MINISTRY OF HEALTH

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Pursuant to Article 26, paragraph 7, Article 43 paragraph 9, Article 51, paragraph 3, Article 52 paragraph 5, Article 53 paragraph 6, Article 56 paragraph 3, Article 60 paragraph 4, Article 63 paragraph 6, Article 69 paragraph 4, Article 98 paragraph 5, Article 100 paragraph 4 of the Medicinal Products Act (Official Gazette 76/2013), the Minister of Health hereby issues the

ORDINANCE

ON GRANTING MARKETING AUTHORISATIONS FOR MEDICINAL PRODUCTS

I. GENERAL PROVISIONS

Article 1

This Ordinance lays down the procedure, conditions and documentation required for granting, renewal, revocation, and transfer of authorisations for the marketing of medicinal products in the Republic of Croatia, the contents of the Summary of Product Characteristics, package leaflets, and labelling of medicinal products, registration, form and content of documentation, proof of traditional use and the rules of labelling traditional herbal medicinal products and registration and content of documentation for the registration of homeopathic medicinal products.

Article 2

(1) This Ordinance transposes the following directives into the legislation of the Republic of Croatia:

1. 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 (SL L 311, 28.11.2001.),

2. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (SL L 33/30, 8. 2. 2003.),

3. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (SL L 159, 27. 6. 2003.),

4. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 on traditional herbal medicinal products (SL L 136, 30. 4. 2004.),

5. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (SL L 136, 30. 4. 2004.),

6. Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the implementing powers conferred on the Commission (SL L 81, 20. 3. 2008.),

7. Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products,

8. Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products (SL L 168, 30. 3. 2009.),

9. Commission Directive 2009/120/EC of 14 October 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal product (SL L 242. 15. 9. 2009).

(2) This Ordinance regulates the implementation of the following regulations:

1. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (SL L 18, 22. 1. 2000),

2. Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’ (SL L 103, 28. 4. 2000),

3. 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 (SL L 136, 30. 4. 2004),

4. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (SL L 324, 10. 12. 2007),

5. Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council (SL L 155, 15. 6. 2007),

6. Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (SL L 334/7, 12. 12. 2008),

7. Commission Regulation (EU) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (SL L 209, 4. 8. 2012).

Article 3

(1) The provisions of this Ordinance shall appropriately apply to all medicinal products for which marketing authorisation applications are submitted in the Republic of Croatia, with certain specifics for the following groups of medicinal products:

– biological medicinal products,

– radio-pharmaceuticals and precursors,

– medicinal products for the treatment of severe and rare diseases (orphan drugs),

– advanced therapy medicinal products,

– homeopathic products,

– traditional and herbal medicinal products.

(2) The specific content of the documentation for the groups of medicinal products referred to in paragraph 1, subparagraphs 1-4 of this Article are provided in Annex II which forms an integral part of this Ordinance, while for groups from indents 5-6 are prescribed in Articles 65 – 76 of this Ordinance.

Article 4

In the sense of the Medicinal Products Act (hereinafter: Act) and this Ordinance, the same medicinal products shall be deemed medicinal products of the same applicant for the granting of marketing authorisation / marketing authorisation holder, having the same quantitative and qualitative composition of active compound and the same pharmaceutical form.

Article 5

(1) In preparing the medicinal product dossier, the applicant is obliged to follow the general chapter, special and general monographs of the European Pharmacopoeia.

(2) In the preparation of the dossier, the applicant shall take consideration of the guidelines of the *European Medicines Agency* (hereinafter: EMA), *European Commission, Coordination Group for Mutual Recognition and Decentralised Procedure, Human Medicinal Products* (hereinafter: CMD(h)) and the *Heads of Medicines Agencies* (hereinafter: HMA).

(3) All significant information on the assessment of the medicinal product, either positive or negative, must be included in the dossier.

(4) The dossier should include all important details on incomplete or terminated preclinical or clinical trials relating to therapeutic indications not reported in the dossier.

(5) For the purpose of monitoring and assessing the cost to benefit ratio of medicinal products, all new information not contained in the application for the granting of marketing authorisation for a medicinal product and all information on the safety of administration of a medicinal product of the marketing authorisation holder shall be submitted to the Agency for Medicinal Products and Medical Devices (hereinafter: Agency).

Article 6

(1) The dossier is submitted with the application pursuant to the provisions of the Act and ordinances adopted pursuant to the Act, and in line with the type of application, group of medicinal product and legal basis for the granting of marketing authorisation for the medicinal product.

(2) The dossier from paragraph 1 of this Article is submitted in the form of the Common Technical Document (hereinafter: CTD), in line with the instructions of the European Commission: *Volume 2B, Notice to Applicants, Medicinal Products for Human Use, Presentation and Content of the Dossier.*

(3) The fundamental sections of the CTD are:

Module 1: Administrative data and medicinal product information

Module 2: CTD summaries

Module 3: Quality

Module 4: Non-clinical study reports

Module 5: Clinical study reports

(4) The structure of individual CTD modules is stipulated in Annex I which forms an integral part of this Ordinance.

(5) The fundamental principles and requirements for the preparation of Module 1 are prescribed in Articles 77–86 of this Ordinance.

(6) The fundamental principles and requirements of the preparation of Modules 2, 3, 4 and 5 are stipulated in Annex I which forms an integral part of this Ordinance.

(7) The dossier in electronic form is submitted to the Agency in an electronic form of the CTD with advanced search possibilities through the dossier (hereinafter: eCTD form) or in temporary electronic form of the CTD without advanced search options (hereinafter: NeeS form).

(8) Exceptionally, if the applicant does not possess the electronic documentation from paragraph 7 of this Article, the applicant shall be obliged to submit Modules 1, 2, 3, 4 and 5 in written form, and additionally Modules 4 and 5 on an electronic medium.

(9) After submission of the dossier in NeeS form, the dossier for all future applications should be submitted exclusively in NeeS or eCTD form.

(10) After submission of the dossier in eCTD form, the dossier for all future applications should be submitted exclusively in eCTD form.

(11) The dossier is submitted as a photocopy, if this Ordinance does not prescribe the original, or a photocopy certified by a notary public.

(12) Exceptionally, the Agency may request the applicant bring the original dossier in for review.

(13) The prescribed dossier may be submitted by the applicant in Croatian or in English, except for the documentation which is prescribed by this Ordinance that is shall be submitted in Croatian.

(14) The Agency may release further instructions regarding the content, form and manner of submission of dossiers on its website.

Article 7

(1) The Agency shall inform the EMA of each denial or revocation of a marketing authorisation for the medicinal product by official duty, every stoppage of marketing a medicinal product or recall of a medicinal product.

(2) If the Agency decision on the marketing of a medicinal product impacts human health in a third country, the Agency shall inform the World Health Organisation therefore, and forward the said notification to the EMA for its information.

(3) The report on the assessment of the dossier from Article 42, paragraph 3 of the Act shall be publicly released on the Agency's website.

(4) The Agency shall act appropriately within 30 days with a decision of the European Commission passed after arbitration proceedings, which pertains to medicinal products that are approved for marketing or are in the marketing authorisation granting procedure in the Republic of Croatia.

II. GRANTING MARKETING AUTHORISATIONS FOR MEDICINAL PRODUCTS

Article 8

(1) The procedure for granting authorisation is initiated with a written application that is submitted to the Agency pursuant to the provisions of the Act and this Ordinance.

(2) The application for granting marketing authorisation for a medicinal product in the Republic of Croatia shall be submitted by the applicant as an original, in Croatian.

(3) The written application from paragraph 1 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product.

(4) The application for granting marketing authorisation for a medicinal product shall contain:

1. name of medicinal product,

2. active substance,

3. pharmaceutical form and strength,

4. pharmacotherapeutic group according to the ATK classification,

5. number of mutual recognition procedures (hereinafter: MRP) or decentralised procedures (hereinafter: DCP), if applicable,

6. information on applicant (name and seat),

7. outline of legal basis for granting the authorisation,

8. data on the form of dossier (eCTD, NeeS, hardcopy),

9. data on whether based on the same dossier an application for granting marketing authorisation for the same medicinal product of a different name (duplicate) has been submitted to the Agency previously or at the same time, with reference to the second application/procedure of granting marketing authorisation,

10. date and signature of the responsible person in the applicant,

11. list of dossiers submitted with the application.

(5) In addition to the application for the granting of marketing authorisation, the applicants is obliged to also submit Modules 1, 2, 3, 4 and 5, unless otherwise stipulated by this Ordinance.

(6) In addition to the application for the granting of marketing authorisation, the applicant is obliged to also submit all parts of Module 1 which are prescribed by Annex I of this Ordinance, except the parts of Module 1, points 1.3.3, 1.3.5, 1.5, 1.7, 1.9 and 1.10 which are to be submitted, if applicable.

(7) The applicant may, pursuant to the identical dossier, submit multiple applications for the granting of marketing authorisation for the same medicinal product having different names (duplicates).

(8) In addition to the application for the granting of marketing authorisation from paragraph 7 of this Article, the applicants is obliged to also submit the dossier as stipulated by the Act and this Ordinance.

(9) In the sense of the Act and this Ordinance, the same applicant or marketing authorisation holder is defined pursuant to the Commission Communication on the Community Marketing Authorisation Procedures for Medicinal Products (98/C 229/03).

Article 9

(1) In addition to the application for the granting of marketing authorisation from Article 8 of this Ordinance, the applicant is also obliged to submit the filled in application form for the

granting of authorisation of the European Commission in English, or a translation of the form provided on the Agency website.

(2) The form from paragraph 1 of this Article shall be submitted by the applicant as an original, signed by the responsible person in the applicant.

(3) The application form from paragraph 1 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product.

(4) In addition to the application form from paragraph 1 of this Article, the applicant is required to submit the data and documents prescribed by the Act and this Ordinance and all data and documents listed in the application form, as applicable.

(5) In addition to the data and documents from paragraph 4 of this Article, the applicant is obliged to submit the following:

– proof of the seat of the applicant, and if the future marketing authorisation holder is a natural or legal persons other than the applicant, proof that the seat of the future marketing authorisation holder is within the territory of the European Union, such proof must be less than six months old as of the date of submission of the application,

– written authorisation of the responsible person in the applicant authorising the person for submission of the application, signing the application form and communications on behalf and for the account of the applicant during the authorisation granting procedure, either as an original or certified photocopy,

– written authorisation of the responsible person of the future authorisation holder, if the future authorisation holder is not also the applicant, authorising the applicant to submit the application for the granting of authorisation on its behalf, either as an original or certified photocopy,

– written authorisation of the responsible person of the applicant authorising the person for submission of the application, signing the application form and communication on behalf and for the account of the applicant after the granting of marketing authorisation, either as an original or certified photocopy,

– written statement of the marketing authorisation holder that is not seated in the Republic of Croatia of the appointment of a local representative that is seated in the Republic of Croatia and the appropriate contact information,

– contract between the manufacturer of the medicinal product responsible for the release of batches of medicinal products onto the market and the future marketing authorisation holder or applicant, if the manufacturer and future authorisation holder or applicant are not the same person,

– proof that the future authorisation holder has a person approved by the Agency for pharmacovigilance with residence in the Republic of Croatia, or proof of a submitted request to the Agency for authorisation of a person responsible for pharmacovigilance with residence in the Republic of Croatia,

– proof of payment of expenses of the marketing authorisation granting procedure,

– proof of payment of the administrative fee.

(6) For persons from paragraph 5, subparagraphs 2, 3 and 4 of this Article, authorisation must also be given by the responsible person of the legal person employing the authorised person.

Article 10

(1) In the marketing authorisation granting procedure, the Agency shall assess the acceptability of the proposed name of the medicinal product.

(2) The Agency may assess a proposed name of a medicinal product as unacceptable if it is not in compliance with Article 3, points 8 and 9 of the Act and the provisions of this Ordinance.

(3) A newly invented name of a medicinal product may not:

– create confusion due to a similarity with a scientific name / international non-proprietary name or common name,

– create confusion due to a similarity with an approved name of another medicinal product,

– created confusion due to suggesting the therapeutic effect of the medicinal product in its name,

– created confusion pertaining to the composition of the medicinal product,

– create confusion pertaining to the safety of the medicinal product,

– contain messages of a promotional character.

(4) If more than one application for marketing authorisation is submitted for the same medicinal product, the proposed names of the medicinal product must differ.

(5) In the authorisation procedure, amendments to the proposed name of the medicinal product in the dossier must meet the criteria from paragraph 3 of this Article.

Article 11

(1) In the national procedure for the grating of authorisation, the applicant is obliged to submit to the Agency a mock-up of the external and internal packaging of the medicinal product in Croatian.

(2) In the mutual recognition and decentralised procedures for granting authorisation, the applicant is obliged to submit to the Agency at the time of submitting the application for the granting of marketing authorisation a mock-up of the external and internal packaging of the medicinal product in one of the languages of the European Union, and in Croatian within 5 days of the completion of the mutual recognition or decentralised procedure.

(3) The mock-up of the external and internal packaging may not:

– create confusion concerning the dosage and manner of application of the medicinal product,

– create confusion concerning the composition of the medicinal product,

– create confusion concerning the safety and efficacy of the medicinal product,

– contain messages of a promotional character,

– create confusion due to the similarity of appearance with another medicinal product.

(4) In the procedure for approval of amendments to the dossier, the proposed mock-up of the external and internal packaging of the medicinal product must meet the conditions from paragraph 3 of this Article.

Article 12

(1) The Agency confirms the validity of the submitted application and assesses the submitted documentation on the medicinal product, in line with the provisions of the Act and of this Ordinance.

(2) Pursuant to Article 27 of the Act, the applicant is obliged at the request of the Agency to submit samples of the medicinal product and the prescribed reference standards, and in the case the applicant fails to submit the same, the deadline from Article 37, paragraph 1 of this Act shall cease to run until the date of submission of the requested materials.

(3) If pursuant to Article 40 of the Act, the Agency deems it necessary to conduct supervision, the deadline from Article 37, paragraph 1 of the Act shall cease to run from the notification of the performance of supervision to the date of completion of the supervision.

Article 13

The Agency shall grant or deny the marketing authorisation for the medicinal product pursuant to the procedure carried out and the assessment of the dossier, pursuant to the provisions of the Act and the ordinances adopted pursuant to the Act.

Article 14

The decision on granting the marketing authorisation for the medicinal product shall contain the following:

1. number of the authorisation,

2. name and seat of the authorisation holder for the medicinal product,

3. name of the medicinal product, the name shall be accompanied by the international non-proprietary name (hereinafter: INN), or if there is no INN, another common name,

4. pharmaceutical form, dosage, type and size(s) of the packaging of the medicinal product;

5. declared composition of the medicinal product;

6. the name and address of the manufacturer responsible for market release of the medicinal product;

7. validity term of the marketing authorisation;

8. manner and place of dispensing the medicinal product;

9. method of prescribing the medicinal product;

10. the method of advertising to general public,

11. conditions pursuant to Article 46, 47 and 48 of the Act which the authorisation holder is obliged to fulfil,

12. frequency of submission of PSURs, where applicable.

Article 15

(1) In the sense of the provisions of Article 54 and 55 of the Act, the date of marketing the medicinal product is the date when one of the types or sizes of packaging of the pharmaceutical form and strength of the medicinal product is released onto the market for the Republic of Croatia.

(2) For medicinal products having marketing authorisation, and for whose reference medicinal product the protection period for the marketing of the medicinal product has not yet expired pursuant to Article 29, paragraphs 2 and 3 of the Act or the appropriate intellectual rights protection period, the start of the three-year period from Article 54, paragraph 1 of the Act commences to run as of the date of the expiry of the appropriate protection period.

(3) The Agency shall release information on the manner of submission of data on the marketing of medicinal products on its website.

Specifics of dossiers for individual types of applications for granting marketing authorisation with regard to the legal basis

Article 16

In accordance with the outline of the legal basis in the application for granting marketing authorisation, the applicant also submits written substantiation for the individual types of applications for granting authorisation and dossiers as prescribed by the Act and this Ordinance.

Article 17

(1) Module 4 and/or 5, which are submitted with the application for the granting of authorisation pursuant to Article 26 of the Act may, where justified, consists of a combination of reports on conducted clinical and/or preclinical trials and data from the scientific literature.

(2) During the authorisation granting procedure, the Agency shall determine the legitimacy of the documentation and the justification for the lack of conducting certain trials from paragraph 1 of this Article.

Article 18

(1) Pursuant to Article 29 of the Act, alongside the application for the granting of marketing authorisation for a generic medicinal product, the applicant is obliged to append Modules 1, 2 and 3 that contain the data prescribed by the Act and this Ordinance, and data on bioavailability and bioequivalence with the reference medicinal product, in line with the guidelines of the European Union.

(2) The applicant requesting the granting of marketing authorisation for a generic medicinal product is obliged to prove that the application and dossier are in compliance with Article 29 of the Act and, if applicable, with Article 31 of the Act.

(3) The proposed Summary of product characteristics of the medicinal product and package leaflets for the Republic of Croatia must be aligned with the Summary of product characteristics of the medicinal product and package leaflets of the reference medicinal product authorised in the Republic of Croatia or a European Union Member State, as listed in the Application form for the granting of authorisation.

(4) The appended expert report/summary on preclinical and clinical documentation in Module 2 must be particularly directed at:

– an assessment of the foundedness of claims of the equivalence of the medicinal product with the reference medicinal product,

– an assessment of the acceptability of impurities present in the active substance(s) and impurities in the medicinal product (including degradation products arising during storage) for medicinal products under preparation,

– an assessment of the conducted bioequivalence testing or substantiation as to why such testing was not conducted in accordance with the valid guidelines of the European Union for testing bioavailability and bioequivalence,

– a new review of the published literature pertaining to the active substance and the submitted application (for this purpose, articles from peer-reviewed scientific journals may be accepted),

– for each claim in the Summary of product characteristics of the medicinal product not ensuing from the properties of the medicinal product and/or its therapeutic groups, a critical overview should be provided and supported by the published literature and/or additional testing.

(5) In the case from Article 29, paragraph 6 of the Act, alongside the application for the granting of marketing authorisation for a generic medicinal product, the applicant is obliged to append additional data for the purpose of confirming the equivalent safety of application and efficacy of the active substances and its salts, esters, ethers, isomers, isomer mixtures, complexes and derivatives.

Article 19

(1) Pursuant to Article 32 of the Act, alongside the application for the granting of marketing authorisation for a medicinal product, the applicant is required to append Modules 1, 2, 3, 4 and/or 5 containing the information stipulated by the Act and this Ordinance. Module 4 and/or 5 should contain a combination of reports on the appropriate pre-clinical and/or clinical trials conducted.

(2) If, based on the conducted trials from paragraph 1 of this Article 1, the applicant cannot confirm the equivalent safety and/or efficacy of the active substance of the reference medicinal product and its salts, esters or derivatives that are contained as an active substance of the medicinal product for which the application for marketing authorisation is requested, the salt, ester or derivative of the active substances of the reference medicinal product shall be considered a new active substance.

Article 20

(1) Pursuant to Article 33 of the Act, alongside the application for marketing authorisation for a medicinal product, the applicant is obliged to append Modules 1, 2, 3, 4 and 5 that contain the information stipulated by the Act and by this Ordinance. Module 4 and Module 5 should contain additional information on the preclinical and/or clinical trials conducted for the purpose of proving the similarity of the two biological medicinal products.

(2) In addition to the documentation from paragraph 1 of this Article, the scope and type of additional data (e.g. toxicological and other non-clinical and the appropriate clinical data) to be submitted shall be determined by the Agency in the procedure of assessing individual applications, in line with the appropriate scientific findings.

(3) Due to the variety of biological medicinal products, the applicant is obliged in Modules 4 and 5 to submit data on the trials conducted, taking into account the specific characteristics of each biological medicinal product.

(4) In the case the reference medicinal product has more than one indication, the safety of use and efficacy of the biosimilar medicinal product must be substantiated/justified or, if necessary, proven separately for each listed indication.

Article 21

(1) Alongside the application for the granting of marketing authorisation for a medicinal product whose active substance(s) have well-established medicinal use pursuant to Article 34 of the Act, the applicant is obliged to append Modules 1, 2, 3, 4 and 5 containing the data prescribed by the Act and by this Ordinance. Module 4 and Module 5 should contain comprehensive scientific data from the literature.

(2) In proving the well-established medicinal use, the applicant is obliged to follow the following rules:

a) factors to be taken into consideration when establishing the well-established medicinal use of the substances in the medicinal product:

– time period of application of the substance,

– frequency and extent of its use,

– degree of scientific interest for the application of the substance (reflected in the published scientific literature), and

– coherence of scientific assessments.

b) the attached documentation on the medicinal product must contain all data that enables an assessment of the safety and/or efficacy of a medicinal product and contains or refers to a review of the corresponding literature, taking into account both pre- and post-marketing studies of the medicinal product, and the published scientific literature that pertains to experiences in the form of epidemiological trials, and particularly comparative epidemiological trials; this documentation must contain data, regardless of whether they are in support of or against the safety and/or efficacy of the medicinal product.

c) special attention should be paid to missing information, and in this case, justification must be given in support of an acceptable safety and/or efficacy level, despite the fact that some information on studies is lacking.

d) expert reports on non-clinical and/or clinical documentation shall contain justification and a critical assessment of any information that differs between the medicinal product as outlined in the scientific literature and the medicinal product for which the marketing authorisation application is submitted; it is necessary to provide an assessment as to whether the medicinal product tested according to literature data can be considered a similar medicinal product for which the marketing authorisation has been requested, despite the existing differences.

e) special consideration should be given to post-marketing experiences with other medicinal products containing the same active substance as the medicinal product for which the marketing authorisation has been requested.

(3) In order to determine the well-established medicinal use of an active substance, the time over which the substance has been used in a medicinal product shall not be less than ten years from its first systematic and documented use as a medicinal product in the European Union.

Article 22

(1) Alongside the application for the marketing authorisation for the medicinal product pursuant to Article 35 of the Act which contains at least two active substances not previously authorised in such combination, the applicant is obliged to submit a full dossier, i.e. Modules 1, 2, 3, 4 and 5 containing the data prescribed by the Act and by this Ordinance.

(2) If applicable, it is necessary to submit data on the safety assessment pertaining to the possible presence of adventitious agents in the medicinal product, with regard to the location of manufacture of the medicinal product.

Article 23

(1) Alongside the application for marketing authorisation of the medicinal product pursuant to Article 36 of the Act, the applicant is obliged to append Modules 1 and 2 containing the data laid down by the Act and by this Ordinance, including an original statement by the responsible person in the authorisation holder for the medicinal product in the Republic of Croatia on the permitted use of pharmaceutical, non-clinical and clinical documentation of the medicinal product.

(2) The marketing authorisation holder granted authorisation pursuant to Article 36 of the Act is obliged to report to the Agency all amendments to the authorisation reported to the Agency for the medicinal product for which the statement from paragraph 1 of this Article is submitted.

Medicinal products containing a combination of medicinal products and medical devices

Article 24

If a medicinal product contains a combination of medicinal product and medical device that enables the application of the medicinal product and with the medicinal product comprises an integral product, the documentation for the medical device is also submitted and must meet the requirements prescribed for the appropriate risk class of medical devices pursuant to the Act on Medical Devices and the ordinances adopted pursuant to the said Act.

III. AMENDMENTS TO THE DOSSIER

Article 25

For the purpose of application of the provisions of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (hereinafter: Commission Regulation (EC) No 1234/2008), the competent body in the Republic of Croatia that performs the procedure of approvals of variations to dossiers is the Agency.

Article 26

(1) The approval procedure for variations is initiated by a written request submitted to the Agency pursuant to the provisions of the Act.

(2) The applicant requesting the approval of a variation is required to submit as an original, in Croatian.

(3) The written request from paragraph 1 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product

(4) The request for approval of the variation(s) contains:

1. name of the medicinal product,

2. active substance,

3. pharmaceutical form and strength,

4. pharmacotherapeutical group according to the ATK classification,

5. types of variation in the dossier,

6. data on the application of grouping and/or worksharing,

7. authorisation number,

8. number of the MRP/DCP procedure, if applicable,

9. data on the applicant (name and seat),

10. data on the form of the dossier (eCTD, NeeS, hardcopy),

11. data on whether a request for the same variation to a marketing authorisation has been submitted to the Agency for another medicinal product previously or at the same time,

12. date and signature of the responsible person in the applicant,

13. list of documentation appended with the application.

Article 27

(1) Alongside the request for approval of variations to the dossier which has received marketing authorisation, the applicant is also required to append:

1. filled-out form for reporting the authorisation of the variation to the European Commission in English, or the translation of the application form available on the Agency website, in the original, signed by the responsible person in the applicant,

2. documentation on the variation in CTD form,

3. proof of payment of procedural costs, and

4. proof of payment of the administrative fee.

(2) The instructions for filling out the form and preparing the documentation in the procedure to approve variation(s) are provided on the Agency website.

Article 28

For variations to the dossiers that require an amendment to data in the approved Summary of product characteristics, package leaflets and labelling of the medicinal product, the applicant is required to submit a proposal of the Summary of product characteristics, package leaflets and labelling of the medicinal product in Croatian, outlining the variation(s) in comparison with the previous approved version, and the proposal of the same in a clean copy.

Article 29

The applicant, in classifying the variations, conditions to be met and the dossier that must be submitted to the Agency with the request for the approval of variation(s), is obliged to act in accordance with the valid guidelines on classifications of variations in the European Union.

Article 30

(1) The expansion of approval as stipulated by Annex I of Commission Regulation (EC) No 1234/2008 requires the initiation of a new procedure for granting marketing authorisation for the medicinal product.

(2) Alongside the application for expansion of approval, the applicant is obliged to append a filled out application form for the granting of marketing authorisation for the medicinal product.

(3) Alongside the request from paragraph 2 of this Article, the applicant is obliged to submit the appropriate dossier in line with the provisions of the Act and ordinances adopted pursuant to the Act, and to refer to sections of the previously submitted dossier pertaining to the new request.

Article 31

The Agency website provides recommendations for the classification of approved variation(s) given pursuant to the national procedure, whose classification is not encompassed by the valid guidelines on the classification of variations in the European Union.

Article 32

The authorisation holder is obliged without delay to submit to the Agency the request for the approval of a change in the person responsible for pharmacovigilance seated in the Republic of Croatia, pursuant to Articles 26 and 27 of this Ordinance.

Article 33

(1) The conditions, documentation and manner of approving changes to the manner of dispensing medicinal products is conducted pursuant to the valid guidelines of the European Commission, recommendations of the European Directorate for the Quality of Medicines (hereinafter: EDQM) and the provisions of this Ordinance.

(2) Alongside the documentation on the medicinal product from paragraph 1 of this Article, the authorisation holder is obliged to submit:

– the proposal of the Summary of product characteristics, package leaflets and labelling of the medicinal product, including a mock-up of the external and internal packaging of the medicinal product,

– risk management plan that defines the possible risks stemming from the changes to the manner of dispensing the medicinal product, and the proposal for managing those risks, if necessary,

– results of testing the comprehensibility and simplicity of the package leaflet.

(3) The authorisation holder is obliged to submit the request for approval of the changes from paragraph 1 of this Article in accordance with Articles 26 and 27 of this Ordinance.

Article 34

Alongside the request for a change of the place of dispensing the medicinal product, the authorisation holder is obliged to submit the following documentation:

– expert report on the clinical documentation that should contain a critical review of the safety of the medicinal product, with regard to the dispensing of the medicinal product outside of pharmacies (Module 2, point 2.5),

– data on the expert for the clinical documentation (Module 1, point 1.4.3),

– proposal of the Summary of product characteristics, package leaflets, labelling of the medicinal product and mock-up of the external and internal packaging of the medicinal product,

– risk management plan that defines the possible risks stemming from changes to the place of dispensing the medicinal product, and proposals for managing those risks, if necessary,

– results of testing the comprehensibility and simplicity of the package leaflets, if applicable.

Article 35

(1) The Agency website provides the conditions for approval of the place and/or manner of dispensing the medicinal product, taking into account the safety profile of the active substance, application route of the medicinal product, pharmaceutical form, size of packaging, maximum individual daily dose, indications or other conditions of use of the medicinal product.

(2) For medicinal products meeting the conditions prescribed under paragraph 1 of this Article, in the expert reports from Articles 33 and 34 of this Ordinance, the authorisation holder is obliged to confirm that all the prescribed conditions have been met in full.

Article 36

(1) The authorisation holder is obliged to submit a request for the approval of changes to the labelling of the medicinal product and/or package leaflet, including changes to the mock-up of the external and internal packaging, and which are not associated with changes to the Summary of product characteristics and which are not encompassed by the valid guidelines on classification of variations in the European Union.

(2) Alongside the request from paragraph 1 of this Article, the authorisation holder is obliged to submit:

– form to report the changes from paragraph 1 of this Article that is available on the Agency website for national procedures and for the national part of the mutual recognition procedure or decentralised procedure, or the reporting form available on the CMD(h) website for the joint part of the mutual recognition or decentralised procedure,

– approved labelling of the internal and/or external packaging of the medicinal product and/or package leaflets, including a mock-up of the internal and external packaging of the medicinal product,

– proposal of the new labelling of the internal and/or external packaging of the medicinal product and/or package leaflets, including a mock-up of the internal and/or external packaging of the medicinal product,

– proof of payment of the procedural costs, and

– proof of payment of the administrative fee.

(3) The authorisation holder is obliged to submit a request for the approval of the amended mock-up of the internal and/or external packaging of the medicinal product from paragraph 1 of this Article in the case that:

– the variation influences the legibility of the text on the packaging of the medicinal product, or

– includes a variation/addition/deletion of text, logo, symbol, pictogram and/or images on the packaging of the medicinal product.

(4) If within 90 days of the date of receipt of the request for approval of variations from paragraph 1 of this Article the Agency does not contest the proposed variation, it shall be deemed accepted.

(5) The authorisation holder and manufacturer of the medicinal product shall not be exempt from legal liability if the Agency does not contest the variation from paragraph 1 of this Article within the deadline from paragraph 4 of this Article.

(6) The authorisation holder and manufacturer of the medicinal product shall not be exempt from legal liability if the Agency does not reject the granting of marketing authorisation for a medicinal product whose labelling or product leaflets are not in accordance with the provisions of the Act, this Ordinance, or with the Summary of product characteristics of the medicinal product.

Article 37

(1) The Agency establishes the validity of the submitted request for the approval of variation(s) in the documentation, pursuant to the provisions of the Act, this Ordinance and Commission Regulation (EC) No 1234/2008.

(2) In the national procedure, the Agency gives its approval for the variation(s) with the Report on the approval of variation(s).

(3) In the mutual recognition and decentralised procedures, the notification on the approval of variation(s) is given by the competent body of the reference state.

Article 38

After the approval of the variation(s) to the dossier, the medicinal product manufactured and marketed in the Republic of Croatia according to the previously granted authorisation may remain on the market until its expiry date, unless the Agency decides otherwise in the variation approval procedure, of which the applicant shall be duly informed.

IV. RENEWAL OF MARKETING AUTHORISATIONS

Article 39

(1) The authorisation renewal procedure for a medicinal product is initiated by a written request submitted to the Agency pursuant to the provisions of the Act.

(2) The authorisation renewal request from paragraph 1 of this Article shall be submitted by the applicant as an original, in Croatian.

(3) The written request from paragraph 1 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product.

(4) The marketing authorisation renewal request for a medicinal product shall contain:

1. name of the medicinal product,

2. active substance,

3. pharmaceutical form and strength,

4. pharmacotherapeutic group according to the ATK classification,

5. authorisation number,

6. number of the MRP/DCP procedure, if applicable,

7. data on the applicant (name and seat),

8. data on the form of dossier (eCTD, NeeS, hardcopy),

9. date and signature of responsible person in the applicant,

10. list of documentation on the medicinal product enclosed with the application.

(5) Alongside the application for renewal of the marketing authorisation, the authorisation holder is obliged to submit the documentation of Modules 1 and 2 containing the data and documents pursuant to Article 40 and 41 of this Ordinance.

Article 40

(1) Alongside the authorisation renewal request from Article 39 of this Ordinance, the applicant is obliged to submit a filled-out reporting form for authorisation renewal of the European Commission in English or a translation of the reporting form available on the Agency website.

(2) The applicant is obliged to submit the form from paragraph 1 of this Article as an original, signed by the responsible person in the applicant.

(3) The form from paragraph 1 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product.

(4) Alongside the form from paragraph 1 of this Article, and alongside the data and documents stipulated by the Act and by this Ordinance, the applicant is also obliged to submit all data and documents listed on the form, as applicable.

(5) With the data and documents from paragraph 4 of this Article, the applicant is also obliged to submit the following:

– written authorisation of the responsible person in the applicant authorising the person to submit the request, sign the application form and communicate on behalf of and for the account of the applicant during the authorisation renewal procedures, as an original or certified copy,

– written authorisation of the responsible person of the authorisation holder, if the authorisation holder is not also the applicant, authorising the applicant to submit the form for the authorisation renewal on its behalf, as an original or certified copy,

– written authorisation of the responsible person of the applicant authorising the person for submission of the request, signing the form and communication behalf of and for the account of the applicant after the renewal of authorisation, as an original or certified copy,

– written statement by the authorisation holder not seated in the Republic of Croatia on the appointment of a local representative seated in the Republic of Croatia and the appropriate contact information,

– contract between the manufacturer of the medicinal product responsible for the release of batches of the medicinal product onto the market and the authorisation holder or applicant, if the manufacturer and authorisation holder or applicant are not the same person,

– proof that the authorisation holder has an Agency approved person responsible for pharmacovigilance with residence in the Republic of Croatia,

– proof of payment of the procedural costs for the authorisation renewal,

– proof of payment of the administrative fee.

(6) For persons from paragraph 5, subparagraphs 1, 2 and 3 of this Article, the authorisation must also be given by the responsible person in the legal person where they are employed.

Article 41

(1) Alongside the application for authorisation renewal, the applicant is also obliged to submit the following sections of Module 2:

– 2.3. Expert's report on quality that should contain:

– expert's statement confirming that in the period since the granting of marketing authorisation, all the newest scientific and technical progress made has been followed, and that all the necessary amendments have been made to ensure that the medicinal product is manufactured and that its quality is verified in line with the generally accepted scientific methods,

– statement that all amendments regarding quality of the medicinal product have been reported and approved, and that the medicinal product is compliant with the valid European guidelines on medicinal product quality,

– statement on the approved quality requirements for the active substance and medicinal product (with date and number of procedure/authorisation),

– qualitative and quantitative composition of active substance(s) and excipient(s) (with date and number of the procedure/authorisation);

– 2.4. Expert's report on preclinical documentation that should contain:

– data supporting the reassessment of the risk-benefit ratio for the medicinal product based on preclinical data collected after the grant or latest marketing authorisation renewal or based on any new data. In absence of recent preclinical data that could affect the risk-benefit ratio, this should be stated in the expert’s report on the clinical documentation, in which case it is not necessary to append the annex on the expert’s report on preclinical documentation with the authorisation renewal request;

– 2.5. Expert's report on clinical documentation that should reflect current risk-benefit ratio based on the safety data from the Periodical Safety Update Reports and safety and efficacy data collected after the grant or latest renewal of the marketing authorisation or after any newly available information, and must contain the following information:

– data on conducted controls of the pharmacovigilance system (date, competent authority conducting the control, site of control, type of control, data on whether the control was conducted for an individual medicinal product, list of medicinal products in question) and analysis of results of controls to the risk-benefit ratio for the medicinal product,

– data on the status of approval of medicinal products around the world: list of countries where the medicinal product has been approved and marketed,

– data on post-marketing measures taken for safety reasons, or since the last authorisation renewal, concluding 90 days prior to the date of submission of the renewal application,

– description of significant measures associated with the safety of the medicinal product that have had a potential influence on the risk-benefit ratio of the approved medicinal product, such as temporary terminations, recalls, temporary stoppages or early conclusions of clinical trials due to the safety reasons, etc.

– significant variations to the Summary of product characteristics of the medicinal product (warnings, counterindications, limitations in indications) after the granting of authorisation or after the last renewal, concluding 90 days prior to the data of submission of the renewal application or variations to the reference data on the safety of the medicinal product that have

not yet been accepted in the approved Summary of product characteristics of the medicinal product. It is necessary to list the significant differences between reference data on the safety of the medicinal product and the proposed summary description of the medicinal product properties,

– data on the assessed exposure of the medicinal product, containing data on the cumulative exposure of subjects in clinical trials and in patients in the post-marketing phase. If the authorisation holder observes that a certain use of the medicinal product requires the introduction of new safety data, it is necessary to append a short description of the said use of the medicinal product, i.e. use of the medicinal product outside the approved indications,

– data from the table summaries should contain a tabular overview of the serious adverse events from clinical trials and the post-marketing adverse reactions since the last authorisation renewal, concluding 90-days prior to the date of submission of the renewal application,

– the summary of significant results on the safety and efficacy of the medicinal product from clinical and non-intervention trials, containing a description of all the significant results of the safety of the medicinal product in the trials that had an influence on the execution of clinical or non-intervention trials. The summaries should state whether the envisaged key objectives from the testing of the safety and efficacy of the medicinal product performed post-marketing, testing concerning the risk management plan and testing conducted as an obligation and condition of the authorisation have been achieved,

– scientific data from the literature: overview of the significant scientific papers published since the first authorisation or since the last authorisation renewal, concluding 90 days prior to the date of submission of the authorisation renewal, which have a possible impact on the risk-benefit ratio of the medicinal product,

– data on the assessment of the risk containing a summary overview of data significant for the safety of the medicinal product, assessment and characterisation of risks, and efficacy of measures to minimise risks since the first authorisation or since the most recent authorisation renewal, concluding 90 days prior to the submission of the authorisation renewal request,

– data on the assessed use of the application of the medicinal product containing a summary overview of data on the efficacy of the medicinal product (including data on shortcomings in efficacy) since the first authorisation or since the most recent authorisation renewal, concluding 90 days prior to the submission of the authorisation renewal request,

– data on the assessment of the risk-benefit ratio of the medicinal product for the approved indication,

– most recently available data on the safety and efficacy of the medicinal product that became available during the preparation of the report.

The expert on the clinical documentation should confirm:

– that there are no new clinical data (or preclinical data if an expert's report on preclinical documentation has not been submitted) that alter or would lead to a new assessed risk-benefit ratio for the medicinal product,

– that the authorisation given for the medicinal product with regard to safety can be renewed for an unlimited time or data submitted on the proposed or taken measures on safety of the medicinal product,

– that the competent authorities have received all the additional data necessary to assess the benefit-risk ratio for the medicinal product,

– that the information on the medicinal product is aligned with the current scientific achievements, conclusions and recommendations published on the EMA website.

Article 42

(1) Alongside the request for renewal of authorisation granted in the national procedure, the applicant may also submit an application(s) for the renewal of authorisation of the same medicinal product of a different pharmaceutical form, strength or type and size of packaging, in order to align all the available data and information on the medicinal product.

(2) In the case from paragraph 1 of this Article, independent of the expiry period of the authorisation for which the renewal is requested, the Agency shall resolve the applications simultaneously and renew all authorisations from paragraph 1 of this Article pursuant to Article 53 of the Act.

Article 43

(1) Alongside the authorisation renewal application, the applicant may, exceptionally, report variations in the Summary of product characteristics, package leaflet and labelling of the medicinal product where such variations:

– are due to the alignment of the name for the pharmaceutical form and composition pursuant to the name in the Croatian Pharmacopoeia,

– are due to an alignment of the form of the Summary of product characteristics, package leaflet and labelling of the medicinal product with valid templates, which does not affect the content of the same,

– ensue from the conclusions of expert reports on preclinical and/or clinical documentation, and impact the risk-benefit ratio of the medicinal product.

(2) For any other variations in the dossier, the authorisation holder is obliged to submit a separate application for the approval of variations to the Agency.

Article 44

At the request of the Agency, the applicant requesting authorisation renewal is obliged to submit samples of the medicinal product and the prescribed reference standards necessary to verify the quality of the medicinal product.

Article 45

(1) After the granting of authorisation renewal in line with the provisions of the Act and this Ordinance, the Agency may grant the subsequent authorisation renewal for an unlimited time, except in the case prescribed by Article 53 paragraph 5 of the Act.

(2) In the authorisation renewal procedure, the Agency may, pursuant to the assessment of the submitted documentation, request amendments in the submitted proposal of the Summary of product characteristics, package leaflet and labelling of the medicinal product.

(3) If in the authorisation renewal process the Agency establishes that the risk-benefit ratio of the medicinal product is no longer positive, it shall deny the renewal of marketing authorisation for the medicinal product.

Article 46

In the authorisation renewal procedure, the authorisation holder is obliged at the request of the Agency to submit, in addition to the data from Articles 40 and 41 of this Ordinance, additional data and documents for the assessment of the risk-benefit ratio of the medicinal product.

V. REVOCATION OF MARKETING AUTHORISATIONS

Article 47

(1) Pursuant to Article 56 of the Act, the marketing authorisation holder for a medicinal product initiates the procedure to revoke the marketing authorisation with a written request to the Agency, in Croatian.

(2) The form requesting the revocation of authorisation from paragraph 1 of this Ordinance is available on the Agency website.

(3) The written request from paragraph 1 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product.

(4) With the request from paragraph 1 of this Article, the applicant is also required to append:

– copy of the valid marketing authorisation,

- copy of the notification in line with Article 55, paragraph 2 of the Act,

– proof of payment of the procedural costs for revocation of the authorisation,

- proof of payment of the administrative fees.

Article 48

The Agency shall render a decision in order to either grant or refuse the revocation of the marketing authorisation within 30 days from the receipt of a valid application.

VI. TRANSFER OF MARKETING AUTHORISATIONS

Article 49

(1) Pursuant to Article 60 of the Act, the marketing authorisation holder for a medicinal product shall submit the application for the transfer of the marketing authorisation to the Agency, as an original, in Croatian.

(2) The application form for the transfer of marketing authorisation from paragraph 1 of this Ordinance is available on the Agency website.

(3) The written application referred to in paragraph 1 shall be submitted separately for each pharmaceutical form and strength of the medicinal product.

(4) The following shall be enclosed with the application for the transfer of the marketing authorisation:

1. the original statement given by the responsible person of the marketing authorisation holder consenting with the transfer of the marketing authorisation to another natural or legal person, and with transfer to that person of all rights and obligations of the marketing authorisation holder, transfer of the medicinal product dossier based on which the authorisation was granted and of all post-authorisation amendments approved (indicate the medicinal product concerned, to which natural or legal person, and other data),

2. the original statement by the natural person or the responsible person of the legal person to whom the marketing authorisation for the medicinal product is being transferred, accepting the transfer of the marketing authorisation, as well as of rights and obligations, responsibilities for the medicinal product, and the medicinal product dossier based on which the authorisation and all authorised amendments were granted (indicate the medicinal product concerned, current authorisation holder and date of assumption of rights and obligations of the future authorisation holder),

3. proof that the seat of the natural or legal person to whom the marketing authorisation is being transferred is in the territory of the European Union, not older than six months from the application submission,

4. written authorisation of the responsible person in the future authorisation holder authorising the person to submit the application, sign the application form and communicate on behalf of and for the account of the future marketing authorisation holder following the transfer of the marketing authorisation, as an original or certified copy,

5. statement by the applicant in the mutual recognition procedure and decentralised procedure giving consent with the submitted application for the transfer of marketing authorisation in the Republic of Croatia to another authorisation holder,

6. written statement of the future authorisation holder not seated in the Republic of Croatia on the appointment of local representation seated in the Republic of Croatia and their contact information,

7. contract between the manufacturer of the medicinal product responsible for the release of batches onto the market and the future authorisation holder, if the manufacturer and future authorisation holder are not the same person and if the contract with the manufacturer submitted to the Agency in the marketing authorisation granting procedure is not longer applicable,

8. proof that the future authorisation holder has an Agency approved person responsible for pharmacovigilance with residence in the Republic of Croatia, or proof of the submitted request to the Agency for approval of the person responsible for pharmacovigilance with residence in the Republic of Croatia.

10. proposal of the Summary of Product Characteristics, package leaflet and instructions for medicinal product labelling (with the data on legal person to whom the marketing authorisation is being transferred),

11. proof of payment of the authorisation transferral procedure costs,

12. proof of payment of the administrative fee.

Article 50

(1) The Agency shall be obliged to either grant or refuse the marketing authorisation transfer of a medicinal product within 30 days from the receipt of a valid application.

(2) The decision on the marketing authorisation transfer to a new holder shall be issued prior to the expiry of the validity term of the marketing authorisation whose transfer was applied for.

VII. MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES

Article 51

The provisions of the Act and of this Ordinance relating to the procedures of granting, renewal, amendments, revocation and transferral of marketing authorisations shall apply appropriately in the mutual recognition and decentralised procedures, with certain specificities as outlined in this Ordinance.

Article 52

When the Republic of Croatia participates in the mutual recognition or decentralised procedures, the applicant, authorisation holder and Agency are obliged to follow the valid guidelines and recommendations of the European Union, including the guidelines and recommendations of the CMD(h).

Article 53

When the Republic of Croatia participates in the mutual recognition or decentralised procedure as a participant state, the Agency either grants or denies marketing authorisations,

renewals or approvals of variations to the marketing authorisations pursuant to the accepted Report on the assessment of the dossier of the reference state in the procedure.

Article 54

(1) Prior to the initiation of a mutual recognition or decentralised procedure in which the Republic of Croatia is the reference state, the applicant is obliged to request the Agency, as the competent authority of the Republic of Croatia, to consider the possibility of initiating such a procedure, and to reach a prior agreement thereto with the Agency.

(2) The Agency is not obliged to accept the request for the initiation of the procedure from paragraph 1 of this Article with the Republic of Croatia as the reference state.

(3) During the consideration of the possibility of initiating the procedure from paragraph 1 of this Article, the Agency may request the applicant align the dossier and to prepare a consolidation of the documentation with the most recent valid data and documents.

Article 55

(1) When the Agency acts as the competent authority of the reference state in the mutual recognition procedure, it is obliged to prepare the repeated report on the assessment of the dossier within a period of 90 days from the agreement reached with the applicant.

(2) The Agency is obliged to forward the Report on the assessment of the dossier from paragraph 1 of this Article, with the approved Summary of product characteristics, package leaflet, and labelling to the participant states in the mutual recognition procedure and to the applicant.

Article 56

(1) When the Agency acts as the competent authority of the reference state in the decentralised procedure, it is obliged to prepare the final draft of the report on the assessment of the dossier, Summary of product characteristics, package leaflets and labelling within a period of 120 days from receipt of the valid application.

(2) The Agency is obliged to forward the Report on the assessment of the dossier, Summary of product characteristics, package leaflet, and labelling from paragraph 1 of this Article to the participant states in the decentralised procedure and to the applicant.

Article 57

(1) After the participant states in the mutual recognition or decentralised procedure accept the report on the assessment of the dossier, Summary of product characteristics, package leaflets and labelling prepared by the Agency as the competent body of the reference state, the Agency completes the procedures and informs the applicant thereof.

(2) When the Agency acts as the competent authority of the reference state in the mutual recognition procedure, upon completion of the procedure, the Agency does not grant new marketing authorisation pursuant to the completed procedure, though the existing authorisation may be amended or revoked.

(3) When the Agency acts as the competent authority of the reference state in the decentralised procedure, it shall grant or deny authorisation within a period of 30 days from the completion of the procedure.

Article 58

(1) When the Agency acts as the competent authority of a participant state in the mutual recognition or decentralised procedure, it is required within a period of 90 days from the date of receipt of the report to accept the report on the assessment of the dossier and the approved Summary of product characteristics, package leaflets and labelling prepared by the reference state, except in the cases stipulated by Article 44 of the Act.

(2) When the Agency participates in the procedure from paragraph 1 of this Article as the competent authority of the participant state, it is obliged within a period of 30 days from the completion of the procedure to grant or deny the marketing authorisation for the medicinal product.

Article 59

For medicinal products for which the authorisation has been granted pursuant to the mutual recognition or decentralisation procedure, the authorisation holder is obliged to submit all requests for the approval or amendments and renewals of authorisation, if applicable, to all competent authorities of the European Union Member States that have granted the marketing authorisation pursuant to the said procedure.

Article 60

In the mutual recognition or decentralised procedure, the competent authority of the reference state may agree with the applicant on a joint date for the renewal of authorisation for all participant states in the procedure, pursuant to which an authorisation was given for a period of shorter than 5 years.

Article 61

(1) The mutual recognition procedure, except in the cases from Article 43 of the Act, is also carried out in the following cases:

– after an arbitration procedure pursuant to Article 44, paragraph 5 of the Act,

- after an arbitration procedure pursuant to Article 44, paragraph 8 of the Act.

(2) The arbitration procedure carried out in accordance with Article 44, paragraphs 1-10 of the Act may be initiated in the procedure for variations to the authorisation.

Repeated procedure

Article 62

The provisions of the Act and of this Ordinance relating to the mutual recognition procedure shall apply appropriately to the repeated procedure.

Abbreviated repeated procedure

Article 63

(1) The abbreviated repeated procedure for the granting of marketing authorisation for medicinal products in the Republic of Croatia as a participant state may only be initiated for a medicinal product for which the authorisation was granted pursuant to the Ordinance on special conditions for the marketing of medicinal products in the Republic of Croatia having marketing authorisation in European Union states (Official Gazette 10/2008).

(2) The marketing authorisation holder granted the marketing authorisation pursuant to the Ordinance from paragraph 1 of this Article is obliged to submit to the Agency a list of the authorisation for which it plans to initiated the abbreviated repeated procedure within a period of 30 days from the date of entry of this Ordinance into force.

Article 64

(1) The application for authorisation from Article 63 paragraph 1 of this Ordinance, in addition to the data listed in Article 8, paragraph 4 of this Ordinance, contains:

– name of the medicinal product and class of marketing authorisation granted pursuant to the Ordinance from Article 63, paragraph 1 of this Ordinance, and

– data on the intent of the authorisation holder to submit an application for the termination of authorisation for the same medicinal product granted pursuant to the Ordinance from Article 63, paragraph 1 of this Ordinance

(2) Alongside the application from paragraph 1 of this Article, the applicant is obliged to submit the following data and documents to the Agency:

a) documentation from Article 9 of this Ordinance,

b) statement of the applicant that the dossier for which authorisation was granted pursuant to the Ordinance on special conditions for the marketing of medicinal products in the Republic of Croatia having marketing authorisation in European Union states is identical to the dossier currently approved in the reference state,

c) list of all amendments and renewals of authorisations approved in the reference state that are submitted to the Agency for the medicinal product authorised pursuant to the Ordinance on special conditions for the marketing of medicinal products in the Republic of Croatia having marketing authorisation in European Union states,

d) proposed date of the joint renewal of authorisations in the mutual recognition procedure.

(3) If the dossier authorised in the reference state is in eCTD or NeeS form, it is necessary to submit all sequences of the documentation in electronic form from the mutual recognition or decentralised procedure.

(4) If the procedure is underway in the Agency to approve variations to the medicinal product authorised in the Republic of Croatia pursuant to the Ordinance on special conditions for the

marketing of medicinal products in the Republic of Croatia having marketing authorisation in European Union states, prior to submitting the request from paragraph 1 of this Article, the applicant is required to contact the Agency to agree to a plan to resolve all unauthorised requests for variations to the authorisation.

(5) During the abbreviated simplified procedure, the Agency shall request the following documentation from the reference state:

a) currently authorised Summary of product characteristics, package leaflet and labelling of the medicinal product in English,

b) list of all variations and renewals of the authorisation approved in the reference state,

c) date of joint renewal of authorisation,

d) as needed, the report on the assessment of the dossier not previously submitted to the Agency.

(6) In the abbreviated repeated procedure, the applicant is not obliged to submit to the Agency the repeated report on the assessment of the dossier by the reference state.

(7) If the Agency accepts the valid Summary of product characteristics, package leaflet and labelling of the medicinal product without reserve in the abbreviated repeated procedure, and with the consent of all participant states, the deadline for completion of the procedure by the reference state may be reduced to 30 days.

VIII. HOMEOPATHIC MEDICINAL PRODUCTS

Article 65

(1) The applicant for the granting of marketing authorisation for homeopathic medicinal products and for issuing a decision on the registration on homeopathic medicinal products is obliged, instead of the application form from Article 9 paragraph 1 of this Ordinance, to submit the filled out application form for the granting of authorisation/issuing of a decision on the registration of a homeopathic medicinal product of the European Union in English, or the translation of that form available on the Agency website.

Article 66

(1) Alongside the application, the applicant from Article 65 of this Ordinance is obliged to submit Module 3 with the following specific requirements and principles:

a) Name

– Latin name of the homeopathic source listed in the dossier must be aligned with the Latin name in the monograph of the European Pharmacopoeia or, if the absence of the same, in the pharmacopoeia of the European Union Member State. If necessary, the traditional/accepted name is also listed.

b) Verification of starting materials

– the appended data and documents on starting materials, i.e. all raw materials used including the starting material and intermediary products up until the final dilution into the medicinal product, should contain information on the homeopathic source,

– general quality standards should be applied to all starting raw materials and in the intermediate steps in production until the final dilution into the medicinal product. If possible, it is necessary to perform a determination of contents if toxic substances are present and if the quality cannot be verified in the final dilution of the medicinal product due to the high degree of dilution. Each dilution step should be carried out in accordance with the homeopathic production methods stipulated by the valid monograph of the European Pharmacopoeia or, in the absence of the same, the Pharmacopoeia of the member state.

c) Verification/testing of medicinal products

– it is necessary to apply the general quality requirements to homeopathic medicinal products, and every exemption should be justified by the applicant. It is necessary to identify and determine the content of toxic substances. If it can be justified that the identification and/or determination of the content of toxic substances is not possible due to their dilution in the medicinal product, the quality should be verified through the comprehensive validation procedure of production and dilution.

d) Stability testing

– it is necessary to append data on stability testing. Data on the stability of homeopathic sources are usually transferrable to dilution/titration. If due to the degree of dilution it is not possible to identify and determine the contents of active substances, data on the stability of the pharmaceutical form may also be considered.

Article 67

For homeopathic medicinal products for which the application is submitted for issuing a decision on the registration of the applicant, it is also necessary to append Module 4, and all missing data must be justified, i.e. justification must be appended that despite the lack of certain testing an acceptable level of safety of the medicinal product can be proven.

Article 68

For homeopathic medicinal products for which an application is submitted for issuing a decision on registration, the applicant is obliged in Module 5 to submit the documentation proving the homeopathic use of the homeopathic source(s) based on the appropriate literature data.

Article 69

The authorisation holder of a homeopathic medicinal product and the holder of the decision on registration of a homeopathic medicinal product is obliged in the authorisation renewal procedure and the decision on registration renewal procedure, instead of the application form from Article 40, paragraph 1 of this Ordinance to submit the filled out application form for authorisation renewal/decision on registration renewal that is available on the HMA website in English, or the translation of that form available on the Agency website.

Article 70

(1) The holder of the decision on registration of the homeopathic medicinal product is obliged in the variation approval procedure, instead of the application form from Article 27, paragraph 1 of this Ordinance, to submit the filled out application form for the approval variations to the registration decision of the homeopathic medicinal product available on the Agency website, in which it is mandatory to give a short description of the variations and to submit the appropriate data and documents or documentation.

(2) The Agency shall grant or deny the approval of variations from paragraph 1 of this Article within a period of 60 days from the receipt of the valid application.

IX. HERBAL MEDICINAL PRODUCTS

Article 71

(1) The applicant requesting marketing authorisation for an herbal medicinal product is obliged to also append the dossier, with the following specificities:

1. Herbal substance and herbal preparations

– the phrase 'herbal substances and preparations' should be considered equivalent to the phrases 'herbal drugs and herbal preparations', in accordance with the definition in the European Pharmacopoeia,

– in the sense of the names of herbal substances, the binomial scientific name of the plant (genus, species, subspecies and authority) and chemotype (where applicable), parts of the plant, description of the plant substances, other names (synonyms listed in other pharmacopoeias) and laboratory codes should be listed,

– in the sense of the names of herbal preparations, the binomial scientific name of the plant (genus, species, subspecies and authority) and chemotype (where applicable), parts of the plant, description of the plant preparations, ratio of plant substances in the preparation, extraction solvent(s), other names (synonyms listed in other pharmacopoeias) and laboratory codes should be listed,

– for an overview of the part of the structure of the herbal substances and preparations, where applicable, the physical form and description of components of known therapeutic activity or markers (molecular formula and relative molecular mass, structural formula including relative and absolute stereochemistry) and other elements should be appended,

– for an overview of the part of the production of herbal substances, it is necessary to append, where applicable, the name, address and responsibility of individual suppliers, including cooperation/responsible suppliers, and every proposed location or plant participating in production/collection and the verification of herbal substances.

For an overview of the part of production of herbal preparations, it is necessary to append, where applicable, the name, address and responsibility of individual manufacturers, including those cooperative/responsible, and every proposed location or plant participating in production/collection and the verification of herbal preparations.

– in the sense of the description of the production process and process controls for herbal substances, the appended data need to appropriately describe the manner of obtaining and collecting the plant species, including the geographical origin of medicinal plants and the conditions of growing, collection, drying and storage,

– in the sense of the description of the production process and process controls for herbal preparations, the appended data need to appropriately describe the production process of the preparation, including a description of obtaining, solvents and reagents, the purification and standardisation phases,

– in the sense of the development of production procedures, it is necessary to append, where appropriate, a short summary that describes the development of herbal substances and preparations, taking into consideration the proposed manner and route of administration of the medicinal product,

– it is necessary to consider, where appropriate, the comparative results of the photochemical composition of the herbal substances and herbal preparations used in the accompanying literature data and herbal substances and preparations contained within the herbal medicinal product,

– in the sense of explaining the structure and other properties of herbal substances, it is necessary to append the data on the botanical, macroscopic, microscopic and phytochemical characteristics and, where necessary, the biological activity,

– in the sense of explaining the structure and other properties of the herbal preparation, it is necessary to submit data on the phyto- and physico-chemical characteristics and, where necessary, the biological activity,

– if applicable, quality requirements and analytical procedures for testing herbal substances and preparations should be appended,

– if applicable, the analytical procedures used in the testing of herbal substances and herbal preparations should be listed,

– in the sense of validation of the analytical procedures, it is necessary to append, where appropriate, the documentation on the analytical validation, including the experimental data on the analytical procedures used in testing the herbal substances and herbal preparations,

– in the sense of the analysis of batches, it is necessary to append, where applicable, a description of the batch and results of the batch analysis of herbal substances and herbal preparations, including those for Pharmacopoeia substances,

– if applicable, justification of the quality requirements of the herbal substances and herbal preparations should be appended,

– if appropriate, data on the reference standards or materials for the testing of herbal substances and herbal preparations should be appended,

– if the herbal substance or herbal preparation is described by a monograph of the European Pharmacopoeia, the applicant may submit a request to obtain the Certification of compliance of the monograph of the European Pharmacopoeia.

2. Herbal medicinal products

– in the sense of the development of formulations, it is necessary to append, where appropriate, a short summary describing the development of the herbal medicinal product, taking into account the proposed manner and application route of the medicinal product,

– if appropriate, the results of comparisons of the phytochemical composition of the product used in the literature and the herbal medicinal product for which the application is submitted should be considered.

Traditional herbal medicinal products

Article 72

(1) The registration of traditional medicinal products is performed in the national procedure for the granting of marketing authorisation in the Republic of Croatia pursuant to the provisions of this Ordinance.

(2) Exceptionally from paragraph 1 of this Article, if the *Committee for Herbal Medicinal Products* (hereinafter: HMPC) adopts the Community monograph for the herbal substance or preparation contained in the herbal medicinal product in question, or when the herbal medicinal product contains herbal substances, preparations or a combination thereof from the *Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products* (hereinafter: Community list), the registration procedure for the traditional medicinal product is carried out pursuant to the provisions stipulated by the mutual recognition and decentralised procedures.

(3) The Community list from paragraph 2 of this Article contains a list of the herbal substances, preparations and combinations thereof that are applied as traditional herbal medicinal products, with data on their indications, strength, dose, administration route and other pertinent data for the safe use of traditional herbal medicinal products.

Article 73

(1) The procedure to issue decisions on the registration of traditional medicinal products is initiated by a written request pursuant to Article 8 of this Ordinance.

(2) Alongside the application from paragraph 1 of this Article, the applicant is obliged to append:

– application form and documentation from Article 9 of this Ordinance,

– data and documents from Article 26, paragraph 3, points a) to h) of the Act,

– results of pharmaceutical testing from Article 26, paragraph 3, point k) of the Act,

– data and documents from Article 26, paragraph 3, points o) and p) of the Act,

– data on the granting of marketing authorisation in another European Union Member State or third country, the reasons for denial of marketing authorisation or revocation of authorisation within or outside the European Union and the reasons for such decisions,

– bibliographic evidence or expert evidence that the traditional medicinal product or corresponding medicinal products have been in medicinal use for at least 30 years to the date of submission of the application, of which at least 15 years in the European Union, including data on the traditional area of use, traditional indications, strength, dosage, manner and duration of use that should be listed in the expert's report on the clinical documentation.

– bibliographic overview of data on safety, together with the expert's report on preclinical documentation and, at the request of the Agency, additional data necessary to assess the safety of the medicinal product (e.g. data on genotoxicity),

– evidence that the applicant has a qualified person responsible for pharmacovigilance seated in the Republic of Croatia, and who meets the criteria relating to reporting on all suspected adverse reactions,

– expert report on the quality of the medicinal product,

– expert report (signed and dated) which confirms that the reports on medicinal product quality, i.e. the report on preclinical documentation or the report on clinical documentation which are an integral part of the dossier, have been compiled in accordance with the provisions of this Ordinance,

– short resume of the expert on the medicinal product quality, on the preclinical and clinical documentation containing the name and surname, education, additional training and work experience of the expert.

(2) The Summary of product characteristics of the traditional herbal medicinal product need not contain the data prescribed by Article 100, paragraph 1, point 4 of the Act.

(3) The applicant requesting registration of the traditional herbal medicinal product is obliged to submit the documentation for the registration of the traditional medicinal herbal product in CTD form, pursuant to the valid EMA guidelines.

(4) If the application for registration of the traditional herbal medicinal product pertains to an herbal substance, preparation or combination thereof contained within the Community list, the applicant is not obliged to submit the data prescribed in paragraph 2, subparagraphs 5, 6 and 7 of this Article.

(5) If the application for registration of a traditional herbal medicinal product pertains to an herbal substance, preparation or combination thereof contained on the Community list, the Agency may not deny the decision for registration of the traditional herbal medicinal product for the reasons laid down by Article 64, paragraph 1, subparagraphs 3 and 4 of the Act.

(6) If the herbal substance, preparation or combination thereof is no longer on the Community list, the Agency shall revoke the approval for registration of the traditional herbal medicinal

product if the authorisation holder does not submit all the data and documents pursuant to paragraph 2 of this Article within a period of three months.

(7) If the traditional herbal medicinal product contains a combination of active substances, the applicant is obliged to submit data from Article 63, paragraph 2, subparagraph 5 of the Act for the combination in question, and data on the individual active substances if they are insufficiently well known.

(8) The external use from Article 63, paragraph 2, subparagraph 3 of the Act includes application to the skin, membranes of the oral and nasal cavities, rectal and vaginal membranes, external auditory canal and ocular application, with the condition that this primarily relates to local activity and that there are no barriers concerning the safety of the medicinal product.

(9) Traditional herbal medicinal products are not products containing chemically defined active substances (synthetic compounds or substances isolated from plant materials, such as camphor, menthol, cineol, etc.) or substances of biological or animal origin (e.g. fish oil, bee products, etc.).

Article 74

(1) For the purpose of determining the period of traditional use, the applicant is obliged to submit bibliographic evidence or expert evidence that the traditional herbal medicinal product or similar medicinal product has been in medicinal use for at least 30 years to the date of submission of the application, including at least 15 years in the European Union.

(2) The Agency may request the opinion of the HMPC on the adequacy of evidence on the long-term use of the herbal medicinal product or similar product, and shall submit the accompanying documentation with its request.

(3) The traditional use of a medicinal product may be proven in the case when the marketing of the product is not based on a specific authorisation procedure, and when the number of quantity of ingredients of the medicinal period in that period is reduced.

(4) If the medicinal product has been in use in the European Union for less than 15 years, but is suitable for registration as a traditional herbal medicinal product, the Agency shall forward the application for registration of the traditional herbal medicinal product to the HMPC with the accompanying documentation. The HMPC will consider whether the remaining criteria for the registration of the traditional herbal medicinal product have been fully met. If the HPMC assesses that the application is founded, it will draft a Community monograph that the Agency shall consider when making the final decision on the application for issuing the decision on registration of the traditional herbal medicinal product.

(5) When the herbal substance, preparation or combination thereof is included on the Community list, or after the adoption of their Community monographs, the authorisation holder for a traditional herbal medicinal product containing the said active substances is obliged to align the data on the medicinal product (Summary of product characteristics, package leaflets and labelling) with the said documents and submit an application to the Agency for approval of the variations to the registration.

Article 75

(1) The labelling and leaflet on the traditional herbal medicinal product, together with the data and requirements prescribed by the Act and this Ordinance, must also contain the following claims:

– that the product is a traditional herbal medicinal product for use in the marked indications based on the experience of long-term use, and

– that the patient should consult a physician or pharmacist if the symptoms do not cease with the administration of the medicinal product or in the case of appearance of undesired effects listed in the leaflet of the medicinal product.

(2) The Agency may request the registration holder to list the types of traditional uses of the medicinal product in question in the labelling and package leaflet.

Article 76

(1) Instead of the application form from Article 27, paragraph 1 of this Ordinance, the applicant is obliged to submit the filled out application form for the amendment of the decision on registration of the traditional herbal medicinal product available on the Agency website in which it is necessary to give a short description of the amendment, with submission of the appropriate data and documents.

(2) The Agency shall approve or deny the amendments to the decision on registration of the traditional herbal medicinal product within a period of 60 days from receipt of the valid application.

X. FUNDAMENTAL PRINCIPLES AND REQUIREMENTS FOR THE PREPARATION OF MODULES AND THE COMMON TECHNICAL DOCUMENT

Article 77

(1) The applicant is obliged in Module 1 to use the names according to the European Pharmacopoeia and Croatian Pharmacopoeia for the active substances and excipients in the composition of the medicinal product, while for pharmaceutical forms, manner of administration of the medicinal product and containers, it is necessary to use standard phrases.

(2) When a substance is not listed in the Croatian Pharmacopoeia, its name in the documents in the Croatian language should be created according to the same rules by which the Croatian names in the Croatian Pharmacopoeia have been created.

(3) When there is no standard term for a pharmaceutical form, manner or route of administration or container, and the Croatian standard term is not listed in either the Croatian Pharmacopoeia or in the publication *Standard terms: Pharmaceutical dosage forms, Routes of administration, Containers*, then the used Croatian term for the pharmaceutical form, manner or route of administration or container should be accompanied by a detailed description and the English term.

Article 78

The applicant is obliged to draft a proposed Summary of product characteristics for the medicinal product in accordance with the instructions and template available on the Agency website.

Article 79

(1) The applicant is obliged to draft proposed package leaflets in accordance with the instructions and template available on the Agency website.

(2) The package leaflet for a medicinal product authorised pursuant to the national procedure, mutual recognition procedure and decentralised procedure, in addition to the data from Article 98 of the Act, must also contain the following data:

1. manner and place of dispensing the medicinal product,

2. name, address and telephone number of the representative of the authorisation holder for the Republic of Croatia, if one is appointed.

Article 80

(1) The applicant is obliged to draft a proposal of the external and internal labelling of the medicinal product in accordance with the instructions and template available on the Agency website.

(2) With the data stipulated by the Act, the proposed external and internal labelling of the medicinal product must also include the following data:

– price of medicinal product,

– obtaining the right to a refund for the medicinal product,

– EAN code (barcode).

(3) The addition of a QR code or 2D code on the external labelling of the medicinal product is permitted under the following conditions:

– the code is intended for monitoring the production procedure, stocks of the medicinal product or as a means of protection from counterfeiting of the medicinal product,

– all data accessible to the public must contain only data in accordance with the approved Summary of product characteristics, package leaflets or labelling of the medicinal product in the Republic of Croatia,

– the code may not affect the legibility of other data contained on the external labelling of the medicinal product,

– the code may not be associated with internet content.

(4) If the criteria from paragraph 3 of this Article are met, the authorisation holder is not required to submit an application for the approval of variation(s) for the addition of the QR code on the external labelling of the medicinal product.

Article 81

The provisions of this Ordinance on the labelling and package leaflets shall not apply to medicinal products imported pursuant to the provisions of Article 129 of the Act.

Article 82

(1) Upon assessing the comprehensibility and simplicity of the package leaflets conducted in cooperation with target groups of patients, the applicant is obliged to act in accordance with the valid guidelines of the European Commission and instructions provided on the Agency website.

(2) Upon adding information in Braille on the packaging of medicinal products and preparing a package leaflet that is appropriate for blind and vision impaired persons, the applicant is obliged to abide by the valid guidelines of the European Commission and instructions provided on the Agency website.

Article 83

The applicant is obliged to submit the following information about the experts from Article 5, paragraph 1, point 1.4 of this Ordinance:

– statement of the expert, signed and dated, confirming that the reports on the quality of the medicinal product, report on the preclinical documentation or reports on clinical documentation that are an integral part of the dossier have been compiled in accordance with the provisions of this Ordinance,

– short curriculum vitae of the expert, including name and surname of the expert, information on education, additional training and work experience.

Article 84

(1) Alongside the application for the granting of marketing authorisation for a medicinal product, the applicant is also obliged to submit an assessment of the risk the medicinal product could have on the environment.

(2) The risk assessment from paragraph 1 of this Article should contain an overview of the possible hazards that the use and/or disposal of a certain medicinal product could present to the environment, and list the same on the labelling.

(3) The applicant is obliged to consider the threat to the environment presented by medicinal products containing or consisting of genetically modified organisms (hereinafter: GMO).

(4) The data on the risk a medicinal product may have on the environment must be compliant with Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the intention introduction of genetically modified organisms into the environment

replacing Council Directive 90/220/EEC (hereinafter: Directive 2001/18/EC) and the European Union guidelines.

(5) Data on the risk the medicinal product may have on the environment consist of:

– introduction;

– copy of the written consent with the intended release of GMO into the environment for research and development purposes in accordance with Part B of Directive 2001/18/EC;

– data prescribed by Annexes II to IV of Directive 2001/18/EC, including the detection and recognition methods and a single symbol for GMO, and all additional data on the GMO in question or the medicinal product that are important for the assessment of the risk the medicinal product can have on the environment,

– report on the environmental risk assessment of the medicinal product (ERA) prepared pursuant to the data listed in Annexes III and IV of Directive 2001/18/EC and in line with Annex II of Directive 2001/18/EC;

– conclusions that propose the appropriate risk management strategy, taking into account the abovelisted data included in the ERA, and with regard to the GMO and the medicinal product in question, post-marketing monitoring plan and determination of all specificities that should be included in the Summary of product characteristics, labelling and package leaflet;

– appropriate public information measures.

(6) The data on the environmental risk assessment of the medicinal product must also contain the list of experts who drafted the assessment, including the date of drafting, information on the experts' education, professional training and work experience, and a statement on the relations between the expert and the applicant.

Article 85

(1) The summary of the pharmacovigilance system, risk management plan and manner of drafting and frequency of submitting the Periodic Safety Update Report of the medicinal product (hereinafter: PSUR) shall be drafted pursuant o the regulations on pharmacovigilance.

(2) During the assessment of the dossier, the Agency may request that the applicant submit the latest available PSUR if the medicinal product is marketed in any of the states for at least nine (9) months prior to the submission of the application for the marketing authorisation in the Republic of Croatia.

Article 86

In the manufacture of medicinal products, the manufacturer may only use those colours approved for use in the production of food.

XI. DEROGATIONS IN LABELLING AND PACKAGE LEAFLETS

Article 87

(1) The authorisation holder shall submit derogations in labelling and package leaflets from Article 101 of the Act to the EMA.

(2) The procedure for the authorisation of derogations in labelling and package leaflets from Article 102, paragraph 1 of the Act may be carried out during the granting procedure or approval of variations, if additional requested and justified by the applicant.

(3) The procedure for the authorisation of derogations in labelling and package leaflets from Article 102, paragraph 2 of the Act is initiated by a written request in the Croatian language submitted to the Agency as an original.

(4) The written request from paragraph 3 of this Article is submitted separately for each pharmaceutical form and strength of the medicinal product.

(5) The authorisation holder may submit the request from paragraph 3 of this Article upon completion of the authorisation granting procedure, under the condition that the medicinal product for which the approval of the derogation from Article 102, paragraph 2 of the Act is requested is dispensed only with a physician's prescription.

(6) The applicant shall append the following data and documents to the request from paragraph 3 of this Article:

– name of the medicinal product,

– active substance,

– pharmaceutical form and strength, type and size of packaging,

– substantiation of the request,

– data on the size of the production batch of the medicinal product for which the derogation is requested,

– expiry period of the medicinal product,

– data on the annual consumption of medicinal products in the area of the Republic of Croatia, or the assessment of the annual consumption of medicinal products for the territory of the Republic of Croatia, if the medicinal product has been marketed in the Republic of Croatia for at least one year or has not yet been marketed in the Republic of Croatia,

– number of individual packages of the medicinal product for which the derogation is requested,

– statement by the marketing authorisation holder that the medicinal product has been produced and that its quality has been controlled in line with the marketing authorisation for the Republic of Croatia,

– mock-up of the external and internal packaging of the medicinal product in a foreign language,

– proof of payment of the procedural costs,

– proof of payment of the administrative fee.

(7) The Agency shall grant or reject the consent for the derogation from paragraph 3 of this Article.

(8) The Agency may give the consent for the derogation from paragraph 3 of this Article for individual batches of a medicinal product for a maximum period of one year.

(9) The agency may give its consent for the partial derogation from the obligation to include the package leaflet in Croatian in such a way that with the package leaflet in a foreign language, the package leaflet in Croatian must be appended to the medicinal product packaging.

(10) The Agency may give its consent for the partial derogation from the obligation of labelling in Croatian in such a way that the external packaging is equipped with a sticker label in Croatian.

(11) In the derogation approval procedure from paragraph 3 of this Article, the Agency may also approve derogations from Article 102, paragraph 1 of the Act, if so requested and substantiated by the applicant.

XII. SUPPLEMENTATION OF DOCUMENTATION FOR APPROVED MEDICINAL PRODUCTS IN THE REPUBLIC OF CROATIA

Article 88

(1) The supplementation of documentation on the medicinal product is the procedure of aligning the content of the dossier for the medicinal product authorised in the Republic of Croatia prior to its accession to the European Union with the provisions of the Act and this Ordinance.

(2) For supplementation of the dossier, the authorisation holder is obliged to submit the following to the Agency:

– written request,

- application form for the supplementation of the dossier available on the Agency website,

– dossier to be supplemented when applicable,

– substantiation for individual types of applications (Module 1, point 1.5.1 or 1.5.2),

– Summary of product characteristics, package leaflet and labelling of the medicinal product, if applicable.

(3) The dossier to be submitted by the authorisation holder for the purpose of supplementation of the documentation shall depend on the alignment of the documentation at the time of submission of the application for the supplementation, taking into account the documentation

pursuant to which the marketing authorisation was initially granted, documentation for the approved variations and supplemented documentation through the renewal procedure.

(4) After the completion of the procedure to assess the application for supplementation of the dossier, the Agency issues notification on the supplemented dossier or revokes the marketing authorisation.

(5) The Agency shall publish instructions on its website on the content, form and manner of submitting documentation for the supplementation of the dossier.

XIII. TRANSITIONAL AND FINAL PROVISIONS

Article 89

As of the date of entry of this Ordinance into force, the Agency shall initiate the procedure of revoking the marketing authorisation for medicinal products authorised in the Republic of Croatia prior to the accession to the European Union, and for which the procedure of supplementation of the dossier has not been carried out pursuant to the Ordinance on the procedure and manner of granting marketing authorisations for medicinal products (Official Gazette 113/08 and 155/09) and which are not listed on the List of medicinal products from Annex V of the Treaty on the Accession of the Republic of Croatia to the European Union and which do not have marketing authorisation in compliance with the provisions of the Medicinal Products Act (Official Gazette 71/07, 45/09 and 124/11), Ordinance on the procedure and manner of granting marketing authorisations for medicinal products (Official Gazette 113/08 and 155/09, and Ordinance on special conditions for the marketing of medicinal products in the Republic of Croatia that have marketing authorisation in the European Union states (Official Gazette 10/08).

Article 90

The marketing authorisations for medicinal products in the Republic of Croatia granted pursuant to the abbreviated repeated procedure and authorisation for the same medicinal product granted pursuant to regulations valid prior to 1 July 2013 may remain simultaneously valid, on the condition that the names of the medicinal products differ.

Article 91

As of the date of entry of this Ordinance into force, the Ordinance on the procedure and manner of granting marketing authorisations for medicinal products (Official Gazette 113/08 and 155/09), Ordinance on the testing of bioavailability and bioequivalence of medicinal products (Official Gazette 71/99), Ordinance on the criteria for the production and marketing and the manner of controlling quality and keeping the record log on homeopathic products (Official Gazette 62/05) and the Ordinance on the marketing, labelling and advertising of traditional herbal medicinal products (Official Gazette 89/10) shall cease to have effect, except in the part pertaining to the advertising of traditional herbal medicinal products.

Article 92

This Ordinance is published in the Official Gazette, and enters into force on 2 July 2013.

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Zagreb, 26 June 2013

Minister

Professor Rajko Ostojić, MD, PhD., m. p.

ANNEX I

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2. BASIC PRINCIPLES AND REQUIREMENTS OF PREPARATION OF MODULES 2, 3, 4 AND 5 OF THE COMMON TECHNICAL DOCUMENT

MODULE 2

SUMMARIES OF THE COMMON TECHNICAL DOCUMENT

2.1 Contents of the Common Technical Document (Modules 2-5)

Module 2 lists the content of the documentation of Modules 2 through 5.

2.2 Introduction

Information on the pharmacological class, mechanism of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be provided.

2.3, 2.4 and 2.5 Expert reports

Experts are required to provide comprehensive reports on their observations concerning the documents and data that make up the documentation for the granting of marketing authorisation, and in particular for Modules 3, 4 and 5.

Experts are required to address the critical parameters relating to the quality of the medicinal product and testing conducting on animals and humans, and to outline all data necessary for the assessment of the dossier.

The experts prepared the Expert report on quality of the medicinal product (Module 2.3), Expert report on pre-clinical documentation (Module 2.4) and Expert report on clinical documentation (Module 2.5) which are appended to the application for the granting of marketing authorisation for the medicinal product.

2.3 Expert Report on the Chemical, Pharmaceutical and Biological Documentation

The report shall contain an overview of data on the chemical, pharmaceutical and biological documentation.

Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases of deviation from requirements.

The report shall be drawn up in compliance with the content and format of the corresponding data presented in Module 3.

2.4 Expert Report on Non-clinical Documentation

The report shall present an integrated and critical assessment of the pre-clinical evaluation of the medicinal product in animals (*in vitro*).

Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.

Except for biological products, an assessment of the impurities and degradation products along with their potential pharmacological and toxicological effects shall be included.

The implications of any difference in the chirality, chemical form, and impurity profile between ingredients used in non-clinical studies and the medicinal product for which the marketing authorisation is required shall be discussed.

For biological medicinal products, comparability of material used in non-clinical studies and clinical studies and the medicinal products for which the marketing authorisation is required should be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated in the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in humans shall be discussed.

2.5 Expert Report on Clinical Documentation

The clinical documentation overview is intended to provide a critical analysis of the clinical data included in the clinical documentation summary and Module 5.

The approach to the clinical development of the medicinal product, including the study protocol and performance of the studies should be described.

Besides, a brief overview of the clinical findings, including important restrictions and benefits and risks assessment based on conclusions of relevant clinical studies shall be provided.

An interpretation of the way the efficacy and safety findings support the proposed dosage and target indications and an evaluation of how the Summary of Product Characteristics and other approaches will optimise the benefits and manage the risks is required.

Efficacy or safety issues encountered in the development of the medicinal product and unresolved issues shall be explained.

2.6 Summary of Non-clinical Documentation

The results of pharmacology, pharmacokinetics and toxicology studies carried out in animals (*in vitro*) shall be provided in the form of written and tabulated summaries which shall be presented in the following order:

Introduction

– Pharmacology Written Summary

– Pharmacology Tabulated Summary

– Pharmacokinetics Written Summary

– Pharmacokinetics Tabulated Summary

– Toxicology Written Summary

– Toxicology Tabulated Summary.

2.7 Summary of Clinical Documentation

A detailed, factual summarisation of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutical studies, of clinical pharmacology studies, and of clinical efficacy and safety studies.

A synopsis of the individual studies is also required.

Summarised clinical data shall be presented in the following order:

– Summary of bio-pharmaceutics studies and associated analytical methods

– Summary of clinical pharmacology studies

– Summary of clinical efficacy

– Summary of clinical safety

– Synopsis of individual studies

MODULE 3

QUALITY

for medicinal products containing chemical and/or biological active substances

The appended documentation on quality shall contain all the relevant data on the active substance(s) and the medicinal product on: the pharmaceutical development and manufacturing process, the structure elucidation and other properties, the specifications and quality control methods, the stability, and the composition and type of packaging.

Separate sets of information should be provided for the active substance and for the medicinal product.

Detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the medicinal product should be provided.

All the procedures and methods used for manufacturing and quality control of the active substance and the medicinal product shall be described in sufficient details to enable them to be repeated if required. All test methods and procedures shall correspond to the current

scientific progress and shall be validated, and the results of the validation studies shall be provided. In the case of test methods included in the European Pharmacopoeia, the method description shall be replaced by the appropriate reference to the monograph(s) and general chapter(s) of the European Pharmacopoeia.

The monographs of the European Pharmacopoeia shall be applicable to all substances and pharmaceutical forms appearing in it. However, where a material declared in accordance with the European Pharmacopoeia has been prepared by a method liable to leave impurities not described in the European Pharmacopoeia monograph, these impurities and their tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia is insufficient to determine the quality of the substance, the Agency may request more appropriate specification from the applicant. The Agency shall inform the authorities responsible for the pharmacopoeia accordingly, and the applicant shall provide the authorities with the details of the alleged insufficiency and the specifications applied.

In the case of testing methods included in the European Pharmacopoeia, the corresponding monograph (s) and general chapter(s) of the European Pharmacopoeia shall be indicated instead of the description.

In case where starting and raw materials, active substance(s) or excipients are not described in the European Pharmacopoeia, compliance with the monograph of an EU Member State pharmacopoeia may be accepted. Where such monographs are not available, compliance with a monograph of a valid pharmacopoeia of another country may be accepted, but in such case a copy of the monograph shall be submitted accompanied by the testing procedures contained in the monograph, and by a translation where appropriate.

If the active substance and/or a starting and raw material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant may apply for a Certificate of suitability issued by the European Directorate for the Quality of Medicines & Healthcare (EDQM), which is to be attached to the appropriate section of Module 3. The Certificates of suitability of the monographs of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections in this Module. The manufacturer is required to provide a written guarantee to the applicant that the production procedure has not been altered after the issuance of the Certificate of suitability of the monograph of the European Pharmacopoeia.

For a completely defined active substance, the active substance manufacturer or the applicant may arrange for:

(i) detailed description of the manufacturing process,

(ii) quality control during manufacture, and

(iii) process validation

The manufacturer of the active substance directly submits this information to the Agency as an *Active Substance Master File* (ASMF). In this case, the manufacturer shall provide the applicant with all of the data, which may be necessary for the latter to take full responsibility for the finished medicinal product. The manufacturer of the active substance shall confirm in

writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the Agency, and when they concern the open part of the active substance master file these documents and particulars shall be also supplied to the applicant.

For materials which may present risk of transmitting animal spongiform encephalopathy– TSE/BSE (materials of ruminant origin), the applicant must prove compliance of the used materials with the relevant guidelines on minimising the risk of transmission of animal spongiform encephalopathy agents via medicinal products and its subsequent amendments, published by the Commission in the Official Journal of the European Union. Demonstration of safety/compliance can be preferably done by submitting a certificate of suitability to the relevant general Article of the European Pharmacopoeia, granted by EDQM, or by the supply of scientific data to substantiate this compliance.

Information assessing the risk with respect to potential contamination with adventitious agents that are usually not contained in a medicinal product composition, whether they are of viral or non-viral origin, shall be provided, as laid down in the European Pharmacopoeia and relevant guidelines of the European Union.

Any special apparatus or equipment, which may be used at any stage of the manufacturing process and quality control of the medicinal product, shall be described in adequate detail.

For a medical device which is used together with the medicinal product, if appropriate, the certificate of suitability of the medical device (CE mark) shall be attached to the relevant section of the documentation in accordance with the provisions of the Medical Devices Act (Official Gazette 76/13) and ordinances adopted pursuant to that Act.

3.2.S. Active Substances

3.2.S.1. General information

In the sense of this Ordinance, starting materials are considered all those substances from which the active substance is produced or extracted. For biological medicinal products, starting materials are considered all those substances of biological origin, such as microorganisms, organs and tissues of plant or animal origin, cells or fluids (including plasma and blood) of human or animal origin and biological construct of cells (cell substrates, regardless of whether they are of recombined or other origin, including primary cells).

All other substances used in the production or abstraction of active substances, but from which the active substance is not directly extracted, such as reagents, cell culture media, bovine foetal serum, additives and chromatographic buffers, etc. are described as raw materials.

Information on the nomenclature of the active substance should be provided, including the International Non-proprietary name (INN), compendial name in accordance with the Croatian and/or European Pharmacopoeia (if relevant), and chemical name of the substance.

Also, the structural formula, including the data on relative and absolute stereochemistry should be attached, as well as the molecular formula and the relative molecular mass.

For biotechnological medicinal products, if appropriate, the schematic amino acids sequence and the data on relative molecular mass shall be provided. In addition, a list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

3.2.S.2. Manufacturing procedure

(a) For the description of manufacturing process and quality control during the process appropriate information shall be provided in accordance with the latest scientific and technical progress and with the valid guidelines of the European Union.

b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process, together with the data on the quality and control of these materials. Also, information demonstrating that materials meet standards appropriate for their intended use shall be provided. Raw materials shall be listed and their quality and controls shall also be documented. The name, address, and the part of the manufacturing process which is the responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

c) Additional requirements shall apply for biological medicinal products, i.e. data on the source/origin of starting materials shall be described and documented, and data indicating that the active substance is compliant with the valid guidelines on reducing the threat to the transfer of agents of animal spongiform encephalopathy via the medicinal product, and their subsequent amendments, as published by the Commission in the Official Journal of the European Union. When cell banks are used, it must be demonstrated that cell characteristics remain unchanged during the manufacture and later. Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested on the presence of adventitious agents. If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

Whenever possible, the production of vaccines shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on seed.

Also, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on seed, and where such proof is insufficient, the attenuation characteristics shall also be demonstrated at the production stage.

For medicinal products derived from human blood or plasma, relevant information on the origin, criteria and procedures of collection, transportation and storage of the starting materials shall be provided in accordance with Annex II of this Ordinance.

The manufacturing facilities and equipment shall be described.

d) Relevant information on tests (with indication of acceptance criteria) carried out at every critical step, information on quality and control of intermediates and data on validation and/or evaluation of the manufacturing process shall be provided.

e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation while data on validation of such processing shall be provided in the section dealing with viral safety evaluation.

f) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.S.3. Characterisation of the active substance

Information on the structure and other characteristics of the active substance shall be provided, i.e. confirmation of the structure of the active substance based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.S.4. Quality Control of the Active Substance(s)

Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, and description of methods of analysis shall be provided, alongside with validation data. Also, the results of control carried out on individual batches manufactured during development shall be presented.

3.2.S.5. Reference Standards or Materials

Reference standards shall be identified and described in detail. Where relevant, chemical and biological reference standards of the European Pharmacopoeia shall be used.

3.2.S.6. Immediate Packaging

A description and specification of the immediate packaging for active substance keeping shall be provided.

3.2.S.7. Stability

a) The summary of conducted stability studies, used protocols and results of the studies shall be provided.

b) Detailed results of the stability studies, including information on the analytical procedures used and information on validation of those procedures shall be presented in an appropriate format.

c) Also, the post-authorisation stability protocol and stability commitment for the active substance shall be provided.

3.2.P. Medicinal product

3.2.P.1. Description and composition of the medicinal product

A description and the composition of the medicinal product shall be provided, including information on the pharmaceutical form and constituents of the finished medicinal product as well as their amount on a per-unit basis and function (role in formulation) for:

– the active substance(s),

– excipients, whatever their origin or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickening agents, emulsifiers, taste enhancers and aromatic substances, etc.,

– the constituent of the outer covering of the medicinal product, intended to be ingested/ administered to the patient (hard and soft capsules, rectal capsules, coated tablets and film-coated tablets, etc.)

These particulars shall be supplemented by any relevant data concerning the type of immediate packaging and manner of closure, together with details of medical devices with which the medicinal product will be used or administered used.

The usual terminology to be used in describing the constituents of medicinal products where the documentation is submitted in:

a) Croatian:

– in respect of substances which appear in the Croatian Pharmacopoeia, the main title of the constituent should be indicated and the current European Pharmacopoeia containing the relevant monograph should be cited; in respect of substances which do not appear in the Croatian Pharmacopoeia but appear in the European Pharmacopoeia or other pharmacopoeias, the main title at the head of the monograph in question and the relevant pharmacopoeia shall be indicated (together with the name of the substance in Croatian);

– in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation or an exact scientific name shall be given; if none of those data are available, their origin and manufacturing method shall be described and those data shall be supplemented by any other relevant details;

– in respect of colouring matter, designation by the "E" code assigned in the European Union to colouring matters which are authorised for use in medicinal products and to colouring matters authorised for use in foodstuffs shall be indicated.

b) English:

– in respect of substances which appear in the European Pharmacopoeia, the main title shall be indicated and the current European Pharmacopoeia containing the relevant monograph shall be quoted; in respect of substances which do not appear in the European Pharmacopoeia but appear in some other pharmacopoeia, the main title at the head of the monograph in question and the relevant pharmacopoeia shall be indicated (together with the name of the substance in English);

– for other substances, the international non-proprietary name (INN) recommended by the World Health Organisation or an exact scientific name shall be indicated; if none of those data

are available, their origin and manufacturing method shall be described and those data shall be supplemented by any other relevant details;

– in respect of colouring matter, designation by the "E" code assigned in the European Union to colouring matters which are authorised for use in medicinal products and to colouring matters authorised for use in foodstuffs shall be indicated.

When indicating the quantitative composition of active substance(s) in medicinal products, it is necessary to specify the mass or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance. Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule. For medicinal products containing a novel active substance, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products shall have their quantitative composition stated in the same way for the same active substance. International Units of biological activity defined by the World Health Organisation shall be used for substances which cannot be defined molecularly. However, where no International Unit has been defined for a particular substance, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

3.2.P.2. Pharmaceutical development

This chapter should contain information on the studies conducted to establish that the dosage form, the formulation, manufacturing procedure, immediate packaging, microbiological attributes and usage instructions are appropriate for the intended use of the medicinal product specified in the documentation.

The studies described here are distinct from routine quality control tests conducted according to specifications.

Critical parameters of the formulation and manufacturing process that can influence batch reproducibility, medicinal product performance and its quality should be identified and described.

Additional supportive data, where appropriate, shall be provided for the relevant parts of the Module 4 and Module 5 of the documentation.

The evidence should be provided on the compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished medicinal product, or on the compatibility of different active substances with each other in the case of combination products.

The choice of excipients should be explained, in particular relative to their intended role and concentration in the medicinal product.

Information on the development of the medicinal product shall be included, taking into consideration the proposed route of administration and usage.

Any overages in the medicinal product formulation should be justified/ explained.

Any physicochemical and biological parameter relevant to the performance of finished product shall be addressed and documented.

Information on the selection and optimisation of the manufacturing process as well as information on differences between the manufacturing process(es) used to produce clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided (if available).

The data on the suitability of the immediate packaging should be provided and possible interaction between the medicinal product and immediate packaging should be considered.

The microbiological attributes of the medicinal product in relation with sterile and non-sterile preparations shall be in accordance with requirements of the European Pharmacopoeia.

In order to provide appropriate information for the labelling, the compatibility of the finished medicinal product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.P.3. Manufacturing process

The description of the manufacturing method should be drafted in such a way as to give an overview and the type of manufacturing operations employed.

The description shall include:

– indication of all parts of the manufacturing process, including the process control and relevant specifications, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

– in the case of continuous manufacture, full details concerning precautions to ensure the homogeneity of the medicinal product,

— the results of studies validating the manufacturing process where a non-standard method of manufacture is used or where it is critical for the product,

– for sterile medicinal products, details of the sterilisation process and/or aseptic procedure used,

– a detailed batch formula.

The name, address, and role of each manufacturer in the manufacturing process, including contractors, and the list of all production sites or facilities involved in manufacturing and quality control shall be provided.

The data relating to the tests/controls that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.

These tests are essential for checking the conformity of the medicinal product with the formula when an analytical method for testing the finished product which does not include the assay of all the active substances is used (or of all the excipients subject to the same specifications as the active substance). The same applies to cases where the quality of the finished medicinal product depends on process control tests, particularly when the product is defined by it method of preparation.

Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.P.4. Quality control of excipients

All materials used in the production of excipients shall be listed, identifying where each material is used in the process. In addition, information demonstrating that the materials meet standards appropriate for their intended use shall be provided. Used colouring matters must comply with Directives 78/25/EEC and/or 94/36/EC. Furthermore, colouring matters must meet purity criteria as stipulated in Directive 95/45/EC with its amendments.

Specifications and elucidations shall be provided for all excipients, while the analytical procedures shall be described and validation data submitted.

Excipients of human or animal origin should be addressed with particular care. The applicant must prove for excipients that the medicinal product is manufactured in compliance with the valid guidelines on reducing the threat of transmission of the agents of animal spongiform encephalopathy via the medicinal product and with its subsequent amendments, as published by the Commission in the Official Journal of the European Union. The most appropriate manner for confirming the non-risk, i.e. compliance with the above guidelines, is to submit the appropriate Certificate of suitability with the European Pharmacopoeia issued by the EDQM or to submit scientific evidence that proves such compliance.

Novel excipients:

For excipients used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and quality controls, with cross references to supporting safety data (preclinical and/or clinical) shall be provided.

It is also necessary to provide a document containing detailed chemical, pharmaceutical and biological information about excipients.

Information on novel excipients must be structured in the same order as described in the part of Module 3 for the active substance(s).

Information on novel excipients may be provided presented as a stand-alone document following the format of other parts of the documentation. When the applicant is not also the manufacturer of the novel excipient, this stand-alone document must be available to the applicant for submission to the Agency.

Additional information on toxicity studies of novel excipients shall be provided in Module 4, and data on clinical studies in Module 5.

3.2.P.5. Quality control of the medicinal product

For the quality control of the medicinal product, the manufacturing batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5% at the time of manufacture.

Detailed information on the specifications, (market release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.P.6. Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be described in detail, if not previously provided in the section related to the active substance.

3.2.P.7. Immediate packaging of the medicinal product

A description of the container and closure system including the list and quality specifications of each material that comes into contact with the product shall be provided.

The quality specifications shall include chemical description and identification of the relevant materials.

A description and validation of non-compendial methods, together with information on their validation, shall be included where appropriate.

For non-functional outer packaging materials only a brief description should be provided. For functional outer packaging materials additional information shall be provided.

3.2.P.8. Stability

a) Summarised stability studies (with types of studies conducted), protocols used, and the results of the studies shall be submitted.

b) Detailed results of the stability studies, including information on analytical procedures used to generate the results, and data on validation of these procedures shall be presented in an appropriate format. In case of vaccines, information on cumulative stability of vaccines shall be provided where appropriate.

c) Also, the data on post marketing authorisation protocol and stability commitment shall be provided.

MODULE 4

REPORTS ON NON-CLINICAL TRIALS

4.1. Format and presentation

Contents

Study reports:

Pharmacology

– Primary Pharmacodynamics

– Secondary Pharmacodynamics

– Safety Pharmacology

– Pharmacodynamic Drug Interactions

Pharmacokinetics

– Analytical Methods and Validation Reports

– Absorption

– Distribution

– Metabolism

– Excretion

– Pharmacokinetic Drug Interactions (preclinical)

– Other Pharmacokinetic Studies

Toxicology

– Single-Dose Toxicity

– Repeat-Dose Toxicity

– Genotoxicity:

- *In vitro*

- *In vivo* (including supportive toxico-kinetics evaluations)

– Carcinogenicity:

- Long-term studies

- Short- or medium-term studies

- Other studies

Reproductive and Developmental Toxicity Studies:

- Fertility and early embryonic development

- Embryo-foetal development

- Prenatal and postnatal development

- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

– Local Tolerance

– Other Toxicity Studies:

- antigenicity,

- immuno-toxicity,

- mechanistic studies,

- dependence,

- metabolites,

- impurities, and

- other studies,

Literature references

4.2. Contents: basic principles and requirements

Special attention shall be paid to the following selected elements.

The pharmacological and toxicological tests must show:

a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, information about the therapeutic and toxicological potential of the medicinal product should be provided.

For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to

be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

- all tests requiring repeated administration of the medicinal product shall be designed to take account of the possible induction of, and interference by, antibodies;

– examination of reproductive function, of embryo/foetal and peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

The toxicology and pharmacokinetics of a novel excipient shall be investigated.

Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1. Pharmacology

The pharmacology study shall follow two distinct lines of approach:

- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both *in vivo* and *in vitro*, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.

- Secondly, the potential undesirable pharmacodynamic effects of the substance on physiological functions should be investigated. These investigations shall be performed at exposures in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmacodynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmacodynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

4.2.2. Pharmacokinetics

Pharmacokinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.

The study of these different phases may be carried mainly by means of physical, chemical or biological methods, and by observation of the actual pharmacodynamic activity of the substance itself.

Information on distribution and elimination shall be necessary:

– in all cases where such data are indispensable to determine the dosage for humans;

– in respect of chemo-therapeutic substances (antibiotics, etc.), and

– in respect of whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

Pharmacokinetic investigation of all pharmacologically active substances is necessary.

In the case of new combinations of known substances, which have been investigated in accordance with the most recent scientific information, pharmacokinetic studies may not be required, if the toxicity tests and therapeutic justification justify their omission.

The pharmacokinetic program shall be designed to allow comparison and extrapolation between animal and human studies.

4.2.3. Toxicology

a) Single-dose toxicity

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The single dose toxicity test must be carried out in accordance with the most recent scientific information from the field of toxicology.

b) Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use and on the valid guidelines in the European Union. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies.

c) Genotoxicity

The purpose of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.

d) Carcinogenicity

Tests to reveal carcinogenic effects shall normally be required for:

1. Any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner;

2. Some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeat-dose toxicity studies,

3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be transspecies carcinogens, implying a hazard to humans. However, if such a medicinal product is intended to be administered chronically to humans, a chronic toxicity study may be necessary to detect early tumorigenic effects.

e) Reproductive and development toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing foetal development when administering the medicinal product may be warranted.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and post-natal studies shall be conducted in at least one species.

If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeat-dose toxicity studies.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.

f) Local tolerance

The purpose of the local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body which may come into contact with the product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmacodynamic ones. Local tolerance testing should be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference standards may be included where necessary.

The design of local tolerance tests (choice of species, duration, frequency and route of administration, dosages) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Evaluation of reversibility of local lesions should be included where relevant.

Studies in animals can be substituted by validated *in vitro* tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.

For chemicals applied to the skin or administered rectally or vaginally, the sensitising potential should be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

MODULE 5

REPORT ON CLINICAL TRIALS

5.1. Form and presentation

The general outline of the Module 5 is as follows:

– Table of contents for clinical studies

– Tabular Listing of All Clinical Study Reports

– Clinical Study Reports

– *Reports of Bio-pharmaceutical Studies*

– Bio-availability study reports

– Comparative Bio-availability and Bio-equivalence Study Reports

– *In vitro-In vivo Correlation Study Report*

– Reports of Bio-analytical and Analytical Methods

– *Reports of Studies Pertinent to Pharmacokinetics using Human Bio-material*

– Plasma Protein Binding Study Reports

– Reports of Hepatic Metabolism and Drug Interaction Studies

– Reports of Studies Using Other Human Bio-materials

– *Reports of Human Pharmacokinetic Studies*

– Healthy subjects Pharmacokinetic and Initial Tolerability Study Reports

– Patient Pharmacokinetic and Initial Tolerability Study Reports

– Intrinsic Factor Pharmacokinetic Study Reports

– Extrinsic Factor Pharmacokinetic Study Reports

– Population Pharmacokinetic Study Reports

– *Reports of Human Pharmacodynamic Studies*

– Healthy subject Pharmacodynamic and Pharmacokinetics/Pharmacodynamic Study Reports

– Patient Pharmacodynamic and Pharmacokinetic-/Pharmacodynamic Study Reports

– *Reports of Efficacy and Safety Studies*

– Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

– Study Reports of Uncontrolled Clinical Studies

– Reports of Analyses of Data from More than One Study, including any formal integrated analyses, meta-analyses and bridging analysis

– Other Study Reports

– *Reports of Post-Marketing Experience*

– Literature References

5.2. Content: basic principles and requirements

Special attention shall be paid to the following:

a) The clinical particulars must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's

brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) to be kept by the owners of the data:

– for at least 15 years after completion or discontinuation of the trial,

– or for at least two years after the granting of the last marketing authorisation for the medicinal product in the European Union and when there are no applications for marketing authorisations in plan or procedure in the European Union,

– or for at least two years after formal discontinuation of clinical development of the investigational product.

The Subjects' medical files shall be retained in accordance with the valid regulations and for the longest possible period permitted by the hospital, institution or private clinic. Documents may be kept for longer if so required by the valid regulations or agreement with the client. The client informs the hospital, institution or private clinic of the cessation of the need to hold the documents.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised.

This documentation shall include:

- the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used;

- standard operating procedures;

- all written opinions on the protocol and procedures;

- the investigator's brochure;

- case report forms on each trial subject;

- the final report;

- audit certificate(s), if available.

The sponsor of the trial or subsequent owner shall keep the final report for five years after the expiry of the marketing authorisation.

Furthermore, for clinical trials conducted in the European Union, the marketing authorisation holder is obliged to ensure that the documentation is kept in line with the provisions of Directive 2001/20/EC and the guidelines for its implementation.

Any change of ownership of the data shall be documented.

All data and documents shall be made on request, in accordance with the provisions of the Ordinance on clinical studies and good clinical practice.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

– the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used,

– audit certificate(s), if available,

– the list of investigators (with following data: name, address, qualifications and clinical duties in the clinical trial), country in which the trial was performed, information assembled in respect of each patient individually, including case report forms on each trial subject

– the final report signed by the investigator and for multi-centre trials, by all investigators or the co-ordinating (principal) investigator.

e) The particulars of clinical trials referred to above shall be shall be forwarded to the Agency upon request. In agreement with the Agency, the applicant may leave out a part of the data listed in this point, and in that case, the entire documentation is submitted to the Agency upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

f) The clinical observations shall be summarised for each trial indicating:

1) the number and sex of subjects treated;

2) the selection and age-distribution of the groups of patients being investigated and the comparative tests;

3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;

4) where controlled trials were carried out under the above conditions, whether the control group:

– received no treatment

– received a placebo

– received another medicinal product of known effect

– received treatment other than medicinal products;

5) the frequency of observed adverse reactions;

6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or patients whose physiological or pathological condition requires special consideration;

7) parameters or evaluation criteria of efficacy and the in terms of these parameters;

8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved;

g) In addition, the investigator shall always indicate his observations on:

1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;

2) any interactions that have been observed with other medicinal products administered concomitantly;

3) the criteria determining exclusion of certain patients from the trials;

4) any deaths which occurred during the trial or within the follow-up period.

h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.

i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre-clinical toxicological and pharmacological tests must be undertaken or the available ones reviewed.

j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.3.1. Reports on biopharmaceutical testing

Bio-availability study reports, comparative bio-availability and bio-equivalence study reports, reports on *in vitro* and *in vivo* correlation studies, and bio-analytical and analytical methods shall be provided.

Additionally, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for a generic medicinal product.

5.3.2. Reports of studies pertinent to pharmacokinetics using human bio-materials

Human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmacokinetics properties of drug substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.3.3. Reports on pharmacokinetic testing on humans

The following pharmacokinetic characteristics shall be described:

– absorption (rate and extent),

– distribution,

– metabolism,

– excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the preclinical studies, shall be described.

In addition to standard multiple-sample pharmacokinetics studies, population pharmacokinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmacokinetics response relationship. Reports of pharmacokinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmacokinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmacokinetic studies shall be provided.

If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacokinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.3.4. Reports of human pharmacodynamic studies

The pharmacodynamic action correlated to the efficacy shall be demonstrated including:

− the dose-response relationship and its time course,

− justification for the dosage and conditions of administration,

− the mode of action, if possible.

The pharmacodynamic action not related to efficacy shall be described.

The demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

If the medicinal product is normally administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacokinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.3.5. Reports of efficacy and safety studies

In general, clinical trials shall be done as controlled clinical trials if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and will also depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.

The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed, taking into account the valid guidelines of the European Union, with particular attention to events resulting in changes of dosage or need for concomitant medication, serious adverse events, events resulting in withdrawal of subjects from the trial, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, elderly, people with established metabolic or excretory abnormalities, etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

It is necessary to submit reports on uncontrolled clinical trials, reports on analyses of data from one or more trials and other reports on clinical trials, where they exist.

5.3.6. Reports of post-marketing experience

If the medicinal product is already authorised in other countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the doses used in practice.

5.3.7. Case reports forms and individual patient listings

Case report forms and individual patient data listings from clinical trials shall be provided (in accordance with the valid guidelines of the European Union), and presented in the same order as the clinical study reports and indexed by study.

ANNEX II

REQUIREMENTS AND CONTENT OF DOCUMENTATION FOR GROUPS OF PARTICULAR MEDICINAL PRODUCTS

1. *BIOLOGICAL MEDICINAL PRODUCTS*

1.1 BLOOD AND BLOOD PLASMA-DERIVED MEDICINAL PRODUCTS

The data on starting materials for medicinal products derived from human blood or plasma may be provided within Module 3 of the CTD documentation or in a separated filed entitled Plasma Master file (PMF), which the competent authority must assess and issue confirmation in accordance with this Ordinance.

If the main documentation on plasma pertains to medicinal products from human blood/plasma that are approved only in the Republic of Croatia and that are not approved in any other European Union Member State, the Agency is the competent authority for the assessment and issuance of confirmations pursuant to the provisions of this Ordinance. If the medicinal product has been approved in another European Union Member State, the competent authority is the EMA.

The Plasma Master File is a separate document, separate from the dossier of the medicinal product for the granting of authorisation. The PMF contains all the relevant, detailed data on the characteristics of human plasma used as a starting material and/or raw materials for the production of fractions and ingredients of excipients and active substances that form an integral part of the medicinal product or medical device.

Every centre or institution for the fractioning/processing of blood plasma prepares and updates the relevant, detailed data from the Plasma Master File.

The applicant requesting the marketing authorisation for the medicinal product or the marketing authorisation holder submits the Plasma Master File to the competent authority. If the applicant or authorisation holder is not also the owner of the PMF, it should be available to the applicant or authorisation holder for submission to the competent authority. In any case, the applicant or authorisation holder is responsible for the medicinal product.

If the assessment of the PMF is conducted by the EMA, the Agency does not decide on the application for the granting of authorisation before the EMA can assess and issue a certificate for the PMF.

The documentation on the medicinal product containing components obtained from human plasma must refer to the Plasma Master File for the plasma that is used as starting materials/raw materials for the medicinal product in question.

The Plasma Master File must contain the following data on plasma that is used as a starting material/raw material:

a) Origin of plasma:

– Information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections,

– Information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status,

– Selection/exclusion criteria for blood/plasma donors,

– System in place which enables the path taken by each donation to be traced from the collection establishment through to finished products and vice versa.

b) Plasma quality and safety

– Compliance with European Pharmacopoeia Monographs,

– Data on testing of blood/plasma donations and pools relating to markers for infectious diseases, including information on test methods, and in the case of plasma pools, validation data on the tests used,

– Technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used,

– Conditions of storage and transport of plasma,

– Any inventory hold and/or quarantine period,

– Characteristics of plasma pools.

c) Data on system in place between the blood/plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

d) In addition, the PMF shall provide a list of blood/plasma derived medicinal products with valid PMF (whether marketing authorisations have been granted or are in the process of being granted, including medicinal products in clinical trials).

For Human blood/plasma derived medicinal products that do not have marketing authorisation, the applicant requesting the marketing authorisation is required to submit the full documentation on the medicinal product to the competent authority, to which the PMF is appended, if the same has not previously been submitted to the competent authority.

The Plasma Master File is subjected to scientific and technical assessment by the competent authority.

When the competent authorisation for the Plasma Master File is the Agency, after its assessment, the Agency issues a certificate on the Plasma Master File.

The Certificate for the Plasma Master File issued by the EMA is valid for the entire territory of the European Union.

The Plasma Master File must be renewed, submitted to the competent authority and reauthorised by the competent authority once per year.

Amendments to the Plasma Master File are also subjected to the scientific and technical assessment by the EMA, or the agency, pursuant to which the EMA, or Agency issues the certificate.

1.2. VACCINES

Data on the active substance(s) for vaccines intended for human use can be presented within Module 3 of the CTD documentation, or as a separate Vaccine Antigen Master File (VAMF).

If the documentation is based on the Vaccine Antigen Master File, the principles outlined in this section are followed.

Documentation submitted for the purpose of granting marketing authorisation for a vaccine, except in cases for flu vaccines for humans, must contain the Vaccine Antigen Master File for each antigen that is an active substance in the components of the vaccine.

The Vaccine Antigen Master File is a separated part of the documentation for the granting of marketing authorisation for vaccines, that contains all significant data on the biological, pharmaceutical and chemical nature for each active substance (antigen) in the components of the vaccine. The same Vaccine Antigen Master File may be submitted for one or more single-component and/or combined vaccines of the same applicant or authorisation holder.

The Vaccine Antigen Master File must contain the following data on quality from the appropriate sections of Module 3 that pertain to active substances:

a) General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia

b) Information on the manufacture of the active substance: information on the manufacturing process, information on the starting/source materials, raw materials, specific measures on TSEs and adventitious agents, and data on facilities and equipment

c) Characterisation of the active substance

d) Quality control of the active substance

e) Reference standard and materials

f) Container/immediate packaging

g) Stability of the active substance

For new vaccines containing new antigens, the applicant requesting the marketing authorisation submits the complete documentation on the medicinal product to the Agency,

including the Vaccine Antigen Master File for each antigen in the composition of the new vaccine for which a VAMF has not yet been submitted to the Agency. The VAMF is subject to scientific and technical assessment by the EMA. Upon granting a positive assessment, the EMA issues a Certificate on the Vaccine Antigen Master File. The Certificate on the VAMF issued by the EMA is valid for the entire territory of the European Union.

The provisions of the preceding paragraph pertain to all vaccines that contain new antigen combinations, regardless of whether one or more of those antigens is in the composition of an already approved vaccine in the EU or not.

If the Vaccine Antigen Master File pertains to an application for marketing authorisation for a vaccine that is not approved, or that will not be approved in the centralised procedure, and if the vaccine does not contain antigens that have been assessed or that need to be assessed by the European Medicines Agency, the scientific and technical assessment of the VAMF is conducted by the Agency. In this case, the Agency issues the Certificate on the VAMF.

Amendments to the VAMF are also subject to scientific and technical assessment by the EMA or the Agency, pursuant to which the EMA or Agency issues a Certificate.

2. RADIOPHARMACEUTICALS AND PRECURSORS

2.1. Radiopharmaceuticals

In addition to the requirements for the granting of authorisation pursuant to Article 22, point 6 and Article 28 of the Medicinal Products Act, it is necessary to submit the complete documentation that contains the following specific data:

Module 3

In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described. For radio-nuclides, the nuclear reactions involved shall be discussed.

In a generator, both mother and daughter radio-nuclides shall be considered active substances.

Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

Starting materials include irradiation target materials.

Considerations on chemical/radiochemical purity and its relationship to bio-availability shall be provided.

Radio-nuclide purity, radiochemical purity and specific activity shall be described.

For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.

The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclide purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

Module 4

It is considered that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

Module 5

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.1 Radio-pharmaceutical precursors for radio-labelling purposes

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labelling efficiency or in vivo dissociation of the radio-labelled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.

If applicable, the following information where applicable shall be provided:

Module 3

The provisions of Module 3 apply to the granting of authorisation for radio-pharmaceutical precursors, in line with the provisions of indents (a) to (i), if applicable.

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice as laid down by Council Directive 87/18/EEC and 18/320/EEC, unless otherwise justified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant "cold" nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. MEDICINAL PRODUCTS FOR RARE AND SEVERE DISEASES (ORPHAN MEDICINAL PRODUCTS)

In the case of medicinal products for rare and serious diseases (orphan medicinal products) in the sense of Regulation (EC) No 141/2000, the provisions of Article 47 of the Act may apply, in which it is laid down that under exceptional circumstances, the Agency may provide provisional marketing authorisation (authorisation under exceptional circumstances).

The provisional marketing authorisation, pursuant to Article 47 of the Act, may be issued if the applicant is able to prove that it is not possible to submit comprehensive data on the efficacy and safety of the medicinal product under the usual circumstances of use, because:

– the indications for which the medicinal product is intended appear so rarely that the applicant cannot expect the collection of comprehensive evidence, or

– with the current scientific knowledge, it is not possible to list comprehensive information, or

– the collection of such information would be contrary to the generally accepted principles of medical ethics.

The criteria or obligations that are defined with the marketing authorisation for the medicinal product pursuant to Article 47 of the Act may include the following:

– the applicant is obliged to complete the established research programme in the period defined by the competent authority, whose results must form the basis for a re-assessment of the risk to benefit ratio of the use of the medicinal product,

– the medicinal product is dispensed exclusively by physician's prescription and, in certain cases, is administered exclusively under the strict watch of a physician, where possible in a hospital, and in the case of radio-pharmaceuticals, it is administered by an authorised person,

– the package leaflet and all information about the medicinal product inform the physician to the fact that the available details about the medicinal product are currently lacking, in a certain extent,

In the case of the provisional authorisation from Article 47 of the Act, the applicant is required in the summaries of the preclinical and clinical documentation to list the reasons why it is not possible to submit the full information, and to give a substantiation of the risk to benefit ratio for the orphan drug.

If the applicant in applying for the marketing authorisation for an orphan drug refers to the provisions of Article 34 of the Act and Article 21 of this Ordinance, in proving the systematic and documented use of the active substances, they may exceptionally refer to the use of those substances pursuant to the provisions of Article 5 of Directive 2001/83 of the European Parliament.

4. ADVANCED THERAPY MEDICINAL PRODUCTS

4.1 INTRODUCTION

Applications for the dossier from Modules 3, 4 and 5 stipulated for biological medicinal products in the annex of this Ordinance shall apply appropriately to advanced therapy medicinal products.

Specific requirements for the dossiers from Modules 3, 4 and 5 for advanced therapy are prescribed in this section.

Considering the specific nature of advanced therapy medicinal products, the approach based on an a risk assessment may be applied in order to determine the scope of data on quality, preclinical and clinical data on the medicinal product which is necessary to be submitted, with the submission of an application for the granting of marketing authorisation in line with the valid scientific guidelines.

The risk assessment may pertain to the integral development of the medicinal product. Risk factors that may be considered include: cell origin (autologue, allogene, xenogene), ability of proliferation and/or differentiation, and ability to stimulate an immune response, level of cell manipulation, cell combination with biologically active molecules or structural materials, nature of the medicinal product for gene therapy, scope of the ability for the replication of viruses or microorganisms used *in vivo*, level of integration of nucleic acid sequences or genes in the genome, long-term functionality, risk of oncogenocity and manner of application and use of the medicinal product.

The risk assessment may also consider the appropriately available preclinical and clinical data or experiences with other similar medicinal products for advanced therapy.

Each derogation from the requirements prescribed in this annex must be scientifically corroborated in Module 2 of the dossier.

The risk assessment, where applicable, must also be contained and described in Module 2 of the dossier.

In that case, the methodology used, the nature of the established risks and implications of the basic approach based for the risk assessment for the development and the assessment programme must be taken into consideration. Each derogation from the requirements prescribed by this annex ensuing from the risk assessment must be described.

4.2 Definitions

For the purpose of this Annex, alongside the terms laid down by Regulation (EC) No 1394/2007, the following terms shall apply:

4.2.1 GENE THERAPY MEDICINAL PRODUCTS

Gene therapy medicinal product is a biological medicinal product with the following properties:

a) contains an active substance that contains or consists of recombinant nucleic acids used or applied to humans with the goal of regulating, repairing, replacing, supplementing or deleting gene sequences,

b) therapeutic, prophylactic or diagnostic activity of the medicinal product is directly associated with the recombinant nucleic acid sequence that it contains, or with a product of genetic expression of those sequences.

Gene therapy medicinal products shall not be considered vaccines against infectious diseases.

4.2.2 SOMATIC CELL THERAPY MEDICINAL PRODUCTS

Somatic cell therapy medicinal products are biological medicinal products with the following properties:

a) contains or consists of cells or tissues that were subjected to significant manipulations due to which their biological properties, physiological functions or structure properties significant for clinical use have been altered, or from cells and tissues which do not have the same function(s) in the recipient and donor of the same,

b) it is shown that it has the properties for, or is used/applied in humans with the aim of treatment or the prevention of disease or diagnostics via the pharmacological, immunological or metabolic activities of the cells or tissues it contains.

The significant manipulations listed under point a) shall not be considered the manipulations laid down in Annex I of Regulation (EC) No 1394/2007.

4.3 SPECIFIC REQUIREMENTS FOR MODULE 3

4.3.1 Specific requirements that pertain to all advanced therapy medicinal products

It is necessary to submit a description of the tracking system that the authorisation holder intends to establish and use so as to ensure that each medicinal product, including starting materials and raw materials used for its production, and including all substances coming into contact with the cells and tissues that the medicinal product may contain, may be tracked from its origin, production, packaging, storing, transport to the dispatch to the hospital, institution or private medical clinic. The tracking system must, in addition to the stipulations, also be compliant with the requirements laid down in Directive 2004/23/EC and Directive 2002/98/EC.

4.3.2 Specific requirements to gene therapy medicinal products

4.3.2.1 Introduction: medicinal product, active substance and starting materials

4.3.2.1.1. Gene therapy medicinal products that contain recombinant nucleic acid sequences or genetically modified organisms or viruses

Medicinal products containing nucleic acid sequences or genetically modified microorganisms or viruses formulated in their ultimate primary container for medicinal use for which the medicinal product is intended. The medicinal product may be in combination with a medical device or active medical implant.

The active substance contains nucleic acid sequences or genetically modified microorganisms or viruses.

4.3.2.1.2 Gene therapy medicinal product that contain genetically modified cells

Medicinal product contains genetically modified cells formulated in the ultimate primary container for medicinal use for which the medicinal product is intended. The medicinal product may be in combination with a medical device or active medical implant.

The active substance contains genetically modified cells or one of the medicinal products described in point 4.3.2.1.1 of Annex II of this Ordinance.

*4.3.2.1.*3 When a medicinal product contains a virus or viral vector, the starting materials are considered the contents from which the viral vector is obtained, i.e. the main seed viral vector or plasmid used for transfection (or transfer) into the packaging cell line.

4.3.2.1.4 When a medicinal product contains plasmids, non-viral vectors and genetically modified microorganisms (other than viruses), the starting materials are considered the contents used for generating the production cells, i.e. plasmids, bacterial hosts and main cell banks for the packaging cell line.

4.3.2.1.5 For genetically modified cells, the starting materials are considered the contents that are used for obtaining genetically modified cells, i.e. starting materials for the production of vectors, vector and human or animal cells. The principles of good manufacturing practice shall be applied from the system of banks used for the production of vectors thereforth.

4.3.2.2 Special requirements

In addition to the requirements listed in this section, the following requirements shall also apply:

– it is necessary to append all data on the starting materials used in the production of the active substance, including the products necessary for the genetically modified human or animal cells, and, where applicable, data on the subsequent cultivation and storage of genetically modified cells, taking into account the possible omission of purification procedures,

– for medicinal products containing microorganisms or viruses, it is necessary to submit data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, dependence of microorganisms or viruses in the cell cycle, pathogenicity and properties of the parental strain,

– In the appropriate sections of the documentation, it is necessary to describe impurities from the production process and impurities associated with the medicinal product, particularly impurities in the sense of viruses that can replicate if the vector has been constructed as incapable of replication,

– for plasmids, it is necessary to determine the quantity of various forms of plasmids during the shelf life of the medicinal product,

–genetically modified cells should be characterised prior to and after modification, and prior to and after each subsequent freezing/storage procedure.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal product, the quality requirements pertaining to somatic cell therapy medicinal products and medicinal products obtained from tissue engineering shall also apply.

4.3.3 Specific requirements pertaining to somatic cell therapy medicinal products and medicinal products obtained from tissue engineering

4.3.3.1 Introduction: medicinal product, active substance and starting materials

Medicinal products containing an active substance formulated in the primary container for medical use for which the medicinal product is intended and in a final combination for a combined advanced therapy medicinal product.

Active substance consisting of cells and/or tissues obtained through genetic engineering.

Excipients (e.g. carriers, biological matrices, products, biomaterials, biomolecules and/or other contents) that are combined with manipulated cells of which they are an integral part, are considered starting materials, even in the case when they are not of biological origin.

Materials used in the production of active substances (e.g. agar, growth factors) and which are not intended to form an integral part of the active substances are considered raw materials.

4.3.3.2 Special requirements

In addition to the requirements listed in this section, the following requirements shall also apply:

4.3.3.2.1 Starting materials:

– it is necessary to submit the summary of data on donations, procurement and testing of human tissues and cells that are used as starting materials and are obtained in accordance with the requirements of Directive 2004/23/EC. If unhealthy tissues or cells (e.g. carcinoma tissues) are used as a starting material, it is necessary to substantiate the justification of their use,

– if the population of allogenic cells are pooled, it is necessary to describe the pooling strategy and measures taken to ensure traceability,

– as part of the validation of the production procedure, characterisation of active substances and medicinal products, the development of testing and establishing quality and stability requirements, it is necessary to address the potential variability introduced via the human or animal cells and tissues,

– for medicinal products based on xenogenic cells, it is necessary to submit data on the origin of the animal (such as geographic origin, breeding method, age), special acceptability criteria, measures to control and eradicate infectious diseases in the original animal donor, testing of the animal for infectious agents, including vertical transfer of microorganisms and viruses, and proof of suitability of the animal housing,

– for medicinal products based on cells obtained from genetically modified animals, it is necessary to describe the specific characteristics of cells connected with the genetic modification. It is necessary to submit a detailed description of the creation and characterisation of the transgenic animals,

– for genetic modifications, the requirements listed in point 4.3.2 of Annex II of this Ordinance shall apply,

– it is necessary to submit a description and substantiation of the manner of testing of all excipients (carriers, biological matrices, products, biomaterials, biomolecules or other content) that are found in the combination with the cells obtained from genetic engineering and of which they form an integral part,

– for carriers, biological matrices and products that are by definition medical devices or active medical implants, it is necessary to submit the data necessary for the assessment of combined advanced therapy medicinal products listed in point 4.3.4 of Annex II of this Ordinance.

4.3.3.2.2 Production procedure:

– the production procedure should be validated for the purpose of ensuring the consistency of batches and procedures, the functional integrity of the cell during transport and production, to the moment of application or use, and the appropriate degrees of differentiation,

– if the cells grow directly in or on a matrix, carrier or product, it is necessary to submit data on the validation of the cell cultivation procedure with regard to the cell growth and the function and integrity of the combination.

4.3.3.2.3 Strategy for characterisation and control:

– it is necessary to submit the appropriate data on the characterisation of the cell population or mixture of cells in the sense of identity, purity (e.g. foreign microbiological agents or impurities of cell origin), viability, potential, nucleus properties, tumorogenicity and suitability for the intended medical use. It is necessary to prove the genetic stability of the cell,

– it is necessary to submit the qualitative and, where possible, quantitative data on impurities concerning the procedure and medicinal product, and of all substances that have the capacity of introducing a degradation product during the production of the medicinal product. It is necessary to justify the scope of determination of the impurities,

– if individual quality control testing cannot be performed on the active substance or medicinal product, but only on the key inter-products, this should be substantiated,

– when biologically active molecules (such as growth factors, cytokins) are an integral part of the medicinal product based on calls, it is necessary to characterise their influence and interaction with other components of the active substance,

– for medicinal products based on cells whose three-dimensional structure is part of the intended function, as part of the characterisation, it is necessary to list the degree of differentiation, structural and functional organisation of the cells and to generate and extracellular matrix where this is applicable. Where necessary, the physico-chemical characterisation should be corroborated with preclinical trials.

4.3.3.2.4 Excipients:

– for excipients of medicinal products based on cells or tissues (e.g. components of media for transport), the requirements for new excipients in accordance with this Ordinance apply, except where data exist on the interaction between the excipients and the cells and tissues.

4.3.3.2.5 Testing for development purposes:

– in the description of the development programme, it is necessary to substantiate the selection of materials and procedures. It is particularly necessary to substantiate the integrity of cell populations in the final formula.

4.3.3.2.6 Referential standards:

– it is necessary to document and characterise the appropriate reference standard specific for the active substance.

4.3.4 Specific requirements pertaining to advanced therapy medicinal products that contain medical devices

4.3.4.1 Advanced therapy medicinal products that contain medical devices in accordance with Article 7of Regulation (EC) No 1394/2007

It is necessary to append a description of the physical characteristics and active properties of the medicinal product and a description of the procedures of design of the medicinal product.

It is necessary to describe the interactions and compatibility between genes, cells and/or tissues and structural components.

4.3.4.2 Combined advanced therapy medicinal products in accordance with Article 2(1)(d) of Regulation (EC) No 1394/2007

For the cell or tissue part of a combined advanced therapy medicinal product, specific requirements for medicinal products for therapy with somatic cells and for medicinal products obtained through tissue engineering as laid down in this Ordinance shall apply, and in the case that this pertains to genetically modified cells, specific requirements for gene therapy medicinal products as listed in point 4.3.2 of Annex II of this Ordinance shall apply.

The medical device or active medical implant may be an integral part of the active substance. When the medical device or active medical implant is combined with cells at the time of production or application or use of the medicinal product, it is deemed an integral part of the medicinal product.

It is necessary to submit the following data on the medicinal product or active medical implant (that are an integral part of the active substance or medicinal product) that are necessary for the assessment of the combined advanced therapy medicinal product:

– data on the source and intended use of the medical device or active medical implant and proof of compatibility of the produce with the other components of the medicinal product,

– proof of compliance of the medical device with the key requirements listed in Annex I of Directive 93/42/EEC or proof of compliance of the active medical implant with the key requirements listed in Annex I of Directive 90/385/EEC,

– where applicable, proof of compliance of the medical device or active medical implant with the requirements pertaining to BSE (bovine spongiform encephalopathy) / TSE (transmissible spongiform encephalopathy) listed in Directive 2003/32/EEC,

– the results of every assessment conducted by the reporting body according to Directive 93/42/EEC or Directive 90/385/EEC for part of the medical device or active medical implant, where applicable.

The reporting body conducting the assessment of the medical device shall, at the request of the competent authority responsible for the assessment of the application, make available all data relating to their own assessment conducted pursuant to Directive 93/42/EEC or Directive 90/385/EEC. This may also relate to data and documents contained in the said application for the assessment of compliance, when necessary for the assessment of the combined advanced therapy medicinal product as a whole.

4.4 SPECIAL REQUIREMENTS FOR MODULE 4

4.4.1 Special requirements for all advanced therapy medicinal products

Due to the uniqueness and diverse structural and biological properties of advanced therapy medicinal products, the requirements for the documentation on the pharmacological and toxicological testing of medicinal products from Module 4 listed in Annex I of this Ordinance are not always applicable for this type of medicinal product. As part of the technical requirements listed in points 4.4.1, 4.4.2 and 4.4.3, it is outlined how the requirements from Annex I of this Ordinance are applicable for advanced therapy medicinal products. Where applicable, taking into consideration the specificity of the advanced therapy medicinal product, additional requirements are also posed.

As part of the expert's report on preclinical documentation, it is necessary to submit substantiation for the preclinical development of the medicinal product and the criteria that were applied for the selection of the appropriated animal models, and models for *in vitro* and *in vivo* testing. The selected animal models may be immunocompromised, *knock-out* (animals with selectively inactivated genes), humanised or transgenic animals. It is necessary to consider the use of homologous models (e.g. mice cells analysed in mice) or models that mimic the disease, particularly in the testing of immunogenicity or immunotoxicity.

In addition to the requirements listed in Annex I of this Ordinance, it is necessary to submit data on the safety, appropriateness and biocompatibility of all structural components (such as matrices, carriers, products) and all excipients (such as cell products, biomolecules, biomaterials and chemical substances) that are contained within the medicinal product and to take into account their physical, mechanical, chemical and biological properties.

4.4.2 Special requirements for gene therapy medicinal products

For the purpose of determining the scope and type of preclinical trials, it is necessary to determine the appropriate level of data on the safety of use, taking particular consideration of the design and type of gene therapy medicinal product.

4.4.2.1 Pharmacology

– In using the appropriate models and animal species, it is necessary to conduct *in vitro* and *in vivo* testing of the mechanisms of activity related to the therapeutic application of the medicinal product (i.e. testing that proves the established pharmacodynamic concept), designed in such a way so as to prove that the nucleic acids reach the target organ or cells and that they act in line with the envisaged intent (levels of expression and functional activity). It is necessary to submit data on the duration of the function of nucleic acid sequences and the manner of dosing in clinical trials.

– Target selectivity: when the gene therapy medicinal product has a selective or target restricted functionality it is necessary to conduct testing for the purpose of confirming the specificity and duration of the function and activity in the target cells and tissues.

4.4.2.2 Pharmacokinetics

– Biodistribution testing must include testing of the persistence, clearance and mobilisation, and an additional emphasis on the risk of transferral of genetic material,

– It is necessary to submit research on rejection and the risk of transferral to 'third' persons, together with an environmental risk assessment, unless the above has been properly substantiated in the applicant with regard to the type of medicinal product for which the application has been submitted.

4.4.2.3 Toxicology

– It is necessary to address the toxicity of the gene therapy medicinal product. It is further necessary, depending on the type of medicinal product, to take into account the individual testing of the active substances and excipients and to assess the *in vivo* effect of the expression of nucleic acid sequences associated with the medicinal product, which are not intended to have any physiological function.

– Toxicity testing of single doses may be combined with the pharmacological and pharmacokinetic safety testing, e.g. in order to test for persistence.

– When multiple doses are intended to be applied in humans, it is necessary to submit the results of multiple dose toxicity testing. The manner and plan of use must be equivalent for the planned doses in the clinical trials. In the case that the administration of a single dose can achieved extended functionality of the nucleic acid sequence in humans, the need for testing repeated toxicity should be considered. Testing may last longer than in standard toxicity testing, depending on the persistence of the gene therapy medicinal product and the envisaged potential risks of administration. It is necessary to submit substantiation for the justification of duration of the testing,

– It is necessary to test the genotoxicity. Standard genotoxicity testing is conducted only in the case when it is necessary to test for specific impurities or components of the administration system,

– It is necessary to test for carcinogenicity. Standard carcinogenicity testing in rodents during their entire life cycle are not necessary. However, depending on the type of medicinal product, it is necessary to assess the tumorigenic potential of application using the appropriate *in vivo* and *in vitro* models,

– Reproductive and developmental toxicity: it is necessary to submit testing of the effects on fertility and general reproductive function. It is necessary to submit testing of the embryo-foetal and perinatal toxicity and the transfer of genetic material, unless their exemption is not adequately substantiated in the application pursuant to the type of medicinal product for which the application is submitted.

– Additional toxicity testing: for all gene therapy medicinal products, it is necessary to submit testing of the transgene integration into the genome of host cells, except in the case of a scientific justification for not performing such tests, e.g. because the nucleic acid sequence cannot enter into the nucleus. For gene therapy medicinal products for which transgene integration is not expected into the genome of host cells, this testing is performed if the biodistribution data indicate a risk for the transfer of genetic material.

– Immunogenicity and immunotoxicity: it is necessary to test the potential immunogenic and immunotoxic effects.

4.4.3 Special requirements for somatic cell therapy medicinal products and medicinal products obtained through tissue engineering

4.4.3.1 Pharmacology

– The primary pharmacological testing must be designed in such a way as to appropriately prove the set concept. It is necessary to test the interactions of medicinal products based on cells with the surrounding tissues.

– It is necessary to determine the quantity of medicinal product for achieving the desired effect / effective dose and depending on the type of medicinal product, the dosage frequency,

– It is necessary to consider the secondary pharmacological testing for the assessment of the potential physiological effects that are not associated with the desired therapeutic effects of the somatic cell therapy medicinal product, medicinal product obtained through tissue engineering or additional substances such as biologically active molecules, considering that they may secrete biologically active molecules other than the protein in question or if the protein in question could have an undesired target spot.

4.4.3.2 Pharmacokinetics

– It is not necessary to submit pharmacokinetic testing for the purpose of testing absorption, distribution, metabolism and excretion. However, it is necessary to test parameters such as viability, longevity, distribution, growth, differentiation and migration, unless otherwise substantiated in the application, based on the type of medicinal product in question.

– For somatic cell therapy medicinal products and medicinal products produced through tissue engineering that systematically produce active biomolecules, it is necessary to test the distribution, duration and quantity of expression of those molecules.

4.4.3.3 Toxicology

– It is necessary to test the toxicity of the medicinal product. It is necessary to consider the individual testing of the active substance, excipient and other substances and any other impurities that arise from the production procedure,

– The testing duration may be longer than in standard toxicity testing, and it is necessary to consider the expected shelf life of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile. It is necessary to submit justification for the duration of the testing,

– It is not necessary to conduct conventional testing of carcinogenicity and genotoxicity, except in relation to the tumorigenic potential of the medicinal product,

– It is necessary to test the potential immunogenic and immunotoxic effects,

– For medicinal products based on cells containing animal cells, it is necessary to address the specificities associated with the safety of use, such as the transfer of xenogenic pathogens to humans.

4.5 SPECIAL REQUIREMENTS FOR MODULE 5

4.5.1 Special requirements for all advanced therapy medicinal products

Special requirements for the documentation of Module 5 listed in this section shall be applied in addition to the requirements prescribed in Annex I of this Ordinance.

When alongside the administration of the advanced therapy medicinal product, other accompanying treatment or a surgical procedure are simultaneously required, it is necessary to test and describe the treatment procedure as a whole. It is necessary to submit data on the standardisation and optimisation of the said treatment procedure during the clinical development.

When during the surgical procedure for the use, implantation or administration of the advanced therapy medicinal product a medical device is used than may affect the efficacy or safety of use of the advanced therapy medicinal product, it is necessary to submit data on those medicinal products.

It is necessary to define the specific knowledge and skills that are necessary for the application, implantation, use or active monitoring after the administration of the advanced therapy medicinal product. Where necessary, it is required to submit the training plan for health care staff for the procedures of application, implantation or administration of these medicinal products.

Due to the nature of the advanced therapy medicinal product, during the clinical development, there may be a change in production process. In that case, it is necessary to submit additional testing for the purpose of proving comparability.

It is necessary to address the risks of potential infectious agents or risks from the use of materials of animal origin during the clinical development, and on measures taken to minimise those risks.

In testing to determine dosage, it is necessary to define the selection of dose and the schedule of administration.

The efficacy in the proposed indications must be corroborated with the appropriate results of clinical trials in which clinically significant endpoints for the intended use of the medicinal product are used. For certain clinical conditions, it is necessary to prove the long-lasting efficacy and for that purpose, to submit the strategy of assessment of the long-lasting efficacy.

In the risk management plan, it is necessary to include a strategy for the long-term monitoring of safety and efficacy of the medicinal product.

Testing of the safety and efficacy of a combined advanced therapy medicinal product should be designed and conducted for the combined medicinal product as a whole.

4.5.2 Special requirements for gene therapy medicinal products

4.5.2.1 Pharmacokinetic testing on humans

Pharmacokinetic testing on humans must include the following aspects:

–shedding studies so as to determine the excretion of the gene therapy medicinal product,

– biodistribution testing,

– pharmacokinetic testing of the medicinal product and the share of gene expression (e.g. expression of the protein or the genomic signature).

4.5.2.2 Pharmacodynamic testing on humans

Pharmacodynamic testing on humans must contain data on the expression and function of nucleic acid sequences after the application of the gene therapy medicinal product.

4.5.2.3 Safety testing of the medicinal product

Safety testing must include the following aspects:

– creation of vectors with the capacity for replication

– creation of new strains

– reassortment of existing genome sequences,

– neoplastic proliferation caused by mutagenic insertion

4.5.3 Special requirements for somatic cell therapy medicinal products

4.5.3.1 Somatic cell therapy medicinal products in which the manner of activity is based on the production of defined biomolecule(s)

For somatic cell therapy medicinal products in which the manner of activity is based on the production of defined biomolecule(s), it is necessary, where possible, to address the pharmacokinetic profiles of those molecules (particularly the distribution, duration and quantity of expression).

4.5.3.2 Biodistribution, persistence and long-term integration in the tissue of the components of somatic cell therapy medicinal products

It is necessary to address the biodistribution, persistence and long-term integration in tissue of components of the somatic cell therapy medicinal products during the clinical development of the medicinal product.

4.5.3.3 Safety testing of the medicinal product

Safety testing of the medicinal product must include the following aspects:

– distribution and integration into the tissue after use of the medicinal product,

– dislocated (ectotopic) integration into the tissue

– oncogenic transformation and lineage fidelity of the cell/tissue.

.5.4 Special requirements for medicinal products obtained through tissue engineering

4.5.4.1 Pharmacokinetic testing

In the case when conventional pharmacokinetic testing is not significant for the medicinal product obtained through tissue engineering, it is necessary during the clinical development to address the biodistribution, persistence and decomposition of the components of the medicinal product obtained through tissue engineering.

4.5.4.2 Pharmacodynamic testing

Pharmacodynamic testing should be designed and adapted in line with the specificities of the medicinal product obtained through tissue engineering. It is necessary to submit data on the proof of the established concept and the kinetics of the medicinal product necessary to achieve the desired regeneration, repair or replacement. It is necessary to consider the appropriate pharmacodynamic markers associated with the intended function and structure.

4.5.4.3 Safety testing of the medicinal product

The requirements listed in point 4.5.3.3 shall apply.