ROMANIA

Newsletter

Year 15, No. 3 (59), 3rd quarter of 2013

National Agency for Medicines and Medical Devices

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ISSN 1583-347X

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DECISION

No. 18/08.08.2013

on approval of the revised Guideline on evaluation of advertising of medicinal products for human use

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 158/18.02.2013, in accordance with the Regulation on the organisation and operation of the NAMMD Scientific Council, Article 8 (1), adopts through written procedure the following:

DECISION

Article 1. – The revised Guideline on the evaluation of advertising of medicinal products for human use is approved, in accordance with the Annexes which are integral parts of this Decision.

Article 2. – On this Decision coming into force, NAMMD Scientific Council Decision No. 21/08.09.2011 on approval of the Guideline on the evaluation of advertising of medicinal products for human use shall be repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX
(SCD No. 18/08.08.2013)

GUIDELINE
ON EVALUATION OF ADVERTISING OF MEDICINAL PRODUCTS FOR HUMAN USE

CHAPTER I
Introduction, definitions, scope, provisions

SECTION 1
Introduction

Article 1. - The mission of the National Agency for Medicines and Medical Devices (hereinafter, NAMMD) is to contribute to the protection and promotion of public health. The NAMMD is the competent authority in respect of approval of advertising material and any other forms of advertising related to medicinal products for human use, according to provisions of Law no. 95/2006 on healthcare reform, Title XVII – The Medicinal Product.

Article 2. – (1) In all activities regarding medicinal product advertising, standards and regulations shall be defined and observed which would organise and regulate this activity.

(2) The entire activity concerning advertising and promotion of medicinal products shall be carried out responsibly, ethically and at the highest standards in order to ensure safe use of medicinal products, both in self-medication and in case of medicinal products administered under medical guidance and supervision.

Article 3. – (1) Medicinal product advertising for human use is only accepted provided compliance with legislation in force.

(2) This guideline aims at facilitating application of regulations in force by clarifying certain detail aspects, so that advertising for any medicinal product, irrespective of its form (in order to arouse consumers' interest) be at a high standard and observe legal provisions.

(3) Medicinal product advertising not include anything offensive or misleading for the consumer.

SECTION 2
Definitions

Article 4. – For the purposes of this Guideline, the following terms and concepts shall have the following meaning:

1. Administrative staff – decision-making staff in public and private healthcare institutions and members or chairpersons of medicinal product therapeutic commissions;

2. Adverse reaction – a harmful and unwanted response to a medicinal product, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological functions;

3. Advertising agent/agency – any person (physical or legal) appointed by a pharmaceutical company to provide advertising services of any kind to its benefit, on the grounds of an agreement;

4. Advertising (promotional) material – any means used for advertising (promotional) purposes as defined by the concept of "promotion";

5. Common Name – the international non-proprietary name recommended by the World Health Organisation (WHO) or, if one does not exist, the usual common name;

6. Comparative advertising – any form of advertising explicitly or implicitly identifying the competition and/or comparative description;

7. Competent authority – the National Agency for Medicines and Medical Devices;

8. Educational material

a) material targeting the general public and/or healthcare specialists, which aims at target audience information on a certain pathology or medicinal product, used for scientific/educational purposes and not encouraging prescription, delivery, sale, administration, recommendation or consumption of the respective medicinal product;

b) Material as part of consolidated risk management actions and not subject to this Guideline (except for the manner of application submission and fee) shall not be considered educational material.

9. Essential information in the SmPC: minimum information in the summary of product characteristics necessary for a correct use of the medicinal product. This will generally include information in sections 1-4 and 6-7 of the Summary of Product Characteristics: indications, doses and method of administration, contraindications, warnings and cautions, as well as adverse reactions. Abbreviation or removal of information deemed unessential of these sections may be acceptable;

10. Generic medicinal product – medicinal product with the same qualitative and quantitative composition as regards the active substances and the same pharmaceutical form as the reference medicinal product and whose bioequivalence with the reference medicinal product has been proved by proper bioavailability studies. Various salts, esters, ethers, isomers, mixtures of isomers, compounds or derivates of an active substance are considered as the same active substance, if they do not present significantly different properties with respect to safety and/or efficacy. The applicant does not have to provide bioavailability studies, if he/she can prove that the generic medicinal product meets the relevant criteria as defined in the proper detailed guidelines;

11. Healthcare professionals - physicians, dentists, pharmacists and nurses;

12. Healthcare services – the totality of medical or pharmaceutical services accomplished by healthcare professionals in order to treat or prevent disease in humans.

13. Homeopathic medicinal product - any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia; a homeopathic medicinal product can contain number of active principles;

14. Medical events – planned scientific events, organised for healthcare professionals, initiated and organised locally, regionally, nationally or internationally, such as: congresses, symposia, round tables, workshops, classes, Advisory Boards (expert meetings);

15. Medical prescription – any medicinal product prescription issued by a person qualified to this purpose.

16. Medical representative – a person paying visits to healthcare professionals and appropriate administrative staff regarding promotion of medicinal products, such as but not limited to assigned sale managers, product managers, marketing managers etc.;

17. Medicinal product/Medicine:

a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

18. Medicinal product advertising (commercial) – any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products; it shall include in particular:

a) medicinal product advertising to the general public;

b) medicinal product advertising to persons qualified to prescribe or supply them;

c) visits by medical sales representatives to persons qualified to prescribe medicinal products;

d) supply of samples;

e) sponsorship of promotional meetings with participation of persons qualified for medicinal product prescription or supply;

f) sponsorship of scientific congresses with participation of persons qualified for medicinal product prescription or supply and in particular payment of travelling and accommodation expenses in connection therewith;

19. Misleading advertising – any form of advertising which, under any form, presentation included misleads or is liable to mislead any person;

20. Name of the medicinal product – the name assigned to a medicinal product, which can be an invented name not leading to confusions with the common name or a common or scientific name, accompanied by the trademark of the marketing authorisation holder;

21. On prescription medicinal product – any medicinal product for which the consumer shall provide a medical prescription for release to be performed;

22. OTC (over-the-counter) medicinal product – any medicinal product that is available without a medical prescription;

23. Pharmaceutical company – any legal person undertaking and carrying out any sort of activities in the pharmaceutical industry, whether or not a parent-company (for instance main office, control or company office), company subsidiary, branch or any other form of enterprise or organisation;

24. Promotion – it relates to any organised activity encouraging prescription, delivery, sale, administration, recommendation or use of medicinal products;

25. Reference medicinal product - a medicinal product authorised according to Article 700 and 702 of Law no. 95/2006 or a medicinal product authorised in one of the Member States of the European Union or by centralised procedure;

26. Reminder – a short advert meant for the target audience, which by exception from the common law in the field, may include the name of the medicinal product or the international non-proprietary name only, if any, the trademark of the medicinal product, the name of the company or image of the medicinal product. Reminders may only be used within a campaign and via the same communication channel where the full advertising material is presented according to legislation in force;

27. Representative of the marketing authorisation holder – person, usually known as "local representative", appointed by the marketing authorisation holder (MAH) for representation in Romania;

28. Risks related to use of the medicinal product:

a) any risk for the patient's or public health, regarding the quality, safety or efficacy of the medicinal product; and/or

b*)* any risk of unwanted effects on the environment;

29. Sample – medicinal product supplied on free of charge to healthcare professionals in order to become accustomed with the product and acquire experience with its use;

30. Serious adverse reaction - an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect;

31. Strength of the medicinal product – the content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to pharmaceutical form;

32. Subliminal advertising – advertising using adverts whose beneficiary is not aware thereof, for instance expressed with a low acoustic intensity or displayed on a screen for a short period of time, no longer than a second;

33. Unexpected adverse reaction - an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

SECTION 3
Scope

Article 5. – (1) This Guideline regulates advertising of medicinal products for human use (whether original or generic medicinal products, on prescription medicinal products to healthcare professionals or OTC medicinal products).

(2) By "advertising activity" or "promotion", one understands any activity carried out, organised or sponsored by a pharmaceutical company (or by an advertising agency on its behalf by authorisation) resulting in encouragement of prescription, release, sale, administration or use of a medicinal product.

(3) This Guideline relates to promotion and advertising aimed not only at physicians, but also at all other healthcare professionals who, within their professional activities, can prescribe, supply, administer a medicine or encourage its sale, distribution or use.

Article 6. - This Guideline relates to all promotion methods, namely to those mentioned under Article 4 (21), as well as to visits from medical representatives accompanied by delivery of promotional material, advertising in newspapers or magazines, scientific publications, direct e-mail advertising, and other means of electronic communication (sites, web-pages, blogs, forums), use of audio-visual systems (such as films, video recordings, data storage services).

Article 7. - This guideline does not seek to limit or restrict supply of medical or scientific information to healthcare professionals or the public.

Article 8. - This guideline does not cover the following fields:

a) summaries of product characteristics, as provided by relevant legislation, labelling and patient leaflets of medicinal products, if not promotional in nature;

b) mail exchanges, possibly accompanied by material of non-promotional nature, in response to individual questions of healthcare professionals, only if exclusively related to the letter or the question subject and if not promotional;

c) general, non-promotional information about companies (such as information for investors or current/prospective employees), including financial data, descriptions of research and development programs and discussions on regulation affecting the company and its products.

Article 9. - This Guideline has been developed according to provisions of the following documents:

(1) Law no. 95/2006 on healthcare reform, Title XVII – The medicinal product, published in the Official Gazette of Romania, Part I, no. 372 of 28/04/2006, as amended, transposing Directive 2001/83/EC on the Community code relating to medicinal products for human use, published in the Official Journal (OJ) of the European Union no. L 311 of 28 November 2001, as amended;

(2) Law no. 148/2000 regarding advertising, published in the Official Gazette of Romania, Part I, no. 359/2000, as amended;

(3) Law no. 158/2008 regarding misleading advertising and comparative advertising, published in the Official Gazette of Romania, Part I, no. 559/2008;

(4) The Law of audio-visual no. 504/2002, published in the Official Gazette of Romania, Part I, no. 534/2002, as amended;

(5) The Audiovisual Code – Decision no. 220/2011 concerning the regulation of audio-visual content, published in the Official Gazette of Romania, Part I, no. 174/2011, supplemented through National Audiovisual Council no. 459/2011, published in the Official Gazette of Romania, Part I, no. 534/2011;

(6) The European Federation of Pharmaceutical Industries and Associations (EFPIA) Code of Practice on promotion of prescription-only medicinal products to, and interactions with healthcare professionals], adopted in July 2007 and updated in June 2011.

Article 10. – This Guideline applies not only to pharmaceutical companies *per se*, to their affiliated companies or representatives, but to other partners as well (agents, agencies, MAH representatives) with whom agreements are in place for conduct of the respective pharmaceutical company's advertising of any type concerning medicinal products thereof.

Article 11. – (1) Pharmaceutical companies and their representatives are responsible for compliance with this Guideline, even for activities contracted out to third parties (e.g. marketing contractors, consultants, market research companies, advertising agencies), such as promotional, advertising or implementation activities as well as involvement, on their behalf, in advertising activities subject to this Guideline provisions.

(2) Pharmaceutical companies shall ensure that any of the third parties to whom medicinal product advertising activities have been contracted out are compliant with provisions of this Guideline.

(3) Pharmaceutical companies and their representatives shall not be considered liable for promotional activities initiated by third parties outside a contract with the MAH/their representative, clearly stating a promotional activity as an object of the contract.

SECTION 4
Provisions

Article 12. - Medicinal product advertising means any type of organised activity aiming to provide information by direct/indirect means, as well as any type of promotion meant to encourage prescription, distribution, sale, administration, recommendation or use of one or several medicinal products for human use.

Medicinal product advertising may target healthcare professionals or the general public.

Article 13. – (1) Medicinal product advertising shall:

a) be accurate, balanced, unbiased, objective and contain enough information to allow the target audience to form their own opinion concerning the therapeutic value of medicinal product concerned;

b) be based on updated evaluation of all relevant evidence and clearly reflect such evidence;

c) encourage reasonable use of the medicinal product, by objective presentation without undue exaggeration of its properties and therapeutic qualities;

d) not encourage self-medication or the irrational use of the medicinal product;

e) not be misleading, subliminal or misleading by distortion, overstatement, unjustified emphasis, omission or in any other way etc.;

f) not suggest that a medicinal product/active ingredient has any particular merit, quality or property, unless supported by scientific data;

g) not be detrimental to respect for human dignity and public morals;

h) not include any form of discrimination based on race, gender, language, origin, social background, ethnic identity or nationality;

i) not be detrimental to any person's image, honour, dignity and private life.

(2) All information included in medicinal product advertising material shall be compliant with the information stipulated in the SmPC.

Article 14. – (1) As a general rule, advertising to the public is prohibited for the following categories of medicinal products:

a) medicinal products without a marketing authorisation valid in Romania;

b) medicinal products released on medical prescription only.

(2) a) Exceptionally, manufacturing companies or their representatives in Romania may disseminate clearly specified information (e.g. data on new medicinal products or new methods of administration of already authorised medicinal products, with potentially substantial impact on associated costs) to healthcare authorities or authorities in Board of Directors of Healthcare Institutions, such as, for instance persons in charge of establishing institutional budgets required for medium- and long-term planning of estimated healthcare costs.

Distribution of such material is to be performed specifically to the budget decision-making staff.

b) Likewise, manufacturing companies and their representatives in Romania may distribute relevant information when specifically requested by healthcare authorities.

Article 15. – Responsible parties:

(1) The MAH or their representative is responsible for the content of advertising/promotional material developed by the former for a given medicinal product.

(2) The MAH is also responsible for the training and conduct of medical representatives concerning use and distribution of advertising/promotional material.

(3) Apart from an existing contract with a third party, the MAH bears no responsibility with regard to the manner of distribution and use of promotional material.

(4) Pharmaceutical companies set up, internal training systems related to promotional material manner of use by their representatives in promotional campaigns.

(5) Within a company, final approval of all advertising/promotional material is delegated to a responsible person. Moreover, the NAMMD may request MAHs or their representatives to provide the names of the persons delegated for final approval of advertising/promotional material, as well as the names of their alternates.

(6) Although the main responsibility for ensuring compliance with regulations in force of all medicinal product advertising material lies with the MAH, other third parties may be responsible as well, who are involved in the manufacturing and distribution of non-compliant promotional material. This provision also enables sanctioning of third parties involved in the manufacturing and distribution process of non-compliant advertising material.

Article 16. Notification, submission for approval, evaluation and archiving of material:

(1) The MAH is required to submit for NAMMD approval all advertising material to the general public/patients and only place them on the market after grant of advertising approval.

(2) Advertising material for OTC medicinal products, as well as educational material for the general public/patients are subject to Article 16 (1).

(3) Advertising material is submitted together with the application form for assessment of the material and the payment form.

(4) Payment of evaluation fees is performed for each product and each communication channel for the respective advertising material.

(5) NAMMD assessment of advertising material is only commenced after confirmation of respective fee payment; assessment may result in either approval of advertising material submitted or request for their change.

(6) Requests for change or potential non-compliances are notified to the MAH or their appointed representatives, respectively, via e-mail.

(7) For compliance check reasons, when NAMMD approval is obtained for a changed proposal (from the one initially submitted), the MAH is required to submit a printed copy of the finally approved material (the actually marketed version) and another in unprintable electronic format.

(8) The NAMMD assesses advertising material for healthcare professionals, concerning on-prescription/non-prescription medicinal products after distribution, in a random manner or following complaints.

(9) MAH participation in medical events is notified to the NAMMD prior to the event.

(10) To check compliance, the NAMMD hereby establishes a 3-year period as a minimal mandatory period for archiving of advertising material by the MAH, for both printed material and electronic ones.

(11) The period mentioned under Article 16 (10) runs from date of the first use of the advertising material.

Article 17. – The main forms of advertising used in the pharmaceutical industry are as follows:

(1) Printed material (prints):

Such material is defined in Annex 1 to this Guideline.

a) scientific/promotional material for healthcare professionals;

b) advertising material for the general public;

c) educational material for patients and patient organisations/ associations;

d) posters, invitations;

e) reminding material (reminders);

(2) Audio-visual advertising (radio, television)

(3) Billboards or any other form of outdoor advertising or any other form of advertising using a different communication channel than pharmacies, medical practices, audiovisual media, written press, the internet;

(4) Advertising over the Internet (web pages, e-mail, forums, blogs or any other form of electronic support);

(5) Provision of samples;

(6) Promotional objects (relevant for medical practice).

CHAPTER II
Misleading and comparative advertising, encouragement of reasonable use, compliance with SmPC content

SECTION 1
Misleading advertising

Article 18. - (1) Misleading advertising means any form of advertising which, in any way, by presentation method includes, misleads or is likely to mislead any person it is intended for or makes contact with it.

(2) No form of advertising shall suggest that a medicinal product or an active ingredient has any special intrinsic worth, quality or property, if not scientifically documented. This is a general provision.

(3) In order to determine the misleading character of advertising, all its characteristics are considered, particularly such components as:

a) medicinal product characteristics (irrespective of their nature), the extent of their compliance with their intended purpose and outcomes expected from its use;

b) omission of essential information regarding identification and description of that medicine in order to mislead the target audience of the advertising in question.

c) accurately described information, likely to mislead because of the overall impression derived from their contradicting the respective therapeutic indications. Examples may include advertising material showing images related to driving when the respective medicinal product can affect the ability to drive vehicles.

SECTION 2

Comparative advertising

Article 19. - (1) Comparative advertising means any form of advertising explicitly or implicitly identifying a competitor by its comparative description. Any comparison between different medicinal products shall be based on relevant and comparable aspects.

(2) Comparative advertising for the general public is prohibited.

(3) Comparative advertising for healthcare professionals is prohibited if:

a) the comparison is misleading, according to the above-mentioned specifications;

b) the trademark of a competitor is used; only international non-proprietary names are allowed.

c) the comparison is made between/among medicinal products with different therapeutic indications or different pharmaceutical forms;

d) no objective comparison is made between/among essential, relevant, verifiable and representative characteristics of medicinal products, among which the price may also be included;

e) confusion arises in the market between the advertised company and a competitor thereof or between/among the various trademarks, international non-proprietary names or other distinctive marks of the advertised medicinal product and those belonging to a competitor;

f) a competitor's trademark, non-proprietary name, other distinctive marks, activities or any other characteristics are discredited or blamed;

g) a competitor's reputed trademark, international non-proprietary name, distinctive marks or any other characteristics are incorrectly taken advantage from, without evidence to support the advertiser's allegations.

SECTION 3

Encouragement of reasonable use

Article 20. - (1) Any advertising material shall encourage accurate and adequate use of the medicinal product. Therefore, it is compulsory that any advertising material include information regarding:

a) the recommended dose/administration pattern/specific administration instructions if any;

b) the exact indications of the medicinal product according to the SmPC;

c) special warnings and precautions according to the SmPC;

d) contraindications according to the SmPC.

(2) Any piece of information included in advertising material shall be supported by clear scientific reference, without exaggerations or extrapolations not scientifically substantiated. For instance:

a) advertising material for a medicine alleviating symptoms of a disease may not suggest that that medicine can cure the respective disease;

b) advertising material in which data of clinical trials results are not accurately presented or are taken out of context will be deemed as exaggerating the properties of that medicine.

SECTION 4
Compliance with SmPC content

Article 21. - (1) No advertising material shall promote use of the medicinal product outside the therapeutic indications listed in the SmPC approved for that medicine.

(2) No advertising material for a medicine shall promote its use by certain categories of patients for which there is no indication in the SmPC. (For instance, the presence of an infant's image in an advertising material for a medicine not recommended for infants represents a breach of this provision).

CHAPTER III
Advertising for healthcare professionals
General considerations, advertising forms

SECTION 1
General considerations

Article 22. – (1) Promotion of medicinal products is prohibited before grant of a marketing authorisation allowing for their sale or distribution.

(2) Promotion of medicinal products outside approved therapeutic indications is prohibited.

Article 23. – (1) Any form of advertising shall be in compliance with provisions listed in the approved SmPC as well with marketing authorisation terms as granted by the NAMMD or in compliance with the European Commission Decision, as appropriate,.

(2) Any form of medicinal product advertising not compliant with the marketing authorisation is prohibited.

(3) a) Information regarding certain indications of a medicinal product which are not specified in the marketing authorisation (MA) ("non-label indications") and may only be supplied in response to an appropriately documented request from a healthcare professional.

b**)** Use of such information in order to promote the respective medicinal product in unauthorised indications or promote its use under different conditions than included in the approved SmPC is prohibited.

c**)** In this case, the MAH ensures that the data provided are purely informative, non-promotional, clearly specifying that the respective information regards "non-label" use.

Article 24. – (1) Any form medicinal product advertising for persons qualified to prescribe or supply such products shall include:

a) essential information compatible with the approved SmPC;

b) the classification for supply of the respective medicine;

c) mentions regarding the date of the latest set-up or revision of the documentation used for development of the advertising material or of any other form of advertising.

(2) All information included in the documentation under Article 24 (1) shall be accurate, updated, verifiable and comprehensive enough to allow the recipient to develop their own opinion regarding the therapeutic quality of the medicine concerned.

(3) Quotations as well as tables and other illustrative material taken from medical literature or other scientific works for use in the above-mentioned documentation shall be faithfully reproduced, with exact indication of the source (references).

(4) All illustrations in promotion material, including graphs, various images, photographs and tables, taken from published studies shall meet the following conditions:

a) clearly indicate their exact source/ sources;

b) be faithfully reproduced, except when adjustment or change is needed (for instance, to comply with any applicable code/codes), in which case any such adjustment/change shall be clearly specified.

c) Not be misleading regarding the nature of the medicine (for instance, concerning appropriateness use in children or not) or regarding a statement or comparison (for example, by use of incomplete, statistically irrelevant information or inappropriate comparisons).

Article 25. - Without appropriate scientific arguments, such words as "safe" or "risk-free" shall never be used to describe a medicinal product.

Article 26. - The word "new" shall be avoided to describe a product or presentation form generally available previously or a therapeutic indication generally promoted for longer than one year (in Romania).

Article 27. - No product may be presented as having no adverse reactions, toxicity or addiction risks, except for those cases mentioned in the SmPC.

Article 28. - The design and presentation of advertising shall allow clear and effortless understanding. When footnotes are used, these shall be obvious, be proper in size, be easily legible and have a duration which allows reading.

Article 29. - Advertising for persons qualified for medicinal product prescription or supply shall not promise gifts, advantages in cash or in kind.

SECTION 2
Advertising forms

Article 30. - Printed advertising material meant for healthcare professionals

(1) Advertising (promotional) material for on-prescription medicinal products shall be distributed to healthcare professionals only.

a) Display of such promotional material is prohibited in places accessible to the general public such as, but not limited to, pharmacies, waiting rooms of medical practices, hospital and clinic halls etc.

b) Liability for display of such promotional material, to the general public is presumed to lie with the pharmaceutical company, which may prove the contrary with documents.

(2) Any printed advertising material meant for healthcare professionals shall include at least the following information:

a) the name of the medicinal product and active substance (INN = international non-proprietary name);

b) the pharmaceutical form and strength;

c) the dosage for each administration route and each therapeutic indication, as appropriate;

d) the date of the first authorisation or of authorisation renewal;

e) the other essential information in the SmPC;

f) the date of the text revision (for the SmPC);

g) the mention: "This promotional material is meant for healthcare professionals."

h) the classification for release and the type of prescription required for release;

i) Information in the SmPC is printed using font size *10*, irrespective of the font type.

(3) Inclusion into printed advertising material of messages stating or suggesting that use of the respective medicine is risk-free is prohibited, except for the cases mentioned in the SmPC.

(4) Unless scientifically supported, all steps shall be taken for healthcare professionals not to be misled by allegations that a product is better or safer than another.

Article 31. – Posters, invitations to medical events:

(1) If not related to the therapeutic effects of a medicinal product, invitations to medical events organised for healthcare professionals can only include the name of the product or its international non-proprietary name, if any, or its trademark and, if necessary, a plain statement of the indications meant to designate the therapeutic category of the product or its route of administration. Otherwise, such material is subject to regulations provided in Article 30, **"**Printed advertising material meant for healthcare professionals".

(2) Posters as well as invitations aimed at promoting certain undertakings, activities, scientific medical events, educational programs, or meant to increase the recognition of a certain pathology and displayed in public places shall comply with regulations provided in Article 51 "Printed advertising material meant for the public".

Article 32. – Short commercials (reminders):

By way of exemption from provisions of Article 30,"Printed advertising material meant for healthcare professionals", for short commercials meant as reminders, medicinal product advertising for healthcare professionals may only include the name of the medicinal product or its International Non-proprietary Name, if any, or its trademark.

Article 33. - International literature for healthcare professionals

Promotional material included in international literature to be distributed by the MAH or their representatives in Romania shall be in compliance with regulations in force.

Article 34. – Advertising over the Internet

(1) Since advertising over the internet is normally accessible to the general public, Internet advertising of on-prescription medicinal products is only allowed if compliant with regulations in force.

a) In such cases, the MAH shall prove restriction of access to this information for all other persons except healthcare professionals, by a valid and verifiable system of password protection. A complete SmPC is mandatory for the information included.

b) Likewise, web-site providers shall ensure that the material posted on the site does not contain information non-compliant with national and international rules in force. As for other advertising forms, this channel for promotion to the general public of on-prescription medicinal products is prohibited.

(2) As for the other advertising material, medical information shall be endorsed by scientific references compatible with the approved SmPC.

(3) When links are included on certain web-sites that are meant for foreign users, Romanian users shall be specifically informed thereof..

(4) The following represent good practice rules for medicinal product advertising for human use:

a) Romanian users have to be provided direct access to any web-page containing medicinal product related information (SmPC – for web-sites intended for healthcare professionals, leaflet – for web-sites intended for the general public);

b) the web-site shall mention the category of targeted users;

c) any information about web-sites targeting healthcare professionals representing an advertising form be compliant with legal provisions regulating the content and format of the commercials, as well as the manner of medicinal product advertising.

Article 35. – **Hospitality**

Hospitality to healthcare professionals is allowed at scientific/professional events only and under the terms provided by regulations in force. Therefore, it shall be limited to the main objective of the meeting and may not be extended to other people outside healthcare professionals or for whom the scientific field of the event has no professional relevance.

Article 36. – Sponsorship

(1) Any type of sponsorship provided to healthcare professionals shall not be correlated with the name of a medicinal product, regardless of its status for release (on- or non-medical prescription).

(2) Sponsorship activities shall not involve use of direct/indirect promotional messages for medicinal products, regardless of their release status for release (on- or non-medical prescription).

Article 37. - Facilitation of access to educational programs, scientific material, medical goods or services

(1) Programs initiated by the MAH or their legal representatives, which are aimed at providing sponsorship for scientific research activities, study visits etc. are allowed provided that:

a) they do not include promotional elements regarding a medicine;

b) they are not provided on condition of prescription or stimulation of a prescription of a medicine.

(2) Supply of goods and services to hospitals or other healthcare institutions:

a) shall have as a sole aim the welfare of the patients;

b) shall not be provided on condition of prescription, stimulation of a prescription or distribution of a medicine;

c) shall not in general be related to a medicinal product.

Article 38. – Advertising in medical events

(1) Local, regional, national or international medical events are subject to this provision. These are forms of advertising intended for healthcare professionals only and therefore the MAH or their representatives shall notify the NAMMD with respect to the following aspects:

a) the type of event in which the MAH participates;

b) The material to be distributed during or after the event (must be listed, not presented as such);

c) The medical information supplied during these events – the set of slides only with reference to product characteristics and not the entire presentation;

d) Romanian specialists participating in international events, who provide medical information on certain product characteristics in the event, shall only submit the set of slides referring on product characteristics as such and, not to the entire presentation;

e) the promotional objects distributed (to be listed);

f) Specialisation of healthcare professionals for whom the information is intended.

(2) Irrespective of the information support, none of the advertising material used in this context shall go against regulations in force. The MAH or their representatives shall ensure that all advertising material contains all recommended information .

(3) Should a single set of studies be used during a medicinal product advertising campaign, a single notification will suffice, submitted at the beginning of the campaign and accompanied by a plan of all events in the campaign.

(4) Should prizes be offered in such events, these shall be of no significant value and not be provided on condition of medicinal product prescription. Notification is to be made 10 days prior to the event.

Article 39. – The granting of samples

Exceptionally, free samples are only offered to persons qualified for prescription of such products and under the terms imposed by the legislation and regulations in force.

Article 40. – Promotional objects

(1) Healthcare professionals may not be supplied with, offered or promised any gifts, financial advantages or in kind benefits as stimulant for the prescription, purchase, supply, sale or administration of a medicinal product.

(2) a) When medicinal products are promoted to healthcare professionals, such promotional objects may be supplied or offered if only not costly (not exceeding RON 150, VAT included, before personalisation) and relevant for the practice of medicine and pharmacy.

b) Objects of general use, used as promotional objects, may include pens, notebooks, calendars, watches or other similar stationary items (parasols, bath towels etc. are excluded).

(3) Promotional objects may only bear:

a) the name and logo of the pharmaceutical company;

b) the name of the medicine, or its international non-proprietary name, if any, or the trademark;

c) The strength, pharmaceutical form and a simple statement of the indications meant to designate the product therapeutic category;

(4) Imprinting of the trade name of medicinal products under promotion on gowns offered to healthcare professionals as promotional objects is prohibited.

CHAPTER IV
Advertising to the general public
General considerations, recommendations related to statements contained in the advertising material for the general public, advertising forms

SECTION 1

General considerations

Article 41. - Advertisement to the general public is only allowed for those medicinal products, which, by their composition and purpose, are meant for use without a physician's intervention in diagnosis, prescription or treatment monitoring, a pharmacist's advice being sufficient in case of need.

Pharmacies are allowed to present commercial catalogues and lists of prices to the general public provided that such material does not contain promotional offers whatsoever, and it is only displayed in pharmacies and medical practices.

Article 42. – (1) Advertisement to the general public is prohibited for medicinal products which:

a) are released on medical prescription only;

b) contain substances defined as narcotic or psychotropic within the meaning established by the United Nations Organisation conventions of 1961 and 1971, as well as the national legislation.

(2) Advertisement to the general public is prohibited in Romania for medicinal products prescribed and dispensed within the health insurance system. Such prohibition does not apply to vaccination campaigns carried out by the pharmaceutical industry and approved by the Ministry of Health.

(3) Manufacturers are not allowed to directly distribute medicinal products to the population for promotional purposes.

Article 43. – Advertisement for the general public performed by the MAHs and contracted third parties acting on their behalf is prohibited for medicinal products containing promotional offers (e.g.: "buy one and get .....", or "buy X + Y" and get a gift, discount etc.) or references to discounts, price cuts, special prices.

Trade companies (authorised pharmacies or third parties) are also prohibited from such advertising to the public.

Article 44. – Any form of public medicinal product advertising shall:

(1) be designed in such a way as to clearly outline the advertising character of its message and allow unambiguous identification of the product as a medicinal product;

(2) include at least the following information:

a) the name of the medicinal product, and the non-proprietary name should the medicine contain a single active substance;

b) all necessary information for correct medicinal product use (therapeutic indication(s), recommended dose according to therapeutic indication(s) it refers to);

c) an explicit and legible invitation to careful reading of instructions in the patient leaflet or the outer packaging, worded as follows: *"This medicinal product is available without medical prescription. Careful reading of the patient leaflet or the information on the package is recommended. In case of any unpleasant manifestations, please contact your physician or pharmacist."*

d) 'reminder' material shall include the name of the medicinal product and the invitation to read the instructions in the patient leaflet or the outer package, as appropriate.

3) be submitted to the NAMMD for approval; the NAMMD grants an approval valid for a 6 month/1 year period, depending on the applicant's request; the number of the approval and the date of its grant shall be imprinted and displayed. Further to grant of approval for advertising visa maintenance, the inscription of the visa number needs no changing.

Small advertising material such as change trays, wobbler etc. (as detailed in Annex 1 to this Guideline) are exempted from mandatory visa number inscription.

4) shall not contain any element, material, date or information which:

a) leaves the impression that no medical advice, medical intervention or surgical procedure is necessary, especially by offering diagnosis suggestions or remote treatment;

b) suggests that treatment with the medicine in question has *guaranteed* effect or is free from occurrence of adverse reactions (e.g.: *"rids one from……"*);

c) suggests that the effect of the respective medicinal product is better or equivalents to that of a different treatment or active substance, unless scientifically grounds are provided for such statements;

d) suggests that the patient's health can only be improved by use of the respective medicinal product;

e) suggests that the patient's health may be harmed unless the respective medicinal product is used; such prohibition does not apply to immunisation campaigns;

f) targets children exclusively or especially;

g) relates to a recommendation by scientists, healthcare professionals or persons not part of these categories, but whose celebrity may encourage consumption of medicinal products;

h) suggests that the medicinal product is a food, cosmetic or other product for consumption;

i) suggests that medicinal product safety or efficacy is owed to its being non-synthetic;

j) by detailed description or representation of a case, be likely to induce inaccurate self-diagnosis;

k) provide, in inadequate or misleading terms, insurance regarding healing;

l) inaccurately, alarmingly or misleadingly use visual representations of disease or lesion induced changes or medicinal product action on the human body as a whole or in part;

m) allege that a marketing authorisation has been granted for that medicinal product;

n) expresses violence (even if not explicitly).

o) uses diminutives or other words (phrases) meant to trigger users' emotional response;

p) represents messages, images from campaigns related to other types of products (cosmetics, food supplements, medical devices etc.).

SECTION 2

Recommendations regarding statements in advertising material meant for the general public

Article 45. - Statements suggesting the product is the most efficient (e.g. *"No other medicine acts as fast as ……"*) are prohibited because of their capacity to mislead consumers with respect to therapeutic benefits of the medicinal product as compared to those associated to other medicinal products in the same category.

Article 46. – (1) Such terms as “safe” or “risk-free” shall never be used to describe a medicinal product, unless appropriate scientific arguments are given.

(2) The word “new“ shall never be used to describe a product or a presentation form generally available or a therapeutic indication generally promoted for longer than one year on the Romanian market.

Article 47. – (1) The advertising material shall not suggest that the medicinal product is completely free from adverse reactions.

(2) Moreover, allegations on medicinal product manufacturing resulting in lower residual content or higher quality than a similar product shall not be misleading as regards its therapeutic benefits.

Article 48. - The medicinal product’s high action or absorption rate are characteristics resulting from the product’s SmPC (e.g. action setting in less than 30 minutes).

Article 49. - The NAMMD does not encourage use of advertising material promoting medicinal products together with others with similar trade names, marketed by the same company. Such reference to other products in the advertising material can be misleading.

Article 50. - Manufacturing companies or their representatives in Romania shall not directly or indirectly communicate the idea that their product is better than others for having been granted a marketing authorisation.

SECTION 3

Advertising forms

Article 51. – Printed advertising material for the general public

Printed advertising material for the general public:

(1) may mention the name of the pharmaceutical company supporting development of the material without other reference but its identification data;

(2) may contain non-promotional information regarding human health or diseases, provided there is no direct or indirect reference to specific medicinal products (educational material);

(3) may contain advice (recommendations) for a better life quality of patients, however without referring to any medicinal product (educational material);

(4) does not encourage self-medication or unreasonable use of medicinal products;

(5) if medicinal products are concerned, the presentation is objective, realistic, supported by arguments, without exaggerating their properties and curative effects;

(6) the design and presentation of advertising shall allow for clear and straightforward understanding; when footnotes are used, these shall be obvious, of sufficient size, in order to be easily legible;

(7) shall be subject to NAMMD approval;

(8) shall contain the approval visa number and date of its release, in the following form: *”advertising approval no. /date*….”.

Article 52. - Posters, invitations, catalogues

(1) Posters and invitations are compliant with recommendations for advertising material to the general public, including the recommendation regarding inscription of the approval number and date of release, in the following form: *”advertising approval no. /date*….”.

(2) Catalogues in pharmacies:

a) may only mention non-prescription medicinal products;

b) may include the shelf price of the products, without mentioning promotional offers (e.g. ”buy one, get .....”, or ” buy X + Y and get a gift, discount” etc.), or reference to price, discounts, price reductions.

c) shall be submitted for NAMMD approval; the approval is valid for 6 months;

d) shall contain the approval number and the date of its release, in the following form: *"advertising approval no. /date*….".

Article 53. Audio-visual advertising

Medicinal product advertising broadcast on radio and television programmes, by radio-electric means, cable or any other assimilated technical system is subject to legal provisions regarding audiovisual advertising.

(2) Audiovisual medicinal product and medical treatment advertising refers to any form of promotion performed in the frame of program services, meant to stimulate their distribution, consumption or sale.

(3) Advertising is only allowed for medicinal products not requiring medical prescription.

(4) Medicinal product advertising shall encourage their rational use, present them objectively, without exaggerating their therapeutic qualities.

(5) Promotion of medicinal products in audiovisual programs will necessarily include the following:

a) the name of the medicinal product;

b) the non-proprietary name if the medicinal product contains a single active ingredient;

c) the therapeutic indication (conditions in which the medicinal product is used);

d) an express, legible invitation to careful reading of instructions in the patient leaflet or on the packaging;

e) verbal warning: *"This is a medicinal product. Careful reading of the patient leaflet is recommended";*

f) approval number and date of its grant, in the following form: *"advertising approval no. /date*….".

(6) By exemption from provisions of the previous paragraph, medicinal product advertising broadcast in a short form (reminders) shall include the warning: *"Careful reading of the patient leaflet is recommended."*

(7) Warnings mentioned under paragraph (5) e) and (6) shall be broadcast under the following terms:

a) where the main TV advertisement is concerned, the warning text is presented at the end of the TV advertisement, visually, for a time long enough to ensure clear perception;

b) for reminders, the warning text is presented during the broadcast of the TV advertisement, in terms allowing for clear perception of the message.

(8) Broadcast of medicinal product advertising presented or recommended by public figures, cultural, scientific, sports figures or other people who, on account of their fame, can encourage the use of these products or treatments is prohibited.

(9) Likewise, no broadcast of advertising and teleshopping is allowed showing physicians, pharmacists or nurses recommending or expressing approval for medicinal products.

(10) No broadcast of medicinal product advertising during children's shows or advertising breaks before or after such shows is allowed.

(11) Medicinal product manufacturers and distributors may not be sponsors of children's programs or shows .

(12) Broadcast of advertising is prohibited suggesting the necessity that any person supplement their diet with vitamins and minerals and that such supplements can improve otherwise regularly good physical or mental functions.

(13) Advertising for any kind of medicinal product or treatment for weight loss or maintenance will observe the following conditions:

a) it shall not address people under 18 years of age and shall warn the public thereof in writing and / or sound;

b) it may not be broadcast in children's shows or advertising breaks before or after such shows;

c) it shall not be directed towards obese people, will not include examples of cases with reference to or appearance of formerly obese people before using the products or services advertised for;

d) it shall not suggest or assert that being underweight is adequate or desired.

(14) The design and presentation of advertising shall allow for clear and easy understanding, and include the transposition, understandable by patients/final consumers, of SmPC indications in the advertising material (e.g. varicose syndrome, pain, swelling, sensation of weight etc., if proven that these are the symptoms of the reference action).

Article 54. - Billboards or any other form of outdoor advertising or any type of advertising provided using any other communication channels than pharmacies, medical practices, audiovisual, the written press, the internet;

(1) For the above forms of advertising, special attention shall be given to their presentation manner and placement, to avoid misleading advertising because of various associations with other surrounding promotional elements.

(2) This type of advertising material is assessed within the NAMMD scientific council.

(3) The NAMMD does not encourage outdoor advertising **or any other form of advertising provided using any other communication channels than pharmacies, medical practices, audiovisual, the written press, the internet.**

Article 55. – Short commercials *(reminders):*

(1) Reminder material shall include:

a) the name of the medicinal product;

b) an express, legible invitation to careful reading of instructions in the patient leaflet or on the packaging, worded as follows: *"Careful reading of the patient leaflet or information on the package is recommended".*

(2) For TV advertisement, a reminder means that an advertising clip cumulatively meeting the following conditions:

a) it is a part, sequel and/or supplementation of the same advertising campaign for a certain medicinal product, carried out at the same time and within the same audiovisual media service;

b) it reminds the audience of elements in the message broadcast in the main advertisement of the campaign;

c) is no more than 10 seconds in length;

d) it conveys the same information and messages as the whole commercial;

e) it contains the approval visa number and its date of its release, as "*advertising approval no. /date*….".

Article 56. – **Advertising over the Internet**

As any other form of advertising, irrespective of its form, advertising over the Internet shall be subject to NAMMD evaluation and approval.

(1) **Web pages:**

a) Each web page shall clearly establish:

- the identity and material and electronic address of the sponsor (sponsors) for the web-page;

- the source(s) of all information on the web-page;

- the target audience of the web-page (for instance, healthcare professionals, patients and the general public, or a combination thereof);

- approval visa number and date of its release, as *"advertising approval no. /date* …."

b) Webpage content:

- Information provided on the web-page will be updated with any significant changes in MA and/or medical practice and be subject to NAMMD approval; for each page and/or subject, as applicable, the date of the most recent update shall is will clearly displayed.

- Information that may be included on a single website or on multiple sites is as follows:

1. General information about the company:

- The webpages may contain information of interest for investors, news media and the general public, including financial data, descriptions of research and development programs, discussions of regulatory developments concerning the company and its products, information for prospective employees etc.

- The content of this information falls out of the scope of this guideline or legal provisions on medicinal products advertising.

2. Information regarding health education

- Webpages may contain non-promotional information regarding health education, characteristics of diseases, prevention methods, screening and treatment methods and other information aimed at promoting public health. These can relate to medicinal products, provided the discussion is balanced and accurate.

- Relevant information may be provided on therapeutic alternatives, including, if necessary, surgical procedures, diet, behavioural change and other interventions not requiring use of medicinal products.

- Web-pages containing information on health education shall always recommend visitors to require further information from healthcare professionals.

3. Promotional information for the patients and the general public

- Any information on web-sites for patients and the general public, which constitute a form of promotion shall be compliant with provisions of this Guideline, particularly with those mentioned under Article 53, "Audio-visual advertising", with regulatory provisions in force and with other codes of practice of the industry, regulating the content and format of commercials and the manner of medicinal product promotion.

- Such information shall be clearly labelled as advertising information for the general public.

- Such promotional information shall always recommend visitors to seek further information from healthcare professionals and include an express, legible invitation to carefully read the instruction in the leaflet or on the package, as follows: *„This medicinal product can be released without medical prescription. Careful reading of the patient leaflet or information on the package is recommended. In case of any unpleasant manifestations, please contact your physician or pharmacist."*

4. (1) Non-promotional information for the patients and the general public

- According to Romanian laws and regulations in force, web-sites may include non-promotional information for patients and the general public, regarding products in the pharmaceutical company's OTC portfolio (including information on indications, adverse reactions, interactions with other medicinal products, correct use, clinical research reports etc.) provided that the information is balanced, accurate and in line with the approved summary of product characteristics.

- For each product discussed, the web-page shall contain complete, unchanged examples of the currently approved summary of product characteristics and patient leaflet. These documents shall be posted in conjunction with other product information or connected to the respective discussion by a visible link recommending reference for readers.

- Additionally, the web-page may supply a link to a full, unchanged copy of any public evaluation report issued by the Committee for Medicinal Products of Human Use (CHMP) of the European Medicines Agency (EMA) or a relevant competent national authority.

- Trademarks shall be accompanied by non-proprietary international names.

- The web-page may include links to other web pages containing reliable medicinal product information, including web-pages of governmental authorities, medical research entities, patient organisations etc.

- The web-page shall always recommend visitors to seek further information from healthcare professionals.

(2) Advertising by electronic mail (e-mail) or text messages (SMS):

Advertising of medicinal products for human use (SMS) is not recommended.

(3) Links from other web-sites:

- Links can be created to a web-site sponsored by a pharmaceutical company from web-sites sponsored by other people; however, pharmaceutical companies shall not create links from web-sites meant for the general public to company sponsored web-sites, meant for healthcare professionals.

- In the same way, links may be created to separate web-sites, including web-sites sponsored by pharmaceutical companies or other people.

- Links shall direct to the initial page (homepage) of the intended web-page or be treated in such to ensure reader awareness as to the web-page sponsor's identity.

(4) **Revision of scientific information**

- Pharmaceutical companies and/or their representatives shall provide revision of scientific and medical information prepared for posting on the web-site, compliant with this guideline provisions.

- This function shall be accomplished by the scientific department in charge of information related to MAH marketed medicinal products, set up in accordance with legal provisions.

(5) **Confidentiality**

Web-sites shall be compliant with legislation and applicable codes of conduct regulating the private character, security and confidentiality of personal information.

Article 57. – Awareness raising and prevention campaigns concerning certain diseases

(1) Campaigns classified as 'medical education' are encouraged (campaigns targeting general public health education, awareness raising and prevention of certain diseases).

(2) MAH shall ensure that the material included in the respective campaign does not contain advertising messages for on-prescription medicinal products and does not encourage abusive or excessive use of the given medicinal products.

(3) Promotion of messages which restricting the therapeutic range of a given disease is prohibited.

(4) MAH shall also ensure that patients and the general public clearly understand that the therapeutic decision lies with the physician.

Article 58. - Sponsorship

(1) Sponsorship of any kind concerning the general public may not be related to the name of any medicinal product available without medical prescription.

(2) Moreover, sponsorship actions shall not contain direct or indirect promotional messages concerning the medicinal products available without medical prescription.

(3) Mutual aid or charity programs may not be performed in the name of a specific medicinal product.

Article 59. - Provision of samples

(1) MAHs and contracted persons/entities acting on their behalf are prohibited to provide the public with samples for advertising purposes.

(2) Commercial companies (authorised pharmacies or third parties) are not allowed to provide samples to the public for advertising purposes.

(3) Supply of samples by means of publications delivered directly or by mail or addition of samples in the publication packaging, as well as distribution of vouchers or tickets for access to free medicinal products or discounted medicinal products are prohibited.

Article 60. – Promotional objects

(1) Promotional objects given to the public shall be inexpensive and promote health and wellbeing.

(2) May only be offered for promoting non-prescription medicinal products.

Article 61. – **Promotion of medical and pharmaceutical services**

(1) Clinics, medical practices, pharmacies or other organisations providing healthcare services shall strictly limit themselves to provision thereof and may not include activities related to advertising of on-prescription products. The appropriate therapeutic approach of disease is the result of physician-patient cooperation.

(2) An example illustrating Article 61 (1) is beauty salons, which may promote "treatments against wrinkles", which is a non-specific, neutral indication, while not referring to a certain product however (botox or the botulinum toxin).

Article 61[1]. – Co-funding discount programs. All co-funding discount programs shall comply with the principles mentioned under Annex 2 to this Guideline.

Cards will be imprinted with information about the manner of adverse reaction reporting to the NAMMD.

CHAPTER V

Supervision and penalties

General considerations, notifications and potential non-compliances with the norms on the advertisement of medicinal products

SECTION 1
General considerations

Article 62. - The NAMMD is the authority entitled to take adequate and efficient steps for evaluation and monitoring of all forms of medicinal product advertising, as follows:

(1) a) for non-prescription medicinal products, **advertising material meant for the general public** is subject to prior NAMMD approval;

b) **Educational material intended for patients** is subject to prior NAMMD approval.

(2) a) **Advertising material intended for healthcare professionals**, promoting both on- and non- prescription medicinal products is reviewed by the NAMMD further to dissemination, randomly or following complaints.

b) **Educational material intended for healthcare professionals** are submitted for NAMMD prior approval.

(3) On applicant request, the NAMMD may grant advertising approval visa, valid for 6/12 months for advertising/educational material intended for the general public and for educational material meant for healthcare professionals, for fees in line with regulations.

Article 63. – (1) Generally, the deadline for review of all medicinal product advertising forms submitted for NAMMD approval in accordance with Article 62 (1) and (2) b) provisions or requested by the NAMMD in accordance with provisions of Article 62 (2) a) is 30 days from confirmation of payment/submission to the NAMMD (excluding the time used by the MAH to respond to potential NAMMD questions).

The MAH is notified on evaluation requirements.

(2) The 30-day deadline may be brought forward or extended, depending on the quality and/or complexity of the advertising material originally submitted for evaluation.

If data submitted for assessment of the various forms of advertising are substantial and evaluation is not possible to perform within the specified deadline, the NAMMD provides an estimate of the time necessary to complete the evaluation, however not exceeding 60 days.

(3) For advertising material submitted for reapproval, if NAMMD response/approval is not granted in 30 days, they shall be deemed as implicitly approval and continued on the market.

(4) Following reapproval, advertising material already printed need not be reprinted to include the approval visa number and date; assessment of compliance is performed based on the new approval granted by the NAMMD.

(5) As regards advertising material requiring reapproval, the application and fee shall be undertaken at least 30 days prior to expiry of approval.

Article 64. – In addition to the advertising form submitted for evaluation, the MAH shall indicate its target audience.

Article 65. – All advertising forms shall have already been submitted for evaluation by the internal scientific service responsible for monitoring of information concerning medicinal products marketed by the MAH.

Article 66. – When receipt of any type of advertising material, all units involved in medicinal product distribution are required to ascertain inclusion of the given product advertising NAMMD approval or its notification with the NAMMD.

Article 67. – The NAMMD may request counselling from other bodies responsible for evaluation of various advertising forms, concerning advertising type/form, target audience, as well as the date and duration foreseen for presentation/broadcast/transmission of each advertising form submitted for evaluation.

Article 68. - Natural and legal persons with legitimate interest in prohibiting any medicinal products advertising form noncompliant with legal provisions and regulations in force may notify the NAMMD in this respect, who shall answer in 60 days.

SECTION 2
Complaints and penalties for potential non-compliance with medicinal product advertising rules

Article 69. – To ensure implementation of proper, correct, unexaggerated advertising for medicinal products for human use marketed in Romania, in accordance with the legal provisions and regulations in force, for the general public as well as healthcare professionals, the NAMMD takes all required measures to insure compliance with the legal framework in that respect. Therefore:

(1) NAMMD qualified staff carries out inspections in units undertaking distribution of medicinal products for human use (community pharmacies, hospital pharmacies, druggist's shops, wholesale distributors), as well as MAH sites, for assessment of promotional material they hold or provide.

(2) NAMMD qualified staff also evaluates compliance with legal provisions of advertisement for healthcare professionals as displayed in scientific events (symposia, conference, congresses) attended by healthcare professionals.

(3) In case of non-compliance with legal provisions and regulations in force related to advertisement of medicinal products for human use, after responsible parts involved have been determined, the NAMMD applies penalties in accordance with provisions of Article 836 c) of Law no. 95/2006 on healthcare reform – Title XVII – The medicinal product.

Article 70. – (1) Any natural/legal person with legitimate interest in prohibition of any advertising form non-compliant with legal dispositions may submit a complaint to the NAMMD on breach of regulations for medicinal product advertising.

(2) The complaint may be in writing, according to the following requirements:

a) inclusion of the claimant's contact data (for easy identification and contact by the competent authorities for communication of the investigation status and results);

b) clear and comprehensive presentation of details regarding the type, moment and place where form of advertising in question has been encountered;

c) clear and specific presentation of the claimant's underlying reasons for concern;

d) if possible, a copy of the form of advertising (commercial) making the subject of the inquiry;

e) copies of any documents as proof of possible prior contact with the MAH or advertising agent for amiable resolution of the disagreement.

Article 71. – (1) Although all inquiries submitted are deemed similarly important, the NAMMD is particularly concerned for complaints regarding cases of possible negative impact of advertising upon public health.

(2) Alternatively, a complaint may be submitted to any other regulatory body.

Article 72. – (1) The NAMMD records all complaints received and notifies the claimant thereof.

(2) Over the entire the investigation, the claimant's identity is unknown to the defendant (whether pharmaceutical company or advertising agent).

(3) The NAMMD shall respond to the complaint received within 60 days as of its registration.

(4) If, after evaluation, the NAMMD ascertains that legal provisions have been breached with respect to medicinal product advertising, considering the interests of all parties involved, but particularly taking public interests into account, the NAMMD may take all the necessary steps for the law to be observed, including by ruling termination of the advertising and withdrawal of the advertising material.

Article 73. - (1) In case the misleading or illegal advertising material has not been published yet, but the publication is impending, the NAMMD may rule that this advertising be prohibited.

(2) In case of serious violation of public health, the measure provided for in Article 73 (1) can be instituted by expedited procedure and may be temporary or permanent.

Article 74. - (1) When the NAMMD ascertains that a form of advertising is based on inconclusive or false evidence (clinical trials, epidemiological studies or any other scientific arguments), it shall be ruled that the broadcasting of that form of advertising and the incriminated evidence and arguments be prohibited.

(2) Moreover, in order to remove the effects of misleading advertising whose termination has been ruled by the NAMMD, the latter may request:

a) full or partial publication of the final decision under the form considered adequate;

b) publication of a corrective statement.

CHAPTER VI
Final provisions, emergency restrictions or variations to MA terms for safety reasons

SECTION 1
Final provisions

Article 75. – MAHs have the following obligations:

(1) keep available for or provide to the NAMMD a sample of all advertising material they have initiated, together with a statement as to its intended audience, the manner of notification and the date of the first notification;

(2) ensures that the advertising material drafted for its medicinal products are in compliance with legal provisions for public information, provide clear and legible information, in sufficient detail to allow readers a correct opinion as regards the efficacy, safety and manner of administration of a medicinal product;

(3) check whether their legal representatives have been appropriately trained and whether they fulfil their legal obligations;

(4) provide the NAMMD with the information and assistance necessary to accomplish its responsibilities;

(5) ensure that NAMMD decisions are enforced immediately and fully.

Article 76. - The NAMMD takes adequate steps to ensure application of legal provisions and regulations in force on advertising of medicinal product for human use and, in case of breach thereof, applies penalties in accordance with the law.

SECTION 2

Urgent restrictions or variations to MA terms for safety reasons

Article 77. – (1) The MAH or its legal representatives have to ensure that prescribers are immediately and fully informed on any important or relevant change of available product information as used in promotional campaigns.

(2) As a result of an urgent restriction required by changes in the safety profile or following a variation to MA terms for similar reasons, persons in charge of advertising campaigns shall take all necessary steps for advertising material subsequent to such change to reflect the new form and, where necessary, reflect possible differences in a relevant and clear manner.

ANNEX 1
(SCD no.18/08.08.2013)

Names/Definitions of advertising material

Advertising material for shelf display	**Description of the material**
Wobbler/Stopper/Shelf talker	- applicable at the product shelf
Wobbler	- size: 10-15 cm + metal/PVC hook to hang outside the shelf
Stopper	- size: 10-15 cm + fixing system between two shelves, placed perpendicularly on the shelf, to allow sideways viewing
Shelf talker	- size: 30 – 70 cm – to be applied on the entire length of the shelf
Counter advertising material	**Description of the material**
Counter Display	- Of various visual forms; may or may not include shelves of various sizes, placed on the counter (LAMA displays or totem counters are also available, about 50 cm in height)
Change tray **Change tray branding**	- tray for the change - product poster or package (included in the change tray plastic), of the same size as the change tray, incorporated in the change tray material (PVC)
LAMAdisplay/ **Totem/Floor display**	- cardboard tube printed on both sides, 1.54 – 2.00 m in size
Floor sticker	- sticker applied on the floor, at the entrance of the pharmacy or in the counter area
Advertising material for window display	**Description of the material**
Pharmacy poster	- Can be printed on paper/cardboard/ poliplan/ backlite of various sizes and shapes, depending on pharmacy specificity – framed, or luminous boxes

Set of window material*: - ***Self-adhesive labels**** - ***Open/Closed or Pull/Push sign or pharmacy working hours**** - ***Window frame as a brand sticker****	- posters directly applied on pharmacy windows; their size may vary. - Sticker applied on pharmacy doors

Other advertising material	Description of the material
Security door covers	- Covers made of cardboard/fabric/PVC used for security doors
Dummy box	- a much larger mock-up made of cardboard/PVC, compliant with the product's artwork;
Floor display	- cardboard/ glass/plexiglass shelf, placed on the floor, regardless of the pharmacy's furniture; it may contain various information and may act as support for other advertising material; (it may contain mini-dummy boxes)
Ceiling hanger	- hanging material, visible to the consumer
Flyer	- information material intended for the consumer, displayed in pharmacies or waiting rooms of medical practices, clinics or hospitals
Branding water dispenser	- sticker applied on the water dispenser
Press layout	- information material in magazines/newspapers, intended for the general public and/or healthcare professionals
Press release*	- medicinal product information material providing brief information to the media (magazines/ newspapers/ other publications); may contain the product image of the packaging / artwork accompanied or not by other information, meant for the general public and/or healthcare professionals; may coexist or not with the initial press layout and may be established as reminders of other types of material (e.g. TV advertising)

Banners may be: ***- Conference/Exhibition banner**** ***- Out-door banner*,*** ***- Online banner **** ***- Spider type banner****	- advertising screen of different formats and sizes (roll-up, poster) with reduced amount of information - flexible advertising screen (usually large), placed on a foldable metallic structure, used in scientific events - display set consisting of several fixed/flexible advertising screens, possible also including display windows, projection screens, monitors, display tables used in scientific events. This set of advertising material shall not contain the advertised product SmPC, either in full or in part.
- Stand/Booth type*	- information material announcing a launch, a new indication, an approval/authorisation of a new product, an event
Newsletter – information material announcing a release (press release)**	
Press dossier	- set of material used in a press conference, whose content is adjusted to the target audience
Promotional flyer for healthcare professionals	- promotional material size A4 format or smaller, provided to healthcare professionals, consisting of a single sheet; it contains promotional messages more comprehensive than reminders
Information flyer for healthcare professionals	- material provided to healthcare professionals, containing scientific information or information related to changes in medicinal product primary and/or secondary packaging (e.g. information concerning: changes of logo; change in the colour of primary/secondary packaging; other design changes; changes in the wording of a medicinal product etc.). This information material may be considered an abridged version of the educational material.
Leave piece/Leave behind**	- Printed promotional/educational material, for healthcare professionals, meant for target audience information on a pathology/product
Visual aid	- Promotional material containing detailed medicinal product information, intended for healthcare professionals. To be used in the promotional activities performed by medical representatives and are

Promotional presentations	not provided to be preserved by specialists. - Advertising material containing detailed product/disease information intended for healthcare professionals. To be used in promotional activity performed by medical representatives and/or at panels/congresses/symposia.
Other advertising material ***	**Description of the material**
	- To be defined as they emerge

*This type of materials is considered a reminder
**Notified material
***Yet unmarketed

ANNEX 2

to SCD no. 18/08.08.2013

PRINCIPLES

for co-funding discount programs granted for facilitation of patient access to medicinal products prescribed

To facilitate patient access to treatment prescribed at more accessible costs, implementation is required of programs for partial or total cofunding discount concerning patient costs for treatment with certain medicinal products and medical devices, which allows avoidance of the risk of treatment discontinuation and ensuing decline of patients' health.

Development of a platform pertaining to a co-funding discount program involves processes carried out by the following actors: Holders of marketing authorisations for products entered into the co-funding discount program or their representatives, the program administrator, adherent pharmacies and patients.

Co-funding discounts may be granted for any product entered into the program and prescribed by physicians and they can contribute to discounts granted by state/private insurers, to be finally supported by Marketing Authorisation Holders for products in the co-funding discount program or their representatives.

In order not to be considered promotion of medicinal products as per Law 95/2006 as well as an incentive for medicinal product distribution, co-funding discount programs shall be conducted in strict compliance with the following principles:

1- All patients have equal access to the co-funding discounts granted within a program. However, criteria for support of certain social categories can be defined. Each patient entered into a program shall receive a monthly (or quarterly, depending on prescription) maximum (limiting) co-funding discount for a certain product, the limitation depending on the maximum monthly (quarterly) dose as established in accordance with the treatment scheme and product dosage indications.

2- The prescriber must be able to inform patients about the programs and benefits derived from participation in such programs only after the medicinal product included in the program has already been prescribed to the patient, based on professional independence and prescriber's freedom of decision.

3- All Marketing Authorisation Holders and their representatives have equal access to such programs and may include any of their products in co-funding discount programs. Amounts compensated by Marketing Authorisation Holders and their representatives are established independently; this shall represent in absolute figures as reported to the therapeutic unit of the medicinal product concerned.

4- Co-funding discount programs shall be available for any pharmacy willing to adhere to the program.

5- Participation in a co-funding discount program does not allow direct relationships between Marketing Authorisation Holders or their representatives, on one hand and prescriber, pharmacy or patient, on the other hand, nor direct exchange of information between them.

6- Compliance with aforementioned requirements involves presence of an independent administrator to directly manage the co-funding discount program, also ensuring the platform for the settlement of sums associated with co-funding discounts. Settlement of co-funding discounts shall only be performed between the Marketing Authorisation Holder and their representative and the program administrator and between the program administrator and the adherent pharmacy, respectively, according to transactions reported by the pharmacies. Inclusion of other operators (distributors, business agents etc.) in the process for settlement of co-funding discounts is prohibited.

7- Considering the limited access to information related to transactions within the system, Marketing Authorisation Holders and their representatives may appoint an independent auditor to audit accuracy of transactions reported by the program administrator, but they shall not have access to transaction details.

8- All co-funding discount programs shall be based on one personal, nominal single card for each patient, which shall not contain information related to a certain manufacturer, product or treatment.

9- Because of their capacity to directly or indirectly allow transfer of information among patients, other systems for grant of co-funding discounts for patients are not allowed (e.g. vouchers, coupons or other marketing discount mechanisms etc.).

10- Patient entry into the program, distribution and handling of cards shall only be conducted by the program administrator. Marketing Authorisation Holders and their representatives or prescribers are forbidden to enrol patients or issue or release cards.

11- The program administrator can be any independent legal entity, not affiliated with the Marketing Authorisation Holders or their representatives, who ensures program control and management.

12- The program administrator must meet all requirements stipulated by the law for personal data processing. The administrator may not provide information related to the pharmacy, patients or prescribers to other participants in the program.

13- The administrator is responsible for ensuring system safety and the privacy of information processed, ensuring control of informational flows among various participants in the co-funding discount program.

The program administrator must ensure all facilities (hardware, software etc.), as well as logistic support required for program conduct. The administrator shall be responsible for the integrity and accuracy of information processed. To this effect, to ensure enhanced security of managed data, the program administrator shall be ISO 9001 and ISO 27001 certified.

DECISION

No. 19/12.08.2013

on approval of the detailed Gudeline concerning the various categories of variations to the terms of marketing authorisations and on their examination by the National Agency for Medicines and Medical Devices by the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended through Regulation (EU) no. 712/2012

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 158/18.02.2013, in accordance with Article 8 (1) of the Regulation on the organisation and operation of the NAMMD Scientific Council, hereby adopts through written procedure the following

DECISION

Sole article – The detailed Guideline concerning the various categories of variations to the terms of marketing authorisations and on their examination by the National Agency for Medicines and Medical Devices by the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended through Regulation (EU) no. 712/2012 is approved, in accordance with the Annexes which are integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX

(SCD no. 19/12.08.2013)

Detailed Guideline concerning the various categories of variations to the terms of marketing authorisations and on their examination by the National Agency for Medicines and Medical Devices by the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended through Regulation (EU) no. 712/2012

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CHAPTER I

Introduction

Article 1. – (1) This Guideline is a translation and transposition of *Guideline C(2013) 2804 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV 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 and on the documentation to be submitted pursuant to those procedures*, published in the Notice to Applicants *(NTA);* Regulation (EC) no. 1234/2008 of the Commission, hereinafter *The Variations Regulation* has been amended through Regulation (EU) no. 712/2012, which has broadened its scope to medicinal products for human and veterinary use authorised through "purely national" procedure.

(2) The Guideline establishes the procedure of the National Agency for Medicines and Medical Devices, hereinafter the *NAMMD*, for handling of variations to the terms of marketing authorisations of medicinal products for human use, authorised by „purely national" procedure and by the simplified procedures mentioned in the *Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC)/New Collaboration Agreement between Drug Regulatory Authorities in Central and Eastern European Countries* (nCADREAC)].

(3) The „purely national" procedure referred to in this Guideline is the procedure for grant of marketing authorisations by a Member State in accordance with the Community *acquis* conditions outside the Mutual Recognition Procedure.

Article 2. – This Guideline is enforced in accordance with the definitions mentioned in Law 95/2006 on healthcare reform, as amended, Title XVII – The medicinal product, hereinafter the Law, of Regulation (EC) no. 726/2004, as well as those from *The Variations Regulation*.

Article 3. – In accordance with this Guideline, *'variation'* and *'change'* are synonyms, as mentioned in Article 2 (1) of *The Variations Regulation.*

Article 4. – In accordance with this Guideline, applicants belonging to the same mother society or to the same group of societies, as well as applicants who have signed contracts or who have undertaken harmonised practices related to the marketing of the medicinal products concerned should be considered one and the same holder of the marketing authorisation (hereinafter referred to as "holder").

Article 5. - (1) The purpose of this Guideline is to facilitate the interpretation and application of the Variations Regulation and the provision of details on the application of the relevant procedures, including a description of all the relevant steps from the submission of an application for a variation to the final outcome of the procedure on the application.

(2) In addition, Annex 1 to this Guideline provides details of the classification of variations into the following categories as defined in Article 2 of the Variations Regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II.

(3) It also provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented.

(4) Annex 1 to this Guideline will be regularly updated, taking into account the recommendations provided in accordance with Article 5 of the Variations Regulation as well as scientific and technical progress.

CHAPTER II
Recommendations on the handling of variations

Article 6. – A marketing authorisation of a medicinal product in Romania is composed of:

a) a decision granting the marketing authorisation issued by the NAMMD; and

b) a technical dossier with the data submitted by the applicant in accordance with Articles 702 (4) to 708 of the Law, transposing Articles 8(3) to 11 of Directive 2001/83, as well as with Order of the Minister of Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, transposing Annex I of Directive 2001/83/EC.

Article 7. - (1) The Variations Regulation governs the procedures for the amendment of the marketing authorisation and of the technical dossier.

(2) However, in the case of medicinal products for human use, the introduction of changes to the labelling or package leaflet that is not connected with the summary of product characteristics is not governed by the procedures of the Variations Regulation.

(3) In accordance with Article 771 (3) of the Law transposing Article 61 (3) of Directive 2001/83, these changes are to be notified to the NAMMD in accordance with the provisions of Order of the Minister of Health no. 1205/2006.

Article 8. - These guidelines cover the following categories of variations, defined in Article 2 of the Variations Regulation:

- Minor variations of Type IA
- Minor variations of Type IB
- Major variations of Type II
- Extensions
- Urgent safety restriction

Article 9. - It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group; for instance, a group consisting of an extension and a major variation of Type II will be handled as an extension application; a group consisting of minor variations of Type IB and Type IA will be handled as a Type IB notification.

Article 10. - (1) No variation applications for medicinal products undergoing authorisation procedure shall be submitted.

(2) In case of the authorisation procedure, additional documents shall be submitted based on an address for supplementation of the documentation submitted by authorisation procedure.

Article 11. – For grouped variation applications, the fee is established by implementation of the fees for each individual variation, for the variation defining the group (if there are several marketing authorisations for each authorisation in the group affected by the variation) and for each variation included in the group, other than the one defining the group.

Article 12. – The invalidation or request of reclassification of the variation determines the deduction of a percentage of the assessment fee, in accordance with Order of the Minister of Health no. 716/2009 as amended, while the rest remains in the Holder's possession for payment of further services.

Article 13. – Where required, the NAMMD balances the fee for variations to marketing authorisation terms.

Article 14. - The EU application form for variations to a marketing authorisation for medicinal products (human and veterinary) translated into Romanian (Annex 2) is available on the NAMMD website under heading "Forms and fees".

Article 15. - Any information related to the implementation of a given variation should be immediately provided by the holder upon the request of the NAMMD.

II.1 Type IA minor variations

Article 16. - Hereby guidance is provided on the application of Articles 13a, 13d, 13e, 23 and 24 of the Variations Regulation to minor variations of Type IA.

Article 17. - (1) The Variations Regulation and Annex 1 to this Guideline set out a list of changes to be considered as minor variations of Type IA.

(2) Such minor variations do not require any prior approval, but must be notified by the holder within 12 months following implementation ("Do and Tell" procedure).

(3) However, certain minor variations of Type IA require immediate notification after implementation (IAIN), in order to ensure the continuous supervision of the medicinal product.

Article 18. - Annex 1 to this Guideline clarifies the conditions which must be met in order for a variation to follow a Type IA notification procedure, and specifies which minor variations of Type IA must be notified immediately following implementation.

II.1.1. Submission of Type IA variations

Article 19. - (1) Minor variations of Type IA do not require prior examination by the NAMMD before they can be implemented by the holder.

(2) However, at the latest within 12 months from the date of the implementation, the holder must submit simultaneously to the NAMMD a notification of the relevant variation(s).

(3) It is possible for a holder to include a minor variation of Type IA which is not subject to immediate notification in the submission of a minor variation of Type IA for immediate notification or with any other variation.

(4) The conditions laid down in Article 13 (2)(d), a) – c) of the Variations Regulation (as appropriate) should be fulfilled.

Article 20. - The holder may group several minor variations of Type IA under a single notification, as established in Article 13 (2) (d) of the Variations Regulation; specifically, two possibilities exist for the grouping of variations of Type IA:

a) The holder may group several minor variations of Type IA regarding the terms of one single marketing authorisation provided that they are notified at the same time to the NAMMD.

b) The holder may group one or more minor variations of Type IA to the terms of several marketing authorisations under a single notification provided that the variations are the same for all marketing authorisations concerned and they are notified at the same time to the NAMMD.

Article 21. - (1) The 12 months deadline to notify minor variations of Type IA allows holders to collect Type 1A variations for their medicinal products during a year.

(2) However, the notification of these variations in a single submission is only possible where the conditions for grouping apply (same variations for all medicinal products concerned).

(3) Therefore, it may be the case that the submission of variations implemented over a period of 12 months (so called "annual report") requires several submissions; e.g. one referring to a single minor variation of Type IA, another referring to group of minor variations of Type IA to the terms of one marketing authorisation, and another referring to group of the minor variations of Type IA to the terms of several marketing authorisations.

Article 22. - The notification must contain the elements listed in Annex IV to the *Variations Regulation,* presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format and the elements related to the payment of the assessment fee:

a) Cover letter.

b) Payment form of the assessment fee.

c) Proof of payment to the NAMMD (a copy of the document attesting fee payment, containing the identification data of the variation subject to payment);

d) The completed EU variation application form translated into Romanian, including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable; where a variation is the consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.

e) Reference to the variation code as laid down in Annex 1 to this Guideline, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

f) All documentation specified in Annex 1 to this Guideline.

g) In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format, as well as the relevant translations; where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IA, mock-ups or specimens should be provided to the NAMMD.

Article 23. - (1) For grouped minor variations of Type IA concerning several marketing authorisations from the same holder in accordance with Article 13d of the Variations Regulation, a common cover letter and application form should be submitted together with separate supportive documentation and revised product information (if applicable) for each medicinal product concerned.

(2) This will allow the NAMMD to update the dossier of each marketing authorisation included in the group with the relevant amended or new information.

Article 24. - At least 15 days prior to submission of the documents mentioned under Article 22 c) - g), the holder should submit to the NAMMD the cover letter and the completed payment form.

II.1.2. Assessment of Type IA variations

Article 25. - The NAMMD will review the Type IA notification within 30 days following receipt.

Article 26. - (1) By Day 30, the NAMMD will inform the holder of the outcome of its review.

(2) In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, the NAMMD will update the decision granting the marketing authorisation within 6 months following the date of information to the holder of the outcome of the review, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD.

Article 27. - Where one or several minor variations of Type IA are submitted as part of one notification, the NAMMD will inform the holder which variation(s) have been accepted or rejected following its review.

Article 28. - (1) While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately on request of the NAMMD.

(2) It should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned.

II.2. Type IB minor variations

Article 29. - Hereby guidance is provided on the application of Articles 13b, 13d, 13e, 23 and 24 of the Variations Regulation to minor variations of Type IB.

Article 30. - (1) The Variations Regulation and Annex 1 to this Guideline set out a list of changes to be considered as minor variations of Type IB.

(2) Such minor variations must be notified before implementation.

(3) The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the NAMMD before implementing the change ("Tell, Wait and Do" procedure).

II.2.1. Submission of Type IB notifications

Article 31. - Notifications for minor variations of Type IB must be submitted by the holder to the NAMMD in view of approval.

Article 32. - Holders may group under a single notification the submission of several minor variations of Type IB regarding the same marketing authorisation, or group the submission of one or more minor variation(s) of Type IB with other minor variations regarding the same marketing authorisation, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the NAMMD.

Article 33. - In addition, for medicinal products authorised under purely national procedures, the holder may also group several minor variations of Type IB affecting several marketing authorisations released by the NAMMD, or one or more minor variation(s) of Type IB with other minor variations affecting several marketing authorisations released by the NAMMD provided that:

a) the variations are the same for all the marketing authorisations concerned,

b) the variations are submitted at the same time to the NAMMD, and

c) the NAMMD has previously agreed to the grouping.

Article 34. - Furthermore, where the same minor variation of Type IB or the same group of minor variations (as explained above) affect several marketing authorisations owned by the same holder, the holder may submit these variations as one application for 'worksharing' (see Chapter 3 on 'worksharing').

Article 35. - The notification must contain the elements listed in Annex IV to the *Variations Regulation*, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format, as well as the items related to the payment of the assessment fee:

a) Cover letter;

b) Payment form of the assessment fee;

c) Proof of payment to the NAMMD (a copy of the document attesting fee payment, containing the identification data of the variation subject to payment);

d) The completed EU variation application form (published in the Notice to applicants), translated into Romanian, including the details of the marketing authorisations(s) concerned; where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form; where a variation is considered unclassified, a detailed justification for its submission as a Type IB notification must be included.

e) Reference to the variation code as laid down in Annex 1 to this Guideline, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

f) Relevant documentation in support of the proposed variation including any documentation specified in Annex 1 to this Guideline.

g) For variations requested by the NAMMD or by another authority resulting from new data submitted e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the application should be annexed to the cover letter.

h) In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format, as well as the relevant translations. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IB, mock-ups or specimens should be provided to the NAMMD.

Article 36. – At least 15 days prior to submission of the documents mentioned under Article 35 c) – the holder should submit to the NAMMD the cover letter and the completed payment form.

II.2.2. Review of type IB variations

Article 37. - (1) When the proposed variation is not considered a minor variation of Type IB following Annex 1 to this Guideline or has not been classified as a minor variation of Type IB in a recommendation pursuant to Article 5 of the *Variations Regulation*, and the NAMMD considers that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the holder is required to review and fill in the application in accordance with the requirements for a major Type II variation.

(2) Following the receipt of a valid, reviewed application for variation, an assessment procedure for a Type II variation shall be inaugurated (see Subsection II.3.2).

Article 38. - When the NAMMD is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder will be informed of the outcome of the validation and of the start date of the procedure.

Article 39. - (1) Within 30 days following the acknowledgement of receipt of a valid notification, the NAMMD will notify the holder of the outcome of the procedure.

(2) If the NAMMD has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

Article 40. - (1) In case of an unfavourable outcome, the holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the holder does not amend the notification within 30 days as requested, the variation will be deemed rejected by the NAMMD.

Article 41. - Within 30 days of receipt of the amended notification, the NAMMD will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Article 42. - As far as grouped minor variations are concerned, the holder will be informed accordingly by the NAMMD about the variation(s) approved/rejected following assessment.

Article 43. - (1) Where necessary, the NAMMD will update the marketing authorisation within 6 months following approval of the procedure, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD.

(2) However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the marketing authorisation.

II.3. Type II Major variations

Article 44. - Hereby guidance is provided on the application of Articles 13c, 13d, 13e, 23 and 24 of the Variations Regulation to major variations of Type II.

Article 45. - (1) The Variations Regulation and Annex 1 to this Guideline set out a list of changes to be considered as major variations of Type II.

(2) Such major variations require approval of the NAMMD before implementation.

II.3.1. Submission of Type II applications

Article 46. - Notifications for major variations of Type II must be submitted by the holder to the NAMMD in view of approval.

Article 47. - Holders may group under a single notification the submission of several major variations of Type II regarding the same marketing authorisation, or group the submission of one or more major variation(s) of Type II with other minor variations regarding the same marketing authorisation, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the NAMMD.

Article 48. - In addition, for medicinal products authorised under purely national procedures, the holder may also group several major variations of Type II affecting several marketing authorisations released by the NAMMD, or one or more major variation(s) of Type II with other minor variations affecting several marketing authorisations released by the NAMMD, provided that:

a) the variations are the same for all the marketing authorisations concerned,

b) the variations are submitted at the same time to the NAMMD,

c) the NAMMD has previously agreed to the grouping.

Article 49. - Furthermore, where the same major variation of Type II or the same group of variations (as explained above) affect several marketing authorisations owned by the same holder, the holder may submit these variations as one application for ‘worksharing’ (see Chapter III on ‘worksharing’).

Article 50. - The application must contain the elements listed in Annex IV to the *Variations Regulation*, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format, as well as the items related to the payment of the assessment fee:

a) cover letter;

b) payment form of the assessment fee;

c) proof for payment to the NAMMD, containing identification data of the variation subject to the fee);

d) The completed EU variation application form (published in the Notice to Applicants), including the details of the marketing authorisation(s) concerned; where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form;

e) Reference to the variation code as laid down in Annex 1 to this Guideline, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application;

f) Supporting data relating to the proposed variation(s);

g) An updated version to quality summaries, non-clinical overviews and clinical overviews as relevant; when non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

h) For variations requested by the NAMMD or by another competent authority resulting from new data submitted e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.

i) In case that the variations affect the summary of product characteristics, labelling or package leaflet, the revised product information presented in the appropriate format, as well as the relevant translations; where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the major variation of Type II, mock-ups or specimens should be provided to the NAMMD.

Article 51. – At least 15 days prior to submission of the documents indicated under Article 50 c) - i), the holder submits to the NAMMD the cover letter and the completed payment form.

II.3.2. Assessment of type II variations

Article 52. - Upon receipt of a Type II application, the NAMMD will handle the application as follows:

Article 53. - (1) If the application contains the elements the elements listed in subsection II.3.1, the NAMMD assesses the validity of the submitted application and notifies the holder about the validation/invalidation of the application, also stating the grounds for invalidation or the date of onset of the assessment procedure, as required.

(2) The procedure starts from the date of acknowledgement of the receipt of a valid application. The holder will be informed of the timetable at the start of the procedure.

Article 54. - As a general rule, for major variations of Type II, a 60-day evaluation period will apply; this period may be reduced by the NAMMD having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part I of Annex V or for grouping of variations in accordance with Article 13 d) (2)(c) of the Variations Regulation. For variations for veterinary medicinal products listed in Part 2 of Annex V of the Variations Regulation a 90-day period will apply.

The reference Member State will prepare a draft assessment report and a decision on the application according to the communicated timetable and will circulate them to the concerned Member States for comments as well as to the holder for information.

Article 55. - (1) Throughout the evaluation period, the NAMMD may request the holder to provide additional information.

(2) The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

Article 56. - (1) The procedure will be suspended until the receipt of the supplementary information.

(2) In general, a suspension of one month will typically apply.

(3) For longer suspension the holder should send a justified request to the NAMMD for agreement.

Article 57. - The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

II.3.3. Outcome of assessment of type II variations

Article 58. - By the end of the evaluation period, the NAMMD will finalise and submit the assessment report and its decision on the application, and notifies the holder about the approval or rejection of the variation(s) (while stating the grounds for rejection).

Article 59. - (1) Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the NAMMD will inform the holder which variation(s) have been accepted or rejected.

(2) The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the assessment performed by the NAMMD).

Article 60. - After approval of the variation(s), the NAMMD will, where necessary, amend the marketing authorisation to reflect the variation(s) within 2 months, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD.

Article 61. - The accepted major variation(s) of Type II can be implemented after the holder has been informed about the acceptance of the variation(s) by the NAMMD, provided that the necessary documents to amend the marketing authorisation have been submitted to the Member State concerned.

Article 62. - Variations related to safety issues must be implemented within a time-frame agreed between the NAMMD and the holder.

II.4. Extensions

Article 63. - (1) Annex I of the Variations Regulation sets out a list of changes to be considered as extensions.

(2) As established in Article 19 of the Variations Regulation, such applications will be evaluated in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates.

(3) The NAMMD approves the extension as a new marketing authorisation.

II.4.1. Submission of applications for extension

Article 64. - Extension applications must be submitted to the NAMMD in view of approval.

Article 65. - (1) Holders may group under a single notification the submission of several extensions, or one or more extensions with one or more other variations, regarding the same marketing authorisation provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the NAMMD.

(2) However, no worksharing of extensions applications is foreseen in the Variations Regulation.

Article 66. – The application must contain the following elements, as well as elements related to the payment of the fee for assessment of line extension in accordance with the appropriate headings and numbering of the EU-CTD format:

a) cover letter;

b) payment form of the assessment fee;

c) Proof of payment to the NAMMD (a copy of the document attesting fee payment, containing the identification data of the variation subject to payment);

d) The completed EU variation application form (published in the Notice to Applicants) accompanied, if required, by the completed European form for application for variation translated into Romanian, containing the details of the initial marketing authorisation as specified by the line extension;

e) Supporting data relating to the proposed extension; some guidance on the appropriate additional studies required for extension applications is available in Appendix IV to Chapter 1 of Volume 2A or 6A of the Notice to applicants.

f) A full Module 1 should be provided, with justifications for absence of data or documents included in the relevant section(s) of Module 1 or Part 1.

g) Update of quality summaries, non-clinical and clinical overviews, as relevant; when non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

h) In case that the extension affects the summary of product characteristics, labelling or package leaflet: the revised product information, presented in the appropriate format.

Article 67. – The holder submits to the NAMMD the documents shown under Article 66 in accordance with the provisions of Order of the Minister of Health no. 1448/2010 on amendment of the Annex of Order of the Minister of Health no. 895/2006 on approval of the Regulations on marketing authorisation and surveillance of medicinal products for human use.

II.4.2. Assessment of extension

Article 68. - Upon receipt of an extension application under the purely national procedure, it will be handled as an initial marketing authorisation application in accordance with the provisions of the Law and Order of the Minister of Health no. 906/2006.

II.5. Human influenza vaccines

Article 69. - Hereby guidance is provided on the application of Article 13f of the Variations Regulation to the annual update of human influenza vaccines.

Article 70. - (1) Because of the specificities inherent in the manufacturing of human influenza vaccines, a special 'fast track' variation procedure is applicable for the annual change in active substance for the purpose of the annual update of a human influenza vaccine in order to meet the EU recommendation for human influenza virus strain(s) vaccine composition for the coming season.

(2) In addition, a special urgent procedure is foreseen in Article 21 of the Variations Regulation for cases of pandemic situation.

Article 71. - Any other variations to human influenza vaccines follows the variation procedures foreseen in other sections of these Guidelines.

Article 72. - The 'fast track' procedure consists of two steps:

a) The first step concerns the assessment of the administrative and quality data elements (summary of product characteristics, labelling and package leaflet, and the chemical, pharmaceutical and biological documentation).

b) The second step concerns the assessment of additional data where necessary.

Article 73. - Marketing authorisation holders are advised to discuss the annual update submissions in advance with the NAMMD.

II.5.1. Submission of variations for annual update of human influenza vaccines applications

Article 74. - Variations concerning changes to the active substance for the annual update of human influenza vaccines applications must be submitted to the NAMMD for approval.

Article 75. - The application must be presented in accordance with the appropriate headings and numbering of the EU-CTD format, as well as with the aspects related to the assessment fee:

a) Cover letter;

b) Payment form of the assessment fee;

c) Proof for payment to the NAMMD, containing identification data of the variation subject to the fee);

d) The completed EU variation application form translated into Romanian, containing the details of the concerned marketing authorisation(s);

e) Update to quality summaries, non-clinical overviews and clinical overviews as relevant; when non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2;

f) Supporting data relating to the proposed variation(s).

g) The revised product information, presented in the appropriate format.

Article 76. - At least 15 days prior to submission of the documents indicated in Article 75 c) - g), the holder submits to the NAMMD a cover letter and the completed fee form.

II.5.2. Assessment of variations for the yearly update of influenza vaccines for human use

Article 77. - Upon receipt of an application for the annual update, the NAMMD will handle the application as follows:

Article 78. - The NAMMD will acknowledge receipt of a valid application of an annual variation human influenza vaccine and inform the holder accordingly about the validation (invalidation) of the application, while stating the grounds for invalidation or the date of onset of the assessment procedure, as required.

Article 79. - Within the evaluation period, the NAMMD may send the holder a request for supplementary information (notably clinical or stability data); in such a case, the 45 days deadline is stopped until the requested information has been submitted by the holder.

Article 80. - Within 45 days from the receipt of a valid application, the NAMMD will finalise the evaluation including its decision on the application and inform the holder about the approval or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Article 81. – Upon approval of the variation(s), the NAMMD changes the marketing authorisation(s) in view of including the concerned approved variation(s), provided that the required documents for change of the marketing authorisation are sent beforehand.

II.6 Urgent safety restrictions

Article 82. - Article 22 of the Variations Regulation foresees that in the event of a risk to public health in the case of medicinal products for human use, the holder may take provisional "urgent safety restrictions".

Article 83. - (1) Urgent safety restrictions concern interim variation(s) in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product.

(2) These urgent variations must be subsequently introduced via a corresponding variation in the marketing authorisation.

Article 84. - The holder must immediately notify the NAMMD of the restrictions to be introduced.

Article 85. - (1) If no objections have been raised by the NAMMD within 24 hours following receipt of that information, the urgent safety restrictions are deemed accepted.

(2) The NAMMD notifies the holder about the approval of urgent safety restrictions.

(3) They must be implemented within a time frame agreed between the NAMMD and the holder.

Article 86. - Urgent safety restrictions may also be imposed by the NAMMD in the event of a risk to public health in the case of medicinal products for human use.

Article 87. - The corresponding variation application reflecting the urgent safety restrictions (whether requested by the holder or imposed by the NAMMD) must be submitted by the holder as soon as possible within 15 days.

Article 88. – Within 24 hours as of NAMMD approval of the urgent safety restrictions, the holder submits to the NAMMD a cover letter and the completed fee form.

II.7. Statement of compliance under the Paediatric Regulation

Article 89. - Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) no. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1] ("Paediatric Regulation") provides for rewards:

- Under Article 36(1) of Regulation (EC) No 1901/2006, the holder of a patent or supplementary protection certificate is entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) no. 1768/92[2] [now: Regulation (EC) no. 469/2009] under certain conditions, including the addition to the marketing authorisation of the statement referred to in Article 28(3) of the Paediatric Regulation ("compliance statement").

Article 90. - It follows that, for the purposes of benefiting from the rewards provided for under Articles 36 of the Paediatric Regulation, a variation to add the compliance statement in the marketing authorisation may be required.

Article 91. - (1) Article 23a of the Variations Regulation simplifies the procedure to add the compliance statement in the marketing authorisation so that the rewards foreseen under Regulation (EC) 1901/2006 may be sought as soon as possible once the requirements foreseen in the Paediatric Regulation have been complied with.

(2) Specifically, in order to include the compliance statement holders should submit a variation request to the NAMMD.

(3) After verification that all relevant conditions are met, the compliance statement is to be included by the NAMMD in the technical dossier of the marketing authorisation.

Article 92. - For the purposes of legal certainty, the NAMMD will provide the holder with a confirmation that the compliance statement has been included in the technical dossier within 30 days after the relevant assessment has been concluded.

CHAPTER III
Procedural guidance on worksharing

Article 93. - Article 20 of the Variations Regulation allows a holder to submit in one application the same Type IB, the same Type II variation, or the same group of variations corresponding to one of the cases listed in Annex III of the Regulation or agreed with the NAMMD which does not contain any extension affecting:

- (i) more than one purely national marketing authorisation of the same holder in more than one Member State; or
- (ii) one or several purely national marketing authorisations and one or several centralised marketing authorisations of the same holder; or
- (iii) one or several purely national marketing authorisation(s) and one or several mutual recognition marketing authorisation(s) of the same holder; or
- (iv) one or several purely national marketing authorisation(s), one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder.

Article 94. - In order to avoid duplication of work in the evaluation of such variations, a worksharing procedure has been established under which one authority (the 'reference authority'), chosen amongst the competent authorities of the Member States, namely by the European Medicines Agency (hereinafter 'Agency'), will examine the variation on behalf of the other concerned authorities.

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[1] JO L 378, 27.12.2006, p. 1.

[2] From 6 July 2009, this Regulation has been repealed by Regulation (EC) No 469/2009.

Article 95. - (1) Where at least one of the concerned marketing authorisations has been authorised via the centralised procedure, the Agency will be the reference authority (section 3.4).

(2) In all other cases, a national competent authority chosen by the coordination group, taking into account the recommendation of the holder, will act as the reference authority (section 3.2).

Article 96. - In order to facilitate the planning of the procedure, holders are encouraged to inform the Agency or the coordination group and the proposed reference authority in advance of the submission of a variation or group of variations to be subject to a worksharing procedure.

Article 97. - (1) In order to benefit from a worksharing procedure, it is necessary that the same change(s) will apply to the different medicinal products concerned with no need (or limited need) for assessment of a potential product-specific impact.

(2) Therefore, where the 'same' change(s) to different marketing authorisations require the submission of individual supportive data for specific medicinal products concerned or separate product-specific assessment, such changes cannot benefit from worksharing.

III.1. Submission of variation(s) application under worksharing

Article 98. - (1) A variation or group of variations presented for worksharing shall be submitted as shown under sections 2.2 and 2.3 concerning minor variations of Type IB and II of the *Guideline C(2013) 2804 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV 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 and on the documentation to be submitted pursuant to those procedures* and must be transmitted as one integrated submission package covering all variations for all medicinal products.

(2) This must include a common cover letter and application form, together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned.

(3) This will allow the Agency, the NAMMD and the national competent authorities to update the dossier of each marketing authorisation included in the worksharing procedure with the relevant amended or new information.

Article 99. - The worksharing application must be submitted to all relevant authorities, i.e. the NAMMD and all Member States where the products concerned are authorised and the NAMMD and all Member States where the products concerned are authorised and the Agency (for the centralised procedure).

III.2. Worksharing assessment not involving medicinal products authorised under the centralised procedure

Article 100. - (1) When the holder informs the coordination group of an upcoming worksharing procedure that does not affect any centralised marketing authorisation, the coordination group will at the next meeting decide on the reference authority, taking into account the proposal of the holder and, if applicable pursuant to the third subparagraph of Article 20(3) of the Variations Regulation, another relevant authority to assist the reference authority.

(2) The holder will be informed by the coordination group of the decision of which national competent authority will act as reference authority.

Article 101 - Upon receipt of a worksharing application, the reference authority will handle the application as follows:

Article 102. - (1) The reference authority will acknowledge receipt of a valid application for worksharing.

(2) Immediately after acknowledging receipt of a valid application, the reference authority will start the procedure.

(3) The holder and the Member States concerned will be informed of the timetable at the start of the procedure.

Article 103. - (1) As a general rule, worksharing procedures will follow a 60-day period or a 90-day evaluation period for variations listed in Part 2 of Annex V of the Variations Regulation.

(2) This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or Article 13d(2)(c) of the Variations Regulation.

Article 104. - (1) The reference authority will prepare an opinion according to the communicated timetable and will circulate it to the concerned Member States for comments as well as to the holder for information.

(2) Concerned Member States will send their comments within the deadlines set out in the timetable.

Article 105. - (1) Within the evaluation period, the reference Member State may request the marketing authorisation holder to provide supplementary information.

(2) The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and, where appropriate, the extended evaluation period.

(3) In general, a suspension of one month will typically apply.

(4) For longer suspension the holder should send a justified request to the reference Member State for agreement.

Article 106. - (1) The procedure will be suspended until the receipt of the supplementary information.

(2) The assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

Article 107. - After receipt of the holder's response, the reference Member State will finalise the draft opinion and will circulate it to the concerned Member States for comments as well as to the holder for information.

III.3. Outcome of the worksharing assessment not involving medicinal products authorised through the centralised procedure

Article 108. - By the end of the evaluation period, the reference authority will issue its opinion on the application and inform the concerned Member States and the holder.

Article 109. - (1) In case of a favourable opinion, the list of variations that are not considered approvable should be attached in the Opinion (if applicable).

(2) Variations may be considered approvable for some of the concerned products only.

(3) In case of an unfavourable outcome, the grounds for the unfavourable outcome should be explained.

Article 110. - (1) Within 30 days following receipt of the opinion, the concerned Member States will recognise the opinion and inform the reference Member State accordingly, unless a potential serious risk to public health is identified that prevents a Member State from recognising the opinion of the reference Member State.

(2) The Member State that, within 30 days following receipt of the opinion of the reference Member State, identifies such a potential serious risk should inform the reference Member State and give a detailed statement of the reasons for its position.

Article 111. - (1) The reference authority will then refer the application to the coordination group for application of Article 33 (3), (4) and (5) of the Law transposing Article 29 (3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement and will inform the holder and the Member States concerned accordingly.

(2) The holder is not entitled to trigger a referral.

Article 112. - Where a referral to the coordination group is made, the procedure concerning the decision on the worksharing application will be suspended until a decision has been adopted on the referral procedure (including, where relevant, the referral to the Committee for Medicinal Products for Human Use, hereinafter the Committee, in accordance with Articles 32 to 34 of Directive 2001/83/EC).

Article 113. - After a positive opinion is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 days, translations of the product information texts to the NAMMD and to all Member States concerned.

Article 114. - Within 30 days following the approval of the opinion or, where a referral has been triggered, the notification of the agreement of the coordination group or the European Commission decision (as applicable), the NAMMD and the other Member States will amend the marketing authorisation(s) accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD and to the other Member States concerned.

Article 115. - Minor variation(s) of Type IB approved via a worksharing procedure, may be implemented upon receipt of the favourable opinion of the reference authority.

Article 116. - Major variation(s) of Type II (including those which contain grouped minor variation(s) of Type IB) approved via a worksharing procedure may be implemented 30 days after receipt of the favourable opinion from the reference authority provided that the necessary documentation to amend the marketing authorisation has been submitted to the Member States concerned.

Article 117. - In those cases where the application has been the object of a referral, the variation(s) must not be implemented until the referral procedure has concluded that the variation(s) is accepted.

Article 118. - Variations related to safety issues must be implemented within a time-frame agreed between the marketing authorisation holder and the reference authority.

III.4. Worksharing assessment involving medicinal products authorised under the centralised procedure

Article 119. - Upon receipt of a worksharing application that affects at least one centralised marketing authorisation, the Agency will handle the application as follows:

Article 120. - (1) The Agency will acknowledge receipt of a valid worksharing application.

(2) Immediately after acknowledging the receipt of a valid application, the Agency will start the procedure.

(3) The holder will be informed of the adopted timetable at the start of the procedure.

Article 121. - The Agency will appoint a rapporteur (and in some cases also a co-rapporteur) to lead the assessment procedure.

Article 122. - (1) In general, worksharing procedures will follow a 60-day evaluation timetable or a 90-day evaluation timetable for variations listed in Part 2 of Annex V of the *Variations Regulation.*

(2) This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or Article 13d(2)(c).

Article 123. - (1) Within the evaluation period, the Committee may request supplementary information.

(2) The request for supplementary information or follow-on request will be sent to the holder together with the timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

Article 124. - (1) The procedure will be suspended until the receipt of the supplementary information.

(2) In general, a suspension of up to 1 month will typically apply.

(3) For suspension longer than 1 month the holder should send a justified request to the Agency for agreement by the Committee.

Article 125. - For any follow-on request for supplementary information, an additional clock-stop of up to 1 month will be applied in general; a maximum of 2 months may be applied when justified.

Article 126. - The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data provided by the marketing authorisation holder.

Article 127. - An oral explanation can be held at the request of the relevant Committee or the marketing authorisation holder, where appropriate.

III.5. Outcome of the worksharing assessment involving medicinal products authorised through the centralised procedure

Article 128. - (1) By the end of the evaluation period, the Agency will adopt an opinion on the application, including the assessment report.

(2) The Agency will inform the holder and Member States concerned (if applicable).

(3) In case of disagreement with the opinion, holders may request a re-examination thereof in accordance with the procedure set out in Article 9 (2) and 34 (2) of Regulation (EC) No 726/2004.

Article 129. - Where the opinion of the Agency is favourable and the variation(s) affects the terms of the Commission decision(s) granting the marketing authorisation, the Agency will transmit to the Commission its opinion and the grounds for its opinion as well as the necessary documents to amend the marketing authorisation.

Article 130. - (1) If the Agency considers that some variations are not approvable, the list of variations that are not considered approvable should be attached in the Opinion.

(2) Variations may be considered approvable for some of the concerned products only.

Article 131. - Upon receipt of a favourable opinion by the NAMMD and by the Member States concerned, for medicinal products authorised under the purely national procedure, the NAMMD and the other interested Member States must approve the opinion, inform the Agency accordingly and, where necessary, amend the national marketing authorisations within 60 days provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

Article 132. - Minor variation(s) of Type IB (with the exception of those grouped with major variation(s) of Type II) may be implemented upon receipt of the favourable opinion of the Agency.

Article 133. - Major variation(s) of Type II (and those minor variation(s) of Type IB grouped with the Type II variation) may be implemented 30 days after receipt of the favourable opinion from the Agency provided that:

a) the documents necessary for the amendment of the marketing authorisation(s) have been submitted to the NAMMD and to Member States concerned, and

b) the application has not been the object of a referral.

CHAPTER IV
ANNEX 1

Article 134. - This Annex consists of four chapters classifying variations related to: A) Administrative changes; B) Quality changes; C) Safety, Efficacy and Pharmacovigilance changes and D) Specific changes to Plasma Master Files (PMF) and Vaccine Antigen Master Files (VAMF).

Article 135. - Where reference has to be made to specific variations in this Annex, the variation(s) in question should be quoted using the following structure: X.N.x.n ("variation code").

– X refers to the capital letter of the chapter in this Annex where the variation is included (e.g. A, B, C or D)

– N refers to the roman number of the section inside a chapter where the variation is included (e.g. I, II, III…)

– x refers to the letter of the subsection inside a chapter where the variation is included (e.g. a, b, c…)

– n refers to the number given in this Annex to a specific variation (e.g. 1, 2, 3…)

Article 136. – For each chapter this Annex contains:

- A list of variations which should be classified as minor variations of Type IA or major variations of Type II in accordance with the definitions of Article 2 and Annex II to the *Variations Regulation*. It is also indicated which minor variations of Type IA require immediate notification as established in Article 8 (1) of the *Variations Regulation*.
- A list of variations that should be considered as minor variations of Type IB. It is noted that, in accordance with Article 3 of the Variations Regulation, this category applies by default. Accordingly, this Annex does not attempt to establish an exhaustive list for this category of variations.

Article 137. - (1) This Annex does not deal with the classification of extensions as they are exhaustively listed in Annex I of the *Variations Regulation.*

(2) All changes specified in Annex I of the *Variations Regulation* must be considered extensions of the marketing authorisations; any other change cannot be classified as such.

Article 138. - When one or more of the conditions established in this Annex for a minor variation of Type IA are not met, the concerned change may be submitted as a Type IB variation ("Type IB by default") unless the change is specifically classified as a major variation of Type II in this Annex or in a recommendation pursuant to Article 5 of the Variations Regulation, or unless the applicant considers that the changes may have a significant impact on the quality, safety or efficacy of the medicinal product.

Article 139. - If the NAMMD considers that a variation submitted as a Type IB by default may have a significant impact on the quality, safety or efficacy of the medicinal product, it may request that the application be upgraded and processed as a Type II variation.

Article 140. - (1) For the purpose of this Annex “test procedure” has the same meaning as “analytical procedure”; “limits” has the same meaning as “acceptance criteria”.

(2) “Specification parameter” means the quality attribute for which a test procedure and limits are set e.g. assay, identity, water content.

(3) The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

Article 141. - When several minor changes are taking place (e.g. to the same method or process or material) at the same time or in cases of a major update of the quality information for the active substance or the finished product, the applicant should take into account the overall impact of these changes on the quality, safety or efficacy of the medicinal product when considering the appropriate classification and submit them accordingly.

Article 142. - Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change.

Article 143. - (1) Furthermore, if a variation leads to a revision of the summary of product characteristics, labelling or package leaflet (jointly referred to as 'the product information'), this change is considered part of that variation.

(2) In such cases updated product information has to be submitted as part of the application with the relevant translations.

(3) Mock-ups or specimens should be provided to the NAMMD.

Article 144. - (1) There is no need to notify the NAMMD of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.

(2) Applicants are reminded that compliance with the updated monograph should be implemented within six months.

Article 145. – (1) Any change to the content of the dossier that supports a European Pharmacopoeia Certificate of Suitability, should be submitted to the European Directorate for the Quality of Medicines (EDQM).

(2) However, if the certificate is revised following EDQM evaluation of this change, any marketing authorisation concerned must be updated accordingly.

Article 146. - (1) With reference to Section 1, 'Biological medicinal products' of Part III, 'Special medicinal products' of Order of the Minister of Health no. 906/2006 transposing point 1 of Annex I of Directive 2001/83/EC, changes to Plasma Master Files (hereinafter PMFs) and Vaccine Antigen Master Files (VAMFs) follow the evaluation procedures for variations set-out in the Variations Regulation.

(2) Therefore, Chapter D in this guideline provides a list of variations which are specific to such PMFs or VAMFs.

(3) Following review of these variations, any marketing authorisation concerned must be updated in accordance with Chapter B.V of this Annex.

(4) In case the documentation of the human plasma used as starting material for a plasma derived medicinal product is not submitted as a PMF, variations to this starting material as described in the marketing authorisation dossier should also be handled in accordance with this Annex.

Article 147. - (1) References in this Annex to changes to the marketing authorisation dossier mean addition, replacement or deletion, unless specifically indicated.

(2) If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided; it should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

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A. ADMINISTRATIVE CHANGES

A.1 Change in the name and/or address of the marketing authorisation holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	1, 2	IAIN
Conditions			
1. The marketing authorisation holder shall remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			
2. Revised product information.			

A.2 Change in the (invented) name of the medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
b) For Nationally Authorised Products		2	IB
Documentation			
1. Revised product information.			

A.3 Change in name of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1, 2	1, 2	IAIN
Conditions			
1. The active substance/excipient shall remain the same.			
Documentation			
1. Proof of acceptance by WHO or copy of the INN list. If required, a proof attesting that the change is in line with the European Pharmacopoeia. For herbal medicinal product, declaration that the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products, and with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products.			
2. Revised product information			

A.4 Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur.Certificate of Suitability is part of the approved dossier; or of a manufacturer of a new excipient (where specified in the product dossier)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	1, 2, 3	IA
Conditions			
1. The manufacturing site and all manufacturing operations shall remain the same.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned.			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
3. In case of change in the name of the holder of the Active Substance Master File holder, updated 'letter of access'.			

A.5 Change in the name and/or address of the manufacturer/importer of the finished product [including the batch release/batch testing site for quality control]	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The activities for which the manufacturer/importer is responsible include batch release	**1**	**1, 2**	**IAIN**
b) The activities for which the manufacturer/importer is responsible do not include batch release	**1**	**1, 2**	**IA**
Conditions			
1. The manufacturing site undergoing the name and/or address change and all manufacturing operations must remain the same.			
Documentation			
1. Copy of the modified manufacturing authorisation, if available; or a formal document from a relevant official body (e.g. Chamber of Commerce, or if not available, from a Regulatory Agency) in which the new name and/or address is mentioned.			
2. If applicable, amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.			

A.6 Change in ATC Code / ATC Vet Code	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IA**
Conditions			
1. Change following granting of or amendment to ATC Code by WHO / ATC Vet Code.			
Documentation			
1. Proof of acceptance (by WHO).			
2. Revised product information			

A.7 Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)*	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1, 2	**1, 2**	**IA**
Conditions			
1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. Where applicable at least one manufacturer responsible for batch release that is able to certify the product testing for the purpose of batch release within the EU/EEA remains in the EU/EEA.			
2. The deletion should not be due to critical deficiencies concerning manufacturing.			
Documentation			
1. The variation application form should clearly outline the "present" and "proposed" manufacturers (approved in the context of the marketing authorisation or following a variation).			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.			
**Note:* Where notice has been given by the authorities of the intention to perform an inspection, the deletion of the relevant site shall be notified immediately.			

A.8 Changes to date of the audit to verify Good Manufacturing Practice (GMP) compliance of the manufacturer of the active substance*	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			IA
Documentation			
1. Written confirmation from the manufacturer of the finish product stating verification of compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practices.			
**Note:* This variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called "QP declaration").			

B. QUALITY CHANGES

B.I ACTIVE SUBSTANCE

B.I.a) Manufacture

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	**1, 2, 3**	**1, 2, 3, 4, 5, 6, 7**	**IAIN**
b) Introduction of a manufacturer of the active substance supported by an ASMF			**II**
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			**II**
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			**II**
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			**II**
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	**2, 4**	**1, 5**	**IA**
g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier			**II**
h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method		**1, 2, 4, 5, 8**	**IB**
i) Introduction of a new site of micronisation	**2, 5**	**1, 4, 5, 6**	**IA**
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological / immunological / immunochemical method takes place			**II**
k) New storage site of Master Cell Bank and/or Working Cell Banks		**1, 5**	**IB**
Conditions			
1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.			

2.	The active substance is not a biological/immunological substance or sterile.
3.	Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.*
4.	Method transfer from the old to the new site has been successfully completed.
5.	The particle size specification of the active substance and the corresponding analytical method remain the same.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), if applicable.
2.	A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.
3.	Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the NAMMD and shown to comply with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance.
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5.	The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the application form for marketing authorisation.
6.	A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1.
7.	Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.
8.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice. For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority. For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

B.I.a.2 Changes in the manufacturing process of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	Minor change in the manufacturing process of the active substance	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b)	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product			**II**

c)	The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol			**II**
d)	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production			**II**
e)	**Minor change to the restricted/closed part of an Active Substance Master File**		**1, 2, 3, 4**	**IB**
Conditions				
1.	No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2.	The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.			
3.	The specifications of the active substance or intermediates are unchanged.			
4.	The change is fully described in the open ("applicant's") part of an Active Substance Master File, if applicable.			
5.	The active substance is not a biological / immunological substance.			
6.	The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product.			
7.	The change does not refer to the restricted part of an Active Substance Master File.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format) and of the approved Active Substance Master File (where applicable), including a direct comparison of the present process and the new process.			
2.	Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.			
3.	Copy of approved specifications of the active substance.			
4.	A declaration from the marketing authorisation holder or the ASMF Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.			
Note: For B.I.a.2.b For chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.				

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Up to 10-fold increase compared to the originally approved batch size**	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**
b)	**Downscaling down to 10-fold**	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c)	**The change requires assessment of the comparability of a biological/immunological active substance**			**II**
d)	**More than 10-fold increase compared to the originally approved batch size**		**1, 2, 3, 4**	**IB**
e)	**The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line)**		**1, 2, 3, 4**	**IB**
1.	Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			

2.	Test results of at least two batches according to the specifications should be available for the proposed batch size.
3.	The product concerned is not a biological/immunological medicinal product.
4.	The change does not adversely affect the reproducibility of the process.
5.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6.	The specifications of the active substance/intermediates remain the same.
7.	The active substance is not sterile.
8.	The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	The batch numbers of the tested batches having the proposed batch size.
3.	Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
4.	Copy of approved specifications of the active substance (and of the intermediate, if applicable).
5	A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Tightening of in-process limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new in-process test and limits**	**1, 2, 5, 6**	**1, 2, 3, 4, 6**	**IA**
c)	**Deletion of a non-significant in-process test**	**1, 2, 7**	**1, 2, 5**	**IA**
d)	**Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance**			**II**
e)	**Deletion of an in-process test which may have a significant effect on the overall quality of the active substance**			**II**
f)	**Addition or replacement of an in-process test as a result of a safety or quality issue**		**1, 2, 3, 4, 6**	**IB**
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits			
3.	Any change should be within the range of currently approved limits.			
4.	The test procedure remains the same, or changes in the test procedure are minor.			
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way			
6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods)			
7.	The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Comparative table of current and proposed in-process tests.			

3.	Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters.
5.	Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, attesting that in-process tests are non-significant, or that the in-process tests are obsolete.
6.	Justification from the MAH or ASMF Holder as appropriate for the new in-process test and limits.

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza			II

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Tightening of specification limits for medicinal products subject to Official Batch Release	**1, 2, 3, 4**	**1, 2**	**IAIN**
b) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
c) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter(e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 6**	**IA**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
f) Change outside the approved specifications limits range for the active substance			**II**
g) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 7**	**IB**
Conditions			
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.			
3. Any change should be within the range of currently approved limits.			
4. The test procedure remains the same, or changes in the test procedure are minor.			
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia microbiological methods).			

7.	For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH limits, any new impurity control should be in line with the Ph. Eur. or National Pharmacopoeia of a Member State.
8.	The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format
2.	Comparative table of current and proposed specifications.
3.	Details of any new analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6.	Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.
7.	Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits.

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Minor changes to an approved test procedure**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorised.**	**7**	**1**	**IA**
c)	**Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance**	**1, 2, 3, 5, 6**	**1, 2**	**IA**
d)	**Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological active substance**			**II**
e)	**Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate**		**1, 2**	**IB**

Conditions	
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2.	There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4.	The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The active substance is not biological/immunological.
7	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA (IN) notification.
Documentation	

1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2.	Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c) Container closure system

B.I.c.1 Change in immediate packaging of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Qualitative and/or quantitative composition**	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
b)	**Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances**			**II**
c)	**Liquid active substances (non sterile)**		**1, 2, 3, 5, 6**	**IB**
Conditions				
1.	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
2.	Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).			
3	Sterile, liquid and biological/immunological active substances are excluded.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Appropriate data on the new packaging (e.g. comparative data on permeability e.g. for O2, CO2, moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic materials and objects in contact with foodstuff.			
3.	Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuff.			
4.	A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
5.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).			
6.	Comparison of the current and proposed immediate packaging specifications, if applicable.			

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Tightening of specification limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new specification parameter to the specification with its corresponding test method**	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**

c)	**Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)**	**1, 2**	**1, 2, 5**	**IA**
d)	**Addition or replacement of a specification parameter as a result of a safety or quality issue**		**1, 2, 3, 4, 6**	**IB**
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.			
2.	The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.			
3.	Any change should be within the range of currently approved limits.			
4.	The test procedure remains the same, or changes in the test procedure are minor.			
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Comparative table of current and proposed specifications.			
3.	Details of any new analytical method and validation data, where relevant.			
4.	Batch analysis data on two batches of the immediate packaging for all specification parameters.			
5	Justification/risk-assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, showing that the parameter is non-significant or obsolete.			
6.	Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits.			

B.I.c.3 Change in test procedure for the immediate packaging of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Minor changes to an approved test procedure**	**1, 2, 3,**	**1, 2**	IA
b)	**Other changes to a test procedure (including replacement or addition)**	**1, 3, 4**	**1, 2**	IA
c)	**Deletion of a test procedure if an alternative test procedure is already authorised**	**5**	**1**	IA
Conditions				
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
3.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
4.	The active substance/ finished product is not biological/immunological.			
5.	There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA(IN) notification.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data.			
2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.			

B.I.d) Stability

B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur.Certificate of Suitability covering the retest period is part of the approved dossier.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Re-test period/storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**

	2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH guidelines (*)			**II**
	3. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol.			**II**
	4. Extension or introduction of a re-test period/storage period supported by real time data		**1, 2, 3**	**IB**
b)	**Storage conditions**			
	1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
	2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			**II**
	3. Change in storage conditions of the active substance		**1, 2, 3**	**IB**
c)	**Amendment of an approved stability protocol**	**1, 2**	**1, 4**	**IA**
Conditions				
1.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
2.	The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorised packaging material and covering the duration of the requested re-test period or requested storage conditions.			
2.	Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.			
3.	Copy of approved specifications of the active substance.			
4.	Justification for the proposed changes.			
* *Note*: Retest period not applicable for biological/immunological active substance.				

B.I.e) Design space

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		1, 2, 3	II
b)	Test procedures for starting materials/reagents/ intermediates and/or the active substance		1, 2, 3	II
Documentation				
1.	The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.			
2.	Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the active substance.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.I.e.3 Deletion of an approved change management protocol related to the active substance	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	**1, 2**	**IAIN**
Conditions			
1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol and does not have any effect on the already approved information in the dossier.			
Documentation			
1. Justification for the proposed deletion.			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.I.e.4 Changes to an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**
Documentation			
1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			

B.I.e.5 Implementation of changes foreseen in an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) **The implementation of the change requires no further supportive data**	**1**	**1, 2, 4**	**IAIN**
b) **The implementation of the change requires further supportive data**		**1, 2, 3, 4**	**IB**
c) **Implementation of a change for a biological/immunological medicinal product**		**1, 2, 3, 4, 5**	**IB**
Conditions			
1. The proposed change has been performed fully in line with the approved change management protocol.			
Documentation			
1. Reference to the approved change management protocol.			
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			
3. Outcomes of trials performed in accordance with the approved protocol for handling changes.			
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
5. Copy of approved specifications of the active substance			

B.II. FINISHED PRODUCT

B.II.a) Description and composition

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Changes in imprints, bossing or other markings	**1, 2, 3, 4**	**1, 2**	**IAIN**
b) Changes in scoring/break lines intended to divide into equal doses		**1, 2, 3**	**IB**
Conditions			
1. Finished product release and end of shelf life specifications have not been changed (except for appearance).			
2. Any ink must comply with the relevant pharmaceutical legislation.			
3. The scoring/break lines are not intended to divide into equal doses.			
4. Any product markings used to differentiate strengths should not be completely deleted.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a detailed drawing or written description of the current and new appearance, and including revised product information as appropriate.			
2. Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).			
3 Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.			

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Immediate release tablets, capsules, suppositories and pessaries	**1, 2, 3, 4**	**1, 4**	**IAIN**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses		**1, 2, 3, 4, 5**	**IB**
c) Addition of a new kit for a radiopharmaceutical preparation with another fill volume			**II**
Conditions			
1. If appropriate, the dissolution profile of the reformulated product is comparable to the current one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the current one.			
2. Release and end of shelf-life specifications of the product have not been changed (except for dimensions).			
3. The qualitative or quantitative composition and mean mass remain unchanged.			
4. The change does not relate to a scored tablet that is intended to be divided into equal doses.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a detailed drawing of the current and proposed situation, and including revised product information as appropriate.			
2. Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant guidance on Bioavailability of medicinal products for human use). For herbal medicinal product comparative disintegration data may be acceptable.			
3. Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability of medicinal products for human use.			
4. Medicinal product samples, if required (see NTA, Requirements for samples in Romania).			
5. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.			
Note: For B.II.a.2.c Applicants are reminded that any change to the "strength" of the medicinal product requires the submission of an Extension application.			

B.II.a.3 Changes in the composition (excipients) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) **Changes in components of the flavouring or colouring system**			

	1. Addition, deletion or replacement	**1, 2, 3, 4, 5, 6, 7, 9, 11**	**1, 2, 4, 5, 6**	**IAIN**
	2. Increase or reduction	**1, 2, 3, 4, 11**	**1, 2, 4**	**IA**
b)	**Other excipients**			
	1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**IA**
	2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			**II**
	3. Change that relates to a biological/immunological product			**II**
	4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			**II**
	5. Change that is supported by a bioequivalence study			**II**
	6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**

Conditions

1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.
3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test.
4. Stability studies have been started under ICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.
5. Any new proposed components must comply with the relevant Directives (e.g. Directive 94/36/EC and 2008/128/EC for colours for use in foodstuff and Directive 88/388/EEC for flavours).
6. No new component includes the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current *Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.
7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.
8. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the current one (no significant differences regarding comparability, see the relevant guidance on Bioavailability of medicinal products for human use). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the current one.
9. The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths.
10. The product concerned is not a biological/immunological medicinal product.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including identification method for any new colorant, where relevant, and including revised product information as appropriate.

2.	A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
3.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4.	Sample of the new product, where applicable (see NTA, Requirements for samples in Romania).
5.	Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
7	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
8.	For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.
9.	Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence.*

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Solid oral pharmaceutical forms**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism**			**II**
Conditions				
1.	The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the current one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the current one.			
2.	The coating is not a critical factor for the release mechanism.			
3.	The finished product specification has only been updated in respect of weight and dimensions, if applicable.			
4.	Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at the time of implementation and assurance that these studies will be finalised; data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.			

B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II

B.II.a.6 Deletion of the solvent / diluent container from the pack	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1, 2	**IB**
Documentation			
1 Justification for the deletion, including a statement regarding alternative means to obtain the solvent / diluent as required for the safe and effective use of the medicinal product.			
2. Revised product information.			

B.II.b) Manufacture

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Secondary packaging site	**1, 2**	**1,3, 8**	**IAIN**
b) Primary packaging site	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IAIN**
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			**II**
d) Site which requires an initial or product specific inspection			**II**
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products		**1, 2, 3, 4, 5, 6, 7, 8**	**IB**
Conditions			
1. Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EU/EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.			
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).			
3. Product concerned is not a sterile product			
4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.			
5. Product concerned is not a biological/immunological medicinal product.			
Documentation			
1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice; For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority; For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.			

2.	Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3.	The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in section 2.5 of the application form.
4.	Copy of approved release and end-of-shelf life specifications if relevant.
5.	Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).
6.	For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.
7.	i) If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union. ii) In addition, if the new manufacturing site is located within the EU/EEA and uses the active substance as a starting material – A declaration by the Qualified Person (QP) of the new manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.
8.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
9.	If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.

Notes

In case of a change in or a new manufacturing site in a country outside the EU/EEA without an operational GMP mutual recognition agreement with the EU, marketing authorisation holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous EU/EEA inspection in the last 2-3 years and/or any planned EU/EEA inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a GMP inspection by an inspection service of one of the Member States if needed.

QP Declarations in relation to active substances

Manufacturing authorisation holders are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP so a declaration is expected from each of the manufacturing authorisation holders that use the active substance as a starting material. In addition, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the above.

In many cases only one manufacturing authorisation holder is involved and therefore only one declaration will be required. However, when more than one manufacturing authorisation holder is involved rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP. This will be accepted provided that:

The declaration makes it clear that it is signed on behalf of all the involved QPs.

The arrangements are underpinned by a technical agreement as described in Chapter 7 of the GMP Guide and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the active substance manufacturer(s). *Note:* These arrangements are subject to inspection by the competent authorities.

Applicants are reminded that a Qualified Person is at the disposal of a manufacturing authorisation holder according to Article 749 (1) d) of the Law transposing Article 41 of Directive 2001/83/EC, located in the EU/EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within MRA partner countries are not acceptable.

According to Article 755 (1) of the Law, transposing Article 46a of Directive 2001/83/EC, the manufacture of active substances used as starting materials includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including re-packaging or re-labelling as carried out by a distributor. A declaration is not required for blood or blood components they are subject to the requirements of Directive 2002/98/EC.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Replacement or addition of a site where batch control/testing takes place**	**2, 3, 4, 5**	**1, 2, 5**	**IA**
b)	**Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method**			**II**
c)	**Replacement or addition of a manufacturer responsible for importation and/or batch release**			
	1. Not including batch control/testing	**1, 2.5**	**1, 2, 3, 4, 5**	**IAIN**
	2. Including batch control/testing	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IAIN**
	3. Including batch control/testing for a biological/immunological product and any of the test methods performed at that site is a biological / immunological / immunochemical method			**II**

Conditions	
1.	The manufacturer responsible for batch release must be located within the EU/EEA. At least one batch release site remains within the EU/EEA that is able to certify the product testing for the purpose of batch release within the EU/EEA.
2.	The site is appropriately authorised.
3.	The product is not a biological/immunological medicinal product.
4.	Method transfer from the old to the new site or new test laboratory has been successfully completed.
5.	At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purpose of batch release within the EU/EEA.
Documentation	
1.	For a site within the EU/EEA: Attach copy of manufacturing authorisation(s) or where no manufacturing authorisation exists a certificate of GMP compliance issued within the last 3 years by the relevant competent authority. For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate, issued within the last 3 years by the relevant competent authority. Where no such agreement exists a GMP certificate issued within the last 3 years by a EU/EEA competent authority.
2.	The variation application form should clearly outline the “present” and “proposed” finished product manufacturers, importer, batch control/testing and batch release sites as listed in section 2.5 of the application form for marketing authorisation.
3.	A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorisation operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1.
4	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD), including revised product information as appropriate.

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product		Conditions to be fulfilled	Documentation to be supplied	Variation type
a)	**Minor change in the manufacturing process**	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5, 6, 7, 8**	**IA**
b)	**Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product**			**II**
c)	**The product is a biological/immunological medicinal product and the change requires an assessment of comparability**			**II**
d)	**Introduction of a non-standard terminal sterilisation method**			**II**
e)	**Introduction or increase in the overage that is used for the active substance**			**II**
f)	**Minor change in the manufacturing process of an aqueous oral suspension**		**1, 2, 4, 6, 7,8**	**IB**
1.	No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2.	Either the change relates to: - an immediate release solid oral dosage form / oral solution and the medicinal product concerned is not a biological /immunological or herbal medicinal product; or to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form).			
3.	The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.			
4	The already authorised product should undergo relevant in-process controls and does not require changes (limit extension or deletion).			
5.	The specifications of the finished product or intermediates are unchanged.			
6.	The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.			
7.	Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a direct comparison of the present process and the new process.			
2.	For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.			
3.	For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.			
4.	Justification for not submitting a new bioequivalence study according to the relevant guidance on Bioavailability (of medicinal products for human use).			
5.	For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.			
6.	Copy of approved release and end-of-shelf life specifications.			
7.	Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).			
8.	Declaration that relevant stability studies have been started under ICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least three months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product		Conditions to be fulfilled	Documentation to be supplied	Variation type
a)	**Up to 10-fold compared to the originally approved batch size**	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA**
b)	**Downscaling down to 10-fold**	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c)	**The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study**			**II**
d)	**The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes**			**II**
e)	**More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms**		**1, 2, 3, 4, 5, 6**	**IB**
f)	**The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)**		**1, 2, 3, 4, 5, 6**	**IB**

Conditions	
1.	The change does not affect reproducibility and/or consistency of the product.
2.	The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms.
3.	Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.
4.	Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.
5.	The product concerned is not a biological/immunological medicinal product.
6.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
7.	The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specifications (with proposed action).
3.	Copy of approved release and end-of-shelf life specifications.
4.	Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5.	The validation results should be provided.
6.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product		Conditions to be fulfilled	Documentation to be supplied	Variation type
a)	**Tightening of in-process limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of new tests and limits**	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c)	**Deletion of a non-significant in-process test**	**1, 2, 7**	**1, 2, 6**	**IA**
d)	**Deletion of an in-process test which may have a significant effect on the overall quality of the finished product**			**II**

e)	**Widening of the approved IPC limits, which may have a significant effect on the overall quality of the finished product**			**II**
f)	**Addition or replacement of an in-process test as a result of a safety quality issue**		**1, 2, 3, 4, 5, 7**	**IB**
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.			
3.	Any change should be within the range of currently approved limits.			
4.	The test procedure remains the same, or changes in the test procedure are minor.			
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).			
7.	The in-process test does not concern the control of a critical parameter. e.g.: assay, impurities (unless a particular solvent is definitely not used in the manufacture) any critical physical characteristics (particle size, bulk, tapped density…) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Comparative table of current and proposed in-process tests and limits.			
3.	Details of any new analytical method and validation data, where relevant.			
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.			
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal medicinal products, comparative disintegration data may be acceptable.			
6	Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete.			
7.	Justification of the new in-process test and limits.			

B.II.c) Control of excipients

B.II.c.1 Change in the specification parameters and/or limits of an excipient		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Tightening of specification limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new specification parameter (e.g. deletion of an obsolete parameter)**	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c)	**Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)**	**1, 2, 8**	**1, 2, 7**	**IA**
d)	**Change outside the approved specifications limits range**			**II**
e)	**Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product**			**II**
f)	**Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue**		**1, 2, 3, 4, 5, 6, 8**	**IB**

g) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 6, 8**	**IB**
Conditions			
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.			
3. Any change should be within the range of currently approved limits.			
4. The test procedure remains the same, or changes in the test procedure are minor.			
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).			
7. The change does not concern a genotoxic impurity.			
8. The specification parameter does not concern the control of a critical parameter. e.g.: impurities (unless a particular solvent is definitely not used in the manufacture of the excipient) any critical physical characteristics (particle size, bulk, tapped density…) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2. Comparative table of current and proposed specifications.			
3. Details of any new analytical method and validation data, where relevant.			
4. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.			
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products comparative disintegration data may be acceptable.			
6. Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Guideline on *Bioavailability*, if appropriate.			
7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.			
8. Justification of the new specification parameter and the limits.			

B.II.c.2 Change in test procedure for an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
c) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biochemical reagent			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.			
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).			

5.	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.c.3 Change in source of an excipient or reagent with TSE risk	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) **From TSE risk material to vegetable or synthetic origin**			
1. **For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product**	**1**	**1**	**IA**
2. **For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product**		**1, 2**	**IB**
b) **Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability**			**II**
Conditions			
1. Excipient and finished product release and end of shelf life specifications remain the same.			
Documentation			
1. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.			
2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. Dissolution characteristics) of the finished product.			

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product.			**II**
c) The excipient is a biological/immunological substance			**II**
Conditions			
1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH limits), or in physico-chemical properties.			
2. Adjuvants are excluded.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.			
3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.			

4.	Copy of approved and new (if applicable) specifications of the excipient.

B.II.d) Control of finished product

B.II.d.1 Change in the specification parameters and/or limits of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening of specification limits for medicinal products subject to batch release performed by the official competent authority	**1, 2, 3, 4**	**1, 2**	**IAIN**
c) Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	**1, 2, 9**	**1, 2, 6**	**IA**
e) Change outside the approved specifications limits range			**II**
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
g) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
h) **Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product***	**1, 2, 3, 4, 7, 8**	**1, 2**	**IAIN**
i) **Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass). or Ph. Eur. 2.9.6 (Uniformity of content)**	**1, 2,10**	**1, 2, 4**	**IA**

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.
7.	The change does not concern any impurities (including genotoxic) or dissolution.
8.	The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are in line with the pre January 2008 (non harmonised) situation and does not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form and the proposed controls are in line with the harmonised monograph.
9.	The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product) any critical physical characteristics (hardness or friability for uncoated tablets, dimensions…) a test that is required for the particular dosage form in accordance with the general notices of the Ph. Eur.;

	any request for skip testing.
10	The proposed control is fully in line with the Table 2.9.40.-1 of Ph. Eur. 2.9.40 monograph, and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Comparative table of current and proposed specifications.
3.	Details of any new analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6	Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
7.	Justification of the new specification parameter and the limits
* Note: There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the technical dossier and the variation is made to make reference to the updated version.	

B.II.d.2 Change in test procedure for the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4,**	**1,2**	**IA**
b) Deletion of a test procedure if an alternative method is already authorised	**4**	**1**	**IA**
c) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biochemical reagent or replacement of a reference biological preparation and which is not a part of an approved protocol			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
e) Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	**2, 3, 4, 5**	**1**	**IA**
f) To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number*	**2, 3, 4, 5**	**1**	**IA**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected			
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method);			
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).			
5. The registered test procedure already refers to the general monograph of the Ph. Eur. and any changes are minor in nature and require update of the technical dossier.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).			

2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.
* Note: There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.	

B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

B.II.e) Container closure system

B.II.e.1 Change in immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
2. Semi-solid and non-sterile liqui pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological/ immunological medicinal products.			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			**II**
b) **Change in type of container or addition of a new container**			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological/ immunological medicinal products			**II**
3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	4	**1, 8**	**IA**

Conditions	
1.	The change only concerns the same packaging/container type (e.g. blister to blister).
2.	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
3.	Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging e.g. thicker blister packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4.	The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.
2.	Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture).
3.	Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
4.	A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
6.	Comparative table of the current and proposed immediate packaging specifications, if applicable.
7.	Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States/EMA).
8.	Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.
Note: For B.II.e.1.b) applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application.	

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2.	The change does not result from unexpected events arising during manufacture
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Comparative table of current and proposed specifications.
3.	Details of any new analytical method and validation data, where relevant.

4.	Batch analysis data on two batches of the immediate packaging for all specification parameters.
5.	Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
6.	Justification of the new specification parameter and the limits.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) **Minor changes to an approved test procedure**	**1, 2, 3**	**1, 2**	**IA**
b) **Other changes to a test procedure (including replacement or addition)**	**1, 3, 4**	**1, 2**	**IA**
c) **Deletion of a test procedure if an alternative test procedure is already authorised**	**5**	**1**	**IA**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
4. The active substance/ finished product is not biological/immunological.			
5. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data.			
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.			

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			**II**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**
Conditions			
1. No change in the qualitative or quantitative composition of the container.			
2. The change does not concern a fundamental part of the packaging material, which affects the delivery**,** use, safety or stability of the finished product.			
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least three months (six months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including description, detailed drawing and composition of the container or closure material, and including revised product information as appropriate.			
2. Samples of the new container/closure system, where applicable (see NTA, Requirements for samples in Romania).			

3.	Re-validation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the re-validation studies should be indicated, where applicable.
4.	In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.e.5 Change in pack size of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	**1, 2**	**1, 3**	**IAIN**
2. Change outside the range of the currently approved pack sizes		**1, 2, 3**	**IB**
b) Deletion of pack size(s)	**3**	**1, 2**	**IA**
c) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/ immunological medicinal products.			**II**
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		**1, 2, 3**	**IB**
Conditions			
1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics.			
2. The primary packaging material remains the same.			
3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format) including revised product information as appropriate.			
2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics			
3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).			
Note: For B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.			

B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Change that affects the product information	**1**	**1**	**IAIN**
b) Change that does not affect the product information	**1**	**1**	**IA**
Conditions			
1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			

Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Deletion of a supplier**	**1**	**1**	**IA**
b)	**Replacement or addition of a supplier**	**1, 2, 3, 4**	**1, 2, 3**	**IA**
c)	**Any change to suppliers of spacer devices for metered dose inhalers**			**II**
Conditions				
1.	No deletion of packaging component or device.			
2.	The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.			
3.	The specifications and quality control method are at least equivalent.			
4.	The sterilisation method and conditions remain the same, if applicable.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	For devices for medicinal products for human use, proof of CE marking.			
3.	Comparative table of current and proposed specifications, if applicable.			

B.II.f) Stability

B.II.f.1 Change in the shelf-life or storage conditions of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Reduction of the shelf life of the finished product**			
	1. As packaged for sale	**1**	**1, 2, 3**	**IAIN**
	2. After first opening	**1**	**1, 2, 3**	**IAIN**
	3. After dilution or reconstitution	**1**	**1, 2, 3**	**IAIN**
b)	**Extension of the shelf life of the finished product**			
	1. As packaged for sale (supported by real time data)		**1, 2, 3**	**IB**
	2. After first opening (supported by real time data)		**1, 2, 3**	**IB**
	3. After dilution or reconstitution (supported by real time data)		**1, 2, 3**	**IB**
	4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines*			**II**
	5. Extension of the shelf-life of a biological/ immunological medicinal product in accordance with an approved stability protocol.		**1, 2, 3**	**IB**
c)	**Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol**			**II**
d)	**Change in storage conditions of the finished product or the diluted/reconstituted product**		**1, 2, 3**	**IB**

e) **Change to an approved stability protocol**	**1, 2**	**1, 4**	**IA**
Conditions			
1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
2. The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches[1] of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included. [1]Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.			
2. Revised product information			
3. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.			
4. Justification for the proposed change(s).			
*Note: extrapolation not applicable for biological/immunological medicinal product			

B.II.g) **Design Space and post approval change management protocol**

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for excipients / intermediates and/or the finished product.		**1, 2, 3**	**II**
Documentation			
1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.			
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the finished product.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.II.g.3 Deletion of an approved change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IAIN**

Conditions	
1.	The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol and does not have any effect on the already approved information in the dossier.
Documentation	
1.	Justification for the proposed deletion.
2.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

B.II.g.4 Changes to an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**
Documentation			
1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			

B.II.g.5 Implementation of changes foreseen in an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IAIN**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**
Conditions			
1. The proposed change has been performed in full accordance with the approved change management protocol, stating that the change must be immediately notified after enforcement.			
Documentation			
1. Reference to the approved change management protocol.			
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			
3. Results of the studies performed in accordance with the approved change management protocol.			
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
5. Copy of approved specifications of the finished product.			

B.II.h Adventitious Agents Safety

B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			**II**
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			**II**

2) without modification of risk assessment		**1, 2, 3**	**IB**
Documentation			
1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents.			
2. Justification that the studies do not modify the risk assessment.			
3. Amendment of product information (where applicable).			

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: **For an active substance** **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**
b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient			
1. New certificate for an active substance from a new or an already approved manufacturer	**3, 5, 6, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	**3, 6, 9**	**1, 2, 3, 4, 5**	**IA**
3. Updated certificate from an already approved manufacturer	**7, 9**	**1, 2, 3, 4, 5**	**IA**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			II
Conditions			
1. The finished product release and end of shelf life specifications remain the same.			

2.	Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4.	For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5.	The active substance/starting material/reagent/intermediate/excipient is not sterile.
6.	The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE
7.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
8.	If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should **only** be manufactured in compliance with the relevant country requirements.
9.	At least one manufacturer for the same substance remains in the dossier.
10.	If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.
Documentation	
1.	Copy of the current (updated) Ph. Eur. Certificate of Suitability.
2.	In case of an addition of a manufacturing site, the variation application form should clearly outline the "present" (approved under the marketing authorisation or following a variation) and "proposed" manufacturers.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
4.	Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/ excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
5.	Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.
6.	Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) **Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State**			

	1. Active substance	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA$_{IN}$**
	2. Excipient/active substance starting material	**1, 2,4**	**1, 2, 3, 4**	**IA**
b)	**Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State**	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c)	**Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.**	**1, 4, 5**	**1, 2, 3, 4**	**IA**
Conditions				
1.	The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.			
2.	Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or e.g. bioassays, aggregates).			
3.	No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened			
4.	Additional validation of a new or changed pharmacopoeial method is not required			
5.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Comparative table of current and proposed specifications.			
3.	Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch**.** For herbal medicinal products, comparative disintegration data may be acceptable**.**			
4.	Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.			
Note: There is no need to notify the NAMMD of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.				

B.IV Medical devices

B.IV.1 Change of a measuring or administration device		**Conditions to be fulfilled**	**Documenta-tion to be supplied**	**Variation type**
a)	**Addition or replacement of a device which is not an integrated part of the primary packaging**			
	1. Device with CE marking	**1, 2, 3, 6, 7**	**1, 2, 4**	**IA$_{IN}$**
	2. Device without CE marking for veterinary products only			
	3. Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)			**II**
b)	**Deletion of a device**	**4, 5**	**1, 5**	**IA$_{IN}$**
c)	**Addition or replacement of a device which is an integrated part of the primary packaging**			**II**
Conditions				
1.	The proposed measuring or administration device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.			
2.	The new device is compatible with the medicinal product.			

3.	The change should not lead to substantial amendments of the product information.
4.	The medicinal product can still be accurately delivered.
5.	For veterinary medicinal products, the device is not crucial for the safety of the person administering the product.
6.	The medical device is not used as a solvent of the medicinal product.
7.	If a measuring function is intended the CE marking should cover the measuring function.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.
2.	Proof of CE marking and if a measuring function is intended the proof of CE marking should also include the 4 digit notified body number.
3.	Data to demonstrate accuracy, precision and compatibility of the device.
4.	Samples of the new device where applicable (see NTA, Requirements for samples in Romania).
5.	Justification for the deletion of the device.
Note: For B.IV.1.c), applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application.	

B.V. Changes to a marketing authorisation resulting from other regulatory procedures

B.V.a) PMF/VAMF

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) First-time inclusion of a new Plasma Master File affecting the properties of the finished product			**II**
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions	
1.	The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Order of the Minister of Health no. 906/2006 transposing Annex I of Directive 2001/83/EC.
Documentation	
1.	Declaration that: - the PMF Certificate and Evaluation Report are fully applicable for the authorised product; - PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder; the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation.
2.	PMF Certificate and Evaluation Report.
3.	An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments.
4.	The variation application form should clearly outline the "present" and "proposed" PMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other PMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) First-time inclusion of a new Vaccine Antigen Master File			**II**
b) Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions

1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Order of the Minister of Health no. 906/2006 transposing Annex I of Directive 2001/83/EC.

Documentation

1. Declaration that:
   - VAMF Certificate and Evaluation Report are fully applicable for the authorised product;
   - VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder);
   - the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation.
2. VAMF Certificate and Evaluation Report.
3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments.
4. The variation application form should clearly outline the "present" and "proposed" VAMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.b) Referral

B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) The change implements the outcome of the referral	**1**	**1, 2**	**IA_{IN}**
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it			**II**

Conditions

1. The outcome does not require further assessment.

Documentation

1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned.
2. The changes introduced during the referral procedure should be clearly highlighted in the submission.

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I HUMAN MEDICINAL PRODUCTS

C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) The medicinal product is covered by the defined scope of the procedure	**1**	**1, 2, 3**	**IA_{IN}**

b) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH		**1, 2, 3**	**IB**
c) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH		**1, 3**	**II**
Conditions			
1. The variation implements the wording requested by the authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: a reference to the Commission Decision concerned or to the agreement reached by the CMDh (as applicable) with the annexed Summary of Product Characteristics, Labelling or Package Leaflet.			
2. A declaration that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Commission Decision or to the agreement reached by the CMDh (as applicable).			
3. Revised product information.			

C.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	**Conditions to be fulfilled**	**Documenta-tion to be supplied**	**Variation type**
a) Implementation of change(s) for which no new additional data is required to be submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)			**II**
Documentation			
1. Attached to the cover letter of the variation application: EMA/NCA request, if applicable.			
2. Revised product information.			

C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	**Conditions to be fulfilled**	**Documenta-tion to be supplied**	**Variation type**
a) Implementation of wording agreed by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH		**2**	**II**
Conditions			
1. The variation implements the wording requested by the competent authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: reference to the agreement/assessment of the competent authority.			

2. Revised product information.

C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II
Note: This variation does not apply when the new data has been submitted under variation C.I.13. In such cases, the change(s) in the SmPC, labelling and/or package leaflet is covered by the scope of variation C.I.13.			

C.I.5 Available for medicinal products authorised through the centralised procedure	Variation type

C.I.6 Change(s) to therapeutic indication(s)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Addition of a new therapeutic indication or modification of an approved one			**II**
b) Deletion of a therapeutic indication			**IB**
Note: Where the change takes place in the context of the implementation of the outcome of a referral procedure, or -for a generic/hybrid/biosimilar product- when the same change has been done for the reference product, variations C.I.1 and C.I.2 apply, respectively.			

C.I.7 Not available for medicinal products authorised by the NAMMD (see *Note*)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Pharmaceutical forms		**1, 2**	**IB**
b) Strengths		**1, 2**	**IB**
Note: In cases where a given pharmaceutical form or strength has received from the NAMMD a marketing authorization which is separate to the marketing authorization for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorization.			

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use*	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location		**1, 2**	**IA_{IN}**
Documentation			
1. Summary of the pharmacovigilance system, or update of the relevant elements (as applicable): • Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and an affidavit signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC; • Contact details of the QPPV, Member States in which the QPPV resides and carries out his/her tasks; • PSMF location.			
2. PSMF (if available)			
Note: This variation covers the introduction of a PSMF irrespective of whether or not the technical dossier of the MA contained a DDPS.			

Once the database mentioned in Article 57 of Regulation (EU) no. 1235/2010 on amendment of Regulation (EC) no. 726/2004 is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and email address) and changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation).

Where the MAH makes use of the possibility to update the above information through the Article 57 database, the MAH must indicate in the marketing authorisation that the updated information of those particulars is included in the database.

C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Change in the QPPV and/or QPPV contact details and/or back-up procedure	**1**	**1**	**IA_{IN}**
b) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undergoing pharmacovigilance activities	**1, 2, 3**	**1**	**IA_{IN}**
c) Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes)	**1**	**1**	**IA**
d) Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	**4**	**1, 2**	**IA_{IN}**

Conditions

1. The pharmacovigilance system itself remains unchanged.
2. The database system has been validated (when applicable).
3. Transfer of data from other database systems has been validated (when applicable).
4. The same changes to the DDPS are introduced for all medicinal products of the same MAH (same final DDPS version)

Documentation

1. Latest version of the DDPS and, where applicable, latest version of the product specific addendum. These should include for changes to the QPPV a) summary CV of the new QPPV, b) proof of QPPV EudraVigilance registration, and c) a new statement of the MAH and the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and the MAH, and reflecting any other consequential changes, e.g. to the organisational chart.

   When the QPPV and /or QPPV contact details are not included in a DDPS or no DDPS exists, the submission of a revised DDPS version is not required and the application form is to be provided.
2. Reference of the application/procedure and product in which the change(s) were accepted.

Note: C.I.9 covers changes to an existing pharmacovigilance system for human medicinal products that have not yet introduced a PSMF.

Note for a): Once the Article 57 database is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and email address) may be updated through the Article 57 database only (without the need for a variation). Where the MAH makes use of the possibility to update this information through the Article 57 database, the MAH must indicate in the marketing authorisation that the updated information of those particulars is included in the database.

Note for d): The assessment of a DDPS submitted as part of a new MAA/Extension/Variation may give rise to changes at the request of the NAMMD in this DDPS. Where this occurs, the same change(s) can be introduced to the DDPS in other marketing authorisations of the same MAH by submitting a (grouped) Type IA_{IN} variation.

C.I.10 Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	1, 2	IA_{IN}
Conditions			
1. The change in the frequency and/or date of submission of the PSUR has been agreed by the CHMP/CMDh/NAMMD			
Documents			
1. Attached to the cover letter of the variation application: A reference to the agreement of the NAMMD			
2. Revised frequency and/or date of submission of the PSUR.			
Note: This variation applies only when the PSUR cycle is specified in the marketing authorisation by other means than a reference to the EU list of reference data and where PSUR submission is required.			

C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) **Implementation of wording agreed by the NAMMD**	1	1, 2	IA_{IN}
b) **Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the NAMMD is required***			II
Conditions			
1. The variation implements the action requested by the authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: A reference to the relevant decision of the NAMMD.			
2. Update of the relevant section of the dossier.			
Note: This variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the risk management plan and the conditions and/or obligations of marketing authorisations under exceptional circumstances and conditional marketing authorisation. *The introduction of a risk management plan requested by the NAMMD always requires significant assessment.			

C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	1, 2	IA_{IN}
Conditions			
1. The medicinal product is included or removed from the list of medicinal products that are subject to additional monitoring (as applicable)			
Documentation			
1. Attached to the cover letter of the variation application: A reference to the list of medicinal products that are subject to additional monitoring			
2. Revised product information			
Note: This variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal or variation procedure affecting the product information).			

C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the NAMMD*	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II

Note: In cases where the assessment by the competent authority of the data submitted leads to a change of the Summary of Product Characteristics, Labelling or Package Leaflet, the relevant amendment to the Summary of Product Characteristics, Labelling or Package Leaflet is covered by the variation. The inclusion of the Compliance Statement provided for under Article 28(3) of Regulation 1901/2006 is likewise covered by this variation (provided that the requirements under Regulation 1901/2006 have been met). * This variation does not apply to variations that can be considered as Type IB by default under any other section of this Annex.

C.II Not available for medicinal products for human use	**Variation type**

D. PMF/VAMF

D.1 **Change in the name and/or address of the VAMF certificate holder**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA_{IN}**
Conditions			
1. The VAMF certificate holder must remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

D.2 Change in the name and/or address of the PMF certificate holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA_{IN}**
Conditions			
1. The PMF certificate holder must remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder -i.e. different legal entity).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2, 3, 4, 5, 6	**IA_{IN}**
Documentation			
1. A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date – signed by both companies.			
2. Copy of the latest PMF Certificate page 'EMA Plasma Master File (PMF) Certificate of compliance with Community legislation'.			
3. Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) - signed by both companies.			
4. Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee - signed by both companies.			
5. Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder - signed by the transferee.			
6. Letter of Undertaking to fulfil all open and remaining commitments (if any) - signed by the transferee.			

D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1, 2	**1, 2, 3**	**IA**
Conditions			
1. The blood establishment must remain the same legal entity.			
2. The change must be administrative (e.g. merger, take over); change in the name of the blood establishment/ collection centre provided the blood establishment must remain the same.			
Documentation			
1. Signed declaration that the change does not involve a change of the quality system within the blood establishment.			
2. Signed declaration that there is no change in the list of the collection centres.			
3. Updated relevant sections and annexes of the PMF dossier.			

D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1, 2, 3	**IB**
Documentation			
1. Epidemiological data for viral markers related to the blood/plasma collection centre covering the last 3 years. For newly opened centre(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s).			
2. Statement that the centre is working under the same conditions as the other centres belonging to the blood establishment, as specified in the standard contract between blood establishment and PMF holder.			
3. Updated relevant sections and annexes of the PMF dossier.			

D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1, 2	**1**	**IA**
Conditions			
1. The reason for deletion or change of status should not be related to a GMP issue.			
2. The establishments(s)/centre(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II

D.8 Replacement or addition of a blood centre for testing of donations and/or plasma pools within an establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1, 2	**IB**
Documentation			
1. Statement that the testing is performed following the same SOPs and/or test methods as already accepted.			

2. Updated relevant sections and annexes of the PMF dossier.

D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II

D.10 Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1, 2	**IB**
Documentation			
1. Statement that the storage centre is working following the same SOPs as the already accepted establishment.			
2. Updated relevant sections and annexes of the PMF dossier.			

D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	**1**	**IA**
Conditions			
1. The reason for deletion should not be related to a GMP issues.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.12 Replacement or addition of an organisation involved in the transport of plasma.	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1	**IB**
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.			

D.13 Deletion of an organisation involved in the transport of plasma	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	**1**	**IA**
Conditions			
1. The reason for deletion should not be related to GMP issues.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	**1, 2**	**IA**
Conditions			
1. The new test kit is CE-marked.			
Documentation			
1. List of testing site(s) where the kit is used.			
2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations			**II**
b) The new test kit has been approved in the PMF for other blood centre(s) for testing of donations		**1, 2**	**IA**
Documentation			
1. List of testing centre(s) where the kit is currently used and a list of testing centre(s) where the kit will be used.			
2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II

D.17 Introduction or extension of inventory hold procedure.	Conditions to be fulfilled	Documentation to be supplied	Variation type
	1	**1**	**IA**
Conditions			
1. The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation			
1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.			

D.18 Removal of inventory hold period or reduction in its length.	Conditions to be fulfilled	Documentation to be supplied	Variation type
		1	**IB**
Documentation			
1. Updated relevant sections of the PMF dossier			

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) The new blood containers are CE-marked	**1, 2**	**1**	**IA**
b) The new blood containers are not CE-marked			**II**
Conditions			
1. The container is CE-marked.			
2. The quality criteria of the blood in the container remain unchanged.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.			

D.20 Change in storage / transport	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) storage and/or transport conditions	**1**	**1**	**IA**

b) maximum storage time for the plasma	**1, 2**	**1**	**IA**
Conditions			
1. The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation.			
2. The maximum storage time is shorter than previously.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).			

D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

D.22 Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1	**IB**
Documentation			
1. Updated relevant sections of the PMF dossier.			

D.23 Change in the steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing ("look-back" procedure).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

ANNEX 2
to SCD no. 19/12.08.2013

APPLICATION FORM FOR
VARIATION TO A MARKETING AUTHORISATION

HUMAN ☐ **VETERINARY** ☐
Variation procedure number(s)[3]:.....

☐ **NATIONAL AUTHORISATION IN MRP**
☐ **CENTRALISED AUTHORISATION**
☐ **NATIONAL AUTHORISATION**

Reference Member State / Reference Authority for worksharing

☐AT ☐BE ☐BG ☐CY ☐CZ ☐DE ☐DK ☐EE ☐EL ☐ES ☐FI ☐FR ☐HR ☐HU ☐IE☐IS ☐IT ☐LI ☐LT
☐LU ☐LV ☐MT ☐NL ☐NO ☐PL ☐PT ☐RO ☐SE ☐SI ☐SK ☐UK ☐EMA

Concerned Member State(s)

☐AT ☐BE ☐BG ☐CY ☐CZ ☐DE ☐DK ☐EE ☐EL ☐ES ☐FI ☐FR ☐HR ☐HU ☐IE☐IS ☐IT ☐LI ☐LT
☐LU ☐LV ☐MT ☐NL ☐NO ☐PL ☐PT ☐RO ☐SE ☐SI ☐SK ☐UK ☐NICIUNUL

Type of application (tick all applicable options)

☐ **Type IAIN**
☐ **Type IA**
☐ **Type IB unforeseen[4]**
☐ **Type IB**
☐ **Type II**
☐ **Type II Art. 29[5]**

☐ **Single variation**
☐ **Grouping of variations**
☐ **Including a line extension[6]**
☐ **Worksharing**

[3] Human Medicinal Products: Number to be completed by the Marketing Authorisation Holder, reflecting the correct sequential Mutual Recognition Procedure Number according to Chapter 1 of the 'Best Practice Guides for the submission and processing of variations in the Mutual Recognition Procedure' (http://www.hma.eu).
Veterinary Medicinal Products: Variation number to be issued by the Reference Member State before submission of the application according to the corresponding VMRFG Best Practice Guide (http://www.hma.eu).
Centralised procedure: The sequential EMA procedure number (not the MAH's internal number) should be provided here, when known to the Marketing Authorisation Holder. For worksharing procedures with EMA as reference authority, the 'high-level' EMEA worksharing procedure number needs to be provided.

[4] A variation is considered 'unforeseen' when the proposed variation is not considered a minor variation of Type IB following the Commission classification Guideline, or has not been classified as a Type IB variation in an Article 5 recommendation. When one or more of the conditions established in the guideline for a Type IA variation are not met, the concerned change may be submitted as a Type IB variation unless the change is specifically classified as a major variation of Type II.

[5] Type II variation submitted under Article 29 of Regulation (EC) No 1901/2006.

[6] If the variations are part of a grouped submission including a line-extension, this application form should be considered an annex to the application form for the extension application.

Change(s) concern(s) for (for Type IB and Type II variations only, tick all changes applicable):

- ☐ **Indication**
- ☐ **Paediatric indications**
- ☐ **Safety**
- ☐ **Following Urgent Safety Restriction**
- ☐ **Quality**
- ☐ **Annual variation for human influenza vaccines**
- ☐ **Non-food producing target species**
- ☐ **Other**

Name and address of the Applicant/MA holder[7]:	Name and address of contact person[8]: Telephone number: Fax number (optional): E-mail:

MEDICINAL PRODUCTS CONCERNED BY THIS APPLICATION[9]

Invented name(s) of the medicinal product(s):	Active substance(s)	Pharmaceutical form	Strength	MA Holder name(s)	MA number(s)[10]	MRP variation number

[7] For worksharing or grouped variations affecting more than one Marketing Autorisation (MA), indicate the MAH to be used as reference MAH for the handling of the procedure.

[8] In accordance with the provisions of section 2.4.3 of Part IA/Module 1 *Application form*. If different, attach letter of authorisation. For worksharing or grouped variations affecting more than one MA, a single contact should be designated for the application (see also Signatory box below).

[9] If the List is very long (longer than one page), it could be attached as an annex to the variation application.
For centrally authorised medicinal products, Annex A of the medicinal product(s) subject to the application should be attached as and annex to the variation application.
For the worksharing procedure submitted to the EMA, including nationally authorised medicinal products, the details referring to the medicinal products and to the concerned Member States should be attached as Annex B to the variation application (please check the mock-up on the EMA website).

[10] State MA numbers subject to the application (an interval, if appropriate). For variation number, specific to the medicinal product, see the *Best Practice Guide for the handling of variations*, Chapter 1, e.g. NL/H/0123/001-004/IB/033/G

TYPE OF CHANGE(S)

☐ Copy of the relevant page(s) from the Guideline for this/these change(s) is attached and the relevant boxes for conditions and documentation (both for Type IA and Type IB) are ticked

VARIATIONS INCLUDED IN THIS APPLICATION:

Number and title of variation, as per the Classification Guideline		Variation type
☒ a)	Specific variation applied for, as per the classification guideline	type

***(Select and include** in this section the applicable variation(s) from the list presented at the end of this application form template (see detailed instructions provided with the list). The above example and the list of variations at the end of the form should subsequently be deleted from the completed form to be submitted).*

PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES (if applicable)

(*Include a description and background of all the proposed changes. In case of grouping and worksharing a justification should be provided in a separate paragraph. If a variation concerns an unforeseen change, include a justification for its proposed classification).*

PRESENT [10],[11]	**PROPOSED**
D-U-N-S number:[11] EU or national ASMF number:[12]	D-U-N-S number:[11] EU or national ASMF number:[12]

OTHER APPLICATIONS[13]

[11] If needed, the D-U-N-S number shall be included. The Data Universal Numbering System (D-U-N-S)] is a system developed by Dun & Bradstreet (D&B), assigning an unique digital identifier to a single commercial entity. In this case, it is used to facilitate the manufacturing sites outside the EEA.

[12] If needed, the EU or national ASMF number shall be included (only if the reference EU ASMF is unavailable)

[13] Due to complexity it is not necessary to complete this section for worksharing or grouped variations affecting more than one MA.

Type II variations – new indications – orphan medicinal product information:
(For human medicinal products only; delete this section if the variation does not relate to a new indication)

HAS ORPHAN DESIGNATION BEEN APPLIED FOR, FOR THIS NEW THERAPEUTIC INDICATION?

❍ No
❍ Yes Orphan designation procedure number:

❍ Pending

❍ Orphan designation granted
Date (yyyy-mm-dd):
Based on the criterion of „significant benefit": ❍ Yes
❍ No
Number in the EU Register of Orphan Medicinal Products:
☐ Attach copy of the Designation decision

❍ Orphan designation refused
Date (yyyy-mm-dd):
Reference number of the European Commission Decision:

❍ Orphan designation withdrawn
Date (yyyy-mm-dd):

INFORMATION RELATING TO ORPHAN MARKET EXCLUSIVITY

Has any medicinal product been designated as an Orphan medicinal product for a condition relating to the new indication proposed in this variation application?

❍ No
❍ Yes
Please specify the EU Orphan Designation Number(s):

If YES, has any of the designated Orphan medicinal product(s) been granted a marketing authorisation in the EU?

❍ No
❍ Yes
Please specify:

- Name, therapeutic indications, strength, pharmaceutical form of the authorised medicinal product:
- Name of the Marketing Authorisation Holder:
- Marketing Authorisation Number(s):
- Date of authorisation:

If yes, is the medicinal product, subject of this application, considered as "similar" to any of the authorised Orphan medicinal product(s)? *(as defined in Article 3 of Commission Regulation (EC) no. 847/2000)*

❍ No (module 1.7.1 to be completed)
❍ Yes (modules 1.7.1 and 1.7.2 to be completed)
Note: Please repeat, if required

Type II variations – Paediatric Requirements:
(For human medicinal products only; section to be completed only for variations concerning a new indication or for variations related to PIP implementation)
(*Note: The notion of 'global marketing authorisation' as stated in Article 700 (3) of Law 95/2006, as amended, transposing Article 6 (1), the second subparagraph of Directive 2001/83/EC, as amended, should be taken into account for products belonging to the same [14] Marketing Authorisation Holder).*

❍ **ARTICLE 8 OF THE PAEDIATRIC REGULATION APPLIES TO THIS VARIATION APPLICATION, SINCE:**
- ❍ The application relates to a new indication for an authorised medicinal product, which:
- ❍ Is protected by a supplementary protection certificate under Regulation (EEC) No 469/2009
- ❍ Is protected by a patent which qualifies for the granting of the supplementary protection certificate
- ❍ The application relates to a previous/ongoing/parallel procedure which triggered the Article 8 requirement. Competent authority/EMA procedure number:

❍ **THIS APPLICATION DOES NOT FALL WITHIN THE SCOPE OF ARTICLE 8 OF THE PAEDIATRIC REGULATION, SINCE:**
- ❍ The medicinal product is not protected by a supplementary certificate under Regulation (EC) no. 469/2009 or by a patent which qualifies for granting of the supplementary protection certificate
- ❍ This application relates to a marketing authorisation for a medicinal product with a well-established medical use, generic, a hybrid, biosimilar or herbal medicinal product

❍ **THIS APPLICATION RELATES TO A NEW INDICATION FOR A PAEDIATRIC USE MARKETING AUTHORISATION** (PUMA)**].**

☐ **THIS APPLICATION RELATES TO PAEDIATRIC STUDIES SUBMITTED ACCORDING TO ARTICLE 45 OR 46 OF THE PAEDIATRIC REGULATION.**

☐ **THIS APPLICATION RELATES TO PAEDIATRIC STUDIES INCLUDED IN THE PAEDIATRIC INVESTIGATION PLAN**

THIS APPLICATION INCLUDES:
❍ PIP[15] PIP Decision Number(s):
❍ Product-specific waiver[16] Waiver decision number(s):
❍ Class waiver Waiver decision number(s):
(Note: a copy of the PIP/Waiver decision is to be included in Module 1.10, as well as a copy of the opinion of the Paediatric Committee (PDCO))
HAS THIS APPLICATION BEEN SUBJECT TO PIP COMPLIANCE VERIFICATION?
❍ No
❍ Yes
If YES, please specify the reference compliance report:
(Note: If available, a copy of the PDCO opinion + report, document issued by the national competent authority is to be included in Module 1.10)
☐ The summary of PIP outcomes in a tabulated form is included in module 1.10

Type II variations – Extended data/market exclusivity:

[14] Same "applicant/marketing authorisation holder: as per the Commission Communication (98/C 299/03) (i.e. belonging to the same mother company or group of companies or which are "licencees")
[15] Check if PIP opinion refers to a waiver
[16] Check only if this is about a product-specific waiver opinion, covering all subgroups of the paediatric population

(Delete this section if not applicable)

THIS REQUEST IS ALSO SUPPORTED BY THE FOLLOWING ARTICLES OF LAW 95/2006 ON HEALTHCARE REFORM, AS AMENDED (HEREINAFTER THE LAW) OR BY REGULATION (EC) 726/2004:

CONSIDERATION OF THIS APPLICATION IS ALSO REQUESTED UNDER THE FOLLOWING ARTICLE IN DIRECTIVE 2001/83/EC OR REGULATION (EC) N° 726/2004:

❍ Article 704 (1) of the Law/Article 14 (11) of Regulation (EC) no. 726/2004 (one year of data exclusivity for a new indication)
❍ Article 704 (5) of the Law (one year of data exclusivity for a new indication)
❍ Article 785 of the Law (one year of data exclusivity for a change in classification)

(Note: The report justifying the claim for extended data/market exclusivity is to be provided in Module 1.5.3)

The following amended product information proposals are provided in the relevant sections of the EU-CTD format or NTA volume 6B format, where applicable:

☐ Summary of Product Characteristics

☐ Manufacturing Authorisation Holder responsible for batch release and conditions of the Marketing Authorisation[17]

☐ Labelling

☐ Package leaflet

☐ Mock-ups[18]

☐ Specimens

[17] Only for centrally authorised products (Annex II of EU MA).

[18] See Chapter 7 of Volume 6A of the *Notice to Applicants* or of the *Transfer of Information* from the *Notice to Applicants*, Volume 2A, Chapter 7 (http://www.hma.eu) or *Requirements concerning the dossier of centrally authorised medicinal products* (http://www.ema.europa.eu).

Declaration of the applicant:

I hereby submit a notification/application for the above Marketing Authorisation(s) to be varied in accordance with the proposals given above. I declare that (*Please tick the appropriate declarations*):

- ☐ There are no other changes than those identified in this application (except for those addressed in other variations submitted in parallel;
- ☐ Where applicable, all conditions as set for the variation(s) concerned are fulfilled;
- ☐ For type IA notifications: the required documents as specified for the changes concerned have been submitted;
- ☐ The evaluation fee has been paid;
- ☐ This notification/application has been submitted simultaneously in RMS and all CMSs *(for products within the Mutual Recognition Procedure and worksharing)* or both to EMA and (Co-)Rapporteur *(for products within the Centralised Procedure) or, in case of worksharing involving the EMA, to both the RMS/CMS (as required) and the EMA;*
- ☐ For worksharing or grouped variations affecting more than one MA: the MAs concerned belong to the same MAH.

Change(s) will be implemented from[19]:

☐ Next production run/next printing

☐ Date: _____

[19] Only to be completed for Type IB and Type II variations.

Fees paid *Amount*[20] _____

Please specify fee category in accordance with national regulations _____

Main signatory[21]_____ Status (job title) _____

Print name _____ Date _____

☐ For worksharing/grouping for more than one MA: the main signatory confirms authorisation to sign on behalf of the designated contacts as specified in section 2.4.3 in Part IA/Module 1 Application Form for each of the MAs concerned.

Second signatory _____

Print name_____ Status (job title) _____

Date _____

LIST OF VARIATIONS (to be deleted upon completion of the form**)**

Please select the applicable variation(s) from the list presented below and include in the section "Type(s) of Change(s) – Variations included in this application" above, in accordance with the following instructions:

Only the main header of the change with the variation(s) applied for needs to be included.
To apply for variations not foreseen in the guideline, MAHs should declare such other variation ("z") under the specific guideline section concerned at the lowest possible level i.e. either within a specific variation or under the appropriate guideline section title, as appropriate, including its proposed classification. Please indicate whether the variation has been subject to an Article 5 procedure. Examples of such z) variations have been already included in a number of relevant variations and section titles, for convenience.
For Type IA variations the date of implementation by the MAH needs to be added in the last column.
Full details on the precise scope of the variation concerned, should be given in the section 'precise scope' of the application form.

Examples of how the variation(s) should be presented in the section "Type(s) of Change(s)" of the application form.

E.g. when applying for a change outside the approved specification limits for the active substance:

[20] For submissions to the EMA (including worksharing procedures which include MRP products and/or purely national medicinal products), this section can be left blank.
[21] The main signatory is mandatory.

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance		Variation type
☒ f)	Change outside the approved specifications limits range for the active substance	II

E.g. when applying for an 'unforeseen' change concerning specification limits for the active substance:

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance		Variation type	
☒ z)	Other variation	☐IA ☒IB ☐II	☐ **Art 5**

E.g. when applying for an 'unforeseen' change concerning the control of active substance:

B.I.b Change in control of the active substance		Variation type	
☒ z)	Other variation	☐IA ☒IB ☐II	☐ **Art 5**

The full list of variations is to be deleted from the actual submitted application form.

A. Administrative changes		Variation type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

		Variation type		
☐ **A.1**	**Change in the name and/or address of the marketing authorisation holder**	☐IA_{IN}	☐ IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

A.2 Change in the (invented) name of the medicinal product		Variation type		
☐ a)	For centrally authorised products	☐IA_{IN}	☐ IB¤	**Implement. date:**
☐ b)	For nationally authorised products	IB		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
☐ **A.3**	**Change in the name of an active substance or of an excipient**	☐IA_{IN}	☐ IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
☐ **A.4**	**Change in the name and/or address of a manufacturer (including where relevant quality control sites) or holder of the Active Substance Master File (ASMF), supplier of the active substance, starting material (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or of the manufacturer of a new excipient (where specified in the product dossier)**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

A.5 Change in the name and/or address of a manufacturer/importer of the finished product [including quality/testing control sites]		**Variation type**		
☐ a)	Batch release is one of the attributions of the manufacturer/importer	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Batch release is not the attribution of the manufacturer/importer	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
☐ **A.6**	**Change in ATC Code / ATC Vet Code**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
☐ **A.7**	**Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)*.**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.
*Note: If the authorities have announced their intention to perform an inspection, the deletion of a concerned site should be announced immediately.

		Variation type	
☐ **A.8**	**Change in the date of performance of the audit related to checking compliance with Good Manufacturing Practices (GMP) by the manufacturer of an active substance***	☐IA	**Implement. date:**

B.I.a Change in the manufacture of the active substance	Variation type	
☐ z) Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier		Variation type		
☐ a)	The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Introduction of a new manufacturer of the active substance that is supported by an ASMF	II		
☐ c)	The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.	II		
☐ d)	New manufacturer of material for which an assessment is required of viral safety and/or TSE risk	II		
☐ e)	The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product.	II		
☐ f)	Changes to quality control testing arrangements for the active substance: replacement or addition of a site where batch control/testing takes place	☐IA	☐IB¤	**Implement. date:**
☐ g)	Addition of a new manufacturer of the active substance without ASMF requiring a significant update of the dossier section referring to the respective active substance	II		
☐ h)	Addition of an alternative sterilisation site for the active substance, using a method of the European Pharmacopoeia	IB		
☐ i)	Introduction of a new micronisation site	☐IA	☐IB¤	
☐ j)	Changes to the testing process for quality control of a biological active substance: replacement or addition of a site of batch control/testing, including a biological/immunological/immunochemical method	II		
☐ k)	New site for storage of the master cell bank and/or working cell banks	IB		

☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.2 Changes in the manufacturing process of the active substance		**Variation type**		
☐ a)	Minor change in the manufacturing process of the active substance	☐IA	☐IB¤	**Implement. date:**
☐ b)	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	II		
☐ c)	The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product, which may have a significant impact upon the product's quality/safety and efficacy, and is not related to a protocol.	II		
☐ d)	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production.	II		
☐ e)	Minor change to the restricted/closed part of an Active Substance Master File.	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacture of the active substance		**Variation type**		
☐ a)	Up to 10-fold increase compared to the currently approved batch size	☐IA	☐IB¤	**Implement. date:**
☐ b)	Downscaling down to 10-fold	☐IA	☐IB¤	**Implement. date:**
☐ c)	The change requires assessment of the comparability of a biological/immunological active substance.	II		
☐ d)	More than 10-fold increase compared to the currently approved batch size	IB		
☐ e)	The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line).	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		Variation type		
☐ a)	Tightening of in-process limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of new in-process tests and limits	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a non-significant in-process test	☐IA	☐IB¤	**Implement. date:**
☐ d)	Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	II		
☐ e)	Deletion of an in-process test which may have a significant effect on the overall quality of the active substance	II		
☐ f)	Addition or replacement of an in-process test as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza		Variation type
☐ a)	Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	II

B.I.b Changes in the control of the active substance		Variation type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance		Variation type		
☐ a)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ c)	Addition of a new testing parameter with its corresponding test method	☐IA	☐IB¤	**Implement. date:**
☐ d)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ e)	Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product	II		
☐ f)	Change outside the approved specifications limits range for the active substance	II		
☐ g)	Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product	II		

☐ h)	Addition or replacement (excluding biological or immunological active substances) of a specification parameter as a result of a safety or quality issue	IB	
☐ i)	Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance		**Variation type**		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. date:**
☐ b)	Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorised.	☐IA	☐IB¤	**Implement. date:**
☐ c)	Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	☐IA	☐IB¤	**Implement. date:**
☐ d)	Change or replacement to a biological/ immunological/immunochemical test method or a method using a biological reagent for a biological active substance	II		
☐ e)	Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	IB		

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.c Change in container closure system of the active substance		**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

B.I.c.1 Change in immediate packaging of the active substance		**Variation type**		
☐ a)	Qualitative and/or quantitative composition	☐IA	☐IB¤	**Implement. date:**
☐ b)	Qualitative and/or quantitative composition for sterile and nonfrozen biological/immunological active substances	II		

☐ c)	Liquid active substances (non-sterile)	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance		**Variation type**		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ d)	Addition or replacement of a specification parameter as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance		**Variation type**		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. date:**
☐ b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. date:**

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. certificate of suitability covering the retest period is part of the approved dossier.			**Variation type**		
a)	Re-test period/storage period				
☐	1.	Reduction	☐IA	☐IB¤	**Implement. date:**
☐	2.	Extension of the retest period based on extrapolation of stability data not in accordance with ICH guidelines*	II		
☐	3.	Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol.	II		
☐	4.	Extension or introduction of a re-test period/storage period supported by real time data	IB		

	b)	Storage conditions			
☐	1.	Change to more restrictive storage conditions of the active substance	☐IA	☐IB¤	**Implement. date:**
☐	2.	Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol	II		
☐	3.	Change in storage conditions of the active substance	IB		
	c)	Change in an approved stability protocol	☐IA	☐IB¤	
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.e.1		**Introduction of a new design space or extension of an approved design space for the active substance, concerning:**	**Variation type**
☐	a)	One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures	II
☐	b)	Test procedures for starting materials/reagents/ intermediates and/or the active substance	II

			Variation type
B.I.e.2	☐	**Introduction of a post approval change management protocol related to the active substance**	II

			Variation type		
B.I.e.3	☐	**Deletion of an approved change management protocol related to the active substance**	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.e.4		**Change in description and composition of the Finished Product**	**Variation type**
☐	a)	Major changes in the approved protocol concerning the handling of changes	II
☐	b)	Minor changes in the approved protocol concerning the handling of changes, not affecting the strategy defined in the protocol	IB
☐	z)	Other variation	☐IA ☐IB ☐II ☐ **Art 5 Implement. date:**

B.I.e.5		**Implementation of the changes mentioned in an approved protocol related to the management of changes**	**Variation type**	
☐	a)	The implementation of the change does not require additional justifying data	☐IA_{IN}	☐IB¤
☐	b)	The implementation of the change requires additional justifying data	IB	

☐ c)	The implementation of a change concerning a biological/immunological medicinal product	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a Changes in the description and composition of the medicinal product		**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement or addition of inks used for product marking.		**Variation type**		
☐ a)	Changes in imprints, bossing or other markings	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Changes in scoring/break lines intended to divide into equal doses	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form		**Variation type**		
☐ a)	Immediate release tablets, capsules, suppositories and pessaries	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses	IB		
☐ c)	Addition of anew kit for a pharmaceutical preparation with another filling volume	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.3 Changes in the composition (excipients) of the finished product			**Variation type**		
a)	Changes in components of the flavouring or colouring system				
☐	1.	Addition, deletion or replacement	☐IA_{IN}	☐IB¤	**Implement. date:**
☐	2.	Increase or reduction	☐IA	☐IB¤	**Implement. date:**
☐	3.	Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species	II		
b)	Other excipients				

☐	1.	Any minor adjustment of the quantitative composition of the finished product with respect to excipients	☐IA	☐IB¤	**Implement. date:**
☐	2.	Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product.	II		
☐	3.	Change that relates to a biological/immunological product	II		
☐	4.	Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk.	II		
☐	5.	Change that is supported by a bioequivalence study.	II		
☐	6.	Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells			**Variation type**		
☐	a)	Solid oral pharmaceutical forms	☐IA	☐IB¤	**Implement. date:**
☐	b)	Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism.	II		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
☐ **B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same.**	II
	Variation type
☐ **B.II.a.6 Deletion of the solvent / diluent container from the primary packaging**	IB

B.II.b Change in manufacture of the Finished Product			**Variation type**	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	**Variation type**

☐ a)	Secondary packaging site	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Primary packaging site	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ c)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products or for pharmaceutical forms obtained through complex manufacturing processes.	II		
☐ d)	Site which requires an initial or product specific inspection	II		
☐ e)	Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.	IB		
☐ f)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/ immunological medicinal products	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.2 Change to batch release arrangements and quality control testing of the finished product		**Variation type**		
☐ a)	Replacement or addition of a site where batch control/testing takes place	☐IA	☐IB¤	**Implement. date:**
☐ b)	Replacement or addition of a manufacturer responsible for batch release for a biological/immunological medicinal product, any of the test methods performed at the respective site being a biological/immunological method	II		
c)	Replacement or addition of a manufacturer responsible for batch import and/or release			
☐ 1.	Not including batch control/testing	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ 2.	Including batch control/testing	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ 3.	Including batch control/testing for a biological/immunol. product and one of the test methods performed at that site is a biological/immunol./immunochemical method.	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.3 Change in the manufacturing process of the finished product and of an intermediate used in the manufacture of the finished product		Variation type		
☐ a)	Minor change in the manufacturing process	☐IA	☐IB¤	**Implement. date:**
☐ b)	Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	II		
☐ c)	The medicinal product is a biological/immunological medicinal product and the change requires an assessment of comparability.	II		
☐ d)	Introduction of a non-standard terminal sterilisation method	II		
☐ e)	Introduction or increase in the overdosage that is used for the active substance	II		
☐ f)	Minor change in the manufacturing process of an aqueous oral suspension.	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product		Variation type		
☐ a)	Up to 10-fold compared to the originally approved batch size	☐IA	☐IB¤	**Implement. date:**
☐ b)	Downscaling down to 10-fold	☐IA	☐IB¤	**Implement. date:**
☐ c)	The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study	II		
☐ d)	The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	II		
☐ e)	More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms	IB		
☐ f)	The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product		Variation type		
☐ a)	Tightening of in-process limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of new tests and limits	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a non-significant in-process test	☐IA	☐IB¤	**Implement. date:**
☐ d)	Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	II		
☐ e)	Widening of the approved IPC limits, which may have a significant effect on the overall quality of the finished product	II		
☐ f)	Addition or replacement of an in-process test as a result of a safety quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c Change in control of excipients in the finished product		Variation type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

B.II.c.1 Change in the specification parameters and/or limits of an excipient		Variation type		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ d)	Change outside the approved specifications limits range	II		
e)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II		
☐ f)	Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue	IB		
☐ g)	Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country	IB		

☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c.2 Change in test procedure for an excipient		**Variation type**		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. date:**
☐ b)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. date:**
☐ c)	Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biochemical reagent	II		
☐ d)	Other changes to a test procedure (including replacement or addition)	IB		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c.3 Change in source of an excipient or reagent with TSE risk			**Variation type**		
	a)	From TSE risk material to vegetable or synthetic origin			
☐	1.	For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	☐IA	☐IB¤	**Implement. date:**
☐	2.	For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	IB		
☐ b)		Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability	II		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or of a new excipient		**Variation type**		
☐ a)	Minor change in synthesis or recovery of a nonpharmacopoeial excipient or of a new excipient	☐IA	☐IB¤	**Implement. date:**
☐ b)	The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product.	II		
☐ c)	The excipient is a biological/immunological substance	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.d Change in control of the finished product		Variation type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

B.II.d.1 Change in the specification parameters and/or limits of the finished product		Variation type		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ c)	Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ d)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter, e.g. smell and taste, or of the identification test for a colouring/flavouring material)	☐IA	☐IB¤	**Implement. date:**
☐ e)	Change outside the approved specifications limits range	II		
☐ f)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II		
☐ g)	Addition or replacement (excluding biological or immunological products) of a specification parameter and of the corresponding test method as a result of a safety or quality issue	IB		
☐ h)	Update of the dossier in accordance with the provisions of an updated general monograph of the European Pharmacopoeia for the medicinal product*	☐IA_{IN}	☐IB¤	
☐ i)	Introduction of the provisions of the European Pharmacopoeia 2.9.40 (Uniformity of dosage units) for replacement of the currently approved method, either European Pharmacopoeia 2.9.5 (Uniformity of mass) or European Pharmacopoeia 2.9.6 (Uniformity of content)	☐IA	☐IB¤	
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.d.2 Change in test procedure for the finished product		Variation type		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. date:**
☐ b)	Deletion of a test procedure if an alternative method is already authorised	☐IA	☐IB¤	**Implement. date:**
☐ c)	Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biochemical reagent or replacement of a biological reference preparation which is not part of an approved protocol	II		

☐ d)	Other changes to a test procedure (including replacement or addition)	IB	
☐ e)	Update of the test procedure in accordance with the updated general monograph of the European Pharmacopoeia	☐IA	☐IB¤
☐ f)	To reflect compliance with the European Pharmacopoeia And to eliminate the obsolete reference to the internal testing method and to the testing method code*	☐IA	☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
☐ **B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product**	II

B.II.e Change in container closure system of the Finished Product		**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

B.II.e.1 Change in immediate packaging of the finished product			**Variation type**		
a)	Qualitative and quantitative composition				
☐	1.	Solid pharmaceutical forms	☐ IA	☐IB¤	**Implement. date:**
☐	2.	Semi-solid and non-sterile liquid pharmaceutical forms	IB		
☐	3.	Sterile medicinal products and biological/ immunological medicinal products.	II		
☐	4.	The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	II		
b)	Change in the type of recipient or addition of a new one				
☐	1.	Solid, semi-solid and non-sterile liquid pharmaceutical forms	IB		
☐	2.	Sterile medicinal products and biological/ immunological medicinal products	II		
☐	3.	Deletion of a container meant for immediate packaging, which does not lead to the entire deletion of a strength/pharmaceutical form	☐IA	☐IB¤	
☐ z)		Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product		**Variation type**		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. date:**

☐ c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ d)	Addition or replacement of a specification parameter as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product		**Variation type**		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. date:**
☐ b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)		**Variation type**		
☐ a)	Non-sterile medicinal products	☐IA	☐IB¤	**Implement. date:**
☐ b)	The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product	II		
☐ c)	Sterile medicinal products	IB		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.5 Change in pack size of the finished product		**Variation type**		
a)	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
☐	1. Change within the range of the currently approved pack sizes	☐IA_{IN}	☐IB¤	**Implement. date:**
☐	2. Change outside the range of the currently approved pack sizes	IB		
☐ b)	Deletion of a pack size(s)	☐IA	☐IB¤	**Implement. date:**
☐ c)	Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/ immunological multidose parenteral medicinal products.	II		
☐ d)	Change in the fill weight/fill volume of non-parenteral multidose (or single-dose, partial use) products	IB		

☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.6	**Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))**	**Variation type**		
☐ a)	Change that affects the product information	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Change that does not affect the product information	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.7	**Change in supplier of packaging components or devices (when mentioned in the dossier)**	**Variation type**		
☐ a)	Deletion of a supplier	☐IA	☐IB¤	**Implement. date:**
☐ b)	Replacement or addition of a supplier	☐IA	☐IB¤	**Implement. date:**
☐ c)	Any change to suppliers of spacer devices for metered dose inhalers	II		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.f.1	**Change in the shelf-life or storage conditions of the finished product**	**Variation type**		
a)	Reduction of the shelf life of the finished product			
☐ 1.	As packaged for sale	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ 2.	After first opening	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ 3.	After dilution or reconstitution	☐IA_{IN}	☐IB¤	**Implement. date:**
b)	Extension of the shelf life of the finished product			
☐ 1.	As packaged for sale (supported by real time data)	IB		
☐ 2.	After first opening (supported by real time data)	IB		
☐ 3.	After dilution or reconstitution (supported by real time data)	IB		
☐ 4.	Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines*	II		
☐ 5.	Extension of storage period of a biological/ immunological medicinal product in accordance with an approved stability protocol.	IB		

☐ c)	Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	II		
☐ d)	Change in storage conditions of the finished product or the diluted/reconstituted product	IB		
☐ e)	Change in an approved stability protocol	☐IA	☐IB¤	
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, excluding biologicals, concerning:		**Variation type**
☐ a)	One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures	II
☐ b)	Test procedures for excipients / intermediates and/or the finished product.	II

		Variation type		
☐	**B.II.g.2 Introduction of a post approval change management protocol related to the finished product**	II		
		Variation type		
☐	**B.II.g.3 Deletion of an approved change management protocol related to the finish product**	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.g.4 Changes on the approved protocol concerning the handling of changes		**Variation type**	
☐ a)	Major changes in the approved protocol concerning the handling of changes	II	
☐ b)	Minor changes in the approved protocol concerning the handling of changes, not affecting the strategy defined in the protocol	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

B.II.g.5 Implementation of the changes mentioned in an approved protocol for handling of changes		**Variation type**		
☐ a)	The implementation of the change does not require additional supporting data	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	The implementation of the change requires additional supporting data	IB		
☐ c)	The implementation of a change concerning a biological/immunological medicinal product	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.h.1 Update of the information in „ Adventitious Agents Safety Evaluation" (Section 3.2.A.2)		Variation type
☐ a)	Studies related to manufacturing steps investigated for the first time for one or more adventitious agents	II
☐ b)	Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier	
	1) with modification of risk assessment	II
	2) without modification of risk assessment	IB

B.III.1 Submission of a new or updated Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient			Variation type		
a)	**European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.**				
☐	1.	New certificate from an already approved manufacturer	☐IA_{IN}	☐IB¤	**Implement. date:**
☐	2.	Updated certificate from an already approved manufacturer	☐IA	☐IB¤	**Implement. date:**
☐	3.	New certificate from a new manufacturer (replacement or addition)	☐IA_{IN}	☐IB¤	**Implement. date:**
☐	4.	Deletion of certificates (in case multiple certificates exist per material)	☐IA	☐IB¤	
☐	5.	New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free	IB		
b)		European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient			
☐	1.	New certificate for an active substance from a new or an already approved manufacturer	☐IA_{IN}	☐IB¤	**Implement. date:**
☐	2.	New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	☐IA	☐IB¤	**Implement. date:**
☐	3.	Updated certificate from an already approved manufacturer	☐IA	☐IB¤	**Implement. date:**
☐	4.	Deletion of certificates (in case multiple certificates exist per material)	☐IA	☐IB¤	

☐	5. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required	II	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State		**Variation type**		
a)	Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State			
☐ 1.	Active substance	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ 2.	Excipient/active substance starting material	☐IA	☐IB¤	**Implement. date:**
☐ b)	Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	☐IA	☐IB¤	**Implement. date:**
☐ c)	Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	☐IA	☐IB¤	**Implement. date:**
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.IV Change in medical devices		**Variation type**	
☐ z)	Other variations	☐IA ☐IB ☐ II	☐ **Art 5 Implement. date:**

B.IV.1 Change of a measuring or administration medical device		**Variation type**		
a)	Addition or replacement of a device which is not an integrated part of the primary packaging			
☐ 1.	Device with CE marking	☐ IAIN	☐ IB¤	**Implement. date:**
☐ 2.	Device without CE marking (for veterinary products only)	IB		
☐ 3.	Spacer device for metered dose inhalers or another device which may have a major impact on the release of the product's active substance (e.g. nebuliser)	II		
☐ b)	Deletion of a device	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ c)	Addition or replacement of a device which is an integrated part of the primary packaging	II		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products		Variation type		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ c)	Widening of the approved specifications limits, which has a significant effect on the overall quality of the device	II		
☐ d)	Deletion of a specification parameter that has a significant effect on the overall quality of the device	II		
☐ e)	Addition of a specification parameter as a result of a safety or quality issue	IB		
☐ f)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products		Variation type		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. date:**
☐ b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB¤	**Implement. date:**
☐ c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)		Variation type		
☐ a)	First-time inclusion of a new Plasma Master File affecting the properties of the finished product	II		
☐ b)	First-time inclusion of a new Plasma Master File not affecting the properties of the finished product	IB		
☐ c)	Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product	IB		
☐ d)	Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)		Variation type
☐ a)	First-time inclusion of a new Vaccine Antigen Master File	II

☐ b)	Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product	IB		
☐ c)	Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.V.b.1	**Update of the quality dossier in view of enforcement of the outcome of a referral procedure at EU level**	**Variation type**		
☐ a)	The change implements the outcome of the referral*	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it	II		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I	**Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products**	**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

C.I.1	**Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet in view of implementation of the outcome of the referral procedure at EU level**	**Variation type**		
☐ a)	The medicinal product is covered by the defined scope of the referral*	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	The medicinal product is not covered by the defined scope of the referral but the change implements the outcome of the referral and no new additional data are submitted by the MAH	IB		
☐ c)	The medicinal product is not covered by the defined scope of the referral but the change implements the outcome of the referral with new additional data submitted by the MAH	II		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.2	**Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product**	**Variation type**
☐ a)	Implementation of change(s) for which no new additional data are submitted by the MAH	IB
☐ b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)	II

C.I.3 Change(s) in the Summary of Product Characteristics, labelling or leaflet of medicinal products for human use in view of implementation of the outcome of a procedure related to Periodic Safety Update Reports (PSURs) or of Post Authorisation Safety Studies (PASSs) or of the outcome of the assessment performed by a competent authority in accordance with Article 45/46 of Regulation (EC) No 1901/2006		Variation type		
☐ a)	Implementation of the wording change agreed by the competent authority	☐IA_{IN}	☐IB¤	
☐ b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.4 Change(s) in the Summary of Product Characteristics, labelling or package leaflet due in particular to new quality, pre-clinical, clinical or pharmacovigilance data		Variation type
☐		II
C.I.5 Change in the legal status of a medicinal product for centrally authorised products		**Variation type**
☐ a)	For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product	IB
☐ b)	All other legal status changes	II

C.I.6 Change(s) to therapeutic indication(s)		Variation type
☐ a)	Addition of a new therapeutic indication or modification of an approved one	II
☐ b)	Deletion of a therapeutic indication	IB

C.I.7 Deletion of:		Variation type
☐ a)	A pharmaceutical form	IB
☐ b)	A strength	IB

C.I.8 Introduction of a new summary of the Pharmacovigilance system for medicinal products for human use or of its change*		Variation type	
☐ a)	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	☐IA_{IN}	☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.9 Change(s) to an existing pharmacovigilance system as described in the DDPS.		Variation type		
☐ a)	Change in QPPV and/or his/her contact details and/or of the back-up procedure of the QPPV	☐IA_{IN}	☐IB¤	**Implement. date:**

☐ b)	Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and /or change of the site undergoing pharmacovigilance activities	☐IA$_{IN}$	☐IB¤	**Implement. date:**
☐ c)	Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes).	☐IA	☐IB¤	**Implement. date:**
☐ d)	Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH.	☐IA$_{IN}$	☐IB¤	**Implement. date:**
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type	
C.I.10 ☐ **Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products**	☐IA$_{IN}$	☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan		**Variation type**	
☐ a)	Implementation of wording agreed by the NAMMD	☐IA$_{IN}$ ☐IB¤	**Implement. date:**
☐ b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the NAMMD is required*	II	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type	
C.I.12 ☐ **Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring**	☐IA$_{IN}$	☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
C.I.13 ☐ **Other variations which are not specifically included in another section of this Annex and which require the submission of trials to the NAMMD***	II

C.II Changes to veterinary medicinal products		**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

		Variation type
C.II.1 ☐	**Variations concerning a change to or addition of a non-food producing target species**	II

C.II.2 Deletion of a food producing or non-food producing target species.		Variation type
☐ a)	Deletion as a result of a safety issue	II
☐ b)	Deletion not resulting from a safety issue	IB

		Variation type
C.II.3 ☐	**Changes to the withdrawal period for a veterinary medicinal product**	II

		Variation type
C.II.4 ☐	**Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.**	II

		Variation type
C.II.5 ☐	**Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza**	II

		Variation type
C.II.6 ☐	**Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.**	IB
☐	a) Administrative information concerning the holder's representative	☐IA_{IN}
☐	b) Other variation	IB

C.II.7 Introduction of a new pharmacovigilance system		Variation type
☐ a)	Which has been assessed by the relevant national competent authority/EMA for another medicinal product of the same Marketing Authorisation Holder	II
☐ b)	Which has not been assessed by the relevant national competent authority/EMA for another medicinal product of the same Marketing Authorisation Holder	IB

		Variation type	
C.II.8 ☐	**Change in the frequency and/or date of submission of periodic safety update reports (PSUR)**	☐IA_{IN}	☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

D. Changes to PMF/VAMF		Variation type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

		Variation type		
D.1 ☐	**Change in the name and/or address of the VAMF certificate holder**	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
D.2 ☐	**Change in the name and/or address of the PMF certificate holder**	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
D.3 ☐	**Change or transfer of the current PMF certificate holder to a new PMF certificate holder (i.e. different legal entity).**	☐IA_{IN}	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type		
D.4 ☐	**Change in the name and/or address of a blood establishment including blood/plasma collection centres**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type
D.5 ☐	**Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF**	IB

		Variation type		
D.6 ☐	**Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Variation type
D.7 ☐	**Addition of a new blood establishment for the collection of blood/plasma not included in the PMF**	II

		Variation type
D.8 ☐	**Replacement or addition of a blood centre for testing of donations and/or plasma pools within an establishment already included in the PMF**	IB

		Variation type
D.9 ☐	**Addition of a new blood establishment for testing of donations and/or plasma pools not included in the PMF**	II

		Variation type
D.10 ☐	**Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out**	IB

		Variation type		
D.11 ☐	**Deletion of a blood establishment or centre(s) in which storage of plasma is carried out**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
☐ **D.12 Replacement or addition of an organisation involved in the transport of plasma.**	IB

	Variation type		
☐ **D.13 Deletion of an organisation involved in the transport of plasma**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type		
☐ **D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	**Variation type**		
☐ a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations	II		
☐ b) The new test kit has been approved in the PMF for other blood centre(s) for testing of donations	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
☐ **D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).**	II

	Variation type		
☐ **D.17 Introduction or extension of inventory hold procedure.**	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
☐ **D.18 Removal of inventory hold period or reduction in its length**	IB

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	**Variation type**		
☐ a) The new blood containers are EC-marked	☐IA	☐IB¤	**Implement. date:**
☐ b) The new blood containers are not EC-marked	II		

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

D.20 Change in storage / transport	**Variation type**		
☐ a) Storage and/or transport conditions	☐IA	☐IB¤	**Implement. date:**
☐ b) Maximum storage time for the plasma	☐IA	☐IB¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Variation type
☐ **D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.**	II

		Variation type
D.22 ☐	**Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)**	IB

		Variation type
D.23 ☐	**Change in the steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing ("look-back" procedure).**	II

DECISION

No. 22/12.08.2013

on approval of abbreviated Romanian Standard Terms for the labelling of parenteral, eye, ear and nasal preparations, in line with European Pharmacopoeia approved terms

The Scientific Council of the National Agency for Medicines and Medical Devices, established based on Order of the Minister of Health No. 158/18.02.2013, in accordance with the Regulation on the organisation and operation of the Scientific Council of the NAMMD, Article 8 (1), hereby adopts through written procedure the following

DECISION

Sole article - The abbreviated Romanian Standard Terms for the labelling of parenteral, eye, ear and nasal preparations in line with European Pharmacopoeia approved terms are approved, according to the annex which is integral part of this decision.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD No. 22/12.08.2013

ABBREVIATED ROMANIAN STANDARD TERMS

For parenteral, eye, ear and nasal preparations, in line with

abbreviated European Standard Terms

(***Short /Patient friendly Terms)***

approved by

the European Pharmacopoeia Commission,
the European Directorate for the Quality of Medicines (EDQM),
the European Council, Strasbourg

The Lists of European Standard Terms have been set up by the European Pharmacopoeia Commission at the request of the European Commission, to ensure their harmonised use in Marketing Authorisations (MAs), Summary of Product Characteristics (SmPCs), leaflets, labelling and European electronic medicinal product databases.

Standard terms serve a double purpose: to inform the patient/user/physician and make a difference between products with the same invented name. Given the object of the leaflet and labelling, all standard terms and combinations of standard terms must take account of the patient's condition.

Standard terms must express vital information about the properties and use of medicinal products. Vital information to be provided for all medicinal products is the „pharmaceutical form", defined as follows:

The EDQM *Standard Terms Introduction and Guidance for Use* states:

„A pharmaceutical form is a combination between the form of a medicinal product presentation by the manufacturer (*presentation form*) and its manner of administration, including its physical form *(administration form)".*

The List of European standard terms for pharmaceutical forms represents the basic terms required for characterisation of pharmaceutical forms. Standard terms can be used for medicinal products for human and veterinary use. These terms are called *full standard terms*.

Since the size of the label of certain pharmaceutical forms does not allow use of a full standard term, the use of *short standard terms* is exceptionally allowed, as approved by the *European Pharmacopoeia Commission.*

The following **Abbreviated Romanian Standard Terms** can only be used for the labelling of certain pharmaceutical forms, if the label size does not allow print of a full standard term.

Preparate oftalmice *Eye preparations*				
Whole Standard Terms		No.[1] monogr. of Ph. Eur.	**Abbreviated Standard Terms**	
Romanian	**English**		**Romanian**	**English**
Cream oftalmică	*Eye cream*	No. 1163	-	-
Gel oftalmic	*Eye gel*	No. 1163	-	-
Unguent oftalmic	*Eye ointment*	No. 1163	-	-
Picături oftalmice, soluţie	*Eye drops, solution*	No. 1163	Picături oftalmice*	*Eye drops**
Picături oftalmice, suspensie	*Eye drops, suspension*	No. 1163	Picături oftalmice*	*Eye drops**
Picături oftalmice, pulbere şi solvent pentru soluţie	*Eye drops, powder and solvent for solution*	No. 1163	-	-
Picături oftalmice, pulbere şi solvent pentru suspensie	*Eye drops, powder and solvent for suspension*	No. 1163	-	-
Solvent oftalmic pentru reconstituire	*Eye drops, solvent for reconstitution*	-	-	-
Picături oftalmice cu eliberare prelungită	*Eye drops, prolonged-release*	No. 1163	-	-
Soluţie pentru baie oculară	*Eye lotion*	No. 1163	-	-
Solvent pentru baie oculară	*Eye lotion, solvent for reconstitution*	-	-	-
Insert oftalmic	*Ophthalmic insert*	No. 1163	-	-
Bandă oftalmică	*Ophthalmic strip*	-	-	-

Preparate auriculare *Ear preparations*		
Whole Standard Terms	No.[1] monogr. of Ph.	**Abbreviated Standard Terms**

Romanian	English	Eur.	Romanian	English
Cream auriculară	*Ear cream*	No. 652	-	-
Gel auricular	*Ear gel*	No. 652	-	-
Unguent auricular	*Ear ointment*	No. 652	-	-
Picături auriculare, soluţie	*Ear drops, solution*	No. 652	Picături auriculare*	*Ear drops**
Picături auriculare, suspensie	*Ear drops, suspension*	No. 652	Picături auriculare*	*Ear drops**
Picături auriculare, pulbere şi solvent pentru suspensie	*Ear drops, powder and solvent for suspension*	No. 652	-	-
Picături auriculare, emulsie	*Ear drops, emulsion*	No. 652	Picături auriculare*	*Ear drops**
Pulbere auriculară	*Ear powder*	No. 652	-	-
Spray auricular, soluţie	*Ear spray, solution*	No. 652	Spray auricular*	*Ear spray**
Spray auricular, suspensie	*Ear spray, suspension*	No. 652	Spray auricular*	*Ear spray**
Spray auricular, emulsie	*Ear spray, emulsion*	No. 652	Spray auricular*	*Ear spray**
Soluţie pentru spălări auriculare	*Ear wash, solution*	No. 652	Spălări auriculare*	*Ear wash**
Emulsie pentru spălări auriculare	*Ear wash, emulsion*	No. 652	Spălări auriculare*	*Ear wash**
Tampon auricular	*Ear tampon*	No. 1155	-	-
Creion auricular	*Ear stick*	No. 1154	-	-

Preparate nazale *Nasal preparations*				
Whole Standard Terms		No.1) monogr. of Ph. Eur.	**Abbreviated Standard Terms**	
Romanian	**English**		**Romanian**	**English**
Cream nazală	*Nasal cream*	No. 676	-	-

Gel nazal	*Nasal gel*	No. 676	-	-
Unguent nazal	*Nasal ointment*	No. 676	-	-
Picături nazale, soluţie	*Nasal drops, solution*	No. 676	Picături nazale*	*Nasal drops**
Picături nazale, suspensie	*Nasal drops, suspension*	No. 676	Picături nazale*	*Nasal drops**
Picături nazale, emulsie	*Nasal drops, emulsion*	No. 676	Picături nazale*	*Nasal drops**
Pulbere nazală	*Nasal powder*	No. 676	-	-
Spray nazal, soluţie	*Nasal spray, solution*	No. 676	Spray nazal*	*Nasal spray**
Spray nazal, suspensie	*Nasal spray, suspension*	No. 676	Spray nazal*	*Nasal spray**
Spray nazal, emulsie	*Nasal spray, emulsion*	No. 676	Spray nazal*	*Nasal spray**
Soluţie pentru spălări nazale	*Nasal wash*	No. 676	-	-
Creion nazal	*Nasal stick*	No. 676	-	-

Medicinal product batches recalled during the 3rd quarter of 2013

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
1.	TRIDERM	Cream		COMBINATIONS	Schering Plough Labo NV, Belgium/ Merck Sharp & Dohme, Romania SRL	0MCEA07002, 0MCEA11003, 1MCEA01003, 1MCEA04003, 1MCEA08001, 1MCEA10002, 1MCEA11001, 2MCEA02004, 2MCEA03004, 2MCEA04001, 2MCEA06001, 2MCEA10002, 2MCEA12001, 2MCEA15003, 2MCEA19001, 2MCEA19002, 2MCEA20002, 3MCEA01002, 3MCEA06001	Out-of-specification result under parameter "betamethasone dipropionate'' obtained after laboratory testing conducted during the stability trial (12 months after product manufacture)	Recall from wholesale distribution units	05.07.2013
2.	CONVULEX	Gastro-resistant soft capsules	300 mg	Valproic acid and salts	Gerot Pharmazeutika GES.M.B.H., Austria	1J099A (exp. 30.09.2016)	The pharmaceutical form "capsules" is mentioned instead of ,,gastro-resistant soft capsules" on the primary packaging (the blister foil)	Voluntary recall and blister relabelling	24.07.2013
3.	DIANE-35	Lozenges		COMBINATIONS	Bayer Pharma AG, Germany	02028B, 13092A, 14103D, 14114D, 22138B, 23163D, 24173B	Expiry of the three-month period for closure of implementation of the variation approved by the NAMMD on 22.02.2013 (for the leaflet and the information on product labelling)	Voluntary recall and destruction	30.07.2013

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
4.	CLIMEN	Lozenges		Combinations	Bayer Pharma AG, FRANCE/ Bayer Pharma AG, Germany	14334B	Expiry of the two-year period (specified in Order of the Minister of Health No. 279/2005) after approval of the variation to MA No. 3625/2003/01 of 02.08.2011	Voluntary recall and destruction	01.08.2013
5.	SUTENT	Capsules	50 mg	sunitinib	Pfizer Italia SRL, Italy/ Pfizer Ltd., Great Britain	T737E, U299B	Detection of two boxes of counterfeited product in the legal distribution network in Romania and Germany	Voluntary recall of the two batches	06.08.2013
6.	IMODIUM	Capsules	2 mg	Loperamide hydrochloride	Janssen-Cilag, FRANCE/ McNeil Products Ltd C/O Johnson & Johnson, Great Britain	2EV0501 (exp. 04.2017)	The name of the active substance (loperamide hydrochloride) is not imprinted on the primary packaging (Al/PVC blister)	Recall of all inadequately labelled batches	14.08.2013
7.	DUOFILM	Cutaneous solution		Combinations	Stiefel Lab. Ireland Ltd., Ireland/ GSK Consumer Healthcares SRL	All batches manufactured in accordance with MA No. 7224/2006/01	Expiry of the one-year period since the MAH transfer approved by the NAMMD on 31.07.2012, in accordance with Order of the Minister of Health No. 810/2006	Voluntary recall and destruction	04.09.2013

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
8.	ZOVIRAX	Cream	5%	aciclovir	Glaxo Operations UK Ltd, Great Britain/ GSK Consumer Healthcare, Great Britain	All batches manufactured in accordance with MA No. 7384/ 2006/01-02	Expiry of the two-year period (mentioned in Order of the Minister of Health No. 279/2005) after NAMMD approval of the variation to MA No. 7384/2006/01-02 of 02.09.2011 (change of the invented name, pharmaceutical form and strength)	Voluntary recall and destruction	25.09.2013
9.	BYDUREON	Prolonged-release powder and solvent for solution for injection	2 mg	exenatin	Bristol-Myers Squibb/AstraZeneca EEIG	C164001	Out-of-specification results under parameter ‘‘content homogeneity’’	Voluntary recall and destruction	25.09.2013
10.	MELLEVA	film-coated tablets	2 mg/ 0.035mg	COMBINATIONS	Laboratoire Macors, FRANCE/ Ladee Pharma Kft, HUNGARY	All batches	Recall of the specified product MA	Voluntary recall and destruction	25.09.2013

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 2nd quarter of 2013

During the 2nd quarter of 2013, 244 marketing authorisation/renewal applications for medicinal products corresponding to the following therapeutic groups have been submitted:

A02 - Drugs for acid related disorders
A03 – Drugs for functional gastrointestinal disorders
A07 – Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
A10 – Drugs used in diabetes
A13 – Tonics
B01 – Antithrombotic agents
B02 – Antihemorrhagics
B03 – Antianemic preparations
B05 – Blood substitutes and perfusion solutions
C05 – Vasoprotectives
C07 – Beta blocking agents
C08 – Calcium channel blockers
C09 – Agents acting on the renin-angiotensin system
C10 – Lipid modifying agents
D01 – Antifungals for dermatological use
G03 – Sex hormones and modulators of the genital system
G04 - Urologicals
H02 – Corticosteroids for systemic use
J01 – Antibacterials for systemic use
J02 – Antimycotics for systemic use
J05 – Antivirals for systemic use
J07 – Vaccines
L01 – Antineoplastic agents
L04 – Immunosuppressants
M01 – Anti-inflammatory and antirheumatic products
M02 – Topical products for joint and muscular pain
N01 - Anesthetics
N02 - Analgezics
N03 - Antiepileptics
N04 – Anti-parkinson drugs
N05 - Psycholeptics
N06 - Psychoanaleptics
N07 – Other nervous system drugs
R01 – Nasal preparations
R02 – Throat preparations

R03 – Drugs for obstructive airway diseases

R05 – Cough and cold preparations
R06 – Antihistamines for systemic use
R07 – Other respiratory system products
S01 - Ophthalmologicals
V03 – All other therapeutic products
V09 – Diagnostic radiopharmaceuticals

Medicinal products authorised for marketing by the NAMMD during the 2nd quarter of 2013

INN	Invented name	Pharmaceutical form	Strength	Manufacturer	Country	MA number		
ACIDUM IBANDRONICUM	ACID IBANDRONIC SYNTHON HISPAIN 150 mg	film-coated tablets	150mg	SYNTHON HISPAIN S.L.	SPAIN	5588	2013	10
ACIDUM RISEDRONICUM	RISEDRONAT TEVA 35 mg	film-coated tablets	35mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5633	2013	14
ACIDUM URSODEOXYCHOLICUM	UROSOROM 250 mg	capsules	250mg	ROMPHARM COMPANY S.R.L.	ROMANIA	5662	2013	01
ACIDUM ZOLEDRONICUM	ACID ZOLEDRONIC POLIPHARMA 4 mg/5 ml	concentrate for solution for infusion	4mg/5ml	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5582	2013	04
ACIDUM ZOLEDRONICUM	ACID ZOLEDRONIC POLIPHARMA 5 mg	solution for infusion	5mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5583	2013	01
ACIDUM ZOLEDRONICUM	ACID ZOLEDRONIC PFIZER 4 mg/5 ml	concentrate for solution for infusion	4mg/5ml	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5612	2013	01
AMLODIPINUM	NORVASC 10 mg capsule	capsules	10mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5657	2013	10
AMLODIPINUM	ALGENPIN 5 mg	tablets	5mg	ALVOGEN IPCO S.AR.L	LUXEMBURG	5580	2013	02
AMLODIPINUM	ALGENPIN 10 mg	tablets	10mg	ALVOGEN IPCO S.AR.L	LUXEMBURG	5581	2013	02
AMLODIPINUM	NORVASC 5 mg capsules	capsules	5mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5656	2013	11
AMLODIPINUM	NORVASC 5 mg	tablets	5mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5654	2013	16
AMLODIPINUM	NORVASC 10 mg	tablets	10mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5655	2013	17
AMOXICILLINUM + ACIDUM CLAVULANICUM	AMOXIPLUS 1000 mg/200 mg	powder for solution for injection/infusion	1000mg/ 200mg	ANTIBIOTICE SA	ROMANIA	5521	2013	03
ARTEMETHER+ LUMEFANTRINE	ARTEMETHER & LUMEFANTRINE	tablets	20mg/120mg	CN UNIFARM S.A.	ROMANIA	14	2013	01
ARTESUNATE	LARINATE	powder for solution for injection	60mg	CN UNIFARM S.A.	ROMANIA	16	2013	01
BETAHISTINUM	EMPERIN 8 mg	tablets	8 mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5544	2013	04
BETAHISTINUM	EMPERIN 16 mg	tablets	16 mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5545	2013	07
BETAHISTINUM	EMPERIN 24 mg	tablets	24 mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5546	2013	06

BETAHISTINUM	VESTIBO 24 mg	tablets	24mg	ACTAVIS GROUP PTC EHF.	ICELAND	5677	2013	06
BETAMETHASONUM+ GENTAMICINUM+ CLOTRIMAZOLUM	TRESYL	cream		FITERMAN PHARMA S.R.L.	ROMANIA	5506	2013	01
CAPECITABINUM	CAPECITABINA MEDICO UNO 150 mg	film-coated tablets	150mg	MEDICO UNO WORLDWIDE (CYPRUS) LTD	CYPRUS	5569	2013	02
CAPECITABINUM	CAPECITABINA MEDICO UNO 500 mg	film-coated tablets	500mg	MEDICO UNO WORLDWIDE (CYPRUS) LTD	CYPRUS	5570	2013	02
CAPECITABINUM	CAPECITABINA SANDOZ 150 mg	film-coated tablets	150mg	SANDOZ SRL ROMANIA	ROMANIA	5558	2013	13
CAPECITABINUM	CAPECITABINA SANDOZ 500 mg	film-coated tablets	500mg	SANDOZ SRL ROMANIA	ROMANIA	5559	2013	13
CAPECITABINUM	CAPECITALOX 150 mg	film-coated tablets	150mg	PHAROS GENERICS LTD.	CYPRUS	5586	2013	02
CAPECITABINUM	CAPECITALOX 500 mg	film-coated tablets	500mg	PHAROS GENERICS LTD.	CYPRUS	5587	2013	02
CARVEDILOLUM	CARVEDILOL SANDOZ 6.25 mg	tablets	6.25 mg	HEXAL AG	GERMANY	5663	2013	06
CARVEDILOLUM	CARVEDILOL SANDOZ 12.5 mg	tablets	12.5 mg	HEXAL AG	GERMANY	5664	2013	06
CARVEDILOLUM	CARVEDILOL SANDOZ 25 mg	tablets	25mg	HEXAL AG	GERMANY	5665	2013	06
COMBINATIONS	SMOFKABIVEN CENTRAL	emulsion for infusion		FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	5674	2013	18
COMBINATIONS	ALGOPIRIN	film-coated tablets		MEDICIENT S.R.L.	ROMANIA	5652	2013	03
COMBINATIONS	MOLAXOLE	powder for oral solution		MEDA AB	SWEDEN	5679	2013	20
COMBINATIONS	STEROFUNDIN ISO	solution for infusion		B. BRAUN MELSUNGEN AG	GERMANY	5649	2013	18
COMBINATIONS	SMOFKABIVEN CENTRAL FARA ELECTROLITI	emulsion for infusion		FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	5675	2013	18
COMBINATIONS	SMOFKABIVEN PERIPHERAL	emulsion for infusion		FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	5676	2013	12
COMBINATIONS (ATORVASTATINUM+ AMLODIPINUM)	ATORDAPIN 10 mg/10 mg	film-coated tablets	10mg/10mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5508	2013	10
COMBINATIONS (ATORVASTATINUM+ AMLODIPINUM)	AMLODIPINA/ATORVASTATIN A KRKA 10 mg/10 mg	film-coated tablets	10mg/10mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5509	2013	10
COMBINATIONS (ATORVASTATINUM+ AMLODIPINUM)	TORVALIPIN PLUS 5 mg/10 mg	film-coated tablets	5mg/10mg	ACTAVIS GROUP PTC EHF.	ICELAND	5616	2013	12
COMBINATIONS (ATORVASTATINUM+	TORVALIPIN PLUS 10 mg/10 mg	film-coated tablets	10mg/10mg	ACTAVIS GROUP PTC EHF.	ICELAND	5617	2013	12

AMLODIPINUM)								
COMBINATIONS (AZELASTINUM+ FLUTICASONUM)	SYNAZE 137 micrograms/ 50 micrograms/dose	nasal spray, suspension	137micrograms/ 50micrograms/ dose	MEDA PHARMA GMBH & CO. KG	GERMANY	5572	2013	04
COMBINATIONS (AZELASTINUM+ FLUTICASONUM)	DYMOLIN 137 micrograms/ 50 micrograms/dose	nasal spray, suspension	137micrograms/ 50micrograms/ dose	MEDA PHARMA GMBH & CO. KG	GERMANY	5573	2013	04
COMBINATIONS (AZELASTINUM+ FLUTICASONUM)	DYMISTA 137 micrograms/ 50 micrograms/dose	nasal spray, suspension	137micrograms/ 50micrograms/ dose	MEDA PHARMA GMBH & CO. KG	GERMANY	5574	2013	04
COMBINATIONS (AZELASTINUM+ FLUTICASONUM)	DYLASTINE 137 micrograms/ 50 micrograms/dose	nasal spray, suspension	137micrograms/ 50micrograms/ dose	MEDA PHARMA GMBH & CO. KG	GERMANY	5575	2013	04
COMBINATIONS (CLINDAMYCINUM+ TRETINOINUM)	ZANEA 10 mg/g + 0.25 mg/g	gel	10mg/g+ 0.25mg/g	MEDA PHARMA GMBH & CO. KG	GERMANY	5669	2013	02
COMBINATIONS (DROSPIRENONUM+ ETINILESTRADIOLUM)	VEYANN 3 mg/0.02 mg	film-coated tablets	3mg/0.02mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5562	2013	04
COMBINATIONS (ETINILESTRADIOLUM+ DROSPIRENONUM)	YVIDUALLY 00.2 mg/3 mg	film-coated tablets	0.02mg/3mg	BAYER PHARMA AG	GERMANY	5618	2013	05
COMBINATIONS (IBUPROFENUM+ PSEUDOEFEDRINUM)	MUCOGRIP 200 mg/30 mg	film-coated tablets	200mg/30mg	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	5566	2013	02
COMBINATIONS (LAMIVUDINUM+ ZIDOVUDINUM)	LAMIVUDINA/ZIDOVUDINA AUROBINDO 150 mg/300 mg	film-coated tablets	150mg/ 300mg	AUROBINDO PHARMA (MALTA) LIMITED	MALTA	5565	2013	02
COMBINATIONS (NORGESTIMATUM+ ETINILESTRADIOLUM)	NORGESTIMAT/ETINILESTRADIOL FAMY CARE 250 micrograms/35 micrograms	tablets	250micrograms/ 35micrograms	FAMY CARE EUROPE LIMITED	GREAT BRITAIN	5615	2013	04
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TANYDON HCT 40 mg/12.5 mg	tablets	40mg/12.5mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5602	2013	08
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TANYDON HCT 80 mg/12.5 mg	tablets	80mg/12.5mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5603	2013	08
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TANYDON HCT 80 mg/25 mg	tablets	80mg/25mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5604	2013	08
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/HIDROCLOROTIAZIDA EGIS 40 mg/12.5 mg	tablets	40mg/12.5mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	5619	2013	10

COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/HIDROCLOROTIAZIDA EGIS 80 mg/12.5 mg	tablets	80mg/12.5mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	5620	2013	06
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA EGIS 80 mg/25 mg	tablets	80mg/25mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	5621	2013	06
COMBINATIONS (ZOFENOPRILUM+ HYDROCHLOROTHIAZIDUM)	ZOMEN PLUS 30 mg/12.5 mg	film-coated tablets	30mg/12.5mg	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	5678	2013	07
DESLORATADINUM	DESLORATADINA TEVA 0.5 mg/ml	oral solution	0.5mg/ml	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5551	2013	05
DICLOFENACUM	DICLOFENAC TIS 10 mg/g	gel	10mg/g	TIS FARMACEUTIC S.A.	ROMANIA	5589	2013	01
DOCETAXELUM	TOLNEXA 20 mg/ml	concentrate for solution for infusion	20mg/ml	KRKA, D.D., NOVO MESTO	SLOVENIA	5593	2013	03
DROTAVERINUM	NO-SPA 40 mg	tablets	40mg	SANOFI-AVENTIS ROMANIA S.R.L.	ROMANIA	5578	2013	02
DROTAVERINUM	NO-SPA FORTE 80 mg	tablets	80mg	SANOFI-AVENTIS ROMANIA S.R.L.	ROMANIA	5579	2013	05
DUTASTERIDUM	DUTASTERIDA TEVA 0.5 mg	soft capsules	0.5mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5557	2013	07
ENTACAPONUM	ENCAPIA 200 mg	film-coated tablets	200mg	MEDOCHEMIE LTD.	CYPRUS	5632	2013	09
ESCITALOPRAMUM	ESTAN 5 mg	film-coated tablets	5mg	MEDOCHEMIE LTD.	CYPRUS	5549	2013	14
ESCITALOPRAMUM	ESTAN 10 mg	film-coated tablets	10mg	MEDOCHEMIE LTD.	CYPRUS	5550	2013	14
ESCITALOPRAMUM	ESCITALOPRAM TORRENT 5 mg	film-coated tablets	5mg	TORRENT PHARMA SRL	ROMANIA	5534	2013	01
ESCITALOPRAMUM	ESCITALOPRAM TORRENT 10 mg	film-coated tablets	10mg	TORRENT PHARMA SRL	ROMANIA	5535	2013	01
ESCITALOPRAMUM	ESCITALOPRAM TORRENT 15 mg	film-coated tablets	15mg	TORRENT PHARMA SRL	ROMANIA	5536	2013	01
ESCITALOPRAMUM	ESCITALOPRAM TORRENT 20 mg	film-coated tablets	20mg	TORRENT PHARMA SRL	ROMANIA	5537	2013	01
ESOMEPRAZOLUM	REMESOLIN 20 mg	gastroresistant tablets	20mg	ACTAVIS GROUP PTC EHF.	ICELAND	5670	2013	26
ESOMEPRAZOLUM	REMESOLIN 40 mg	gastroresistant tablets	40mg	ACTAVIS GROUP PTC EHF.	ICELAND	5671	2013	26
ETONOGESTRELUM	NEXPLANON 68 mg	implant	68mg	N.V. ORGANON	HOLLAND	5510	2013	01
GABAPENTINUM	GRIMODIN 100 mg	capsules	100mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5666	2013	03
GABAPENTINUM	GRIMODIN 300 mg	capsules	300mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5667	2013	02
GABAPENTINUM	GRIMODIN 400 mg	capsules	400mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5668	2013	02

GALANTAMINUM	GALANTAMINA ZENTIVA 8 mg	prolonged-release capsules	8mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5554	2013	08
GALANTAMINUM	GALANTAMINA ZENTIVA 16 mg	prolonged-release capsules	16mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5555	2013	08
GALANTAMINUM	GALANTAMINA ZENTIVA 24 mg	prolonged-release capsules	24mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5556	2013	08
GLIMEPIRIDUM	GLIMEPIRIDA ACCORD 1 mg	tablets	1mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5540	2013	06
GLIMEPIRIDUM	GLIMEPIRIDA ACCORD 2 mg	tablets	2mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5541	2013	06
GLIMEPIRIDUM	GLIMEPIRIDA ACCORD 3 mg	tablets	3mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5542	2013	06
GLIMEPIRIDUM	GLIMEPIRIDA ACCORD 4mg	tablets	4mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5543	2013	06
GLUCOSAMINUM	SLIDEFLEX 1178mg	film-coated tablets	1178mg	BLUE BIO PHARMACEUTICALS LIMITED	IRELAND	5533	2013	11
HEPARINUM	HEPARINA POLIPHARMA	solution for injection	5000 IU/ml	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5673	2013	02
HYDROXYETHYL - AMIDON	TETRASPAN 60 mg/ml	solution for infusion	60mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	5519	2013	04
HYDROXYETHYL - AMIDON	TETRASPAN 100 mg/ml	solution for infusion	100mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	5520	2013	04
IBUPROFENUM	INFLANOR 200 mg	soft capsules	200mg	ALVOGEN IPCO S.AR.L.	LUXEMBOURG	5630	2013	04
IBUPROFENUM	INFLANOR 400 mg	soft capsules	400mg	ALVOGEN IPCO S.AR.L.	LUXEMBOURG	5631	2013	04
IBUPROFENUM	BRUFEN 400 mg	effervescent granules	400mg	ABBOTT SCANDINAVIA AB	SWEDEN	5648	2013	03
IMATINIBUM	IMATINIB RICHTER 100 mg	film-coated tablets	100mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5547	2013	07
IMATINIBUM	IMATINIB RICHTER 400 mg	film-coated tablets	400mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5548	2013	07
IMATINIBUM	MEAXIN 100 mg	film-coated tablets	100mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5538	2013	12
IMATINIBUM	MEAXIN 400 mg	film-coated tablets	400mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5539	2013	08
IMATINIBUM	EGITINID 100 mg	capsules	100mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5597	2013	05
IMATINIBUM	EGITINID 400 mg	capsules	400mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5598	2013	04
IMATINIBUM	IMATINIB BIOORGANICS 100 mg	film-coated tablets	100mg	BIOORGANICS BV	HOLLAND	5644	2013	28
IMATINIBUM	IMATINIB BIOORGANICS 400 mg	film-coated tablets	400mg	BIOORGANICS BV	HOLLAND	5645	2013	10

IMATINIBUM	IMATINIB SYNTHON 100 mg	film-coated tablets	100mg	SYNTHON BV	HOLLAND	5646	2013	28
IMATINIBUM	IMATINIB SYNTHON 400 mg	film-coated tablets	400mg	SYNTHON BV	HOLLAND	5647	2013	10
REGULAR IMMUNOGLOBULIN FOR INTRAVASCULAR USE	OCTAGAM 10%	solution for infusion	100 mg/ml	OCTAPHARMA (IP) LIMITED	GREAT BRITAIN	5651	2013	04
INTERFERONUM ALFA (HUIFN-ALFA -LE)	MULTIFERON 3 million IU	solution for injection in pre-filled syringe	3millions IU	SWEDISH ORPHAN BIOVITRUM INTERNATIONAL AB	SWEDEN	5641	2013	01
IRINOTECANUM	IRINOTECAN CSC 20 mg/ml	concentrate for solution for infusion	20mg/ml	CSC PHARMACEUTICALS HANDELS GMBH	AUSTRIA	5601	2013	04
ISOSORBIDI MONONITRAS	MONONITRON EP 60 mg	prolonged-release tablets	60mg	ZENTIVA S.A.	ROMANIA	5599	2013	02
KETOPROFENUM	KETOPROFEN TIS 25 mg/g	gel	25mg/g	TIS FARMACEUTIC S.A.	ROMANIA	5661	2013	01
LEVOCETIRIZINUM	LEVOCETIRIZINA SANDOZ 5 mg	film-coated tablets	5mg	SANDOZ S.R.L.	ROMANIA	5639	2013	36
LEVODOPUM+ BENSERAZIDUM	LEVODOPA/BENSERAZIDE TEVA 200mg/50mg	tablets	200mg/50mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5640	2013	06
LEVONORGESTRELUM	JAYDESS 13.5mg	intrauterine release system	13.5mg	BAYER PHARMA AG	GERMANY	5638	2013	02
LEVONORGESTRELUM	DONASERT 20 micrograms/24 hours	intrauterine release system	20micrograms/ 24 hours	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5672	2013	01
MEMANTINUM	MEMANTINA TEVA 10 mg	orodispersible tablets	10mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5527	2013	17
MEMANTINUM	MEMANTINA TEVA 20 mg	orodispersible tablets	20mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5528	2013	14
METHYLPREDNISOLONUM ACEPONAT	ADVANTAN MILK 1mg/g	cutaneous emulsion	1mg/g	INTENDIS GMBH	GERMANY	5507	2013	02
MONTELUKASTUM	ASTMASAN 4 mg	chewable tablets	4mg	SANDOZ SRL	ROMANIA	5567	2013	17
MONTELUKASTUM	ASTMASAN 5 mg	chewable tablets	5mg	SANDOZ SRL	ROMANIA	5568	2013	17
OCTOCOG ALFA	RECOMBINATE 250 IU/5 ml	powder and solvent for solution for injection	250 IU/5ml	BAXTER AG	AUSTRIA	5590	2013	02
OCTOCOG ALFA	RECOMBINATE 500 IU/5 ml	powder and solvent for solution for injection	500 IU/5ml	BAXTER AG	AUSTRIA	5591	2013	02
OCTOCOG ALFA	RECOMBINATE 1000 IU/5 ml	powder and solvent for solution for injection	1000 IU/5ml	BAXTER AG	AUSTRIA	5592	2013	02

OMEPRAZOLUM	OMEPRAZOL STADA 10 mg	gastroresistant capsules	10mg	STADA ARZNEIMITTEL AG	GERMANY	5605	2013	25
OMEPRAZOLUM	OMEPRAZOL STADA 20 mg	gastroresistant capsules	20mg	STADA ARZNEIMITTEL AG	GERMANY	5606	2013	25
OMEPRAZOLUM	OMEPRAZOL STADA 40 mg	gastroresistant capsules	40mg	STADA ARZNEIMITTEL AG	GERMANY	5607	2013	25
OMEPRAZOLUM	OMEPRAZOL ZENTIVA 10 mg	gastroresistant capsules	10mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5627	2013	12
OMEPRAZOLUM	OMEPRAZOL ZENTIVA 20 mg	gastroresistant capsules	20mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5628	2013	11
OMEPRAZOLUM	OMEPRAZOL ZENTIVA 40 mg	gastroresistant capsules	40mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5629	2013	10
ORLISTATUM	BODIGO 120 mg	capsules	120mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5571	2013	03
OXALIPLATINUM	OXALIPLATINA TEVA 5 mg/ml	concentrate for solution for infusion	5mg/ml	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5650	2013	04
OXALIPLATINUM	ELOXATIN 5mg/ml	concentrate for solution for infusion	5mg/ml	SANOFI-AVENTIS FRANCE	FRANCE	5600	2013	03
OXALIPLATINUM	OXALIPLATIN KABI 5 mg/ml	powder for solution for infusion	5mg/ml	FRESENIUS KABI ONCOLOGY PLC.	GREAT BRITAIN	5613	2013	02
PANTOPRAZOLUM	PIADOR 20 mg	gastroresistant tablets	20mg	ANTIBIOTICE SA	ROMANIA	5576	2013	01
PANTOPRAZOLUM	PANTOPRAZOL ATB 40 mg	gastroresistant tablets	40mg	ANTIBIOTICE SA	ROMANIA	5577	2013	03
PARACETAMOLUM	PARACETAMOL SANDOZ 500 mg	tablets	500mg	SANDOZ SRL	ROMANIA	5584	2013	04
PARACETAMOLUM	PARACETAMOL SANDOZ 1000 mg	tablets	1000mg	SANDOZ SRL	ROMANIA	5585	2013	02
PARACETAMOLUM	PARACETAMOL ARENA 120 mg/5 ml	oral solution for children	120mg/5ml	ARENA GROUP S.A.	ROMANIA	5622	2013	01
PHENYLEPHRINUM	BIOFLU NAZAL 2.5 mg/ml	nasal drops, solution	2.5mg/ml	BIOFARM SA	ROMANIA	5560	2013	01
PHENYLEPHRINUM	BIOFLU NAZAL 5 mg/ml	nasal spray, solution	5mg/ml	BIOFARM SA	ROMANIA	5561	2013	01
NITROGEN PROTOXIDE	NIONTIX 100%	medicinal gas, liquefied		LINDE GAZ ROMANIA SRL	ROMANIA	5660	2013	10
NITROGEN PROTOXIDE	NITROGEN PROTOXIDE YES 100%	medicinal gas, liquefied	100%	YES PHARMACEUTICALS DEVELOPMENT SERVICES GMBH	GERMANY	5614	2013	06
PYRITINOLUM	ENCEPHABOL 80.5 mg/5 ml	oral suspension	80.5mg/5ml	MERCK KGAA	GERMANY	5552	2013	01
QUETIAPINUM	KVENTIAX 150 mg	film-coated tablets	150mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5524	2013	13
QUETIAPINUM	KVENTIAX 200 mg	film-coated	200mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5525	2013	11

		tablets						
QUETIAPINUM	KVENTIAX 25 mg	film-coated tablets	25mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5522	2013	11
QUETIAPINUM	KVENTIAX 100 mg	film-coated tablets	100mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5523	2013	11
QUETIAPINUM	KVENTIAX 300 mg	film-coated tablets	300mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5526	2013	13
QUININE HYDROCHLORIDUM	CINKONA	solution for injection	300mg/2ml	CN UNIFARM S.A.	ROMANIA	15	2013	01
RAMIPRILUM	RAMIPRIL ACCORD 1.25 mg	capsules	1.25mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5511	2013	16
RAMIPRILUM	RAMIPRIL ACCORD 2.5 mg	capsules	2.5mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5512	2013	16
RAMIPRILUM	RAMIPRIL ACCORD 5 mg	capsules	5mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5513	2013	16
RAMIPRILUM	RAMIPRIL ACCORD 10 mg	capsules	10mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5514	2013	16
RIVASTIGMINUM	WERENDI 4.6 mg/24 h	transdermal patch	4.6mg/24h	ACINO AG	GERMANY	5634	2013	04
RIVASTIGMINUM	WERENDI 9.5mg/24 h	transdermal patch	9.5mg/24h	ACINO AG	GERMANY	5635	2013	04
RIVASTIGMINUM	RIVASTIGMIN ACINO 4.6 mg/24 h	transdermal patch	4.6mg/24h	ACINO AG	GERMANY	5636	2013	04
RIVASTIGMINUM	RIVASTIGMIN ACINO 9.5mg/24 h	transdermal patch	9.5mg/24h	ACINO AG	GERMANY	5637	2013	04
ROSUVASTATINUM	CRESTOR 20 mg	film-coated tablets	20mg	ASTRAZENECA UK LIMITED	GREAT BRITAIN	5610	2013	01
ROSUVASTATINUM	CRESTOR 10 mg	film-coated tablets	10mg	ASTRAZENECA UK LIMITED	GREAT BRITAIN	5609	2013	01
ROSUVASTATINUM	CRESTOR 40 mg	film-coated tablets	40mg	ASTRAZENECA UK LIMITED	GREAT BRITAIN	5611	2013	01
ROSUVASTATINUM	CRESTOR 5 mg	film-coated tablets	5mg	ASTRAZENECA UK LIMITED	GREAT BRITAIN	5608	2013	01
ROSUVASTATINUM	ROSUVASTATINA TERAPIA 5 mg	film-coated tablets	5mg	TERAPIA SA	ROMANIA	5623	2013	26
ROSUVASTATINUM	ROSUVASTATINA TERAPIA 10 mg	film-coated tablets	10mg	TERAPIA SA	ROMANIA	5624	2013	26
ROSUVASTATINUM	ROSUVASTATINA TERAPIA 20 mg	film-coated tablets	20mg	TERAPIA SA	ROMANIA	5625	2013	26
ROSUVASTATINUM	ROSUVASTATINA TERAPIA 40 mg	film-coated tablets	40mg	TERAPIA SA	ROMANIA	5626	2013	26
SIMVASTATINUM	SIMVASTATINA TERAPIA	film-coated	10mg	TERAPIA SA	ROMANIA	5594	2013	11

	10 mg	tablets						
SIMVASTATINUM	SIMVASTATINA TERAPIA 20 mg	film-coated tablets	20mg	TERAPIA SA	ROMANIA	5595	2013	11
SIMVASTATINUM	SIMVASTATINA TERAPIA 40 mg	film-coated tablets	40mg	TERAPIA SA	ROMANIA	5596	2013	11
TERBINAFINUM	TERBINAFINA SCHOLL 10 mg/g	cream	10mg/g	RECKITT BENCKISER HEALTHCARE INTERNATIONAL LTD.	GREAT BRITAIN	5643	2013	02
TETRYZOLINUM	VISINE CLASSIC 0.5 mg/ml	eye drops, solution	0.5mg/ml	MCNEIL PRODUCTS LIMITED C/O JOHNSON & JOHNSON	GREAT BRITAIN	5653	2013	01
TIOTROPIUM	SPIRIVA RESPIMAT 2.5 micrograms	solution for inhalation	2.5 micrograms	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	5642	2013	04
TOPIRAMATUM	ZIDOXER 25 mg	film-coated tablets	25mg	LABORMED PHARMA S.A.	ROMANIA	5515	2013	03
TOPIRAMATUM	ZIDOXER 50 mg	film-coated tablets	50mg	LABORMED PHARMA S.A.	ROMANIA	5516	2013	03
TOPIRAMATUM	ZIDOXER 100 mg	film-coated tablets	100mg	LABORMED PHARMA S.A.	ROMANIA	5517	2013	03
TOPIRAMATUM	ZIDOXER 200 mg	film-coated tablets	200mg	LABORMED PHARMA S.A.	ROMANIA	5518	2013	03
TOPIRAMATUM	TOPILEX 25 mg	film-coated tablets	25mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	5529	2013	04
TOPIRAMATUM	TOPILEX 50 mg	film-coated tablets	50mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	5530	2013	04
TOPIRAMATUM	TOPILEX 100 mg	film-coated tablets	100mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	5531	2013	04
TOPIRAMATUM	TOPILEX 200 mg	film-coated tablets	200mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	5532	2013	04
VALSARTANUM	VALSACOR 320 mg	film-coated tablets	320mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5659	2013	11
VANCOMYCINUM	VANCOMICINA FARMAPLUS 500 mg	powder and solvent for concentrate for solution for infusion	500mg	FARMAPLUS AS	NORWAY	5563	2013	01
VANCOMYCINUM	VANCOMICINA FARMAPLUS 1000 mg	powder and solvent for concentrate for solution for infusion	1000mg	FARMAPLUS AS	NORWAY	5564	2013	01

EMA centrally authorised medicinal products for which a marketing price was established in Romania during the 2nd quarter of 2013

INN	Invented name	Pharmaceutical form	Strength	Manufacturer	Country	MA number		
IMATINIBUM	IMATINIB ACTAVIS 100 mg	capsules	100mg	ACTAVIS GROUP PTC EHF	ICELAND	825	2013	01
IMATINIBUM	IMATINIB ACTAVIS 100 mg	capsules	100mg	ACTAVIS GROUP PTC EHF	ICELAND	825	2013	02
IMATINIBUM	IMATINIB ACTAVIS 100 mg	capsules	100mg	ACTAVIS GROUP PTC EHF	ICELAND	825	2013	03
IMATINIBUM	IMATINIB ACTAVIS 100 mg	capsules	100mg	ACTAVIS GROUP PTC EHF	ICELAND	825	2013	04
IMATINIBUM	IMATINIB ACTAVIS 100 mg	capsules	100mg	ACTAVIS GROUP PTC EHF	ICELAND	825	2013	05
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	01
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	02
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	03
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	04
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	05
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	06
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	07
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	08
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	09
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	10
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	11
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	12
MEMANTINUM	MARUXA	film-coated tablets	10mg	KRKA D.D.	SLOVENIA	820	2013	13
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	03
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	04
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	05
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	06
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	07
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	08
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	09
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	10
MEMANTINUM	NEMDATINE 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	824	2013	19
SILDENAFILUM	VIAGRA 50 mg	orodispersible tablets	50mg	PFIZER LIMITED	GREAT BRITAIN	98	2013	20
SILDENAFILUM	VIAGRA 50 mg	orodispersible tablets	50mg	PFIZER LIMITED	GREAT BRITAIN	98	2013	21
SILDENAFILUM	VIAGRA 50 mg	orodispersible tablets	50mg	PFIZER LIMITED	GREAT BRITAIN	98	2013	22
SILDENAFILUM	VIAGRA 50 mg	orodispersible tablets	50mg	PFIZER LIMITED	GREAT BRITAIN	98	2013	23
VACCIN COMBINAT DTPA-HBV-IPV-HIB	HEXACIMA	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	828	2013	02

VACCIN COMBINAT DTPA-HBV-IPV-HIB	HEXACIMA	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	828	2013	03
VACCIN COMBINAT DTPA-HBV-IPV-HIB	HEXACIMA	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	828	2013	04
VACCIN COMBINAT DTPA-HBV-IPV-HIB	HEXACIMA	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	828	2013	05
VACCIN COMBINAT DTPA-HBV-IPV-HIB	HEXACIMA	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	828	2013	06
VACCIN COMBINAT DTPA-HBV-IPV-HIB	HEXACIMA	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	828	2013	07