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National Agency for Medicines and Medical Devices

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MINISTRY OF HEALTH

ORDER no. 1359 of 13 November 2013 on amendment of Order of the Minister of Health No. 716/2009 on approval fees of the National Agency for Medicines and Medical Devices and fee for marketing authorisation maintenance

PUBLISHED IN: THE OFFICIAL GAZETTE OF ROMANIA no. 708 of 19 November 2013

On seeing the Approval report No. E.N. 11.463/2013 of the Pharmaceutical and Medical Devices Directorate,

Taking into account provisions of Article 10 d) of Government Decision no. 734/2010 on the set up, organisation and operation of the National Agency for Medicines and Medical Devices, as amended,

based on Article 7(4) of Government Decision No. 144/2010 on the organisation and operation of the Ministry of Health, as amended,

the minister of health hereby issues the following order:

Article 1. – Order of the Minister of Health no. 716/2009 on approval of fees of the National Agency for Medicines and Medical Devices and marketing authorisation maintenance fee, published in the Official Gazette of Romania, Part I, no. 422 of 19 June 2009, as amended, is hereby amended as follows:

1. Article 2 is amended and reads as follows:

"Article 2 - The marketing authorisation maintenance fee is 230 euro/year and shall be paid to the National Agency for Medicines and Medical Devices every year before the 31 December of the following year."

2. A new article, 4^1, is introduced after Article 4, which reads as follows:

"Article 4^1 – The administrative procedure for the handling of fees received by the National Agency for Medicines and Medical Devices in case of discontinuation of the procedure for clinical trial evaluation, authorisation and amendment is as follows:

a) For notification by applicants on withdrawal of their application for authorisation of a clinical trial on a medicinal product for human use after payment of fee for clinical trial authorisation procedure, the trial authorisation fee paid by applicants according to Annex 3 provisions shall be managed as follows:

(i) For applications for discontinuation of the authorisation procedure concerning a clinical trial on a medicinal product for human use submitted prior to validation of the application, depending on applicant’s request, the respective fee may be returned/directed for payment of a different fee due to the National Agency for Medicines and Medical Devices by the respective applicant;

(ii) For applications for discontinuation of the authorisation procedure concerning a clinical trial on a medicinal product for human use submitted after validation of the application for authorisation, but no later than 25 calendar days as of procedure onset, depending on applicant's request, 90% of the fee may be returned/ directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

(iii) For applications for discontinuation of the authorisation procedure concerning a clinical trial on a medicinal product for human use submitted after day 25 as of procedure onset, the fee paid shall be retained by the National Agency for Medicines and Medical Devices and may no longer be returned;

b) If the application for authorisation of a clinical trial on a medicinal product for human use is rejected following the validation procedure, 90% of the fee may be returned/directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

Notification by applicants on withdrawal of the application for approval of a substantial amendment to a clinical trial on a medicinal product for human use after payment of fees for the procedure for approval of a clinical trial amendment, the fee for evaluation of the clinical trial amendment, as paid by applicants according to Annex 3 provisions, shall be managed as follows:

(i) For applications for discontinuation of the clinical trial amendment approval procedure submitted prior to validation of the application, depending on applicant's request, the respective amount may be returned/directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

(ii) For applications for discontinuation of the clinical trial amendment approval procedure submitted after validation of the application, but no later than 15 calendar days as of procedure onset, 90% of the fee may be returned/ directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

(iii) For applications for discontinuation of the authorisation procedure to the National Agency for Medicines and Medical Devices submitted after day 15 as of procedure onset, the amount paid shall be retained by the National Agency for Medicines and Medical Devices and may not be returned;

d) If the application for authorisation of a clinical trial on a medicinal product for human use is rejected following the validation procedure, depending on applicant's request , 90% of the fee may be returned/directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;"

3. Letter C of Annex 3 is amended and reads as follows:

"C.	Authorisation of clinical trials, approval of substantial amendments and approval of advertising material

28.	Authorisation of clinical trials for investigational medicinal products not authorised on a global scale (new substances). Phases I - III	
29.	Authorisation of clinical trials for investigational medicinal products not authorised in Romania, but authorised in other countries or having a marketing authorisation (MA), (known substances), not used however in the respective clinical trial in accordance with conditions mentioned in the Summary of Product Characteristics (SmPC) in force (as regards indications, dose, route of administration, method of treatment, population group). Phases I - IV	1.000
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NOTE:
Fees established under section 33 and 34 refer to approvals valid 6 months as of issuing date."

4. A new letter, F, is introduced after letter E in Annex 3, which shall read as follows:

"F.	Dossier assessment for scientific opinion, of amendment of the scientific opinion on ancillary active substances	ancillary active substances incorporated in a medical device

55.	Scientific opinion on ancillary active substances incorporated in a medical device for substances not previously assessed by the National Agency for Medicines and Medical Devices (NAMMD)	2.660
56.	Scientific opinion on ancillary active substances incorporated in a medical device for substances not previously assessed by the NAMMD with a different manufacturer	1.330
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ARTICLE II
This order is to be published in the Official Gazette of Romania, Part I.

Minister of health,
Gheorghe-Eugen Nicolăescu

Bucharest, 13 November 2013.
No. 1.359.

DECISION

no. 23/11.10.2013

on approval of the manner of National Agency for Medicines and Medical Devices handling of applications by a notified body for NAMMD scientific opinion on the quality and safety of an ancillary medicinal substance incorporated, as an integral part, into a medical device

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, reunited on summons of the NAMMD President in the ordinary meeting of 11.10.2013, in accordance with Article 12 (5) of Emergency Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Article 1. – The manner of National Agency for Medicines and Medical Devices handling of applications by a notified body for NAMMD scientific opinion on the quality and safety of an ancillary medicinal substance incorporated, as an integral part, into a medical device (hereinafter "ancillary medicinal substance") is approved, in accordance with the provisions of the European Guideline on borderline products, included in the Annex,, which is integral part of this Decision.

Article 2. - (1) Based on Article 7.4.2. of Annex 1 to Government Decision no. 54/2009 on the conditions for the entry of medical devices on the market (hereinafter "Government Decision no. 54/2009"), the NAMMD hereby responds to applications by a notified body relating to grant of a scientific opinion concerning the quality and safety of an ancillary medicinal substance and of the established clinical risk-benefit balance of incorporation of the substance into the device. When issuing the scientific opinion, the NAMMD considers the manufacturing process and data related to the incorporation of the substance into the device, as determined by the notified body.

(2) The NAMMD scientific opinion shall be established within 210 days following receipt of a valid documentation, according to Article 4.3 of Annex 2 to Government Decision no. 54/2009. This period excludes clock stops.

(3) Should changes occur to the ancillary medicinal substance incorporated as an integral part into a medical device, particularly if related to substance manufacturing process, the NAMMD responds to applications of a notified body relating to grant of a scientific opinion concerning the quality and safety of an ancillary medicinal substance, according to Article 7.4.4. of Annex 1 to Government Decision no. 54/2009. The NAMMD takes into account the data referring to the usefulness of the incorporation of a substance into a device, as determined by the notified body, to ascertain that respective changes do not have a negative impact upon the established risk-benefit balance concerning the incorporation of the substance into the medical device.

(4) If, following initial consultation, the NAMMD has obtained information about the ancillary medicinal substance, which may have an impact upon the risk-benefit balance concerning incorporation of the substance into the medical device, according to Article 7.4.5. of Annex 1 to Government Decision no. 54/2009, the NAMMD informs the notified body in this respect, by updating the initial scientific opinion, regardless of the potential impact of the respective information upon the risk-benefit balance of incorporation of the ancillary medicinal substance into the medical device.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

Guideline
on borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

This Guideline is an adapted translation of the MEDDEV 2.1/3 rev. 3 Guideline of the European Commission (EC) on borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative.

This Guideline is part of a set of Guidelines relating to questions of application of EC Directives on medical devices, namely Directive 90/385/EEC of the Council on Active implantable medical devices and Directive 93/42/EEC of the Council on Medical devices, also including their amendment through Directive 2007/47/EC in force as of 21 March 2010.
All these European Directives are transposed into national legislation through Government Decisions (GD) no. 54/2009 on marketing conditions for medical devices (hereinafter Government Decision no. 54/2009) and Government Decision no. 55/2009 on active implantable medical devices (hereinafter Government Decision no. 55/2009). It has been elaborated by an expert group including experts from Member States' Competent Authorities, the Commission' services, as well as industry trade associations. It is therefore intended that the document provide useful guidance, which should assist common positions to be taken throughout the European Union. Due to the participation of the aforementioned interested parties and of experts from Competent Authorities, it is anticipated that these guidelines will be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions.
The present guideline provides non-exhaustive lists of examples of medical devices, accessories to medical devices and medicinal products. Further examples may be found in the manual on borderline and classification in the Community Regulatory framework for medical devices, published on the European Commission website[1]. Particular attention should be given to borderline products (products between medical devices and herbal medicinal products.

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1 http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index_en.htm

A. BORDERLINE PRODUCTS: MEDICAL DEVICES / MEDICINAL PRODUCTS

A.1 Introduction

Establishment of the line between Directive 93/42/EEC on medical devices (MD) and Directive 90/385/EEC on active implantable medical devices (AIMD), transposed into national legislation through Government Decision no. 54/2009 and Government Decision no. 55/2009, and by Directive 2001/83/EC on the medical device (MD), transposed into national legislation through Law 95/2006 on healthcare reform, Title XVII - The medicinal product (hereinafter Law 95/2006), is essential in view of accurate implementation of these Directives and accurate enforcement of national legislation.

Thus, there are several provisions in Government Decision no. 54/2009, Government Decision no. 55/2009 and Law 95/2006 referring to the establishment of a line between the two regulations.
However, it was acknowledged that the subject needs further explanation and exemplification through practical Guidelines.

A.2 General principles

Borderline cases are considered to be those cases where it is not clear from the outset whether a given product falls under the provisions of Government Decision no. 54/2009, Government Decision no. 55/2009 or Law 95/2006.
In order to fall under the regulatory scope of Government Decision no. 54/2009, a medicinal product:

- must fulfil the definition of a medical device, and
- must also not be excluded from the scope of Government Decision no. 54/2009.

It is therefore necessary to examine both prerequisites.
As a general rule, a relevant product is regulated either by Government Decision no. 54/2009 or Law 95/2006. The conformity assessment procedure or the marketing authorization procedure to be followed prior to placing a given product on the market will therefore be governed either by Government Decision no. 54/2009 or by Law 95/2006. The procedures of both regulatory acts do not apply cumulatively.
For defined features, however, some cross-references are made within one regime to specific provisions of the other regime.
The definitions of medical device and medicinal product are reproduced here for reference:

A.2.1 Medical device

A.2.1.1 Definition of medical device

Article 2 (1) point 1 of Government Decision no. 54/2009 MDD defines a medical device as:
"Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
a) diagnosis, prevention, monitoring, treatment or alleviation of disease,
b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
c) investigation, replacement or modification of the anatomy or of a physiological process,
d) control of conception,
and, which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but, which may be assisted in its function by such means;"
In deciding whether a product falls under the Government Decision no. 54/2009, particular account will be taken of the principal mode of action of the product.
Typically, the medical device function is achieved by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions).
The principal intended action of a medical device may be deduced from the scientific data regarding mechanism of action and the manufacturer's labelling and claims.
Although the manufacturer's claims are important, it is not possible to place the product in one or other category in contradiction with current scientific data. Manufacturers may be required to justify scientifically their rationale for the qualification of their product.
The following definitions for pharmacological, immunological or metabolic means are intended only to provide guidance as to the meaning of these terms.

“Pharmacological means” is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or, which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.
“Immunological means” is understood as an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.
“Metabolic means” is understood as an action, which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function.

Note: The fact that a product is, or is not, itself metabolised does not imply that it achieves, or does not achieve, its principal intended action by metabolic means.

Medical devices may be assisted in their function by pharmacological, immunological or metabolic means, but as soon as these means are not ancillary with respect to the principal intended action of a product, the product no longer fulfils the definition of a medical device. The claims made for a product, in accordance with its method of action may, in this context, represent an important factor for its qualification as a medical device.
This principle can be, for example, illustrated by bone cements. Plain bone cement without antibiotics is a medical device since it achieves its principal intended action (the fixation of prosthesis) by physical means. Bone cements containing antibiotics, where the principal intended action remains fixation of prosthesis, are also medical devices. In this case the action of the antibiotic, which is to reduce the possibility of infection being introduced during surgery, is clearly ancillary. If however the principal intended action is to deliver the antibiotic, the product no longer fulfils the definition of a medical device.

A.2.1.2 Examples of medical devices
The following examples should, in view of their principal intended action, generally be considered as medical devices subject to relevant criteria being met; the function of some of the devices indicated in these examples may be assisted by the presence of medicinal substances where such substances have an ancillary action to that of the device.
- Bone cements,
- Dental filling materials,
- Materials for sealing, approximation, or adhesion of tissues (e.g. cyanoacrylates, fibrin-based adhesives not of human origin)
- Resorbable materials used in osteo-synthesis (e.g. pins or bone screws manufactured using polylactic acid),
- Sutures, absorbable sutures,
- Soft and hard tissue scaffolds and fillers (e.g. calcium phosphate, bioglass),
- Bone void fillers intended for the repair of bone defects where the primary action of the device is a physical means or matrix, which provides a volume and a scaffold for osteoconduction,
- Intrauterine devices, except products such as intrauterine contraceptives whose primary purpose is to release progestogens,
- Blood bags,
- Systems intended to preserve and treat blood,

Note: Systems intended for the collection, storage and preservation of blood or blood components and as an ancillary function, the treatment of blood or blood components where this effect is achieved outside the human body, are classified as devices provided that any residual material is not intended to achieve its effect when the blood or cells are reintroduced into the body, e.g. systems incorporating chemicals activated by light to reduce the viral load where the quantity of chemical remaining has no intended effect when transfused.
This note does not cover substances introduced into an extracorporeal circuit.
- Gases and liquids for ocular endotamponades,
- Cell separators, including those incorporating fixed antibodies for cell binding,
- Wound dressings, which may be in the form of liquids, gels and pastes, etc. (e.g. hydrocolloid, hydrogel),
- Haemostatic products, for example patches, plugs and powders where the haemostatic effect results from the product's physical characteristics, or is due to the surface properties of the material. This includes products such as calcium alginate or oxidised cellulose where adhesion of platelets to the surface triggers platelet adhesion and aggregation
- Concentrates for haemodialysis,
- Pressure reducing valves and regulators,
- Irrigation solutions intended for mechanical rinsing (e.g. bladder irrigation solution, ocular irrigation solution),
Note:
If the solution contains a medicinal substance such as chlorhexidine where the principal intended purpose is to provide a local antimicrobial effect, it will be a medicinal product. Solutions incorporating substances for other purposes, e.g. antimicrobial agent for the preservation of the solution remain a medical device.
- Devices such as catheters, guidewires and stents containing or incorporating radio isotopes where the radioactive isotope as such is not released into the body, used for example in cardiology for the prevention of restenosis.

A.2.1.3 Definition of an accessory of a medical device
Article 2. – (1) point 2 of Government Decision no. 54/2009 defines an accessory of a medical device as follows:
”Accessory” means an article, which whilst not being a (medical) device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device.

A.2.1.4 Example of accessories of medical devices
The following products fall under the definition of "accessory".
- Contact lens care products (disinfecting, cleaning, rinsing and hydrating solutions including those, which aid the insertion and/or wearing of contact lenses without therapeutic claim),
- Disinfectants specifically intended for use with medical devices (e.g. endoscopes),
Note:
Multipurpose disinfectants or sterilisation agents are not covered by MDD; they are covered by the directive on biocides.
- Lubricants specifically intended for use together with medical devices (e.g. for gloves, endoscopes, condoms),
- Skin barrier powders and pastes or other skin care products specifically intended for use together with ostomy bags,
- Gases used to drive cryoprobes and surgical tools.

A.2.2. Medicinal product

A.2.2.1 Definition of a medicinal product

Article 695 point 1 of Law 95/2006 defines a medicinal product as follows:

"(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."

This definition comprises two limbs, one relating to presentation and the other to function. A product constitutes a medicinal product if it is covered by one or other or both of those limbs. Due to the definition of medicinal product, substances used in or administered to human beings to make a medical diagnosis, even if they fulfil their function by physical or chemical means and not by pharmacological, immunological or metabolic means in the sense as described above are considered to be medicinal products.

The definition of medicinal product must be applied case by case and must be read in accordance with the case law of the European Court of Justice.

Article 696(2) of Law 95/2006 provides that "in cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other national legislation the provisions of this Title will apply".

The wording of this Article shows that it only applies if, after a case-by-case assessment, taking in consideration all the characteristics of a product, the product in question may fall within the definition of both, medical device and medicinal product. In such a case, the provisions of Law 95/2006 apply. Government Decision no. 54/2009 on medical devices and Law 95/2006 cannot be applied cumulatively.

In deciding whether a product falls under the scope of Law 95/2006 or the scope of Government Decision no. 54/2009, particular account shall be taken of the principal mode of action of the product.

A.2.2.2 Examples of medicinal products:

The following examples should generally be considered as medicinal products subject to relevant criteria being met:

- Spermicidal preparations,
- Gases intended to be used in anaesthesia and inhalation therapy, (e.g. oxygen, medical air supplied in containers) including their primary containers,

Note: These gases are also used in minimal access surgery. However, a product intended exclusively for minimal access surgery would be a medical device.

- Topical disinfectants (antiseptics) for use on patients,
- Haemostatic and sealant products interacting with the coagulation cascade through a pharmacological process, i.e. where the primary mode of action is not mechanical (such as certain collagens, which have a molecular structure capable of surface independent demonstrated interaction with platelet receptors and therefore achieve platelet adhesion through a pharmacological process).
- Water for injections, IV fluids and other fluids for drug injection and plasma volume expanders,
- In vivo diagnostic agents, e.g. x-ray contrast media, NMR enhancing agents, fluorescent ophthalmic strips for diagnostic purposes, carrier solutions to stabilize micro-bubbles for ultrasound imaging, radiopharmaceuticals for diagnostic use
- Gases for in-vivo diagnostic purposes, including lung function, tests, e.g. carbon dioxide for vascular diagnostic purposes,

- Antacids,
- Fluoride dental preparations,

Note:

Dental preparations with a typical device mode of action, such as cements or varnishes incorporating fluoride, are medical devices, where the fluoride is of ancillary action to that of the device.

- Solutions administered in-vivo to the local circulation for the cooling of organs during surgery,

B. DRUG-DELIVERY PRODUCTS AND MEDICAL DEVICES INCORPORATING AS AN INTEGRAL PART, AN ANCILLARY MEDICINAL SUBSTANCE OR AN ANCILLARY HUMAN BLOOD DERIVATIVE

B1. Introduction

The term "Competent Authority" is used in this document to represent a competent body responsible for the evaluation of applications for medicinal products for human use being placed on the market (i.e. national competent authority designated by the Member States or the European Medicines Agency (EMA)).

This guideline aims to provide interested parties with appropriate guidance on procedural aspects to facilitate the consultation procedure to a Competent Authority by notified bodies on:

• Medicinal products, within the meaning of Article 695 (1) of Law 95/2006 incorporated, as an integral part, in a medical device and, which are liable to act upon the body with action ancillary to that of the device.

• Medicinal product constituents or medicinal products derived from human blood or human plasma, within the meaning of Article 695 (1) of Law 95/2006 incorporated, as an integral part, in a medical device and, which are liable to act upon the human body with action ancillary to that of the device.

These substances are referred to hereinafter respectively as ‘ancillary medicinal substances’ and as ‘ancillary human blood derivatives’.

B.2 Drug-delivery products regulated as medicinal products

This category involves a device that is intended to administer a medicinal product in the case where the device and the medicinal product form a single integral product,, which is intended exclusively for use in the given combination and, which is not reusable.

According to the Government Decision no. 54/2009, this single product is governed by Law 95/2006 but the relevant essential requirements of Annex I of Government Decision no. 54/2009 (Articles 1-3) shall apply as far as the safety and performance-related device features are concerned.

B.2.1 Examples of drug-delivery products regulated as medicinal products

- Prefilled syringes,
- Aerosols containing a medicinal product,
- Nebulizers precharged with a specific medicinal product,
- Patches for transdermal drug delivery,
- Implants containing medicinal products in a polymer matrix whose primary purpose is to release the medicinal product, for example plastic beads containing antibiotic for treating bone infections, or a matrix to release osteoinductive proteins into the surrounding bone,
- Intrauterine contraceptives whose primary purpose is to release progestogens,
- Single-use disposable iontophoresis devices incorporating a medicinal product,

- Wound treatment products comprising a matrix whose primary purpose is the administration of medicinal products, for example wound dressings containing an antimicrobial agent where the primary action of the dressing is to administer the agent to the wound for the purpose of controlling infection,
- Temporary root canal fillers incorporating medicinal products, whose primary purpose is to deliver the medicinal product.

B.3 Drug-delivery products regulated as medical devices

This category concerns a device that is intended to administer a medicinal product within the meaning of Law 95/2006.

In this case, that device is governed by Government Decision no. 54/2009 without prejudice to the provisions of Law 95/2006 with regard to the medicinal product (Article 3 (1) of Government Decision no. 54/2009).

B.3.1 Examples of drug-delivery products regulated as medical devices

- Drug delivery pump,
- Implantable infusion pump,
- Iontophoresis device,
- Nebulizer,
- Syringe, jet injector,
- Spacer devices for use with metered dose inhalers,
- Port systems.

B.4 Medical devices incorporating, as an integral part, an ancillary medicinal substance

Government Decision no. 54/2009 also specifies the case of medical devices incorporating, as an integral part, a medicinal substance with ancillary action (Article 4 (1) of Government Decision no. 54/2009).

This case relates to a device that incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 695 of Law 95/2006 and, which is liable to act upon the body with action that is ancillary to that of the device.

That device shall be assessed and authorised in accordance with Government Decision no. 54/2009.

Note: Any substance incorporated in the device must meet the three following conditions:
- The substance, if used separately, may be considered to be a medicinal product;
- The substance is liable to act upon the human body;
- The action of this substance is ancillary to that of the device.

A medical device incorporates a medicinal substance *as an integral part*, within the meaning of Article 4 (1) of Government Decision no. 54/2009, if and only if the device and the substance are physically or chemically combined <u>at the time of administration</u> (i.e. use, implantation, application etc.) to the patient.

B.4.1 Examples of medical devices incorporating, as an integral part, an ancillary medicinal substance

- Catheters coated with heparin or an antibiotic agent,
- Bone cements containing antibiotic,
- Root canal fillers, which incorporate medicinal substances with ancillary action,
- Soft tissue fillers incorporating local anaesthetics,
- Bone void filler intended for the repair of bone defects where the primary action of the device is a physical means or matrix,, which provides a volume and a scaffold for osteoconduction and where an additional medicinal substance is incorporated to assist and complement the

action of the matrix by enhancing the growth of bone cells. In such cases, the ancillary nature would be determined by the performance of the matrix on its own and the extent of the enhancement of growth due to the presence of the substance. With reference to the overall purpose of the product, where the medicinal substance has such an effect that its ancillary nature cannot be clearly established, the product should be considered in accordance with the concept of a drug delivery system,
- Condoms coated with spermicides,
- Electrodes with steroid-coated tip,
- Wound dressings, surgical or barrier drapes (including tulle dressings) with antimicrobial agent,
- Intrauterine contraceptives containing copper or silver.
- Ophthalmic irrigation solutions principally intended for irrigation, which contain components, which support the metabolism of the endothelial cells of the cornea
- Drug eluting coronary stents
It should be noted that the mere coating of a product with a chemical does not imply that the chemical is a medicinal substance. For example, hydroxyapatite, frequently used as coating for orthopaedic and dental implants, is not considered a medicinal substance. Other coatings, which are in use and, which are not medicinal substances are hydromers and phosphorylcholines.

B.5 Medical devices incorporating, as an integral part, an ancillary human blood derivative

The same rule applies when a medical device or an active implantable medical device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma within the meaning of Article 695 of Law 95/2006 and, which is liable to act upon the human body with ancillary action to that of the device.
Such a device shall be assessed and authorised in accordance with Government Decision no. 54/2009.

C. CONSULTATION PROCEDURE ON DEVICES INCORPORATING, AS AN INTEGRAL PART, AN ANCILLARY MEDICINAL SUBSTANCES OR AN ANCILLARY HUMAN BLOOD DERIVATIVE

C.1 Purpose of the consultation procedure on devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

For devices incorporating, as an integral part, an ancillary medicinal substance, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the EMA acting particularly through its committee in accordance with Regulation (EC) No 726/2004 on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device (Article 7.4.2. of Annex 1 to Government Decision no. 54/2009).
For devices incorporating, as an integral part, an ancillary human blood derivative, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device, seek a scientific opinion from the EMA, acting particularly through its committee, on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device (Article 7.4.3. of Annex 1 to Government Decision no. 54/2009).

Note:
The consultation process is only applicable for devices incorporating a substance, which is liable to act upon the body with action ancillary to that of the device.
Therefore, for example, a contact lens solution containing an antiseptic agent, which does not act upon the body with an action ancillary to that of the device but, which aims to preserve the solution does not fall under this procedure.
In accordance with Article 7.4.1. of Annex I to Government Decision no. 54/2009, the quality, safety and usefulness of an ancillary medicinal substance incorporated in a medical device must be verified by analogy with the methods specified in Order of the Minister of Public Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical Rules and protocols in respect of the testing of medicinal products. This is further elaborated in section C.3.
The assessment of "usefulness" and "safety" has a particular implication when applied to a medicinal substance, which has an ancillary action within a device/medicinal product combination.
The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action, and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.
By means of the consultation process, the Competent Authority may make available relevant information concerning risks related to the use of the substance (e.g. resulting from pharmacovigilance).

C. 2 Notified Body actions to initiate consultation process on medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

a) The Notified Body should ensure that data supplied by the manufacturer in relation to the device and its intended use includes a specific segment regarding the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device. Presentation of the data according to the format of the "Notice to Applicants" may facilitate the review by the Competent Authority. (Ref: "The Rules governing medicinal products in the European Union", volume 2B)
b) This segment should include data concerning the quality, safety and usefulness of the ancillary medicinal substance or of the ancillary human blood derivative, also appropriate details regarding information to be supplied with the device when placed on the market to permit the evaluation of the aforementioned features.
c) Except for human blood derivatives and for medicinal products, which fall within the scope of the Annex I to Regulation (EC) N° 726/2004 where consultation with EMA is mandatory, it is at the discretion of the manufacturer to choose the Competent Authority in consultation with its Notified Body. The EMA may also be consulted, e.g. where the substance involved was included in a medicinal product, which has been evaluated by the EMA.

C. 3 Documentation to be provided by the Notified Body to the Competent Authority

Because of the wide range of medical devices, which incorporate, as an integral part, an ancillary medicinal substances or an ancillary human blood derivative, a flexible approach to the data requirements is necessary. Nevertheless the information should be based in principle, to the extent relevant, on Annex I to Directive 2001/83/EC, as amended by Commission

Directive 2003/63/EC, transposed into national legislation through Order of the Minister of Public Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical Rules and protocols in respect of the testing of medicinal products, as amended through Order of the Minister of Health no. 615/2010. It is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation, all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to literature, including standard textbooks, experience and other information generally available. Nonetheless all headings should be addressed; either with relevant data or justification for absence of data. The latter may be based on the manufacturer's risk assessment.
For new active substances and for known substances in a non-established purpose, comprehensive data is required to address the requirements of Order of the Minister of Public Health no. 906/2006, as amended through Order of the Minister of Health no. 615/2010. The evaluation of such active substances would be performed in accordance with the principles of evaluation of new active substances.

Particular attention should be given to, as relevant:
- The "EMEA recommendation on the procedural aspects and dossier requirements for the consultation to the EMEA by a Notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device, EMEA/CHMP/401993/2005[2]."
This recommendation is intended to provide the relevant parties with information about procedural aspects of the consultation procedure to the EMA by Notified Bodies on an ancillary medicinal substance or an ancillary human blood derivative incorporated as an integral part in a medical device, as well as guidance on data requirements and format of such applications for consultation;
- Published guidance from national competent authorities on the documentation requirements for consultations.

1) General information
A general description of the medical device including the manufacturer's claim regarding the purpose of the incorporation of the ancillary medicinal substance or the ancillary human blood derivative, together with a critical appraisal of the results of the risk assessment.

2) Quality documentation
a) For the ancillary medicinal substance or the ancillary human blood derivative itself:
• Relevant parts of CTD-Module 3 in accordance with the format of the "Notice to Applicants" (Ref: "The Rules governing medicinal products in the European Union", volume 2B). Relevant parts should be provided, depending on whether the ancillary medicinal substance or the ancillary human blood derivative is an active pharmaceutical ingredient or a formulated medicinal product.
• Information on the active substance may be provided in the form of an Active Substance Master File (ASMF)[3], structured according to Module 3.2.S of the CTD-format.
Particular attention should be made to current CHMP quality guidelines on ASMF[4].
• Where applicable, reference shall also be made to the European Pharmacopoeia (Ph.Eur.) or in the absence of a Ph.Eur. monograph to a national pharmacopoeia of one of the Member States. If no monograph is available from the Member States reference may be to other national monographs or to the manufacturer's specification and methods of analysis.

[2]http://www.emea.europa.eu/pdfs/human/regaffair/40199305en.pdf
[3]This option does not apply to biological substances.
[4]http://www.emea.europa.eu/htms/human/humanguidelines/quality.htm

• CTD-Module 2.3 (Quality Overall Summary) in accordance with the format of the "Notice to Applicants" (Ref: "The Rules governing medicinal products in the European Union", volume 2B)

b) For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device:

• Qualitative and quantitative particulars of the constituents

A description of the ancillary medicinal substance or the ancillary human blood derivative, and the amount (giving a range where appropriate) of the ancillary medicinal substance or the ancillary human blood derivative incorporated into each medical device. If the medicinal substance or the ancillary human blood derivative is modified during its incorporation into the medical device, relevant information shall be provided.

• Description of method of manufacture

An overall description will already form part of the application to the Notified Body; the section dealing with incorporation of the ancillary medicinal substance or the ancillary human blood derivative in the medical device should be provided.

• Controls of starting materials

The specification for the ancillary medicinal substance or the ancillary human blood derivative shall be provided.

• **Control tests carried out at intermediate stages of the manufacturing process of the medical device**

This information is only necessary if it is directly relevant to the quality of the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device.

• **Final Control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device**

Qualitative and quantitative tests carried out to control the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

• Stability

Information defined to show the ancillary medicinal substance or the ancillary human blood derivative maintains its desired function throughout the defined shelf-life of the medical device including, taking account of the manufacturer's recommended storage conditions, potential interaction with other materials, and potential degradation of the ancillary medicinal substance or the ancillary human blood derivative.

3) Non-clinical documentation

• Non-clinical pharmacology

• Pharmacodynamics

This section should address the intended action of the ancillary medicinal substance or the ancillary human blood derivative in the context of its incorporation into a medical device.

• Pharmacokinetics

It is anticipated that pharmacokinetic studies will not be required in the majority of cases. Some or all of the following are as may need to be addressed as appropriate:

- Description of the pattern of local and systemic exposure to the ancillary medicinal substance or to the ancillary human blood derivative,
- Where the level of exposure fluctuates (AUC), the maximum level and duration of exposure should be considered,

- Where it is considered possible that potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established, taking due consideration of individual variability,
- New active substances will require information on the release from the medical device, and, if relevant, its subsequent absorption, distribution, metabolism and excretion (AUC and eventually metabolites, if relevant).
• Toxicity (including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, as applicable)
Reference to the known toxicological profile of the ancillary medicinal substance or the ancillary human blood derivative may be provided. In the case of new active substances, the results of toxicity tests should be provided, taking into account relevant CHMP guidelines[5].
This may include information on toxicity and biocompatibility of the medical device, which may be available from evaluation in accordance with the EN 10993 series of standards.
• Local tolerance
This is of particular relevance since the route of exposure to the ancillary medicinal substance or the ancillary human blood derivative may be different from its conventional application. The relevant results of medical device testing according to EN ISO 10993 should be provided or, where appropriate, information from the scientific literature.

4) Clinical evaluation
Since these medical devices will be class III, clinical data will form part of the information provided to the Notified Body under annex II or III of the applicable Directive, namely in accordance with Annex 10 of Government Decision no. 54/2009 (national legislation). This data will address the requirements for clinical evaluation of the medical device incorporating an ancillary medicinal substance or an ancillary human blood derivative as required by Annex 10 of Government Decision no. 54/2009. This data will address the safety of the medical device in its entirety. The usefulness of the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device should be addressed by clinical evaluation or by cross-reference to other sections of the dossier, as applicable.
An appropriate methodology for clinical investigations on medical devices is described in EN ISO 14155-2012 - Clinical investigation of medical devices for human subjects. Good Clinical Practice.
Particular attention shall be given to any specific guidelines (e.g. EMA guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug eluting (medicinal substance-eluting) coronary stents[6], MEDDEV guidance 2.7.1 Appendix 1 – clinical evaluation of coronary stents[7]).

5) Labelling
Details supplied by the manufacturer of labelling or information to be provided with the medical device with regard to the ancillary medicinal substance or the ancillary human blood derivative, is to be supplied to the Competent Authority to assist in the understanding of the safety and usefulness of the ancillary medicinal substance or the ancillary human blood derivative together with the medical device.

C. 4 Consultation process on medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

[5]http://www.emea.europa.eu/htms/human/humanguidelines/nonclinical.htm
[6]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003275.pdf
[7]http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/cetf_en.pdf

a) The Notified Body, having requested a Competent Authority to provide an opinion concerning the ancillary medicinal substance or the ancillary human blood derivative and its application, should, together with the Competent Authority, agree such matters as: time-schedules, modalities to obtain further information, including clock stops, fees and practical arrangements for submission of data.
- Further details about the procedure to follow for a consultation to the EMA are detailed in the "EMEA recommendation on the procedural aspects and dossier requirements for the consultation to the EMEA by a Notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device, EMEA/CHMP/401993/2005"[8] .
- National competent authorities may also have published guidance on the procedure to follow for consultations.

b) The Notified Body should make available to the competent Authority relevant data as specified in C.3 together with its own verification of the usefulness of the ancillary medicinal substance or the ancillary human blood derivative incorporated in the device.

c) The Competent Authority should review the data provided by the Notified Body. It should consider the use of the ancillary medicinal substance or of the ancillary human blood derivative by analogy with existing information regarding the known applications and appropriate features of safety, quality and usefulness as they may be relevant to the specific intended purpose of the device incorporating, as an integral part, the ancillary medicinal substance or the ancillary human blood derivative.

d) During the consultation process the Notified Body concerned may withdraw the request and ask for the opinion of an alternative relevant Competent Authority. In this case, the previously consulted Competent Authority should be informed of the name of the new Competent Authority.

e) The Competent Authority should inform the Notified Body of its opinion, taking into account the manufacturing process and the data related to the usefulness of incorporation of the ancillary medicinal substance or of the ancillary human blood derivative into the device as determined by the Notified Body (Article 7.4.2 of Annex 1 to Government Decision no. 54/2009).

f) The scientific opinion on the competent authority must be included in the documentation concerning the device. The opinion of the Competent Authority must be drawn up within 210 days after receipt of a valid documentation (Article 4.3 of Annex 2 to Government Decision no. 54/2009). This time period excludes clock stops.

g) For medical devices incorporating an ancillary medicinal substance, the notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the Competent Authority concerned (Article 4.3. of Annex 2 to Government Decision no. 54/2009).

h) The Notified Body should take into account the opinion of the Competent Authority and use its judgement to either approve the product, after consideration of all aspects of risk/benefit in the intended or expected use of the product, or alternatively to reject the product. It may be that certain suggestions from the Competent Authority may be adopted by the manufacturer to render the product acceptable.

[8]http://www.emea.europa.eu/pdfs/human/regaffair/40199305en.pdf

i) The Notified Body should inform the Competent Authority, which was consulted of the decision reached by the Notified Body, and where this decision deviates from the opinion provided by the Competent Authority this will be shown. Where a Notified Body receives a negative opinion from the Medicinal Product Competent Authority, they should consult with the device Competent Authority before issuing a certificate.

j) For medical devices incorporating an ancillary human blood derivative, the notified body will give due consideration to the opinion of the EMA when making its decision. The notified body may not deliver the certificate if the EMA's scientific opinion is unfavourable. It will convey its final decision to the EMA (Article 4.3. of Annex 2 to Government Decision no. 54/2009).

k) Where changes are made to an ancillary substance incorporated in a device (in particular related to the source, the manufacturing process, the amount and the method of incorporation), the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained. The competent authority shall take into account the data related to the usefulness of the incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance in the device (Article 7.4.5. of Annex 1 to Government Decision no. 54/2009).

l) When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance,, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure (Article 7.4.5. of Annex 1 to Government Decision no. 54/2009).

D. PROCEDURES FOR THE REPORTING OF ADVERSE INCIDENTS

The regulation of a product as a medicinal product or medical device, will determine which procedure should be followed for the reporting of an adverse incident; medicinal products to meet the requirements for pharmacovigilance and medical devices to meet the requirements for medical device vigilance.

Note: Guidelines are available on:

- Medical device vigilance system (MEDDEV. 2.12/1 rev 7)[9].
- Pharmacovigilance requirements[10].

[9] http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_12_1-rev_703-2012_en.pdf
[10] http://ec.europa.eu/health/documents/eudralex/index_en.htm

DECISION

no. 24/11.10.2013

on approval of the Implementation rules related to the NAMMD procedure for consultation by a notified body concerning grant of scientific opinion on the quality and safety of the ancillary medicinal substance incorporated as an integral part into a medical device

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, reunited on summons of the NAMMD President in the ordinary meeting of 11.10.2013, in accordance with Article 12 (5) of Emergency Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, hereby adopts the following

DECISION

Sole article. - The Implementation rules related to the NAMMD procedure for consultation by a notified body concerning grant of scientific opinion on the quality and safety of the ancillary medicinal substance incorporated as an integral part into a medical device are approved, in accordance with the Annexes, which are integral parts 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.24/11.10.2013

IMPLEMENTATION RULES RELATED TO THE NAMMD PROCEDURE FOR CONSULTATION BY A NOTIFIED BODY CONCERNING GRANT OF SCIENTIFIC OPINION ON THE QUALITY AND SAFETY OF THE ANCILLARY MEDICINAL SUBSTANCE INCORPORATED AS AN INTEGRAL PART INTO A MEDICAL DEVICE

CHAPTER I
General provisions

Article 1. – These Rules are issued for implementation of provisions of Article 7.4.2., 7.4.4. and 7.4.5. of Annex 1 to Government Decision no. 54/2009 on marketing conditions for medical devices.

Article 2. – They establish the consultation process of the National Agency for Medicines and Medical Devices (NAMMD) by a notified body for authorisation for placement on the market of medical devices incorporating, as an integral part, an ancillary active substance (hereinafter "ancillary medicinal substance").

CHAPTER II
Consultation procedure

Article 3. - For devices incorporating, as an integral part, an ancillary medicinal substance, the notified body, having verified the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device, will seek a scientific opinion from the NAMMD (competent authority in the field of the medicinal product) on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device.

Article 4. – (1) The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device.

(2) It refers to the suitability of the medicinal substance to achieve its intended action, and to whether the potential inherent risks (aspect of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.

Article 5. - By means of the consultation process, the NAMMD may make available relevant information concerning risks related to the use of the substance (e.g. resulting from pharmacovigilance).

II.1 Submission of application for initial consultations in view of grant of a scientific opinion about the quality and safety of an ancillary medicinal substance incorporated, as an integral part, into a medical device

Article 6. - To start the initial consultation procedure, the notified body submits to the NAMMD, on behalf of the device's manufacturer, a cover letter, signed in original and accompanied by the payment form, at least 15 days prior to submission of the application.

Article 7. – After payment confirmation, the notified body submits to the NAMMD an application for initial consultation for grant of a scientific opinion, as shown in Annex 1, which is integral part of this Decision.

Article 8. – The application for initial consultation must be accompanied by the documents and information mentioned in Annex 2, which is integral part of this Decision, in accordance with the EU Common Technical Document (CTD) specified in the "*Notice to Applicants*", volume 2B "Rules governing medicinal products in the European Union", used in the applications for authorisation of a medicinal product.

Article 9. - An individual application for grant of a scientific opinion is submitted for each medical device incorporating one or several ancillary medicinal substances subject to NAMMD consultation.

Article 10. – (1) The supporting documentation is submitted in electronic format (CD/DVD).

(2) The application for initial consultation for grant of a scientific opinion is submitted on paper and signed in original.

(3) The documentation is submitted in English/Romanian, except for the labelling (submitted in both English and Romanian).

Article 11. – (1) Fees for grant of a scientific opinion are those established through Order of the Minister of Health on approval of NAMMD Scientific Council Decision no. 3/22.08.2013, published in the Official Gazette of Romania, Part I.

(2) If needed, adjustments of the associated tariff are made during/at the end of the consultation procedure.

II.2 Procedure for grant of scientific opinion

Article 12. – Within 30 days as of receipt of the application for initial consultation for grant of scientific opinion and the supporting scientific documentation**,** the NAMMD validates the application.

Article 13. – If, during the application validation stage, it is found that the supporting documentation should be supplemented with administrative and technical documents/information, the notified body receives the list containing the applications for supplementation required in view of validation.

Article 14. – The application for supplementary consultation submitted to the NAMMD is only valid after receipt and assessment of all required documents; otherwise, the application is invalidated, without bringing any prejudice to the notified body's right to submit another consultation application, properly documented.

Article 15. – The NAMMD informs on paper the notified body about the validation/invalidation of the application. The 210-day period specified under Article 4.3 of Annex 2 to Government Decision no. 54/2009 starts passing from the moment of validation.

Article 16. – Following validation, the documentation is allocated in view of assessment, in accordance with the provisions of Article 7.4.1. of Annex 1 to Government Decision no. 54/2009: "the quality, safety and usefulness of the incorporated ancillary medicinal substance must be assessed through analogy with the methods shown in Order of the Minister of Public Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical Rules and protocols in respect of the testing of medicinal products, as amended.

(2) The assessment is performed in accordance with the recommendations of the corresponding scientific guidelines.

Article 17. – If, during the assessment process, new documents/information must be forwarded, the NAMMD will require the notified body to forward the respective documents/information and the procedure will be suspended (*stop-clock*) until a complete response document is received.

Article 18. – (1) The request and submission of supplementary information are performed just once during assessment.

(2) The request for supplementary documents/information is forwarded to the notified body together with a schedule specifying the deadline for submission of the requested information.

Article 19. – Documentation assessment is completed by grant of a final report referring to the favourable/unfavourable scientific opinion.

The supplementary consultation procedure is completed by grant of an updated scientific opinion, irrespective of potential impact of the respective information upon the risk-benefit balance of incorporation of the ancillary medicinal substance into the medical device.

Article 20. – The final assessment report is presented during the meeting of the NAMMD Marketing authorisation Commission and resolves upon grant of a favourable/unfavourable scientific opinion.

Article 21. – The favourable/unfavourable scientific opinion is issued following the Marketing Authorisation Commission respective decision.

Article 22. – The NAMMD decision on grant of an unfavourable scientific opinion is taken if, upon assessment of documentation, the quality and safety of the incorporated ancillary medicinal substance are found noncompliant with the provisions of Order of the Minister of Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical Rules and protocols in respect of the testing of medicinal products, as amended.

Article 23. – (1) The favourable/unfavourable scientific opinion on the NAMMD is forwarded to the notified body.

(2) The unfavourable scientific opinion is accompanied by a justificatory report based on the conclusions of the final assessment report.

II.3 Notification of the National Agency for Medicines and Medical Devices by the notified body concerning the decision taken

Article 24. – The notified body takes into account the NAMMD decision when making a decision for approval of introduction of the medical device on the market.

Article 25. – In accordance with Article 4.3 of Annex 2 to Government Decision no. 54/2009, the notified body informs the NAMMD about the adopted decision. If other than the scientific opinion issued by the Agency, the notified body highlights this fact in the submitted information.

CHAPTER III
The supplementary consultation procedure in case of change of the ancillary medicinal substance incorporated, as an integral part, in a medical device

Article 26. – (1) If there is any change in the design or manufacture of the device, which could have an effect on the quality, safety or usefulness of the drug substance in the device or in respect of amended or additional data, a supplementary consultation is required by the notified body from the NAMMD, in accordance with Article 7.4.4. of Annex 1 to Government Decision no. 54/2009.

(2) The NAMMD assesses the maintenance of the initial quality and safety degree of the ancillary medicinal substance and makes sure that the amendments did not have any impact upon the report established between the benefits and risks of incorporating the substance into the medical device.

Article 27. - Examples of amendments that may require a Supplementary Consultation include:

- Change of the supplier of the ancillary medicinal substance or intermediate processor;
- Change of the formulation or grade of the medicinal substance or an intermediate;
- Significant change of the manufacturing process or change of the specification of the medicinal substance as notified by the manufacturer;

- Changes of quality control tests relevant to the active substance during the manufacturing process;
- Change of the manufacturing process for the incorporation of the medicinal substance into the device;
- Change of packaging;
- Change of the method of sterilisation;
- Extension of shelf life;
- Changes to the intended use of the device;
- Some changes in the design of the device, which may impact on the availability or release of the medicinal substance (e.g. device size increase if the quantity of the medicinal substance per device is increased, change of device surface area);

This list is intended for guidance and is not prescriptive or exhaustive.

III.1 Submission of the applications for supplementary consultation in view of amendment of the terms of the scientific opinion, initiated by the notified body

Article 28. – In view of starting the supplementary consultation procedure, the notified body submits to the NAMMD a cover letter, signed in original and accompanied by the payment form, at least 15 days prior to submission of the application.

Article 29. – After confirmation of the payment, the notified body submits to the NAMMD the application for supplementary consultation, as shown in Annex 3, which is integral part of this Decision.

Article 30. – The application for supplementary consultation is accompanied by supporting documents and information, submitted in accordance with the format of the EU Common Technical Document (CTD) specified in "Notice to Applicants", volume 2B "Rules governing medicinal products in the European Union".

Article 31. – An individual application is submitted for each medical device incorporating an ancillary medicinal substance subject to supplementary consultation.

Article 32. – (1) The documentation for supplementary consultation is submitted in electronic format (CD/DVD).

(2) The application for supplementary consultation is submitted on paper, signed in original.

(3) The documentation is submitted in English/Romanian, except for the labelling (submitted in both English and Romanian).

Article 33. – (1) Supplementary consultation fees are those established through Order of the Minister of Health on approval of NAMMD Scientific Council Decision no. 3/22.08.2013, published in the Official Gazette of Romania, Part I.

(2) If needed, adjustments of the associated tariff are made during/in the end of the supplementary consultation procedure.

III.2 Operation of the supplementary consultation procedure initiated by the notified body

Article 34. – The NAMMD checks the validity of the submitted application and informs in writing the notified body on application validation/invalidation.

Article 35. – If, in the validation stage of the application for supplementary consultation, the supporting documentation is found to require supplementation with administrative and technical documents/information, the notified body is forwarded the list containing the applications for supplementation required in view of validation of the application.

Article 36. – The application for supplementary consultation submitted to the NAMMD is only valid after receipt and assessment of all required documents.

Article 37. – The procedure starts on the date of validation confirmation on paper.

Article 38. – The assessment of applications for supplementary consultation is generally performed in a 60-day term, which can be prolonged by 30 days, in case of substantial amendments. This period excludes *stop-clocks*.

Article 39. – During assessment, the NAMMD may require the notified body to provide supplementary information.

Article 40. – The application for supplementary consultation is forwarded to the notified body together with a schedule specifying the deadline for submission of the requested information and, if required, the extension of the period for assessment.

Article 41. – (1) The procedure is discontinued until receipt of the required supplementary information.

(2) The discontinuation procedure consists of one month.

(3) If a longer discontinuation period is required, the notified body forwards the NAMMD an argumented application in this respect.

Article 42. - The target time for assessment of these applications is 30 to 60 days from receipt, but will vary depending on the complexity of the consultation.

Article 43. – (1) The final assessment report is discussed during the meeting of the Marketing Authorisation Commission, who decides upon grant of an updated favourable/unfavourable scientific opinion.

(2) The final assessment report is forwarded to the notified body.

(3) If an unfavourable updated scientific opinion is issued, it is accompanied by a justificatory document.

III.3.3 Further consultations on the same device initiated by the NAMMD

Article 44. – (1) If, following initial consultation, the NAMMD has obtained information about the ancillary medicinal substance, which may impact upon the established risk-benefit balance of incorporation of the ancillary medicinal substance into the medical device, based on Article 7.4.5. of Annex 1 to Government Decision no. 54/2009, it informs the notified body to that end.

(2) In the information address sent, the NAMMD requires the notified body to submit an application for supplementary consultation in view of updating the scientific opinion, also specifying the supporting documentation to be submitted.

Article 45. – The application validation and the supplementary consultation procedure follow the stages described in subsections III.1. and III.2.

Article 46. – The supplementary consultation procedure is completed by grant of an updated scientific opinion, regardless of the fact that the information has or has not an impact upon the risk-benefit balance of incorporation of the ancillary medicinal substance into the medical device.

III.4 Changes in the ancillary medicinal substance incorporated in a medical device, requiring the initiation of a new complete consultation procedure

Article 47. - Changes to the qualitative or quantitative composition relating to the active substance(s), or indications for use etc. would normally be subject to a new, full consultation.

Article 48. – Examples include:

a) quantitative change to, addition, replacement or deletion of one or several active substances;

b) variations relating to the use of the medical device

- addition of an indication in another therapeutic area;
- addition of or change to the route of administration.

ANNEX 1
to SCD no. 24/11.10.2013

APPLICATION FORM
INITIAL CONSULTATION FOR SCIENTIFIC OPINION

This form is to be filled in and submitted to the National Agency for Medicines and Medical Devices, in view of initial consultation for scientific opinion on the quality and safety of the ancillary active substance(s) incorporated as an integral part in the medical device.

An individual application form is to be submitted for each medical device incorporating one or several ancillary active substance(s).

1. Name of the medical device

2. Name of the ancillary active substance(s)*

**one name only, in the following order of preference: rINN, Ph.Eur. name, Romanian Pharmacopoeia name, Common Name, scientific name.*

3. Status of assessment of the ancillary active substance(s)
(please tick as appropriate)

- First assessment ☐
- Second assessment, with new manufacturer ☐
- Second assessment, with the same manufacturer ☐

4. Notified Body

Declaration and signature:

Name:

Address:

Country:

E-mail address:

Telephone no.:

Fax no.:

Name of the Contact Person assigned for communication with the National Agency for Medicines and Medical Devices during the consultation procedure:

This is to confirm that all data herein on the quality, safety and usefulness of the ancillary active substance(s), the benefit/risk profile included, have been included in the dossier, as required*.

It is also hereby confirmed that the fee has been paid according to Rules and regulations of the National Agency for Medicines and Medical Devices**
On behalf of the Notified Body:

……..
Signature

……..
Name and Surname*

……
Position

Place Date (year, month, day)

*****Please attach the authorisation issued by the Notified Body for the Contact Person in charge of communication with the National Agency for Medicines and Medical Devices/ signatory right granted by the Notified Body (annex 1.2)
****** Please attach the proof of fee payment (annex 1.3).

5. Manufacturer of the medical device

Name:
Address:
Country:
E-mail address:
Telephone no.:
Fax no.:

6. Manufacturer(s)

Authorised manufacturer(s) (or importer) in charge of batch release in the EEA as per Article 748 and 760 of Law no. 95/2006, Title XVII – The Medicinal Product, as amended:

Name:
Address:
Country:
E-mail address:
Telephone no.:
Fax no.:

Manufacturing Authorisation number:
☐ Please attach the copy of the Manufacturing Authorisation(s) (annex 1.4)
or
☐ Please specify the EudraGMP reference number of the Manufacturing Authorisation:

If available:
☐ Please attach the latest GMP Certificate (annex 1.6)
or
☐ Please specify the EudraGMP Certificate reference number: <Number>

Manufacturer(s) of the ancillary active substance(s) and manufacturing site(s)
NOTE:
Please include all manufacturing sites involved in the manufacturing process of the ancillary active substance, including quality in-process testing sites/control. Information on importer(s) and distributor(s) only are not acceptable.

Substance:
Name:
Address:
Country:
E-mail address:
Telephone no.:
Fax no.:

Brief description of the technologic process at the manufacturing site:
☐ Please attach the flow chart, indicating the activities and their succession performed at the various manufacturing sites involved, testing places included (annex 1.5).

☐ For each ancillary active substance, please attach a declaration of the Qualified Person relating to ancillary active substance manufacturing in line with GMP Rules for starting materials (annex 1.9).

- The manufacturing site has been inspected for verification of GMP compliance by a competent authority in the EEA or an authority signatory of a mutual recognition agreement or a different community agreement, according to the provisions of the respective agreement.

❍ Nu ❍ Yes

If Yes, please include the following in annex 1.6:
☐ a declaration no older than 3 years from an inspecting competent authority
or
if available
☐ please attach the latest GMP Certificate (annex 1.6)
or
☐ please specify the EudraGMP Certificate reference number: <Number>

- The manufacturing site has been inspected for verification of compliance with GMP Rules by any other competent authority (including those in countries signatory of a mutual recognition agreement or a different community agreement but not on the territory of the manufacturing site).

❍ No ❍ Yes

☐ If Yes, please include brief data in annex 1.6 (and, if available, a GMP Certificate or a declaration)

- The European Pharmacopeia has issued a *Certification* of Suitability for the ancillary active substance(s)

❍ No ❍ Yes ☐ Please attach a copy of the Certificate in annex 1.7.

If Yes, please specify:
- name of the substance:

- name of the manufacturer:
- reference number:
- date of the latest verification (yyyy-mm-dd):

- There is a Active Substance Master File (ASMF) for the ancillary active substance(s)
❍ No ❍ Yes

If Yes, please specify:
- name of the ASMF holder:
- name of the manufacturer, if different from the above:
- ASMF EU reference number, if available:

- ASMF national reference number, if applicable and only when the ASMF EU reference number is not available:

- number of the ASMF version:

- date of submission (yyyy-mm-dd):
- date of the latest verification (yyyy-mm-dd):

☐ Please attach an access letter for the community competent authority/national competent authority of the Member State where the application has been submitted (see European ASMF procedure for active substances) (annex 1.7).

☐ Please attach a copy of the written confirmation by the active substance manufacturer on medical device manufacturer's notification of changes in the manufacturing process or specifications, as per Law **no.** 95/2006, Title XVII – The Medicinal Product, as amended (annex 1.8)

7. Pharmacotherapeutic classification *(please use current ATC code)*

ATC Code: **Pharmacotherapeutic classification:** <Text>

If no ATC code has been assigned, please specify whether an application has been submitted in that respect: ☐

8. Description of the medical device with ancillary active substance(s)

Description of the medical device

<Text>

Intended purpose of the ancillary medicinal substance as incorporated into the device with scientific explanation that the action of the medicinal substance is only ancillary to that of the device

☐ Please attach the Report of the Notified Body on the usefulness of ancillary active substance(s) incorporation (annex 1.1)

<Text>

Administration route*

<Text>

Ancillary active substance(s)	Quantity	Unit	Reference/ Monograph standards (e.g., European Pharmacopeia
<Text>			
<Text>			
<Text>			

Packaging components, including description of material*

<Text>

Pack size

<Text>

Proposed shelf-life (unopened)

<Text>

Proposed shelf-life (in use)

<Text>

Recommended storage conditions

<Text>

*Please use Romanian Standard Terms in line with European Standard Terms

List of materials of animal origin contained or used in the ancillary active substance(s) manufacturing process

NONE: ☐

Name	Position* AS OI	TSE susceptible material of animal origin	Other animal origin
1.	☐ ☐	☐ Yes** ☐ No	☐
2.	☐ ☐	☐ Yes** ☐ No	☐
3.	☐ ☐	☐ Yes** ☐ No	☐

*AS = ancillary active substance(s), OI = other ingredient (including starting material used in ancillary active substance(s) manufacturing)

** Please attach a copy of the Ph. Eur. Certificate of Suitability as per Resolution AP/CSP (99) 4 of the Council of Europe, if available (annex 1.10)

9. Attachments (where appropriate)

☐ 1.1 Report of the Notified Body on the usefulness of ancillary active substance(s) incorporation

☐ 1.2 Letter of authorisation for communication with the National Agency for Medicines and Medical Devices on behalf of the notified body

☐ 1.3 Proof of fee payment

☐ 1.4. Manufacturing Authorisation(s) required as per Article 748 of Law no**.** 95/2006, Title XVII – The Medicinal Product, as amended (or the equivalent thereof outside the EEA, where a mutual recognition agreement or other community agreement applies); any supporting document in line with Article 702 (4) n) of Law no. 95/2006.

☐ 1.5 Flow chart indicating the different sites involved in the manufacturing process of the ancillary medicinal active substance(s) as incorporated into the device.

☐ 1.6 GMP Certificate(s) or other GMP declarations of compliance; if applicable, a summary of other GMP inspections performed.

☐1.7 Letter of access to Active Substance Master Files or copy of Ph. Eur. Certificate(s) of Suitability

☐ 1.8 Copy of written confirmation from the manufacturer of the ancillary medicinal substance to inform the applicant in case of modification of the manufacturing process or specifications according to Order of the Minister of Health no. 906/2006 for approval of analytical pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products, as amended (transposing annex I to Directive 2001/83/EC)

☐ 1.9 For each ancillary active substance, declaration from the manufacturer's Qualified Person responsible for batch release in the EEA to ancillary active substance(s) manufacturing in line with GMP Rules. Alternatively, such declarations may also be signed by a Qualified Person on behalf of all Qualified Persons involved (on condition this is clearly stated).

☐ 1.10 TSE Certificate of Suitability granted by the European Pharmacopeia.

ANNEX 2
to Scientific Council Decision no. 24/11.10.2013

DOCUMENTATION TO BE SUBMITTED BY THE NOTIFIED BODY TO THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

Section 1

- Application form
- General information on the medical device
  - General description of the medical device
  - Scientific explanation that the action of the medicinal substance is only ancillary to that of the device, as per Scientific Council Decision no. 23/11.10.2013 on approval of National Agency for Medicines and Medical Devices handling of requests by a Notified Body for scientific opinion on the quality and safety of an ancillary medicinal substance incorporated as an integral part into a medical device
- Signed declarations and Curriculum Vitae of Qualified experts.
- Notified Body report on usefulness of the ancillary medicinal substance incorporated as an integral part into a medical device.
- Labelling

Section 2

Module 2.3: Quality Overall Summary (relevant individual documents) concerning the ancillary active substance itself, in line with e-CTD format as set out in "Notice to Applicants", Volume 2B;

- Critical appraisal summaries (or expert reports) on the quality, non-clinical and clinical data of the medicinal substance as incorporated into the medical device, according to. 2b), 3) and 4) of subsection C3 of the Annex to SCD no. 23/11.10.2013.

Section 3

Module 3: For the ancillary medicinal substance itself, relevant information, submitted in one of the three following acceptable formats:

• Relevant parts of Module 3 of e-CTD format in "Notice to Applicants" Volume 2B;

• Active Substance Master File (ASMF), organised as outlined in Module 3.2.S of E-CTD format in "Notice to Applicants" Volume 2B;

• European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP), if available.

Quality documentation, in accordance with the titles and requirements of subsection C.3, 2b) of the annex to SCD no. 23/11.10.2013, for the ancillary medicinal substance as incorporated in the medical device.

Section 4

Non-clinical documentation in accordance with the titles and requirements of subsection C.3, 3) of the annex to SCD no. 23/11.10.2013, for the ancillary medicinal substance as incorporated in the medical device.

Section 5

Clinical documentation in accordance with the titles and requirements of subsection 4) of the annex to SCD no. 23/11.10.2013, for the ancillary medicinal substance as incorporated in the medical device.

ANNEX 3
to SCD no. 24/11.10.2013

APPLICATION FORM
SUPPLEMENTARY CONSULTATION FOR SCIENTIFIC OPINION

An individual application form is to be submitted for each medical device incorporating one or several ancillary active substance(s).

1. Name of the medical device	**2. Number of initial scientific opinion**

3. Name of the ancillary active substance(s)*

**one name only, in the following order of preference: rINN, Ph.Eur. name, Romanian Pharmacopoeia name, Common Name, scientific name.*

4. Status of assessment of the ancillary active substance(s)
(please tick as appropriate)

- First assessment ☐
- Second assessment, with new manufacturer ☐
- Second assessment, with the same manufacturer ☐

5. Notified Body

Declaration and signature:

Name:

Address:

Country:

E-mail address:

Telephone no.:

Fax no.:

6. Name and address of the Contact Person*:

Name and address of the Contact Person:

* *Please attach the authorisation issued by the Notified Body for the Contact Person in charge of communication with the National Agency for Medicines and Medical Devices/ signatory right Granted by the Notified Body*

Fax no. (optional):

Telephone no.:

E-mail address:

7. Manufacturer of the medical device

Name:

Address:

Country:

E-mail address:

Telephone no.:

Fax no.:

8. Description of the medical device with ancillary active substance(s)

Description of the medical device

<Text>

Administration route*

<Text>

Ancillary active substance(s)	Quantity	Unit
<Text>		
<Text>		
<Text>		

Packaging components, including description of material*

<Text>

Pack size

<Text>

**Please use Romanian Standard Terms in line with European Standard Terms*

9. Changes proposed in this application
The change concerns the following section of the Dossier (please check all sections concerned)

☐ Quality
☐ Non-clinical
☐ Clinical
☐ Other

Exact purpose and context of change

<Text>

Current*	**Proposed***
<Text>	<Text>

Support documentation

* *Please provide the exact current and proposed situation of the text or specification, including the number(s) of the dossier section, as detailed as appropriate.*

Applicant's declaration:

This is an application for supplementary consultation concerning change of terms of the initial scientific opinion, according to specified proposals. I hereby declare that (please check as appropriate)

☐ There are no other changes in addition to those specified in this application (except for changes envisaged in other parallel applications);

☐ Changes do not concern the usefulness of the ancillary active substance incorporated as an integral part into a medical device, as originally verified by the notified body;

☐ All conditions set out for the change in question have been met (where appropriate);

☐ The assessment fee has been paid;

☐ The change(s) is/are to be implemented as

☐ The next batch/print

☐ Date: ……..

Fee paid *Please specify the fee type in line with national regulations*_____	
Main signatory*	Position
Name in print	Date
Second signatory	Position
Name in print	Date

* *Signature of the Main signatory is mandatory*

DECISION

no. 25/11.10.2013

on approval of the Guideline on Good Pharmacovigilance Practices, Module IV – Pharmacovigilance audits

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, reunited on summons of the NAMMD President in the ordinary meeting of 11.10.2013, in accordance with Article 12 (5) of Emergency Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, hereby adopts the following

DECISION

Sole article. – The Guideline on Good Pharmacovigilance Practices, Module IV – Pharmacovigilance Audits is approved, in accordance with 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. 25/11.10.2013

Guideline on Good Pharmacovigilance Practices, Module IV – Pharmacovigilance audits

This Guideline is an adapted translation of Guideline EMA/228028/2012 on Good Pharmacovigilance Practices (GVP), Module IV – Pharmacovigilance audits.

Table of contents

IV.C.3. Confidentiality
IV.C.4. Transparency

IV.A. Introduction

The entry into force of the new legislation on pharmacovigilance in July 2012, established legal requirements for competent authorities in the Member States and the European Medicines Agency (EMA) and marketing authorisation holders to perform audits of their pharmacovigilance systems [see Law 95/2006 on healthcare reform, transposing Directive 2001/83/EC (L 95/2006) Article 812(2), Article 815(2), Regulation (EC) 726/2004 (REG) Article 28f], including risk based audits of their quality systems [Regulation for implementation of European Commission Regulation (EU) 520/2012 (RI) Article 13 (1), Article 17 (1).]
For the purposes of this module reference to pharmacovigilance audit(s) and pharmacovigilance audit activity(ies) are deemed to include pharmacovigilance system audits and audit(s) of the quality system for pharmacovigilance activities.
The minimum requirements of the pharmacovigilance systems and the quality system are set out in the Commission Implementing Regulation (EU) No 520/2012 (IR) on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Law 95/2006 on healthcare reform, as amended, transposing Directive 2001/83/EC. Risk-based audits of the pharmacovigilance system should cover all areas listed in Directive 2001/83/EC (DIR) and Regulation (EC) 726/2004 (REG). The specificities of the risk-based audits of the quality system [for pharmacovigilance activities] are as described in the Implementing Measures [IR Art 8,10, 11,12,13(1) for marketing authorisation holders, and IR Art 8,14,15,16,17(1) for national competent authorities and the Agency.] The overall description and objectives of pharmacovigilance systems and quality systems for pharmacovigilance activities are referred to in Module I (SCD no. 15/22.04.2013 on approval of the Guideline on Good Pharmacovigilance Practice – Module I – Pharmacovigilance systems and their quality systems), while the specific pharmacovigilance processes are described in each respective Module of GVP.
This Module provides guidance on planning and conducting the legally required audits, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity. This Module is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonisation, and encourage consistency and simplification of the audit process. The principles in this Module are aligned with internationally accepted auditing standards, issued by relevant international auditing standardisation organisations and support a risk-based approach to pharmacovigilance audits.

IV.A.1. Terminology

Audit, Audit findings, Audit plan, Audit programme, Audit recommendations, Upper management: see Annex I.

Auditee: [entity/unit/organisation] being audited (ISO 19011 (3.7)[1]).

Compliance: Conformity and adherence to policies, plans, procedures, laws, regulations, contracts, or other requirements (*IIA International Standards for the Professional Practice of Internal Auditing*).

Control(s): Any action taken by management and other parties to manage risk and increase the likelihood that established objectives and goals will be achieved. Management plans, organises, and directs the performance of sufficient actions to provide reasonable assurance that objectives and goals will be achieved (*IIA International Standards for the Professional Practice of Internal Auditing*[2]).

Evaluation (of audit activities): Professional auditing bodies promote compliance with standards, including in quality assurance of their own activities, and codes of conduct, which can be used to address adequate fulfilment of the organisation's basic expectations of Internal Audit activity and its conformity to internationally accepted auditing standards.

Finding(s): see Audit findings

Head of the organisation: see Upper management

Auditors' independence: The freedom from conditions that threaten objectivity or the appearance of objectivity. Such threats to objectivity must be managed at the individual auditor, engagement, functional and organisational levels. (IIA International Standards for the Professional Practice of Internal Auditing)

[1]Additional details concerning: **The Institute of Internal Auditors** (IIA) www.theiia.org; the **International Organisation for Standardisation** (ISO) www.iso.org; **Information Systems Audit and Control Association** (ISACA) www.isaca.org; **The International Auditing and Assurance Standards Board** (IAASB) www.ifac.org; **The International Organisation of Supreme Audit Institutions** (INTOSAI) www.issai.org.

[2]**The Institute of Internal Auditors** (IIA) www.theiia.org

Internal Control: Internal control is an integral process that is effected by an entity's management and personnel and is designed to address risk and provide reasonable assurance that in pursuit of the entity's mission, the following general objectives are being achieved: executing orderly, ethical, economical, efficient and effective operations, fulfilling accountability obligations, complying with applicable laws and regulations and safeguarding resources against loss, misuse and damage (for further information refer to COSO standards).
International Auditing Standards: issued by International Auditing Standardisation Organisations.
International Auditing Standardisation Organisations: More details regarding **The Institute of Internal Auditors** (IIA) standards can be found at http://www.theiia.org/guidance/standards-and-guidance/ippf/standards/full-standards; the **International Organisation for Standardisation** (ISO) standard 19011 "Guidelines for quality and/or environmental management systems auditing. http://www.iso.org/iso/home.html; **Information Systems Audit and Control Association** (ISACA) standards can be found at http://www.isaca.org/Standards; **The International Auditing and Assurance Standards Board** (IAASB) standards can be found at http://www.ifac.org/auditing-assurance/clarity-center/clarified-standards; The International Organisation of Supreme Audit Institutions (INTOSAI) can be found at http://www.issai.org/composite-347.htm.
Auditors' objectivity: An unbiased mental attitude that allows internal auditors to perform engagements in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires internal auditors not to subordinate their judgment on audit matters to that of others. (*IIA International Standards for the Professional Practice of Internal Auditing*)[2].

IV.B. Structures and processes

IV.B.1. Audit of pharmacovigilance activities and its objectives

Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.
In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to, which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes.
Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable. Audit criteria are, for each audit objective, the standards of performance and control against, which the auditee and its activities will be assessed. In the context of pharmacovigilance, audit criteria should reflect the requirements for the pharmacovigilance system,

[2] The Institute of In ternal Auditors (IIA) www.theiia.org

including its quality system for pharmacovigilance activities, as found in the legislation and guidance.

IV.B.2. The risk-based approach to pharmacovigilance audits

A risk-based approach is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome and/or likelihood of non-detection by other methods.

The risk-based approach to audits focuses on the areas of highest risk to the organisation's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance.

Risk can be assessed at the following stages:

- strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by upper management;
- tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; and
- operational level audit planning resulting in an audit plan for individual audit engagements, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system [see IV.B.2.3.1.]

Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation (see IV.B.2.1., IV.B.2.2. and IV.B.2.3. respectively).

IV.B.2.1. Strategic level audit planning

The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on, which the audit programme is based.

The audit strategy should cover the governance (management and control), risk management and internal controls of all parts of the pharmacovigilance system including:

- all pharmacovigilance processes and tasks;
- the quality system for pharmacovigilance activities;
- interactions and interfaces with other departments, as appropriate;
- pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other vendors).

This is a non-prioritised, non-exhaustive list of examples of risk factors that could be considered for the purposes of a risk assessment:

- changes to legislation and guidance;
- major re-organisation or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for marketing authorisation holders, this may lead to a significant increase in the number of products for, which the system is used);
- change in key managerial function(s);
- risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organisation, increase in volumes of work, etc.;
- significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements;
- first medicinal product on the market (for the marketing authorisation holder concerned);
- medicinal product(s) on the market with specific risk minimisation measures or other specific safety conditions such as requirements for additional monitoring;
- criticality of the process, e.g.:

- for competent authorities: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;

- for marketing authorisation holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorisation holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorisation holder, in addition to considering the other factors included in this list;

- outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritised depending on criticality); if the area/process has previously been audited, the audit findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;
- identified procedural gaps relating to specific areas/processes;
- other information relating to compliance with legislation and guidance, for example:

- for competent authorities: information from compliance assessment (as described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC), from complaints, from external sources, e.g.

audits/assessments of the competent authority conducted by external bodies;

- for marketing authorisation holders: information from compliance assessment (as described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC), from inspections, from complaints, from other external sources, e.g. audits;

• other organisational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact upon pharmacovigilance activities.

IV.B.2.2. Tactical level audit planning

An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long term audit strategy. The audit programme should be approved by upper management with overall responsibility for operational, management and control structure.

The risk-based audit programme should be based on an appropriate risk assessment and should focus on:

• the quality system for pharmacovigilance activities;

• critical pharmacovigilance processes (see for example NAMMD SCD no. 15/2013 and IR Art 11, 15);

• key control systems relied on for pharmacovigilance activities;

• areas identified as high risk, after controls have been put in place or mitigating action taken.

The risk-based audit programme should also take into account historical areas with insufficient past audit coverage, and high risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

The audit programme documentation should include a brief description of the plan for each audit to be delivered, including an outline of scope and objectives.

The rationale for the timing, periodicity and scope of the individual audits, which form part of the audit programme should be based on the documented risk assessment.

However, risk-based pharmacovigilance audit(s) should be performed at regular intervals, which are in line with legislative requirements.

Changes to the audit programme may happen and will require proper documentation.

IV.B.2.3. Operational level audit planning and reporting

IV.B.2.3.1. Planning and fieldwork

The organisation should ensure that written procedures are in place regarding the planning and conduct of individual audits that will be delivered. Timeframes for all the steps required for the performance of an individual audit should be settled

in the relevant audit related procedures, and the organisation should ensure that audits are conducted in accordance with the written procedures, in line with this GVP Module.
Individual pharmacovigilance audits should be undertaken in line with the approved risk-based audit programme (see IV.B.2.2.). When planning individual audits, the auditor identifies and assesses the risks relevant to the area under review and employs the most appropriate risk-based sampling and testing methods, documenting the audit approach in an audit plan.

IV.B.2.3.2. Reporting
The findings of the auditors should be documented in an audit report and should be communicated to management in a timely manner. The audit process should include mechanisms for communicating the audit findings to the auditee and receiving feedback, and reporting the audit findings to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings should be reported in line with their relative risk level and should be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The grading system should be defined in the description of the quality system for pharmacovigilance, and should take into consideration the thresholds noted below, which would be used in further reporting under the legislation as set out in section IV.C.2:
• **critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.
• **major non-compliance** is a significant non-compliance in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements, which is however not considered serious.
• **minor non-compliance** is a non-compliance in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.
Issues that need to be urgently addressed should be communicated in an expedited manner to the auditee's management and the upper management.

IV.B.2.4. Actions based on audit outcomes and follow-up of audits
Actions referenced in this section of the guideline, i.e. immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the

pharmacovigilance system. Corrective and preventive actions to address critical and major issues should be prioritised. The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on nature of findings and the planned action(s).
The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.
Upper management and those charged with governance, should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to upper management.
Evidence of completion of actions should be recorded in order to document that issues raised during the audit have been addressed.
Capacity for follow-up audits should be foreseen in the audit programme. They should be carried out as deemed necessary, in order to verify the completion of agreed actions. [IR Art 13(2), Art 17(2)]

IV.B.3. Quality system and record management practices

IV.B.3.1. Competence of auditors and quality management of audit activities

IV.B.3.1.1. Independence and objectivity of audit work and auditors

The organisation should assign the specific responsibilities for the pharmacovigilance audit activities.
Pharmacovigilance audit activities should be independent. The organisation's management should ensure this independence and objectivity in a structured manner and document this.
Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results.
The main reporting line should be to the upper management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion.
Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; however auditors should maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires auditors not to subordinate their judgement on audit matters to that of others.

IV.B.3.1.2. Qualifications, skills and experience of auditors and continuing professional development

Auditors should demonstrate and maintain proficiency in terms of the knowledge,

skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, should cover knowledge, skills and abilities in:

- audit principles, procedures and techniques;
- applicable laws, regulations and other requirements relevant to pharmacovigilance;
- pharmacovigilance activities, processes and system(s);
- management system(s);
- organisational system(s).

IV.B.3.1.3. Evaluation of the quality of audit activities

Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, auditee feedback and self-assessment of audit activities (e.g. quality assurance of audit activities, compliance to code of conduct, audit programme, and audit procedures).

IV.B.3.2. Audits undertaken by outsourced audit service providers

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organisation (i.e. within the Agency, competent authority or marketing authorisation holder). Where the organisation decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP module and perform pharmacovigilance audits:

- the requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements should be specified to the outsourced service providers, by the organisation, in writing;
- the scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organisation, in writing;
- the organisation should obtain and document assurance of the independence and objectivity of outsourced service providers;
- the outsourced audit service provider should also follow the relevant parts of this GVP module.

IV.B.3.3. Retention of audit reports

Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in SCD no. 15/2013, section I.B.10., *Record management*

IV.C. Pharmacovigilance audit policy framework and organisational structure

IV.C.1. Marketing authorisation holders in the EU

IV.C.1.1. Requirement to perform an audit

The marketing authorisation holder in the EU is required to perform regular risk-

based audit(s) of their pharmacovigilance system [Law 95/2006, Article 815(2)], including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements [IR Art 8,10,11,12,13(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)]
See IV.C.2. for further details of the requirements for audit reporting by the marketing authorisation holder.

IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the EU (QPPV)

The responsibilities of the QPPV in respect of audit are provided in NAMMD SCD 15/2013. Furthermore, the QPPV should receive pharmacovigilance audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventive actions.
The QPPV should be notified of any audit findings relevant to the pharmacovigilance system in the EU, irrespective of where the audit was conducted.

IV.C.1.2. Competent authorities in Member States and the European Medicines Agency (EMA)

IV.C.1.2.1. Requirement to perform an audit

The Agency shall perform regular independent audits of its pharmacovigilance tasks [REG Art 28f] and competent authorities in Member States shall perform a regular audit of their pharmacovigilance system [Law 95/2006, Article 812 (2)]. Included in their obligation to perform audits of their pharmacovigilance system/tasks, competent authorities in the Member States and the Agency shall perform risk-based audits of the quality system as well, at regular intervals according to a common methodology to ensure that the quality system complies with the requirements [IR Art 8,14,15,16,17(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 17(2)].

IV.C.1.2.2. Common methodology

In order to have a useful audit system, all audits at the competent authorities in the Member States and the European Medicines Agency should have a common ground in terms of methodology. This should ensure harmonised planning, implementation and reporting by every competent authority in Member States and at the Agency.

IV.C.1.2.3. The Pharmacovigilance Risk Assessment Committee (PRAC)

The mandate of the Pharmacovigilance Risk Assessment Committee (PRAC) shall cover all aspects of the risk management of the use of medicinal products for human use, having due regard to the design and evaluation of pharmacovigilance audits [REG Art 61a(6)].

IV.C.2. Community requirements for audit reporting

IV.C.2.1. Reporting by the marketing authorisation holder

The marketing authorisation holder shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system standard master file (PSMF) (see Module II).
Based on the audit findings, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented.
Once the corrective and preventive actions have been fully implemented, the note may be removed [Law 95/2006, Article 815 (2), IR Art 13(2)]. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file (see Module II).
The marketing authorisation holders should ensure that a list of all scheduled and completed audits is kept in the annex to the pharmacovigilance system master file (IR Art 3(5)) and that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies.
The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)].

IV.C.2.2. Reporting by competent authorities in Member States and the Agency

Competent authorities in Member States and the Agency should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies.
Competent authorities in Member States shall report the results [of their pharmacovigilance system audits] to the Commission on 21 September 2013 at the latest and then every 2 years thereafter [Law 95/2006, Article 812 (2)].
The Agency shall report the results [of its pharmacovigilance system audits] to its Management Board on a 2-yearly basis [REG Art 28f].
The reports to the European Commission will follow an agreed format.

IV.C.3. Confidentiality

Documents and information collected by the internal auditor should be treated with appropriate confidentiality and discretion, and also respect Directive 95/46/EC [Regulation (EC) No. 45/2001 for Community institutions and bodies] and national legislation on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

IV.C.4. Transparency

The European Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter [REG Art 29] and on the performance of pharmacovigilance tasks by the competent authorities in Member States on 21 July 2015 at the latest and then every 3 years thereafter [DIR Art 108(b)].

DECISION

no. 26/11.10.2013
on approval of change of classification for release for Telfast 120 mg, film-coated tablets, box containing 1 blister x 10 film-coated tablets

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, reunited on summons of the NAMMD President in the ordinary meeting of 11.10.2013, in accordance with Article 12 (5) of Emergency Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, hereby adopts the following

DECISION

Sole article. - The change of classification for release from release based on medical prescription to release without medical prescription is approved for Telfast 120 mg, film-coated tablets, Marketing Authorisation Holder: Sanofi – Aventis Romania SRL, packaging size: box containing 1 blister x 10 film-coated tablets.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

DECISION

no. 27/11.10.2013

on approval of amendment to the revised version of the Guideline on assessment of advertising of medicinal products for human use, as approved through SCD no. 18/08.08.2013

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, reunited on summons of the NAMMD President in the ordinary meeting of 11.10.2013, in accordance with Article 12 (5) of Emergency Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, hereby adopts the following

DECISION

Sole article. - The amendment of the revised version of the Guideline on assessment of advertising of medicinal products for human use, as approved through SCD no. 18/08.08.2013 is approved, in accordance with the fragments highlighted in blue in 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
(SCD no. 27/11.10.2013)

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 (trade) – 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, except for social networks such as, for instance, Facebook and Twitter etc., or android mobile applications);

(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 trades (reminders):

By way of exemption from provisions of Article 30,"Printed advertising material meant for healthcare professionals", for short trades 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 trades, 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 trade 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.

(4) Advertising to the general public by means of social networks such as, for instance, Facebook and Twitter etc., or android mobile applications is prohibited.

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…."*, printed at the end of the spot, with mandatory update after each advertising visa renewal.

(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 trades *(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 trade;

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 trades 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) Trade 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) Responses to NAMMD requests shall be provided in no longer than 30 days, the *stop-clock* period. Otherwise, material submitted shall be deemed as rejected and the assessment fee shall not be returned.

(4) 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.

(5) 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.

(6) 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 (trade) 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.

DECISION

No.1/22.08.2013
on approval of the 2011 annual report of the National Agency for Medicines and Medical Devices

The Administration Council of the National Agency for Medicines and Medical Devices, summoned through Order of the Minister of Health no. 384/15.03.2013, convened in the meeting of 22 August 2013;

On seeing the need for approval of the 2011 Activity Report of the National Agency for Medicines and Medical Devices;

Based on Article 10 f) of Government Decision No. 734/2010 related to the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Article 1 – Approves the 2011 annual report of the National Agency for Medicines and Medical Devices, as shown in the Annex, which is integral part of this Decision.

Article 2 – The Minister of Health is notified of this Decision.

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

Dr. Marius SAVU

ANNEX
to ACD no. 1/22.08.2013

2011 ANNUAL REPORT
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

INTRODUCTION

The previous year was difficult for both the pharmaceutical market and the medicinal product field and the National Agency for Medicines and Medical Devices (NAMMD). Year 2011 was successful in spite of the issues that the institution had to deal with.

As customary in recent years, the NAMMD has manifested full openness towards cooperation and communication, in the firm belief that this is the only manner for establishing solid partnership between the Agency's management and its employees, as well as between the Agency, the Ministry of Health and all stakeholders.

Evaluation of results obtained in 2011 has proven that, even in the context of the international economic crisis, the NAMMD has managed to accomplish its attributions and duties as a national competent authority in the field of the medicinal product of human use. The efforts of the Agency's employees have been even stronger since, during the past two years, the institution has continually undergone major changes. It is also noteworthy that, in 2011, the NAMMD dealt with a severe shortage of qualified personnel. In spite of the circumstances, the Agency has managed to reach its target goals and continued, during its 5th year since Romania's accession to the EU, to take part and actively get involved in all activities of European bodies in the field of the medicinal product.

The activity of NAMMD departments has proved particularly complex in 2011. Accomplishment of the Agency's priority mission, i.e. assess the authorisation dossier in order to market quality, safe and effective medicinal products for human use and to monitor the safety of medicinal products for human use included in the therapeutic circuit, through inspection and pharmacovigilance related activities, has been at the forefront of the Agency's overall mission.

In the context of 2011 events, one should mention the visit in May 2011 of the audit team of the Heads of Medicines Agencies (HMA) in the context of the BEMA (Benchmarking of European Medicines Agencies) program, meant to measure the overall performance of the agency, as a system, by comparison with standards established within the HMA network and available for all European medicines agencies. This program also allows exchange of experience in the field of Good Practices, as well as identification of areas for improvement at both agency and network level.

This was the second audit visit in this program, following the visit performed in 2005, envisaged as an opportunity to assess the Agency's progress and to identify certain lines for future development.

The institution started the preparation for the BEMA II audit in 2009. In the context of this extensive effort, most of the Agency's activity was allocated to the preparation of this audit.

The BEMA II audit provided for the NAMMD the framework for accurate, realistic self-assessment of its own abilities and performances according to its performance indicators, for identification of lines for improvement and re-establishment of its priorities by implementation of adequate risk management measures.

According to ISO 9004 standards, the BEMA II audit concluded that, although the NAMMD is currently dealing with serious challenges related to staff and finances, the Agency's performance is systematic, approaching by 90% the specific level of a stable and consistent structure.

Year 2011 witnessed the transposition into Romanian legislation of two new European directives, one related to a new pharmacovigilance approach and one to the prevention of entry of falsified medicinal products into the legal supply chain, both having amended Directive 2001/83/EC on the Community code relating to medicinal products for human use. The regulatory acts for transposition of the two directives shall amend and supplement Law 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended. The deadline for transposition is July 2012 for Directive 2010/84/EU on pharmacovigilance and January 2013 for Directive 2011/62/EU on the prevention of entry into the legal supply chain of falsified medicinal products.

Moreover, it was also in 2011 that advertising regulations were reviewed, yielding the revised Guideline on evaluation of advertising of medicinal products for human use, approved through a Decision of the NAMMD Scientific Council (SCD 21/2011). This reviewed Guideline version sheds light on an extended number of advertising related issues and represents the outcome of the activity of a working group consisting of representatives of Marketing Authorisation Holders (MAHs), coordinated by the NAMMD. Thoughtfulness, accuracy and competence in the field of advertising of the medicinal product for human use in both the set-up and assessment of advertising materials has been one of the main requirements. The revised guideline has been intended to clarify, specify and supplement provisions of Law 95/2006, Chapter VIII - Advertising, without exceeding limits imposed by European Directive 2001/83/EC.

Other important NAMMD Scientific Council Decisions are also important to mention:

- Approval of the Guideline on consultation with target patient groups for the package leaflet;
- Approval of criteria for permission of supply of free medicinal product samples;
- Approval of amendment and supplementation of Order of the Minister of Health no. 1483 of 2010 on approval of the Rules on the administrative procedure of the National Agency for Medicines and Medical Devices for handling of variations,, which is to be approved through Order of the Minister of Health.

NAMMD activity of evaluation and authorisation can be illustrated through a number of significant figures:

- The database ensured by the Index of medicinal products for human use has been supplemented with 1085 marketing authorisations granted through the following procedures: national/mutual recognition/decentralised/procedure. Worthy of mention is authorisation for marketing in Romania of new antihypertensive combinations (candesartan and hydrochlorothiazide, valsartan and hydrochlorothiazide, amlodipine and atorvastatin, amlodipine and olmesartan), immunosuppressants (belimumab), antineoplastic monoclonal antibodies (ofatumumab), antivirals (boceprevir), antidiabetics (exenatid), antiepileptics (retigabin).
- MA-related information has been provided: trade name, Marketing Authorisation Holder (MAH), batch release responsible person, packages, Summary of Product Characteristics (SmPC), Leaflet.

Information has been updated for access by external users of the Index of medicinal products, posted on the NAMMD website.

Pharmaceutical inspection related work consisted of 47 inspections for assessment of compliance with God Manufacturing Practice (GMP) rules for authorisation of manufacturing/import/GMP certification, 3 Good Laboratory Practice (GLP) inspections, 6 Good Analytical Laboratory Practice (GALP) inspections for authorisations of independent

control units assessing medicinal product quality, 2 inspections performed prior to grant of Marketing Authorisation at the sites of Romanian medicinal product manufacturers, 10 inspections for assessment of compliance with Good Clinical Practice (GCP) rules, 6 pharmacovigilance inspections, 101 authorisation inspections, resulting in grant of 50 wholesale distribution authorisations.

In 2011, following recommendations of the European Medicines Agency (EMA) and reassessment of the risk/benefit report, rosiglitazone-containing antidiabetics (Avandia, Avandamet and Avaglim) were withdrawn from the market.

As regards the "parallel export" issue, the NAMMD currently is unable to quantify the respective trend. "Parallel export" is known to actually represent intra-community trade performed in the EU and, while it cannot be stopped, it would be preferable for competent authorities to know the real magnitude of the phenomenon.

It is true that, in 2011, aiming at a clear, permanent, objective image of the pharmaceutical market, the NAMMD Scientific Council has adopted a decision on compulsory monthly reporting of placement on the market in Romania, i.e. of sales of medicinal products for human use by authorised wholesale distributors (deadline: 01.11.2011). However, few distributors have complied with this decision although it has apparently been agreed upon by representatives of distributors' association.

In short, whereas "parallel import" is still under-represented (17 parallel import authorisations were issued in 2011 referring to OTCs (released without medical prescription), requests processed of correspondent competent agencies in the EU (Denmark, Poland, Great Britain) for provision of data related to MAs issued in Romania, necessary to the respective agency to issue parallel import authorisations in their respective countries, are numerically significant however (320 applications solved in 2011), targeting both OTCs and prescription-only medicinal products.

Clinical trials, conducted in accordance with European regulations in force, demonstrate the clinical efficacy and safety of medicinal products proposed for authorisation. Several clinical trials are needed for authorisation of a medicinal product; this number depends on product and its development stage. In general, all four clinical trial stages should be covered for each medicinal product.

In Romania, the number of applications for authorisation of clinical trials slightly decreased in 2011, as resulting from comparison between the numbers of applications received every year (246 applications as compared to 266 in 2010, 253 in 2009 or 275 in 2008).

In 2011, a number of 263 clinical trials were authorised. Therapeutic areas covered by applications for authorisation of clinical trials were as follows: psychiatry and neurology, oncology, diabetology, rheumatology, gastroenterology, pneumology, infectious diseases, hematology, cardiology, endocrinology.

It is worth mentioning that, via its representatives, the NAMMD participates in meetings of the working groups of European bodies in the medicinal product field (The European Medicines Agency - EMA, The Heads of Medicines Agencies - HMA, the European Commission – EC) hosting debates for elaboration and harmonisation of clinical trial legislation in all EU member states.

As regards pharmacovigilance, handled by the Pharmacovigilance and Risk Management Service in the European Procedure Department, year 2011 proved that Romanian physicians have become much more interested in adverse reaction reporting. For instance, 280 spontaneous reports were registered in 2004, 525 in 2009 and 939 (serious and non-serious) in 2010. A number of 1011 adverse reactions (448 non-serious and 563 serious) were forwarded to the NAMMD in 2011, by physicians (105 non-serious and 83 serious) and MAHs (343 non-serious and 480 serious reactions), received from physicians in the respective area. In addition to submitting adverse reactions to the Agency, MAHs are required to submit them directly into the European database of adverse reactions to medicinal products (EudraVigilance).

These continually increasing numbers are reason for optimism, revealing the increasing importance attached by physicians to the safety of their patients.

The new European legislation (which is to be transposed into the Romanian legislation by 21 July 2012, amending, under *Pharmacovigilance*, Law 95/2006) will also raise patient awareness related to reporting adverse reactions to medicinal products. The Agency hopes for more effective determination of medicinal product safety profile, through joint physician-patient effort, by detection and reporting of all adverse reactions in due time, meant to enrich information available on medicinal products, aiming at accomplishment of the highest possible level of safety in medicinal product administration in the EU.

In the context of preparatory work related to transposing Directive 2011/62/EU on prevention of the entry into the legal supply chain of falsified medicinal products and on creating the framework for transposition of new provisions into national legislation, one of the main goals was to establish the framework of bilateral cooperation and exchange of information in the field of human medicinal product counterfeiting, with the collaboration of the Romanian Police General Inspectorate.

Lines of NAMMD cooperation with the Romanian Police General Inspectorate were as follows:

- Compliance with legislation concerning medicinal products for human use;
- Exchange of information, for fulfilment of legal assignments of both institutions;
- Surveillance of the operation of markets to identify cases of violation of national and/or community legislation as regards medicinal product counterfeiting and of legal provisions in the field of medicinal products for human use, enabling the two authorities to take the necessary measures, according to each one's abilities and in correlation;
- Media coverage and information of the population and economic agents in medicinal product markets, concerning measures taken in case of violation of national and/or intra-community law in terms of medicinal product counterfeiting;
- Mutual support for efficient operation and safety of medicinal products for human use (required legislative amendments included).

As regards the activity in the field of medical devices, 2011 has proved a busy year, rich in events and efforts of the Technical section – Laboratories Department. As in recent years, in 2011 as well, most of the work involved control of medical devices by periodic check-ups.

This activity envisages all assembly and management of medical devices at high risk employed by all public and private medical device users; the activity consists of assessment of the performance and safety of medical devices in use.

It is worth mentioning that the NAMMD is the only institution accredited and able to assess the performance of medical devices in use, an activity carried out in spite of the understaffing of the Technical-Laboratories Department and the Nuclear Unit.

NAMMD ACTIVITIES PERFORMED IN 2011

1. Activity of the Scientific Council (SC) of the National Agency for Medicines and Medical Devices

In 2011, the Scientific Council was summoned in 5 working sessions; 29 SCDs have been adopted. Out of the 29 decisions, 5 are undergoing approval through Order of the Minister of Health and are to be published in the Official Gazette of Romania, Part I; the remainder of 24 SCDs are posted on the NAMMD website and published in the bilingual NAMMD Newsletter.

Among the regulations, guidelines and procedures debated and adopted by the Scientific Council for improving and streamlining the Agency's activity given the increased

level of complexity of its activity, as shown in the details provided under section 3, the NAMMD Scientific Council has updated and approved the NAMMD Organisational Strategy (SCD no. 14/12.05.2011) establishing the mission, vision and goals of the Agency as competent authority in the Romanian field of the medicinal product for human use and covering the period 2011-2015.

The Scientific Council has also discussed and approved the NAMMD Communication Strategy (SCD no. 15/12.05.2011), establishing the framework for internal and external communication covering the 2011-2015 period, and established the key actions required for communication development during this period.

Both strategies will be subject to second periodic updates, in the context of the same institutional framework.

2. Activity of the NAMMD Administration Council (AC)

In 2011, the Administrative Council (AC) adopted 28 Administration Council Decisions (ACDs).

Thematically speaking, ACDs have covered various aspects of current activities, mainly related to management of current circumstances, and consisted of decision documents regulating organisational issues – consecutive to structure-related changes within the institution, change of the collective labour contract at unit level, approval of the job list and organisational structure, and other issues related to current work.

3. Regulatory activity

Given the enhanced level of complexity of NAMMD activity as competent authority and member of the EU competent authorities network in the field of medicinal products for human use, due to increased patient/consumer awareness of the therapeutic act, the Agency's actions concerning legislative regulation have continued. The continuing character of the Agency's actions in the regulatory field has also been determined by the intense dynamic of the medicinal product field, aiming to enhance the safe use of the medicinal product and improve assessment-authorisation work. Thus, at both European and world level, specific legislation is undergoing continual development/update/amendment, depending on technical-scientific progress across the medicinal product research/development process and on higher expectations.

Of the 29 decisions approved by the Scientific Council in 2011, 5 are regulatory and awaiting approval through Order of the Minister of Health. These SCDs refer to:

- Approval of amendments to Order of the Minister of Health on approval of the Rules on NAMMD administrative procedure for the handling of variations;
- Approval of amendments to the Guideline on Good Wholesale Distribution Practice of medicinal products;
- Approval of the manner of implementation of amendments to marketing authorisations approved by the NAMMD;
- Approval of the new European models of package leaflet, summary of product characteristics and label information for medicinal products authorised for marketing in Romania through national procedure;
- Approval of NAMMD procedure for discontinuation of marketing authorisation/renewal applications for medicinal products for human use.

Other non-regulatory SCDs of 2011 refer to approval/amendment of certain guidelines, namely:

- Approval of Regulations for handling of proposed "umbrella" trade names and other trade names for medicinal products for human use, as related to food supplements and cosmetic products;
- Approval of Regulations for advertising of medicinal products for human use;
- Approval of guidelines on consultations with target patient groups for the package leaflet and documentation on criteria for certification and inspection by the National Agency for Medicines and Medical Devices of operators performing consultations with target patient groups;
- Approval of the Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials; approval of the Guideline on evaluation of advertising in medicinal products for human use;
- Approval of the Guideline on the bioanalytical method validation;
- Approval of amendment of a previous SCD on NAMMD authorisation of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania;
- Approval of the Guideline on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. Various rules/regulations needed in view of conducting various NAMMD activities have also been approved through SCDs, such as:
- Approval of criteria for NAMMD inspectors allowance of supply of free samples and approval of amendment to the Implementation rules on provision of free samples of medicinal products for human use authorised for marketing in Romania; approval of the mandatory monthly reporting of marketing in Romania, i.e. of medicinal product for human use sales by authorised wholesale distributors;
- Approval of new and revised Romanian Standard Terms for pharmaceutical forms, routes of administration and primary packages, in compliance with those adopted by the European Pharmacopoeia Commission;
- Approval of the Community format of the Good Manufacturing Practice (GMP) inspection report;
- Approval of the Regulations on set up of documentation in support of applications for waiver from legal provisions in force on packaging/labelling of medicinal products for human use authorised for marketing, other than mentioned in the Annex to Order of the Minister of Public Health No. 872/2006.

  Another category of objectives requiring regulation through SCD in 2011 consisted of the establishment of NAMMD organisational parameters and strategies, namely:
- Update and supplementation of the Regulation for the organisation and operation of the Scientific Council of the National Agency for Medicines and Medical Devices;
- Approval of the Organisational Strategy of the National Agency for Medicines and Medical Devices (2011-2015);
- Approval of the Communication Strategy of the National Agency for Medicines and Medical Devices (2011-2015).

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions (CAPP)

As a consequence of the setup of 3 commissions for marketing authorisation/marketing authorisation renewal approved through SCD no. 2/23.02.2010 (CAPP-National Procedure, CAPP-European Procedures, CAPP-Renewals, whose structure and manner of operation have been established through Decision no. 165/25.03.2010 of the NAMMD President), assessment

reports are discussed by the Commission, in order to provide an opinion concerning marketing authorisation of various medicinal products, as well as other aspects related to the marketing authorisation of medicinal products for human use.

In 2011, the Marketing Authorisation Commission conducted 29 working sessions for review of 1120 evaluation reports concerning dossiers submitted to the NAMMD for authorisation through national procedure /European procedures.

The commissions decided upon grant of 2030 Marketing Authorisations, out of which 883 issued through European (decentralised and mutual recognition) procedures and 147 through national procedure.

4.2. Commission for the Inspection of Good Manufacturing Practices (GMP), Good Distribution Practice (GDP), Good Laboratory Practices (GLP), Good Analytic Laboratory Practices (GALP), Good Clinical Practices (GCL) and Pharmacovigilance

In accordance with its own regulation for organisation and operation, approved through a NAMMD Administration Council Decision and in the same structure, approved through President Decision, the Commission continued its activity in 2011 as well. The Commission reviews inspection reports issued by Agency inspectors, concerning the manner of compliance by inspected units with Good Manufacturing Practice, Good Distribution Practice, Good Laboratory Practice, Good Analytical Laboratory Practice, Good Clinical Practice rules and/or with other issues concerning work of the Pharmaceutical Inspection Department.

The Commission acts as mediator in cases of inspecting decisions disputed by the inspected unit.

In 2011, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 175 inspection reports, of which:

- 47 inspection reports on compliance with Good Manufacturing Practice rules;
- 101 inspection reports on compliance with Good Distribution Practice rules;
- 10 inspection reports on compliance with Good Clinical Practice rules;
- 2 inspection reports issued prior to the grant of a marketing authorisation at the sites of Romanian manufacturers of medicinal products;
- 3 inspection reports on compliance with Good Laboratory Practice rules;
- 6 inspection reports on compliance with Good Analytical Laboratory Practice rules;
- 6 pharmacovigilance inspection reports.

4.3. Commission for verification of compliance of NAMMD inspection staff with the professional ethic and deontology code

The commission operates in accordance with Decision no. 651/2009 of the NAMMD President and with its own organisational and operation rules, as approved by Administration Council decision.

The goal of the Commission is verification of compliance by Agency inspecting staff with the Code of Ethics, as approved through Order of the Minister of Health no. 160/2004.

In 2010, there were no requests for summons of the Commission.

4.4 Commission for management of crisis situations caused by concerns arising in relation with medicinal product quality, safety and/or efficacy

The Commission for management of crisis situations operates in accordance with Decision of the NAMMD President and with its own organisational and operation rules, as approved through Administration Council Decision.

In 2011, the Commission convened in 2 working sessions to discuss management risk measures to be taken in the context of the potential radioactive contamination of medicinal products for human use as a consequence of radiations occurring in Japan.

5. Marketing authorisation and related activities

In direct relation to the diversification and increasingly stricter regulation of activities specific to a competent authority in the EU medicinal product field, year 2011 witnessed an increase in the level of complexity of work related to assessment of documentation submitted to the NAMMD for marketing authorisation (MA), renewal of marketing authorisation and post-authorisation surveillance of medicinal products.

Performed in accordance with specific provisions related to national and European procedures (mutual recognition, decentralised, repeated mutual recognition procedures), marketing authorisation and related activities have been performed in 2011 in accordance with the organisational structure established the previous year on the organisation and setup of the National Procedure Department and the European Procedures Department, approved through Order of the Minister of Health.

5.1. Marketing authorisation through national and European procedures

In 2011, a number of 2013 marketing authorisation/marketing authorisation renewal applications was received, 1150 through national procedure and 863 through European procedures (Decentralised Procedure-DCP, Mutual Recognition Procedure-MRP and "*repeat use*" procedure).

The assessment activity performed within the European Procedures Department consisted of grant of 883 marketing authorisations and Annexes 1-5, which represents an increase compared to last year (623).

As regards assessment through national procedure, it consisted of grant of 147 marketing authorisations, confirming the decreasing tendency for the number of marketing authorisations granted by the NAMMD in the past three years: MAs through NP: 359 vs. 190 (for 2009 and 2010, respectively), 2011=147. This was caused by the Agency's lesser ability to process documentation because of decreasing number of employees, staff dynamics and diminished number of applications, in favour of European Procedures (EP).

From a global overview, considering the past 3 years, 2011 was the year for grant of the largest number of MAs. Thus: MAs through NP and EP: 2009=927, 2010=813 and 2011 = 1030 MAs.

The same comparative perspective shows an almost stationary concerning the number of decisions for discontinuation of authorisation/renewal procedure, on MAH request for trade reasons, in 2009 and 2011, namely: number of MAs discontinued: 2009=134 and 2011=131, compared to 2010=202.

As regards the "*sunset clause"* provision, in 2011, the "*sunset clause*" was implemented for 177 MAs for medicinal products, which have not been actually marketed during 2007 - 2011. Moreover, the database was brought in line with documents submitted by the MAH, concerning ca. 100 submitted material (dossiers + electronic formats) by 166 MAHs; implementation of the clause will be completed in the first quarter of 2012.

5.2. Assessment of variations to Marketing Authorisation (MA) terms

5.2.1. In 2011, a number of 12427 applications for variation to MA terms were submitted for medicinal products authorised through national and European procedures, of

which 6067 applications for type IA, IB and II variations to MA terms, MA notifications for nationally authorised products and 6360 for type IA, IB and II variations to MA terms, MA notifications through European procedures.

These numbers include neither applications for discontinued variation procedure (involving medicinal products whose marketing authorisation has expired and in relation to which no application has been submitted for renewal as well as medicinal products for which decisions were issued for discontinuation of marketing authorisation or variation procedures on company request), nor variations implemented in accordance with SCD 30/2010 on approval of the manner of handling of Type IA and IB variations not amending marketing authorisation terms for nationally authorised medicinal products.

The NAMMD assessed and approved 4394 applications for variations involving medicinal products authorised through national procedure or undergoing MA renewal procedures, of which:

- 2421 type I variations;
- 435 type II variations;
- 136 applications for MA transfer;
- 232 applications for modification of the design and package labelling;
- 1170 variations on safety and efficacy.

5.2.2. As far as **post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures** is concerned, the Agency received 6360 applications for Type IA, IB, and Type II variation, notifications of marketing authorisations through European procedures in 2010:

In 2011, the following applications have been approved for medicinal products for human use authorised through decentralised/mutual recognition/repeated mutual recognition procedure:

- 726 applications for type IA variations;
- 844 applications for type IB variations;
- 280 applications for type II variations;
- 173 applications for MA transfer;
- 18 notifications in accordance with Article 61 (3) of Directive 2001/83/EC;
- 3 variations on safety and efficacy.

5.3. Assessment of applications and documentation for approval of clinical trials on medicinal products for human use

In Romania, the number of applications for authorisation of clinical trials has slightly decreased in 2011, as evident from comparing the yearly number of applications received (246 in 2011 vs. 266 in 2010, 253 in 2009 or 275 in 2008).

Most of these are Phase III clinical trials, meaning that the respective medicinal products undergo advanced research, thus being close to authorisation. Phase II clinical trials are the second most frequent type of clinical trials; these are exploratory studies concerning the most effective dose for medicinal products whose safety and tolerability have been proven.

There are few applications for performance of Phase I clinical trials in Romania, which requires special conditions.

Therapeutic areas for which clinical trial authorisation was required in 2011 have been the following, in descending order: psychiatry and neurology, oncology, diabetology, rheumatology, gastroenterology, pneumology, infectious diseases, haematology, cardiology, endocrinology.

In 2011, the NAMMD received 263 applications for clinical trial authorisation, mostly for Phase III and II clinical trials.

Moreover, 45 applications for observational clinical trials were received and handled.

In 2011, the Clinical Trial Service approved 788 substantial amendments; 115 assessment reports of clinical bioequivalence studies have been drafted.

5.4. Monitoring and control of advertising material for medicinal products for human use

In 2011, the National Medicines Agency assessed for approval 1085 advertising material to the general public concerning OTC medicinal products.

Of the all advertising material seeking approval, 29 applications were not been approved and 29 notifications were issued on rejection of advertising approval.

As regards advertising material to be used in educational programmes, 186 educational items were assessed and approved.

The content of 1600 advertising material to healthcare professionals was assessed and approved.

Monitoring and control of advertising for medicinal products for human use found further concrete form in the drafting of 2 responses to advertising complaints.

In 2011, special emphasis has been placed upon regulatory, surveillance and control work concerning advertising of medicinal products for human use. Thus, a special heading, "Advertising", has been created on the Agency's website, containing important announcements for stakeholders on this topic as well as MAH penalties applied for non-compliance with advertising rules (e.g. broadcasting of unapproved advertising materials, use of unapproved advertising channels, broadcasting of different advertising materials than approved by the Agency etc.).

5.5. Pharmacovigilance

The NAMMD manages the safety of medicinal products currently authorised in Romania via the Pharmacovigilance and risk management service, which is part of the Agency's European Procedures Department, whose activity is entirely compliant with Law no. 95/2006 and with specific European Guidelines.

As confirmed by recent increasingly marked preoccupations in the regulatory field, pharmacovigilance represents an extremely dynamic and interactive field of activity, developed in time as a requisite for patient safety. According to public documents of the World Health Organisation, pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".

As a representative entity in the field of medicinal products for human use, pharmacovigilance work already has a substantial history in Romania, as detailed in the 2010 Activity report of the NAMMD

Pharmacovigilance activity is conducted in Romania according to European legal frame, transposed into national legislation; this includes, among other activities, assessment and submission of adverse reactions through the EudraVigilance system (the European network for pharmacovigilance data-processing and management), assessment of Periodic Safety Update Reports (PSURs) as forwarded by pharmacovigilance systems of holding companies, assessment of Risk Management Plans, harmonisation of Summaries of Product Characteristics (SmPCs), by implementation of European Commission Decisions based on the recommendations of the Committee for Human Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA).

Moreover, pharmacovigilance activity has ensured (and will continue to ensure) direct healthcare professional communications referring to special warnings for product safety, as

well as translation and posting on the NAMMD website of EMA press releases and Q&A documents, actually representing notifications from the monthly CHMP meetings. An additional pharmacovigilance task is NAMMD response to requests for non-urgent information from the European and international rapid alert system.

In order to safeguard public health, all types of available information related to the safety of the medicinal product are currently posted on the NAMMD website.

To increase physicians' degree of awareness concerning the importance of adverse reaction reporting, the opportunity of symposia, national conferences and congresses is taken to encourage physicians to report spontaneous suspected adverse reactions (AR).

In this context, the incentive designed by the Agency for AR reporting, in cooperation with the Romanian College of Physicians, consists of granting Continuing Medical Education (CME) Credits to reporters, in accordance with the procedure agreed by the two institutions.

As an outcome of all such effort by the Agency and therefore by the National Pharmacovigilance Centre, Romanian physicians have proven increased interest in AR reporting throughout the last year.

If, for example, 280 spontaneous reports were recorded in 2004, 525 were reported in 2009, 938 (serious and non-serious adverse reactions) in 2010 and 1011 (serious and non-serious adverse reactions) in 2011. The numbers are optimistic, since they reveal the increasing healthcare professionals' awareness of the importance attached to safe use of medicinal products.

In 2011, pharmacovigilance activities materialised in the following:

a) handling safety data issued from spontaneous reporting:

- 1011 AR reporting records in Romania, submitted directly to the NAMMD by physicians and MAHs.

Every adverse reaction validated by the NAMMD is confirmed through a thank-you note to the reporter and is accompanied by an Adverse Reaction Reporting Form; the Romanian College of Physicians is quarterly informed about the number of adverse reactions reported by physicians in the country, allowing grant of CME credits.

- 1180 validations/confirmations of adverse reaction reports imposed by the monitoring of the single European electronic database of adverse reactions, EUDRAVIGILANCE, for medicinal products used in Romania and 759 transmissions/retransmissions of adverse reactions.

- 808 electronic transmissions of adverse reactions to the WHO database (the Uppsala Monitoring Centre) via the VigiFlow electronic channel;

- 410 confirmation points of receipt of spontaneous reporting records of adverse reactions from network physicians;

- 405 information points for physicians on granting Continuing Medical Education (CME) credits when reporting adverse reactions;

- 249 responses to MAH requests concerning adverse reactions transmitted to the NAMMD involving medicinal products authorised in Romania;

- 161 response letters on MAH requests concerning pharmacovigilance-related aspects.

b) Collection, validation and archiving of 2115 Periodic Safety Update Reports (PSURs) for medicinal products authorised through national or European procedures (decentralised, mutual recognition, mutual recognition – repeat use procedures).

In 2011, 29 PSUR assessment reports were issued for medicinal products undergoing MA renewal through national procedure.

c) Pharmacovigilance activities in the European national authority system coordinated by the EMA:

- handling of 69 EMA press releases and "Questions and Answers" documents related to medicinal product safety, of 52 "Lines to take" documents proposed by EMA for handling requests for information, 45 Direct Healthcare Professional Communications related to safety

concerns raised in relation with medicinal products;

- transmission of 152 medicinal product safety information letters to the Ministry of Health, the National Health Insurance House, the College of Physicians, the College of Pharmacists;

- 10 information letters to MAHs about the respective application for variation required for implementation of safety measures and for harmonisation of product information;

- 2 information activities for MAHs concerning SmPC and Leaflet harmonisation following referral procedures;

- 2 translations for SmPC harmonisation to be posted on the NAMMD website.

d) Pharmacovigilance activities within actions developed in the rapid alert/non-urgent information system (RA/NUI):

- 27 NUI responses to requests by certain EU authorities;

e) Assessment of compliance with requirements concerning accurate description of the pharmacovigilance system by the MA applicant:

- 1758 assessment reports on summary of the pharmacovigilance system of the applicant for marketing authorisation through European procedures (with Romania as Concerned Member State);

- 274 assessment reports on summary of the pharmacovigilance system of the applicant for marketing authorisation through national procedure.

f) Assessment of requirements concerning description of the pharmacovigilance system.

In this respect, for authorisation through decentralised/mutual recognition/mutual recognition – repeat use procedure, with Romania as Reference and Concerned Member State, 1758 assessment reports of the summary of the applicant's pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) were assessed and drafted by the specialised Service in 2011.

It is worth mentioning that year 2011 meant an intense activity for transposition of the new Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 on amendment, as far as pharmacovigilance is concerned, of Directive 2001/83/EC on the Community code relating to medicinal products for human use, scheduled for entry into force by 21 July 2012.

To this end, through President Decision, a working group has been set up in the NAMMD for transposition into national legislation of the new Directive 2010/84/EU on pharmacovigilance, amending chapter *Pharmacovigilance* of Law 95/2006.

5.6. Other activities

- Handling of the database represented by the Index of medicinal products for human use consisted of introduction of new medicinal products authorised through national/European/centralised procedure, implementation of MA changes for already authorised medicinal products, introduction of approved variations to approved MA terms, keeping track of medicinal products undergoing MA renewal and of MA withdrawal/discontinuation decisions.

In 2011, the database ensured by the Index of medicinal products for human use has been supplemented with 1085 marketing authorisations new to Romania, obtained via national, European (mutual recognition and decentralised) and centralised procedures. Among MAs newly introduced on the Romanian pharmaceutical market, the presence of new antihypertensive combinations is noteworthy: candesartan and hydrochlorothiazide, valsartan and hydrochlorothiazide, atorvastatin and amlodipine, olmesartan and amlodipine, immunosuppressants (belimumab), antineoplastics, monoclonal antibodies (ofatumumab), antivirals (boceprevir), antidiabetics (exenatid), antiepileptics (retigabin).

Moreover, in 2011, on MAH request, 140 MAs were discontinued for financial reasons. The following outcomes reflect the "parallel import" activities performed:

- grant of parallel import authorisations (PIAs) (17 PIAs)
- submission of 23 requests for information to authorities in EU member states needed for parallel import authorisation release and for amendment of the parallel import authorisation;
- requests for information by other authorities in EU Member States, for PIA release and PIA amendment .

"Parallel export" related activities:

- reply to request for information submitted by other competent authorities for PIAs release for concerned Member States (320).

The activities derived from Agency status as competent authority in an EU Member State have continued as follows:

- Management of responses received in application of provisions of Article 729 and 730 of Law no. 95/2006, i.e. notification of temporary or permanent discontinuation of manufacturing and notification of actual medicinal product marketing ("sunset clause"); ca. 100 reports have been received on behalf of 166 MAHs, for implementation of the *"sunset clause"* involving medicinal products not actually placed on the market to 2011;
- Management of the database related to EMA authorised medicinal products based on provisions of Article 127a of Directive 2001/83/EC and monitoring of implementation of conditions and restrictions placed on the MAH by the European Commission;
- Management of European Commission (EC) decisions related to referrals, draft of the letters to MAHs involved for request of transmission of variation applications for the implementation of the EC Decision.

6. Inspection of Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), Good Laboratory Practice (GLP), Good Analytical Laboratory Practice (GALP), Good Clinical Practice (GCP), Good Pharmacovigilance practice and market surveillance

In the course of 2011, the Pharmaceutical Inspection Department (PID) continued to perform the activities mentioned in specific legislation (Law no. 95/2006, Title XVII – The medicinal product and secondary legislation thereof), in accordance with the department's *Standard Operating Procedures (SOPs)*, endeavouring to accomplish its tasks by the deadlines stipulated by law.

The following have been prepared and issued in the pharmaceutical inspection activity:

- 25 Good Manufacturing Practice (GMP) certificates (for Romanian and foreign manufacturers);
- 52 manufacturing authorisations, annexes included;
- 46 import authorisations, annexes included;
- 1 Good Laboratory Practice (GLP) certificate;
- 21 certificates for Qualified Persons;
- 7 authorisations for independent control units;
- 139 dossiers for the inspected units, and for units requesting update of annexes to manufacturing/import authorisations have been issued and handled;
- 123 applications for waiver from legal provisions concerning medicinal product packaging/labelling have been solved;
- management of databases of inspection encoding, the list of authorised/certified manufacturing units, authorised importers, medicinal products for which the export declaration has been approved, and Qualified Persons.

Inspection work in the fields of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Analytical Laboratory Practice (GALP), Good Clinical Practice (GCP), and Good Pharmacovigilance in 2011 consisted of:

- 30 GMP inspections for manufacturing authorisation conducted in Romania;
- 17 inspections for authorisation conducted at the site of medicinal product importers;
- 8 certification inspections for GMP compliance of pharmaceutical companies from third countries;
- 2 unannounced inspections for certification of GMP compliance conducted at the sites of Romanian medicinal product manufacturers;
- 3 GLP inspections to laboratories performing bioequivalence studies;
- 6 GALP inspection at independent quality control units;
- 10 inspections for assessment of compliance with GCP rules;
- 6 pharmacovigilance inspections at Romanian MAH sites, and Romanian MAH representatives sites, according to the yearly inspection plan of the Pharmaceutical Inspection Department.

In May 2011, a NAMMD-PID inspector and an inspector from the Agence Française de Sécurité Sanitaire des Produits de Santé, participated in an inspection requested by the European Medicines Agency (EMA), enforcing the reconfirmation of GMP compliance by an US manufacturer for a centrally authorised product.

In the context of Good Distribution Practice (GDP), inspections conducted in 2011 were as follows:

- 101 inspections for authorisation have been conducted;
- 50 wholesale distribution authorisations have been released;
- 88 follow-up inspections have been conducted to assess the distribution activity and the manner of enforcement of corrective actions proposed through measures submitted to the NAMMD for authorisation;
- 11 unannounced inspections at wholesale distribution units authorised by the NAMMD have been carried out, following which:
- 3 authorisations were suspended;
- 8 breach of law penalties were enforced;
- 24 authorisations were withdrawn following detection of major deficiencies during inspections for authorisation;
- 7 inspections for supervision of the quality of distributed medicinal products were performed, consisting of check of traceability of medicinal products purchased/traded by wholesale distributors. This led to application of a breach of law penalties and suspension of the wholesale distribution authorisation for 1 inspected unit;
- the dossier for 570 applications for approval of export declaration was approved, leading to approval of export declarations for 2043 medicinal products manufactured in Romania.

As regards certification of Qualified Persons, the dossier for grant of the Certificate attesting the Qualified Person status was checked and assessed; 21 such certificates were released.

Activities concerning surveillance of medicinal product quality and handling of rapid alerts consisted of:

a) Carrying out the sampling scheme for medicinal product quality monitoring:

- Of the 39 products proposed, 17 were sampled and 12 were not found in the distribution network;

Laboratory testing results issued have been as follows:

- The 17 samples have been declared appropriate, following laboratory analyses.

In addition to the sampling scheme, the following samples were also provided in 2011:

- 6 medicinal products sampled on request of the Quality Control Department, for

participation in market surveillance studies proposed by the OMCL network (Official Medicines Control Laboratories); all samples of medicinal products have been declared appropriate;

- 4 medicinal products sampled for resolution of medicinal product quality complaints, of, which 3 have been declared noncompliant with quality standards and have been recalled from the market;

- 3 medicinal products sampled from distribution units within the EMA/EDQM coordinated scheme for surveillance of centrally authorised medicinal products; the testing of these products has been performed by laboratories in other EU competent authorities, and the results were found compliant.

b) follow-up inspections of the quality of medicinal products in the distribution network (warehouse, pharmacies):

- 330 thematic inspections in 2306 wholesale and en detail distribution units.

c) inspections of the quality of oxygen used in hospitals:

- 172 were carried out in hospitals across the country to stop use of unauthorised oxygen (liquid oxygen is provided by GMP certified producers, whereas compressed oxygen for 8 hospitals (5%), less than the previous year, is still provided by unauthorised manufacturers). The Ministry of Health has been informed on the situation.

d) Cooperation with other bodies for resolution of issues related to legislation in the field of medicinal products and/or the quality of certain products sold in Romania:

- 10 joint actions with specialised local bodies, carried out by territorial inspectors (7 Cluj, 1 Târgu Mureş, 1 Galaţi, 1 Satu Mare).

e) Resolution of complaints relating to possible quality noncompliances of medicinal products for human use:

- of 22 complaints, 21 have been resolved (for the remaining 1, resolution is pending); of the 21 complaints resolved, 12 had no consequence and 9 were found justified, resulting in recall of the respective medicinal products from the market. Most complaints received (17) have been filed by NAMMD inspectors and referred to inappropriate imprinting of primary/secondary packaging or set up of Leaflets of certain medicinal products. Remaining complaints have been filed by patients or healthcare professionals.

f) Recall from the market of medicinal products displaying quality noncompliances: in 2011, the NAMMD requested recall of 48 medicinal products (fewer than during the previous year), of which:

- 32 medicinal products were identified with intrinsic quality nonconformities and have therefore been proposed for destruction (7 following complaints, 4 due to rapid alert, 21 voluntary recalls performed by manufacturers);

- 8 medicinal products had packaging/leaflet inscription nonconformities and have been proposed for remedy/destruction;

- 8 medicinal products recalled in accordance with Order of the Minister of Health no. 279/30.03.2005.

g) Rapid alert system:

- in 2011, 93 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Of these, 4 have approved products authorised and imported/distributed in Romania; in 2011, the NAMMD issued no Rapid Alert.

h) Cooperation with the EMA, the EDQM, European competent authorities, concerning surveillance of the quality of raw materials/finished products manufactured in third countries:

- 16 cases reported (2 by Romania) of non-compliance with GMP rules by active substances or medicinal products manufacturers from third countries, for,which steps taken were in accordance with joint authorities' decisions;

- 6 certificates of conformity with the European Pharmacopoeia were suspended by the EDQM, for which steps were taken to change active substance suppliers.

i) Creating and updating the databases for all PID services, updating information on the NAMMD website and introducing in the EudraGMP database the information concerning NAMMD activities concerning manufacturing authorisation/import/GMP certification.

j) Coordination of activities of the Territorial Inspection Units (TIU) related to surveillance of medicinal product quality.

7. Quality and control of medicinal products for human use

Quality control of medicinal products for human use is part of the NAMMD general policy aiming to accomplish its mission of ensuring medicinal product quality, safety and efficacy.

This activity is carried out within two departments: the Medicines quality control department (MQCD), and the Biological products control department (BPCD).

Activities in both control departments are carried out in a process-based approach, in line with requirements of standards SR EN ISO 9001/2001 and SR EN ISO 17025/2005.

Both NAMMD control departments are integrated into the European network of Official Medicines Control Laboratories (OMCL), coordinated by the European Directorate for the Quality of Medicines (EDQM), and participate in all related activities.

7.1. The main types of analysis performed by the Medicines Quality Control Department (MQCD) are: physico-chemical analysis, pharmacotoxicological analysis, immunogenetics and pathological anatomy analysis, micro-biological analysis and radio-pharmaceutics analysis.

Core activities in 2011 dealt with:

a) Quality control of non-biological (chemical) and biological medicinal products.

In 2011, 95 medicinal products were analysed, of which:

- 41 obtained through chemical synthesis; 206 laboratory analyses were conducted for quality investigation: cromatographic (HPLC - High Performance Liquid Chromatography and TLC – Thin Layer Cromatography), spectrophotometric (UV, IR) and potentiometric analyses, physico-chemical identifications, dissolution testing and others;

- 54 biological medicinal products (vaccines, sera), the majority of which, except for 2 imported batches, have been manufactured by the “Cantacuzino“ Institute; the analysis of the 54 medicines required physico-chemical, pharmacological, immunological and microbiological determinations.

- To this, 900 internal analyses of environmental checks, calibration of equipment, testing of the suitability of the systems and used equipment were added.

Out of all medicinal products analysed, the quality of 3 was non-compliant; several non-compliances have been reported, e.g. the inappropriate aspect of the solutions.

b) Evaluation of chemical-pharmaceutical documentation (DSSA, clinical studies, finished products).

In 2011, the MQCD assessed documentation for 770 medicinal products undergoing authorisation, most of, which referred to assessment of Active Substance Standard Dossiers (719).

As regards assessment of the clinical trial dossier, 20 full quality studies have been assessed (active substances, Investigational Medicinal Products) all undergoing VHP procedure (Voluntary Harmonisation Procedure, a voluntary harmonised assessment procedure for multinational clinical trials in the EU), as well as 10 amendments to documentation for Investigational Medicinal Products.

Another MQCD activity was evaluation of products included in the Sampling and Testing Plan (STP), sampled by the Pharmaceutical Inspection Department which, as required, involves physical-chemical, pharmacological, microbiological or radiopharmaceutical testing. Laboratory investigations have not evidenced quality deficiencies or noncompliances with MA provisions, except for one product; for the rest of the products, MAHs were recommended to amend and/or supplement control methodologies and submit them for NAMMD approval, as variation to MA terms.

As regards grant of surveys for (medicinal) products with quality deficiencies, counterfeited or from illegal marketing, it is worth these are performed upon request of other state institutions: the Court, the Public Prosecutor's Office, the Ministry of Health, the Police etc.

In that respect, 6 such products, not authorised for marketing, have been analysed, confiscated and sent for analysis for survey purposes by the Ministry of Health and the Ministry of Administration and Internal Affairs; the results will be used as evidence in law courts. Some of the main deficiencies observed were presence of a composition other than declared, labelling and packaging deficiencies, lack of MA.

c) European and international cooperation concerning medicinal product quality.

As in previous years, in 2011 as well, the MQCD continued collaboration with European institutions dedicated to medicines quality control, by taking part in studies initiated and coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM):

- 3 PTS (Proficiency Testing Scheme) studies held annually, testing the capacity and professional ability of each laboratory within the European network (Official Medicines Control Laboratories = OMCL), to resolve highly difficult issues encountered in quality control of medicinal products.

- 1 study on the quality of medicinal products authorised through Mutual Recognition Procedure (MRP): inter-laboratory tests for medicinal products authorised through European procedures, in accordance with the document for cooperation for post-authorisation surveillance of the quality of medicinal products authorised through MRP/DCP. Following testing, the product batches sampled from national territory were found appropriate, the control methodology reproducible; respective results have been registered in the *MRP database*.

- 1 MSS (Market Surveillance Study) for surveillance of the European market, organised by the EDQM. Such studies consist on collection of samples from the market and their testing, by comparison with an EDQM provided standard product, according to a single analytical protocol, irrespective of the methodologies underlying grant of national MAs, which may differ among manufacturers.

The tests performed by the MQCD by comparison with a standard product have been compliant with quality requirements imposed by the protocol; all batches were considered appropriate.

- 3 inter-laboratory studies within the International Pharmaceutical Federation (FIP), with positive conclusions and analytically acceptable results.

7.2. The activity of the **Biological Product Evaluation and Control Department** (BPECD) covers the following aspects:

A. Quality assessment of medicinal products for human use such as: vaccines, therapeutic biological products, *in vivo* diagnostic products.

This important coordinate of BPECD laboratory activity involves:

a) Current laboratory control of quality parameters of national and imported biological products:

- 54 sets of product samples have been analysed corresponding to a number of 412 laboratory tests;

- 103 bulletins have been issued.

As opposed to 2010, laboratory testing work has decreased. The diminished number of applications for testing submitted in 2011 has mainly been determined by manufacturing authorisation only for the seasonal influenza vaccine, for the "Cantacuzino" Institute (internal manufacturer) (whose products underwent "batch to batch testing" for batch release procedure).

In 2011, 18 batches of trivalent influenza vaccine (holding a manufacturing authorisation) and 36 batches of medicinal products already subject to manufacturing/release on the date of manufacturing authorisation expiry have also been sampled from INCDMI "Cantacuzino", for testing by the Biological Product Evaluation and Control Department.

No batches of biological products were rejected after laboratory testing.

b) Official batch release for circulation in Romania of Romanian biological products for human use from third countries and EU Member States for which no official batch release was performed in the EU, for various reasons.

For the purposes of official batch release procedure involving biological products, manufacturer batch summary and batch release certificate (also known as compliance certificate) are also assessed.

Implementation of the official batch release procedure requires sampling for laboratory testing. Finished, intermediate and bulk products were sampled in 5 sampling sessions.

For biological products tested, 54 batch release certificates were issued and no bulletin of non-compliance.

A total number of 216 trading intentions were registered as related to products for which official batch release was performed in the EU.

c) Control of biological products for human use subject to complaint or included in the recall scheme, on PID request.

As regards handling of complaints, testing was conducted on PID request on a human biological product batch, included in the PID sampling plan, following market surveillance.

d) External collaborations concerning biological product quality.

Throughout 2011, via the Cell culture laboratory - measurements and specific microbiology, the BPECD participated in one Proficiency Testing Scheme (PTS) study, performed at the initiative of and coordinated by EDQM (PTS118: *Influenza vaccine potency assay*); the laboratory was rated "*Satisfactory"*, thus ranking among the 9 laboratories awarded positive rating in the context of 15 European laboratories involved in the study, thus reconfirming the competitive level of BPECD laboratory testing.

Moreover, in 2010, 2 batches of biological products for human use included in the sampling plan following PID surveillance of the market were tested within BPCD Laboratories.

B. As regards documentation submitted for assessment/renewal through national, mutual recognition and decentralised procedures for marketing authorisation/marketing authorisation renewal and approval of variations:

- 23 products have been assessed through national procedure and 46 reports have been issued;
- support documentation for 437 variations submitted through national procedure has been assessed;
- 20 products have been assessed through mutual recognition/decentralised procedure; 12 reports have been issued;
- 62 variations have been assessed through mutual recognition/decentralised procedure; 69 reports have been issued.

Moreover, in 2011, the *worksharing* procedure has been initiated (for implementation of provisions of Article 46 of Paediatric Regulation no. 1901/2006) and reports have been drafted in accordance with the established schedule, as Reporting State.

C. Assessment of documentation submitted for approval of applications for clinical trial conduct (assessment of quality and pre-clinical documentation):

- 23 reports (19 assessment reports of the quality documentation, 3 assessment reports for pre-clinical safety and one assessment report for post-authorisation supplementations).

D. Post-authorisation surveillance by registration of all imported biological products for human use:

- 148 batches of authorised marketed biological products have been registered in the BPCD database.

8. Ensuring communication and transparency

The NAMMD pays special attention to ensuring good information transfer and communication with stakeholders and the media, in accordance with Law no. 544/2001 on free access to information of public interest and of Law no. 95/2006, Title XVII – The medicinal product on transparency in the work of EU competent authorities.

8.1. External communication

The agency provides good and accurate information to partner institutions on activities in all domains within its scope.

On its website, the NAMMD publishes bilingual Newsletters, which reflect its busy regulatory work in the area of medicines in line with European legislation and other Agency priority activities. The content of the NAMMD Newsletter includes:

- Laws, ordinances, Government decisions in the field of medicinal products for human use or other areas of NAMMD interest;
- Orders of the Minister of Health for approval of NAMMD Scientific Council decisions and Orders of the Minister of Health in other areas of NAMMD interest;
- Decisions of the NAMMD Scientific Council;
- Decisions of the NAMMD Administrative Council;
- Quarterly list of applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD;
- Quarterly List of EMA newly centrally authorised medicinal products, for which the European Commission issued the decision on translation into Romanian of medicinal product information;
- Quarterly list of medicinal products authorised for marketing by the NAMMD;
- A quarterly list of medicinal product batches recalled by the NAMMD for quality defects.

The NAMMD develops the Index of medicinal products for human use, including all medicines authorised for circulation in the pharmaceutical market in Romania, with data on trade name, International Non-proprietary Name (INN), active substance, marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, manner of release etc. and posts it on its website. In 2011, implementation began, for each medicine, of electronic versions of the Summary of Product Characteristics (SmPC), leaflet and information on labelling and inscription.

The NAMMD develops and keeps updated information available on the Agency's bilingual website. Hence, the NAMMD website has published and continually updated the following information and documents:

- Press releases relating to safety of medicinal products;

- Direct healthcare professional communications;
- Notifications to Marketing Authorisation Holders (MAH) or other interested parties on issues of interest;
- Information related to medicinal products authorised through centralised procedure;
- SmPCs for medicinal products authorised in Romania through mutual recognition procedure and decentralised procedure;
- SmPCs for medicinal products authorised in Romania through national procedure;
- List of NAMMD employees assigned as full members/alternates in the Management Board, scientific committees and working groups of the European Medicines Agency (EMA);

The following information is permanently posted and updated under "Pharmaceutical inspection":

- List of Romanian manufacturers of medicinal products and active pharmaceutical substances;
- List of third country manufacturers, certified by the NAMMD;
- List of Romanian importers of medicinal products;
- List of Romanian distributors of medicinal products;
- List of laboratories of control of medicinal products;
- List of recalled batches;
- List of Qualified Persons approved by the NAMMD,

as well as other contact data for submission of medicinal product quality complaints.

For support of external partners involved in European procedures for the marketing authorisation of medicinal products for human use, the NAMMD website contains two sections dedicated to these procedures,, which have also been posted on the new website:

- <CP> (centralised procedure)
- <MRP and DCP> (mutual recognition procedure and decentralised procedure), containing data on contact persons and useful information for authorisation through these procedures.

The following headings were considered of particular utility by external NAMMD website users:

a) Legislation in the medicinal product field, structured according to the type of regulatory act:

- Laws, Ordinances, Government Decisions;
- Orders of the Minister of Health;
- NAMMD Scientific Council Decisions;
- NAMMD Administration Council Decisions.

b) The Index of medicinal products for human use authorised for marketing on the Romanian pharmaceutical market.

c) Important notifications and EMA and NAMMD Press releases.

The large number of visitors of the NAMMD website, over 100 000 visitors/year, is proof of increased stakeholder interest in information posted.

Moreover, in 2011, the NAMMD continued to inform stakeholders about its activity, otherwise than via NAMMD Newsletters. Thus, several articles were published in Romanian professional magazines ("Farmacist.ro", "Medical Business", "Medica Academia, "Pharma Business") referring to various issues related to Agency work.

NAMMD representatives have participated with professional presentations in numerous scientific/professional manifestations held in Romania and abroad.

8.2. Internal communication

In 2011, the Agency continued supplementation and update of information (available to

NAMMD staff on the Intranet), for best and least time-consuming professional/organisational information.

NAMMD staff has access to the following information available on the "Intranet":

- Instructions of the NAMMD President;
- NAMMD quality-related policies;
- NAMMD regulations;
- Glossary of quality assurance;
- Activity plans of each department;
- Useful forms;
- Information provided by the Pharmacopoeia service;
- Information about training courses organised by the NAMMD or by professional companies;
- Reports issued by the employees receiving training in Romania and abroad;
- Situation of staff training;
- Outcomes of the "staff motivation" poll;
- Useful information;
- Useful addresses etc.

9. Quality management activity

In 2011, taking into consideration the *quality policy and quality objectives*, established by the top management, as well as processes identified and applied, the size and structure of the NAMMD and *SR EN ISO 9001* and *9004* principles in force, the Quality Assurance Bureau, together with the other organisational structures, have taken part in the implementation, development and improvement of the Quality Management System (QMS) in the context of NAMMD organisation.

Activities have been performed as follows:

- The internal quality audit process was carried out in accordance with the Internal Quality Audit Program in 2011, approved by the President of the organisation.

- Findings and conclusions of internal quality audits, whose objectives consisted of ensuring compliance with Standard Operating Procedures (SOPs) applying to audited processes, have been mentioned in internal quality audit reports, submitted to audited organisational structures and top management in order to improve audited processes/products (services). Internal quality audit reports have been accompanied by action plans for improvement issued by audited departments and by reports on the level of implementation of improvement actions proposed due to previously conducted internal quality audits.

- Amendment (review) process of general SOPs (research, set up, drafting, approval, dissemination) was carried out through amendment/review of 1 SOP, in accordance with requirements of international standards in force;

- Grant of quality management-related consultancy to the various NAMMD organisational structures and the processing of objective evidence for good performance of the BEMA II Audit of May 2011, as well as implementation on the Intranet of benchmarking team's recommendation concerning control/communication of general SOPs suited for organisation level;

- New update of declarations of interest, privacy commitments/individual and general job description.

- Set-up and update of Quality Assurance Bureau databases (in electronic format).

- Quality-related counselling.

- Provision of data/information requested by the Romanian Court of Accounts as the audit team, determined by the control of circumstances, evolution and manner of NAMMD administration of the public and private state heritage;

- Participation of NAMMD experts in specialised quality management training.

10. Medical devices

10.1 Control activity through periodic update of medical devices

As of 2010, after merger with the Technical Office for Medical Devices, the NAMMD has become the single institution assigned for assessment of performance and safety of medical devices in use.

The new control activity, namely periodic check-up of medical devices, was thus carried out in 2011 for all medical devices installed and commissioned of high degree of risk, at the sites of all medical device user, both private and public. In 2011, work of the Technical Laboratory Department staff was as follows:

- Number of applications for registration: 1058;
- Number of periodic check-up bulletins issued: 1588;
- Number of notices for use issued: 173;
- Number of medical devices assessed: 5544;
- Number of Mobile intervention units assessed: 658;
- Number of reports on negative laboratory tests (rejected medical devices) issued: 44 (of, which 22 rejected by the Nuclear unit).

In terms of laboratory testing, the following may be mentioned:

- Laboratory testing for certification: 2 ample works, conducted in several stages;
- Participation in technical surveys: 1 action, conducted at the Emergency University Hospital Bucharest;

In 2011, RENAR transferred to the NAMMD the function concerning accreditation and reaccreditation of laboratories for medical device control and testing;

In spite of several (particularly financial) issues, given the need to maintain acceptable safety and performance level of medical devices in use, the Technical section-laboratories made special efforts to ensure constant activity, in line with superior performance parameters.

10.2 The activity of inspection and assessment of technical-medical units

The Technical-Medical Units Assessment Service conducts its activity in accordance with Law No. 176/2000 on medical devices, as amended, and with Order No. 1636/2004 on approval of Methodological rules for implementation of Law No. 176/2000, as amended, referring to notification of medical technique units.

This activity consists of assessing the organisations' ability to perform services requiring notification from the Ministry of Health. Activities assessed deal with optics, medical device commissioning, repair and maintenance, prosthesis (auditory/orthopaedic/other types). The service covers such work throughout the country, performing not only initial unit assessment for approval and surveillance assessments every two years for continued approval, but also detection and application of penalties for infringement of legal provisions as per Law No. 176/2000.

In 2011, staff of this service accomplished the following results:

- Number of registered applications for assessment: 194;
- Number of assessment performed and reports issued: 117;
- Number of activities cancelled (for reason of unsubmitted assessment dossier): 22;
- Number of activities cancelled (for reason of purely trading character of the respective organisation): 11;
- Number of ongoing works: 44;
- Number of assessment-surveillance works: 325;

- Number of conducted assessment-surveillance works, reported: 116;
- Number of ongoing assessment-surveillance works at the end of the year: 110;
- Number of assessment-surveillance works resulting in acknowledgement of cessation of activity or approval of performance: 39.

In the same year, 5 control activities were performed, resulting in application of 3 penalties for breach of legal provisions.

11. International relations

In 2011, NAMMD specialists continued to take part in activities of various cooperating European institutions and organisations:

11.1. Participation in activities of the European Medicines Agency (EMA)

Since 2003, at the initiative of the European Medicines Agency, the NAMMD actively participated through its representatives in the initiative of the European Medicines Agency**,** as active observers to working groups, scientific committees and groups for enforcement of information technology, all related to the medicinal product.

This participation has represented and still represents the optimal means of keeping the Agency connected to European activities in the field of the medicinal product for human use.

Full members since 2007, participating in EMA scientific committees and working parties, NAMMD experts participated in over 100 meetings in 2011. EMA Scientific Committees and Working Groups are:

- The Committee for Medicinal Products for Human Use (CHMP);
- The Committee for Orphan Medicinal Products (COMP);
- The Committee for Herbal Medicinal Products (HMPC);
- The Paediatric Committee (PDCO);
- The Committee for Advanced Therapies (CAT);
  The CHMP Safety Working Party);
- The CHMP Pharmacovigilance Working Party – PhWP, whose activity will be discontinued on entry into force of Directive for amendment and supplementation, in the pharmacovigilance field, of Directive 2001/83/EC, by the beginning of July 2012, on replacement with the Pharmacovigilance Risk Assessment Committee - PRAC; CHMP Blood Products Working Party;
- CHMP Biologics Working Party;
- CHMP Vaccines Working Party;
- The CHMP/CVMP Quality Working Party;
- The GMP/GDP Inspectors Working Group;
- The Subworking Group on the EudraGMP Database;
- The GCP Inspectors Working Group;
- The GLP Inspectors Working Group;
- The Pharmacovigilance Inspectors Working Group;
- The Working Group on the database of medicinal products authorised in the EU (EudraPharm TIG);
- The Working Group on the database of adverse reactions (EudraVigilance TIG);
- The Working Group on the European database for clinical trials (EudraCT Clinical trials TIG);
- The Working Group on the European network (EudraNet TIG);
- The Working Group on the electronic transmission of data (e - Submission);
- The Working Group on European Union Telematics Controlled Terms (EUTCT);

- The Working Group on Product Information Management (PIM);
- The Working Group of the Quality Review of Documents;
- The Invented Name Review Group.

11.2. Participation in activities of the "Heads of Medicines Agencies"

NAMMD representatives are actively involved in meetings of the "Heads of Medicines Agencies" (HMA) European body and in the meetings of the Working Groups of this body, namely:

- The Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD-h);
- The HMA Working Group of Quality Managers;
- The EMACOLEX - European Medicines Agencies Cooperation on Legal Issues;
- The Working Group of Communication Professionals (WGCP);
- The Working Group of Enforcement Officers (WGEO);
- The Clinical Trials Facilitation Group (CTFG);
- The Homeopathic Medicinal Products Working Group (HMPWG).

11.3. Participation in activities of the European Union Council and of the European Commission (EC)

In 2011, NAMMD experts participated in meetings of the Council of the European Union and of the European Commission (EC), i.e. the Working group on medicinal products and medical devices of the EU Council, where proposals for amendment of Directive 84/2010/EU have been discussed, the Permanent Committee for Medicinal Products for Human Use, the Appeal Committee for medicinal products for human use, the Working Group of the European Commission on discussion of amendments to Notice to Applicants on draft of Notice to Applicants updated version.

11.4. Participation in World Health Organisation (WHO) activities

The NAMMD is a member of the WHO Scheme on certification of the quality of medicinal products circulating on the international market.

In 2010, the Agency released the Certificate of the product in WHO format for 490 medicinal products of Romanian manufacturers seeking authorisation for these products in other states.

11.5. Participation in European Council activities

In 2011, NAMMD representatives participated in the two meetings of the Committee of Experts on Minimising the Public Health Risks Posed by Counterfeiting of Medical Products and Related Crimes (CD-P-PH/CMED) of the European Council, organised by the European Directorate for the Quality of Medicines (EDQM), as well as to the Committee of Experts on the classification for release of medicinal products for human use.

11.6. Participation in European Pharmacopoeia Commission activities

NAMMD representatives as members of the European Pharmacopoeia Commission, have been actively involved in specific working sessions in 2011, as well as in the yearly meeting of the secretaries of the national Pharmacopoeias from countries belonging to the Convention on the Elaboration of a European Pharmacopoeia.

The cooperation with the European Directorate for the Quality of Medicines (EDQM) was continued, for issuance and update of the "Romanian Standard Terms", in accordance with those adopted by the European Pharmacopoeia Commission.

11.7. Participation in activities of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)

NAMMD activity as a PIC/S member consisted of participation through its representatives in the two yearly meetings of the PIC/S Committee of Officials, participation in the joint visit organised by the Polish inspectorate, as well as in the annual PIC/S organised training seminar for inspectors on "Good Inspection Practice".

11.8. Participation in the activities of the Official Medicines Control Laboratories (OMCL)

In 2011, in the context of NAMMD cooperation with European institutions in the field of medicinal product control, the Agency laboratory experts participated in 5 trials:

- 3 Proficiency Testing Scheme (PTS) analytical studies performed at EDQM initiative and under coordination of the same, both carried out within the Quality Control Department and the Biological Products Evaluation and Control Department;
- 1 study of surveillance of medicinal product quality authorised through mutual recognition procedure (MRP);
- 1 study of surveillance of medicinal product quality (MSS).

These activities are described under sections 7.1 c) and 7.2 d).

12. Information, Logistics and Electronic Management of Data

In 2011 as well, the Logistics and Information Service managed preservation of optimum parameters of communication channels with the EMA and provision of real-time information exchange between the Agency and external collaborators (MAHs, distributors, healthcare professionals, patients, organisations and associations).

In 2011, maintenance, amendment and update was continued of the Product Index of medicinal products for human use database, for improved work in the field and response to new requirements arising from its use. Moreover, statistical data reports were extracted periodically on request by the Minister of Health, the National Health Insurance House, the NAMMD President and various Agency departments.

As regards cooperation with other institutions, forms have been transmitted as per EMA request containing responses on the preparation stage for submission of data in electronic format and necessary steps have been taken to ensure access to the external experts' database under EMA administration.

Throughout the year, maintenance of connections to the European EudraNet network (EudraCT, EudraLink, EudraMail, EudraPharm, EudraVigilance, PIM, CTS, EPITT) was monitored.

Maintenance of the NAMMD website (*www.anm.ro*) and other software applications has been ensured throughout the year (search engines – Index, search after key words, handling of recalled medicinal products, handling of GMP units - all pending); a new section, "Suggestions", and a new website, "Counterfeiting" (ongoing project – *www.crimemedicine.ro)*. At the same time, many activities concerning setup of the new NAMMD website – *www.anmdm.ro* - have been ensured; the NEWCADREAC (*www.newcadreac.org*) and the Agency's new intranet website have been maintained, amended and updated.

Maintenance and administration of NAMMD servers (folder servers, web-intranet servers, internet servers for several services, accounting servers) have been ensured.

Moreover, an EMAIL server has been set up and configured on the Linux platform for the new domain, anmdm.ro, containing future users' accounts.

Also, maintenance and troubleshooting of software and hardware of existing computers was performed and installation and configuration of new computers were ensured.

The NOD 32 antivirus program and other security programs have been maintained and administered on the Agency's servers.

The implementation of the integrated ROMSYS system benefited from logistics support required for the system's implementation at NAMMD headquarters and lead to the training of NAMMD employees on the informatics system as well as installation and configuration of the "client" application on NAMMD workstations. In the same context of the integrated system for management of document flow, the online submission portal has been presented during a course organised by the NAMMD for the pharmaceutical industry.

The Data and Document Management Service ensures receipt of documents at Agency level and their distribution to concerned offices, release of all documents in the Agency to external collaborators to facilitate swift movement of documents among Agency departments.

A number of 1030 marketing authorisations and their annexes have been issued in 2011.

Also, typing/drafting has been insured for:

- 490 product certificates in WHO format for Romanian medicinal products;
- 185 letters for 761 medicinal products, confirming status of the medicinal product undergoing renewal of marketing authorisation, bearing the "suitable for marketing" specification";
- 516 notification letters sent to manufacturers on MA release in accordance with President directions and maintenance of a copy in the product dossier;
- 103 commitment notifications sent to manufacturers on MA release and their maintenance in the authorisation dossier.

Receipt, administrative assessment and registration in the entry/exit Register and introduction into "Registry A" and the "Pending work" databases of:

- 1150 applications for marketing authorisation/marketing authorisation renewal through national procedure;
- 863 applications for marketing authorisation/marketing authorisation renewal through DCP/MRP;
- 6067 applications for Type IA, IB, II variations, MA notifications through national procedure;
- 6360 applications for Type IA, IB, II variations, MA notifications through decentralised/mutual recognition procedure;
- 6383 drafts and payment forms for issue of invoice for marketing authorisation/marketing authorisation renewal and variations through decentralised/mutual recognition procedure;
- 437 drafts and payment forms followed by submission of the application for approval of clinical trial conduct and amendments;
- 17199 documents (responses to NAMMD requests for MA authorisation/renewal documentation, variations, clinical trials, advertising, adverse reaction reporting etc.);
- 29 meetings of the Marketing Authorisation Commission(s) have been organised and 1120 product dossiers have been assessed.

13. Ensurance of set-up and implementation of NAMMD policies and strategies

In 2011, the Policies and Strategies Department (PSD) contributed to fulfilment of the NAMMD mission, by setting up Agency policies and strategies in its fields of activity, namely by updating:

- *The organisational strategy*, establishing strategic objectives and Guidelines of the Agency's activity, in accordance with the legal framework in force, and the relationship between the NAMMD and the Ministry of Health and between the NAMMD and stakeholders;

- *The communication strategy*, establishing objectives of internal and external Agency communication activity and strengthening its status as expert and reliable source of accurate information in the medicinal product field, provided in due time to stakeholders: healthcare, research and industry professionals, patients, general public and the media.

In 2011, the PSD participated intensely in elaboration of a regulatory act transposing Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, duty assumed by the NAMMD in the context of the transposition schedule requested by the Ministry of Health. This regulatory act for transposition of Directive 2010/84/EU amends Law 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended.

Together with the other professional departments, the PSD participated in proper NAMMD operation in the European network of competent authorities in the field of the medicinal product, acting as interface between the Agency and the European and international authorities in this field through:

- Handling and monitoring of participation of NAMMD staff assigned as full members or alternates to scientific committees and working groups of the EMA, HMA, EDQM, European Council, EU Council, European Commission, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);

- Insuring communication with the EMA for assignment of NAMMD experts as full members/alternates;

- Communication with the secretariats of working groups/scientific committees of the cited bodies in view of form transmission, as well as through:

- Intervention as interface between various NAMMD departments, through monthly monitoring/centralisation of attendance of NAMMD experts assigned in meetings of working groups/committees.

Similar to the previous year, the PSD managed to ensure the secretarial activities for the NAMMD Scientific Council (SC) and organisation (in accordance with the interdepartmental SOP) of the 5 SC meetings through:

- Centralisation and check-up of 29 SC draft decision projects, set up of the SC agenda, forwarding of documents to SC members in electronic format or on paper;

- Handling of the electronic versions of SCDs from draft status to publication (both in the Official Gazette of Romania, Part I, for SCDs approved through Order of the Minister Health, as well as on the NAMMD website, under the headings "Legislation" and "Informative Bulletins") in the directories for Scientific Council meetings;

- Forwarding of documents assessed in electronic format/on paper to SC members; - updating the record of contact coordinates of SC members;

- Drafting of the minutes of SC meetings;

- Out of the 29 SCDs approved in 2011, 4 have been submitted for approval through Order of the Minister of Health and 25, non-regulatory, have been posted on the NAMMD website and published in the Agency's bilingual Informative Bulletins.

The Policies and Strategies Department prepared, issued/ensured final check-up for publication on the Agency's website for:

- 159 regulatory documents, in Romanian and English version;

- 57 amendments, supplementations, recalls of legislative documents published on the website;

- Outline and editorial style of applications and forms to be posted under the heading <Forms> on the website;

- NAMMD informative bulletins in English and Romanian;

- The bilingual brochure containing NAMMD's annual report.

Development of NAMMD Informative Bulletins (IBs) was continued; these were posted on the NAMMD website, namely: 5 IBs in Romanian (no. 3-4/2010, 1-3/2011).

Delays, for objective reasons, of IB translation into English were recovered during this year, as well, and 8 IB issues were completed, covering year 2010 and 2011.

In collaboration with the other NAMMD departments, the PSD updated and improved information on the Agency's website and the NAMMD intranet.

The European Affairs Service ensured, via its trained staff:

- Translation of the NAMMD self-assessment questionnaire for the BEMA II audit in May 2011;

- Translation of the quality manuals of the NAMMD, BPECD and of the Pharmacovigilance and risk management service;

- Translations for elaboration of the consolidated glossary for harmonisation of terms used in medicinal product information in Romania;

- Translation/Review of 15 European guidelines;

- Translation of reports and updates related to the crisis situation determined by radioactive leaks in Japan;

- Checking the translation of 3 evaluation reports and documents in English, for mutual recognition procedures and decentralised procedures;

- Checking translation of /Translating 126 EMA press releases, questions and answers documents and DHPCs as well as action lines proposed by the EMA ("Lines to take") etc.;

- Provision of advice for check of translation of SmPCs and leaflets, message exchanges and communication in English with European bodies;

- Linguistic assessment of EMA's proposals for translation into Romanian of various specialised terms from the legislative field of the medicinal product and proposal of NAMMD agreed terms.

In line with the *NAMMD Communication Strategy*, the following activities were performed in 2011:

- The internal and external communication, namely formulation of views, communication with the written media and the television (by telephone, e-mail, broadcast interviews), relationships with other Romanian and foreign institutions specialised in this field;

- Free access was ensured to public information in accordance with Law 544/2001, *ex officio* and/or upon request, for both the media, and the general public, providing information on NAMMD activities or information on the safety of medicinal products for human use;

- Cooperation with all NAMMD departments for ensured transparency of the Agency's activity by ensuring public accessibility/availability, namely passive transparency by ensuring reactive information following request;

- Notification of media representatives and/or other applicants within deadlines imposed by rules in force, if the information required is already communicated *ex officio* by means of specified under Article 5 of Law No. 544/2001, also stating where the required information can be found;

- Notification of the applicant, according to deadlines imposed by rules in force, if the required information has been identified as waved from free access;

- Cooperation with all NAMMD departments for collection and organisation of information required by the media and/or stakeholders, for draft of the required answer;

- Set-up/Verification and broadcast of official communications and NAMMD standpoints to the media;

- Participation to draft and transmission of mail exchanges with internal and external partners, related to issues specific to NAMMD activity;

- Daily monitoring of the mass-media (TV press and written press) in the healthcare field.

More than 550 e-mails received from the permanent representatives of Romania to the EU and / or the Ministry of Health were monitored / managed in electronic records, regarding participation of NAMMD experts assigned to working groups of the European Council, to the Pharmaceutical Committee and the Standing Committee of the European Commission and redirecting them to NAMMD appointed experts.

The 2009 electronic database of documents in pending review, by theme, as received from the Permanent Representation of Romania to the EU and/or from the Ministry of Health has been maintained in 2011.

Electronic records have been set up for the monitoring/handling of 85 European Commission (EC) Decisions referring to:

- Conditionally authorised medicinal products (based on Article 127a of Directive 2001/83/EC);

- MA suspension/withdrawal/amendment (based on Article 107 of Directive 2001/83/EC);

- Decisions following referral procedures (based on Article 20 and Article 30 of Directive 2001/83/EC).

These European Commission Decisions have been redirected to NAMMD experts appointed for implementation.

The activity of the commission secretariat for handling crisis situations was assured; minutes of operational sessions of Agency's management were written upon Agency request.

14. Legal work of the NAMMD

Regarding areas within the scope of the Legal Department, activities and actions thereof related to all branches of law (labour law, civil law, civil procedure, administrative law, financial law, tax law, administrative law etc.).

Throughout 2011, activities performed concentrated on regulation of ways of resolution of jurisdictional issues pertaining of internal requests and relations with third parties, respectively.

In that respect, 28 draft Administration Council decisions were established covering various issues related to current activities, the main weight resting on provisions for organisational issues: gradual changes in institutional structure, in the collective labour contract at unit level, approval of the job list and of the organisational structure, other current issues.

Activity performed by the Legal department in accordance with the Regulation for NAMMD organisation and operation consisted of the following:

- Set-up by NAMMD management of regulations and instructions or of other regulatory documents;

- Grant of approval concerning the legal character of measures to be taken, and of any other documents possibly involving the institution's patrimonial liability;

- Grant of approval concerning the correct interpretation of regulatory documents applicable to the NAMMD sector of activity;

- NAMMD representation in law courts;

- Insurance of adequate performance of jurisdictional procedures within the institution;

- Set-up/Pooling of documents required for NAMMD employees travels abroad for participation in activities by external partners;

- Set-up of NAMMD Administration Council meetings;

- Set-up of regulations specific to the field of activity;

- Handling of activities ensuring message exchanges for petition resolution in accordance with Ordinance no. 27/30.01.2002 regulating the resolution of petitions.

In the context of the activity performed, the Legal Department set up the dossier representing the institution's legislative initiative, promoted by the chief credit accountant, namely the Ministry of Health. Thus, set up should be mentioned of the dossiers for draft of the Emergency Ordinance concerning transposition of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

The institution was also represented within law courts, which is one of the main assignments of this department; there have been 38 litigations in 2011, subject to complaints concerning breach of legal provisions. As in previous years, the institution has not been incurred patrimonial or financial losses following litigations solved in 2011.

Together with other departments, the Legal Department too contributed to the activity initiated by actions related to protocol no. 5/03.03.2010 for cooperation with the General Inspectorate of Romanian Police for prevention of medicinal product counterfeiting and illegal marketing of counterfeit medicinal products, information and warning of the public in that respect and development of cooperation relationships with other institutions and bodies involved in such activity.

15. Management of human resources

15.1. Human resources policy

Similar to previous years, main HR activities included in the plan of substantial objectives of the Human Resources and Payroll Department, in 2011, managed to:

- Ensure human resources at the level of NAMMD structures, especially in sectors where department and top management reviews evidenced lack of qualified higher education (particularly medico-pharmaceutical) staff, for proper covering of jobs in specialised departments, whose work practically ensures accomplishment of the Agency's scope.

- Improve human resources through employee training and continued professional improvement by:

- Training and professional improvement of existing specialised personnel, for training of highly qualified specialists, able to deal with the entire range of assignments and tasks involved in the NAMMD object of activity;

- Training, improvement and evaluation of NAMMD personnel, performed in accordance with yearly plans established at department level, depending on each employee's work and level of training. Training has been performed for newly hired employees and has been constantly performed both inside and outside the NAMMD by institutions specialised in various fields of activity, such as: quality assurance management (ISO 9001:2000), training specific to pharmaceutical inspection, financial-accounting legislation etc. Moreover, there has been active participation with presentations at various symposia, congresses in the medicinal product field, as well as constant and remarkable participation of NAMMD experts in working groups of international bodies in the medicinal product field.

- Career administration, aiming to ensure long-term balance between the employees' career improvement needs and jobs available in the Agency, to ensure sufficient staff with higher education in the specific field of activity;

- Organisational development, aiming to train employees in terms of anticipation, initiation and management of the change.

- Throughout 2011, staff motivation could not be performed by wage-related compensations (bonuses, pay rises etc.) for special professional merits. Potential solutions:

- stimulating the assigned persons to demonstrate their ability in performance of tasks and responsibilities required by management jobs;

- setting up an adequate system for assessment of performances.

15.2. Ensuring Human Resources within NAMMD structures

In 2011, personnel-related activities were performed within the reorganised Human Resources and Payroll Department. The purpose of this reorganisation has been to ensure more fluent communication between organisational structures, as well as their cooperation for accomplishment of personnel-related duties, optimal resource distribution and decision making. As regards accomplishment of this department's main goal, namely insurance of qualified personnel, one important aspect worth mentioning was the marked burden placed upon HR work by the legal framework set up through Government Emergency Ordinance No. 34/2009 on budget rectification for 2009 and regulation of certain financial-fiscal measures ("Measures on public expenditure" providing for " freeze of hiring proceedings by examination or contest in relation to vacancies in public institutions").

As a consequence, acute understaffing emerging as of 2009 deepened, since the only jobs available for temporary use, on Ministry of Health permission, were labour contracts suspended for strictly determined periods.

15.3. Development of human resources through employee training and professional improvement

Apart from participation in activities organised by various European institutions and bodies, the best manner to maintain the NAMMD connected to European activities in the medicinal product field was for the Agency's specialised personnel to yearly benefit from both a programme for continued training, specific to professional development, on Agency site and from training organised nationally and internationally by various authorities and bodies in the field, such as:

- Training of clinical assessors on DSM V (the *Diagnostic and Statistical Manual of Mental Disorders* V), organised by the European Medicines Agency (EMA);
- Adobe Connect teleconference training of clinical assessors concerning quality of scientific committees opinion, organised by the European Medicines Agencies (EMA);
- Training of pharmacovigilance assessors;
- EMA training of assessors concerning ICH S6 Guideline: Preclinical safety evaluation of biotechnology-derived pharmaceuticals;
- On site Training on Technical validation of documentation submitted in eCTD or NeeS format, organised by TIGes Working Group;
- EDQM organised Training on the 7th edition of the European Pharmacopoeia;
- Training for users of the EudraVigilance database;
- EMA training on "Excellence in Pharmacovigilance: Clinical trials and post-marketing";
- The "Public Internal Audit" course, organised by S.C. Expert Audit Group S.R.L.

16. Economic activity

In 2011, the Economic Department developed and managed a balanced budget of

revenues and expenses from the state budget, amounting to 17,354,000 lei; expenses reached 16,657,821 lei.

These expenses consisted of: staff expenses (12.165.413 lei), expenses on goods and services (3.805.557 lei) and capital expenses (686.851 lei).

All expenses did not exceed the approved 2011 budget in accordance with legal provisions on economic and financial discipline.

Data reveal balanced NAMMD revenue and expenditures, in compliance with budgetary principles and rules according to Law 500/2002 on public finance and in conjunction with specific legislation in force.

All financial activities ensuring optimal and efficient performance of payments and receipts were performed by the Economic Department.

In 2011, through its financial-accounting activities, the Economic Department provided proper accomplishment of its objectives.

17. General administration

In 2011, the General Administration Department managed to fulfil its objectives as well as promptly and efficiently handle requests of other NAMMD structures. Thus, GAD most substantial achievements consisted of performance and completion of activities related to endowment and refurbishment of the NAMMD building. The most important acquisitions have been:

- Extension of the access control and camera surveillance system at the NAMMD headquarters and installation of 2 access barriers, meant to establish safe and effective means for protection of areas by prohibiting unauthorised access to areas where work involves secret or confidential documents;
- Refurbishment of electric equipment in the NAMMD headquarters and the Domneşti farm, as well as ongoing work for replacement of wooden window frames with PVC ones, to lower utility costs and creation of agreeable workplace environment;
- Acquisition of all equipment mentioned in the 2011 Investments List.

The Public Acquisitions Service organised and tracked the planning, performance and acquisition of products, services and works needed for proper NAMMD operation, consistent with its objective needs and the approved budget, developing documentation needed for 426 applications (purchase requisitions).

18. Internal audit

The internal audit structure set up at NAMMD level is subordinated to the NAMMD president, thus ensuring freedom for performance of internal audit activities for objective assessment of deficiencies detected in audited Agency departments and provision of adequate recommendations.

In 2011, the activity of the Internal Audit Bureau consisted of 4 audit and counselling missions conducted in accordance with the yearly internal audit plan.

Audit missions conducted considered the following:

- Assessment of activities of the Information, Logistics and Electronic Management of Data Department;
- Assessment of activities of the Legal Department;
- Assessment of activities of the Economic Department;
- Assessment of activities of the Technical-Laboratory Department.

These audits revealed that the main risks with potential impact upon NAMMD work throughout the period under assessment were organisational, operational, juridical and financial in nature.

At the same time, internal audit missions related to budget related processes, financial-accounting activities, IT system and legal activity have been conducted.

The internal audit missions led to elaboration of recommendations structured by main audited field, contributing to improvement of the respective activities.

For enhanced and improved internal audit activity, Ministry of Health specialists proposed elaboration and publication of procedural guidelines on public internal audit of healthcare activities.

19. Difficulties encountered

In performance of its activities in 2011, the NAMMD encountered several difficulties, the primary of which was recruitment and maintenance of specialised staff, coping with the lack of financial means to ensure continual training of staff and access to the latest scientific progress in general and particularly in their own professional field, insufficient archiving space.

20. Priorities for 2012

As in past years, at the end of 2011 the NAMMD formulated its priorities for the coming year:

- Strengthening of Agency scientific staff following governmental decision on cessation of hiring freeze in the healthcare field;
- Completion, close to the deadline (02.01.2013), of transposition into Romanian legislation of Directive 2011/62/EU on the prevention of the entry of falsified medicinal products into the supply chain;
- Approval through Order of the Minister of Health of the procedure and Rules for NAMMD accreditation of national providers of training related to Good Clinical Practice rules;
- Set-up of the legal framework for NAMMD's activity of authorisation and surveillance of the manufacturing of advanced therapy medicinal products, unsystematically prepared in a Romanian hospital, under the surveillance of a physician; this field involves the priority training of assessors and inspectors in the review of compliance with Good Clinical Practice and Good Manufacturing Practice rules.

In 2012, the NAMMD will envisage:

- Organisation of meetings with the representatives of all stakeholders (manufacturers, distributors) for implementation of regulatory measures for application of a medicinal product traceability system, identification of all elements, which can represent a starting point in finding reliable solutions for such implementation in Romania;
- Revision of the Medical Devices List for periodic control, for sole inclusion of devices of maximum risk to patients and users;
- Revision of Order of the Minister of Health No. 1636/2004 on approval of Methodological Rules for implementation of Law No. 176/2000 on medical devices, as amended, referring to medical technical units, for explanation of certain issues leading to various interpretations of this Order and performance of steps provided, and demonstration of the need to hire more staff for more efficient national implementation of Law 176/2000 provisions.

CONCLUSIONS

In 2011, the NAMMD managed to dutifully fulfil its tasks and duties as a national competent authority in the medicinal product field, in the context of the major changes the Agency has gone through during the past years, which have required a serious adaptive effort.

Through management's permanent availability for cooperation and communication, in view of creating the conditions required for the manifestation of its human resources at full professional capacity, through the efforts undertaken by the Agency's staff (experts and auxiliary staff), the NAMMD managed to maintain its status of regulatory, competent European authority, entirely in line with community requirements, active member in committees and working groups related to the medicinal product for human use.

The activity of the Agency continued at the same pace required by the respective moment: the assessment and marketing authorisation of medicinal products, Good Manufacturing Practice (GMP) inspections, Good Distribution Practice (GDP) inspections, Good Clinical Practice (GCP) inspections, Good Laboratory Practice (GLP) inspections, pharmacovigilance, informing the stakeholders (healthcare professionals, media, patients and, last but not least, the general public) about the latest and most accurate information concerning medicinal products.

As the single habilitated institution able to assess the performances and safety of medical devices in use, the NAMMD carries out the periodic check-up of installed and commissioned medical devices characterised by a high risk degree, at the sites of all medical device users, both in the private and public field. Moreover, the NAMMD has undertaken the duty to authorise and reauthorise medical device control and testing laboratories.

The NAMMD has a solid Quality Management System (QMS), based on *international standards 9001, 9004, 17025* etc. in force. The Agency's top management showed particular interest and ongoing involvement in QMS-related activities, being preoccupied with the enforcement of the process-based approach.

In view of establishing the framework for bilateral cooperation and exchange of information in the field of the counterfeiting of medicinal products for human use, in accordance with the specific attributions and competences stipulated by the legislation in force, the agency has also collaborated with the General Inspectorate of the Romanian Police.

It is a well-known fact that the Agency is one of the decision factors in the field of the medicinal product for human use and, as such, it involves everything related to the set-up of a regulatory framework harmonised with the provisions of the European legislation, in accordance with the recommendations of the European Medicines Agency and with European Commission Decisions. Only in this manner can the NAMMD fulfil its primary mission to grant quality, efficacy and safety of medicinal products authorised for marketing in Romania.

DECISION

No. 3/22.08.2013

on approval of proposed fees for activities conducted by the National Agency for Medicines and Medical Devices

The Administration Council of the National Agency for Medicines and Medical Devices, established through Order of the Minister of Health No. 384/15.03.2013, convened in the meeting of 22 August 2013;

On seeing report no. 7730/17.07.2013 of the Information, Logistics and Electronic Management of Data Department and report no. 7731/17.07.2013 of the National Procedure Department;

Based on Article 10 (d) of Government Ordinance No. 734/21.07.2010 related to the set-up, organisation and functioning of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Article 1 – Approves the proposals for fees for activities conducted by the National Agency for Medicines and Medical Devices, in accordance with the Annex to this Decision.

Article 2 – This Decision is to be communicated to the Minister of Health, for approval through Order of the Minister of Health, which is to be published in the Official Gazette of Romania, Part I.

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

Dr. Marius SAVU

1. Article 2 is amended and reads as follows:

"Article 2 - The marketing authorisation maintenance fee is 230 euro/year and shall be paid to the National Agency for Medicines and Medical Devices every year before the 31 December of the following year."

2. A new article, 4^1, is introduced after Article 4, which reads as follows:

"Article 4^1 – The administrative procedure for the handling of fees received by the National Agency for Medicines and Medical Devices in case of discontinuation of the procedure for clinical trial evaluation, authorisation and amendment is as follows:

a) For notification by applicants on withdrawal of their application for authorisation of a clinical trial on a medicinal product for human use after payment of fee for clinical trial authorisation procedure, the trial authorisation fee paid by applicants according to Annex 3 provisions shall be managed as follows:

(i) For applications for discontinuation of the authorisation procedure concerning a clinical trial on a medicinal product for human use submitted prior to validation of the application, depending on applicant's request, the respective fee may be returned/directed for payment of a different fee due to the National Agency for Medicines and Medical Devices by the respective applicant;

(ii) For applications for discontinuation of the authorisation procedure concerning a clinical trial on a medicinal product for human use submitted after validation of the application for authorisation, but no later than 25 calendar days as of procedure onset, depending on applicant's request, 90% of the fee may be returned/ directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

(iii) For applications for discontinuation of the authorisation procedure concerning a clinical trial on a medicinal product for human use submitted after day 25 as of procedure onset, the fee paid shall be retained by the National Agency for Medicines and Medical Devices and may no longer be returned;

b) If the application for authorisation of a clinical trial on a medicinal product for human use is rejected following the validation procedure, 90% of the fee may be returned/directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

Notification by applicants on withdrawal of the application for approval of a substantial amendment to a clinical trial on a medicinal product for human use after payment of fees for the procedure for approval of a clinical trial amendment, the fee for evaluation of the clinical trial amendment, as paid by applicants according to Annex 3 provisions, shall be managed as follows:

(i) For applications for discontinuation of the clinical trial amendment approval procedure submitted prior to validation of the application, depending on applicant's request, the respective amount may be returned/directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

(ii) For applications for discontinuation of the clinical trial amendment approval procedure submitted after validation of the application, but no later than 15 calendar days as of procedure onset, 90% of the fee may be returned/ directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;

(iii) For applications for discontinuation of the authorisation procedure to the National Agency for Medicines and Medical Devices submitted after day 15 as of procedure onset, the amount paid shall be retained by the National Agency for Medicines and Medical Devices and may not be returned;

d) If the application for authorisation of a clinical trial on a medicinal product for human use is rejected following the validation procedure, depending on applicant's request , 90% of the fee may be returned/directed for payment of a different fee due by the applicant in question to the National Agency for Medicines and Medical Devices;"

3. Under Annex 3, point C is amended as follows:

C.	*Authorisation of clinical trials, approval of substantial amendments and approval of advertising material*	*FEE - EURO*
1.	Authorisation of clinical trials for investigational medicinal products not authorised worldwide (new substances). Phases I–III	1.250
2.	Authorisation of clinical trials for investigational medicinal products not authorised for marketing in Romania, authorised in other countries or authorised for marketing (known substances) but not used according to the Summary of Product Characteristics (SmPC) in force in the respective trial (regarding indications, dose, administration route, treatment method, target group). Phases I – IV	1.000
3.	Authorisation of clinical trials for medicinal products authorised in Romania, used according to SmPC in force. Phase IV	410
4.	Authorisation of bioequivalence studies	600
5.	Authorisation of substantial amendments (mentioned in Scientific Council Decision no. 22/2010 of the National Agency for Medicines and Medical Devices)	200
6.	Approval of advertising material for "Over the Counter" medicinal products (OTCs)	550
7.	Approval of educational material for medicinal products for human use	350

Note:

Fees established under sections 6 and 7 refer to approvals valid for 6 months as of issuance".

4. Under Annex 3, a new point, F, is introduced after point E, which reads as follows:

F.	*Assessment of the dossier for scientific opinion and for amendment of scientific opinion on ancillary medicinal substances incorporated in a medical device*	*TARIFF - EURO*
1.	*Scientific opinion on ancillary medicinal substances incorporated into a medical device for substances not previously assessed by the NAMMD*	*2.660*
2.	*Scientific opinion on ancillary medicinal substances incorporated into a medical device for substances previously assessed by the NAMMD with a different manufacturer*	*1.339*
3.	*Scientific opinion on ancillary medicinal substances incorporated into a medical device for substances previously assessed by the NAMMD with the same manufacturer*	*535*
4.	*Amendment of ancillary medicinal substances for substances not previously assessed by the NAMMD*	*665*

5.	*Amendment of ancillary medicinal substances for substances previously assessed by the NAMMD with the same manufacturer*	*335*
6.	*Amendment of ancillary medicinal substances for substances previously assessed by the NAMMD with the same manufacturer*	*250*

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Medicinal product batches recalled during the 4th quarter of 2013

No. crt.	Product recalled	Pharm. form	Strength	INN	Manufacturer/ MAH	Batch	Grounds for recall	Action proposed	Date of recall
1	AFLEN	capsules	300 mg	triflusalum	Galenica S.A., Greece	H004	Following laboratory retesting, Uriach Spain, the manufacturer of bulk capsules, has discovered occurrence of an out-of-specification result under parameter , “Impurities”	Voluntary recall and destruction	24.10.2013
2	RIGEVIDON 21 + 7	lozenges	0,003 mg /0,15 mg	combinations	Gedeon Richter PLC, Hungary	T93387	Out-of-specification results observed during long-term stability studies	Voluntary recall and destruction	28.10.2013
3	GYNIPRAL	tablets	0.5 mg	Hexoprenalinum	Nycomed Austria GmbH, Austria	All batches	MA renewal procedure discontinued on 19.09.2013	Recall and destruction	06.11.2013
4	KETOCONAZOL ARENA	tablets	200 mg	Ketoconazo-lum	Arena Group SA	All batches	Suspension of marketing authorisation agreed upon at European level due to safety reasons	Recall and destruction	07.11.2013
5	KETOCONAZOL SLAVIA	tablets	200 mg	ketoconazolum	Slavia Pharm SRL	All batches	Suspension of marketing authorisation agreed upon at European level due to safety reasons	Recall and destruction	07.11.2013
6	KETOSTIN	tablets	200 mg	ketoconazolum	AC Helcor SRL	All batches	Suspension of marketing authorisation agreed upon at European level due to safety reasons	Recall and destruction	07.11.2013
7	KETOCONAZOL *Mcc*	tablets	200 mg	ketoconazolum	Magistra CC SRL	All batches	Suspension of marketing authorisation agreed upon at European level due to	Recall and destruction	07.11.2013

No. crt.	Product recalled	Pharm. form	Strength	INN	Manufacturer/ MAH	Batch	Grounds for recall	Action proposed	Date of recall
							safety reasons		
8	NIZORAL	tablets	200 mg	ketoconazolum	Terapia SA	All batches	Suspension of marketing authorisation agreed upon at European level due to safety reasons	Recall and destruction	07.11.2013
9	GRIMODIN	capsules	400 mg	gabapentinum	West Pharma Producoes Farm de Especialidades SA, Portugal/Egis Pharmaceuticals, Hungary	JF0688A	Primary packaging (blister) imprinted in Hungarian, instead of Romanian	Voluntary recall and destruction	12.11.2013
10	BICARBONAT DE SODIU 8.4%	solution for infusion	8.4%	natrii hydrogenii carbonas	B.Braun Melsungen, Germany	121838022, 123528021, 123918082, 124118082, 124638022, 125028022	Detection of isolated cases of dispersion of a solution for infusion	Voluntary recall and destruction	16.12.2013
11	TUSSIN FORTE	tablets	20 mg	Dextrometor-phanum	Europharm SA /GSK SRL, Romania	All batches manufactured until 31.10.2012	Expiry of deadline for implementation of NAMMD approved variation (MA transfer no. 4754/2012/01 from Europharm SA to GSK SRL)	Voluntary recall and destruction	16.12.2013
12	CALMEPAM	tablets	1.5 mg	bromazepamum	Europharm SA, Romania/GSK Romania	006/01, 006/02, 7	Validity of marketing authorisation no. 3102/2010/01-02 expired on 14.09.2012	Voluntary recall and destruction	24.12.2013
13	CALMEPAM	tablets	3 mg	bromazepamum	Europharm SA, Romania/GSK Romania	16, 17, 19, 20	Validity of marketing authorisation no. 3102/2010/01-02 expired	Voluntary recall and destruction	24.12.2013

No. crt.	Product recalled	Pharm. form	Strength	INN	Manufacturer/ MAH	Batch	Grounds for recall	Action proposed	Date of recall
							on 14.09.2012		
14	VIGRANDE	film-coated tablets	50 mg	sildenafilum	Saneca Pharmaceuticals AS Slovakia/Zentiva AS, Slovakia	All batches	Change of trade name into TAXIER 50 mg film-coated tablets, based on a type IB variation approved by the NAMMD on 09.09.2013	Voluntary recall and destruction	24.12.2013
15	VIGRANDE	film-coated tablets	100 mg	sildenafilum	Saneca Pharmaceuticals AS Slovakia/Zentiva AS, Slovakia	All batches	Change of trade name into TAXIER 50 mg film-coated tablets, based on a type IB variation approved by the NAMMD on 09.09.2013	Voluntary recall and destruction	24.12.2013

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 3rd quarter of 2013

During the 3rd quarter of 2013, 310 applications have been submitted for marketing authorisation/ marketing authorisation renewal related to medicinal products, corresponding to the following therapeutic groups:

A02 - Drugs for acid related disorders
A03 – Drugs for functional gastrointestinal disorders
A05 – Bile and liver therapy
A07 – Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
A10 – Drugs used in diabetes
B01 – Antithrombotic agents
B02 – Antihemorrhagics
B03 – Antianemic preparations
B05 – Blood substitutes and perfusion solutions
C05 – Vasoprotectives
C07 – Beta blocking agents
C09 – Agents acting on the renin-angiotensin system
C10 – Lipid modifying agents
D01 – Antifungals for dermatological use
G01 – Gynaecological antiinfectives and antiseptics
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
M05 – Drugs for treatment of bone diseases
N01 – Anesthetics
N02 – Analgesics
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 3rd quarter of 2013

INN	Invented name	Pharm. form	Strength	Manufacturer	Country	MA number		
ACIDUM ACETYLSALICYLICUM	VASOPIRIN 75 mg	gastroresistant tablets	75mg	ICN POLFA RZESZOW S.A.	POLAND	5784	2013	19
ACIDUM ACETYLSALICYLICUM	VASOPIRIN 100 mg	gastroresistant tablets	100mg	ICN POLFA RZESZOW S.A.	POLAND	5785	2013	19
ACIDUM ALENDRONICUM	FOSAMAX 70 mg	tablets	70mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	5778	2013	04
ALBUMINUM HUMANUM	ALBUREX 50 g/l	solution for infusion	50g/l	CSL BEHRING GMBH	GERMANY	5826	2013	03
ALBUMINUM HUMANUM	ALBUREX 200 g/l	solution for infusion	200g/l	CSL BEHRING GMBH	GERMANY	5827	2013	02
ALPRAZOLAMUM	ALPRAZOLAM ATB 0.25 mg	tablets	0.25mg	ANTIBIOTICE S.A.	ROMANIA	5683	2013	03
ALPRAZOLAMUM	ALPRAZOLAM ATB 0.5 mg	tablets	0.5mg	ANTIBIOTICE S.A.	ROMANIA	5684	2013	03
ALPRAZOLAMUM	ALPRAZOLAM ATB 1 mg	tablets	1mg	ANTIBIOTICE S.A.	ROMANIA	5685	2013	03
AMBROXOLUM	AMBROXOL LAROPHARM 15 mg/5 ml	oral solution	15mg/5ml	LAROPHARM S.R.L.	ROMANIA	5699	2013	01
AMBROXOLUM	AMBROXOL FONTANE 15 mg/5 ml	oral solution	15mg/ml	FONTANE PHARMA GMBH	GERMANY	5716	2013	01
AMOXICILLINUM + ACIDUM CLAVULANICUM	AUGMENTIN INTRAVENOS 2000mg/200mg	powder for solution for infusion	2000mg/200mg	BEECHAM GROUP PLC	GREAT BRITAIN	5739	2013	01
ANASTROZOLUM	NUCLIZOL 1 mg	film-coated tablets	1mg	NUCLEOS FARMA SRL	ROMANIA	5687	2013	02
BETAXOLOLUM	BETAXOLOL PMCS 20 mg	tablets	20mg	PRO. MED. CS PRAHA A.S.	THE CZECH REPUBLIC	5782	2013	07
BIOLOGIC (LYSATUM BACTERIALE OM 85 CRYODESICATUM)	BRONCHO-VAXOM COPII 3.5mg	capsules	3.5mg	OM PHARMA S.A.	PORTUGAL	5732	2013	02
BIOLOGIC (LYSATUM BACTERIALE OM 85 CRYODESICATUM)	BRONCHO-VAXOM ADULTI 7 mg	capsules	7mg	OM PHARMA S.A.	PORTUGAL	5733	2013	02
BISACODYLUM	BISACODIL SINTOFARM 10 mg	suppositories	10mg	SINTOFARM S.A.	ROMANIA	5740	2013	02
BISOPROLOLUM	BISOPROLOL THESPIS 5 mg	film-coated tablets	5mg	THESPIS PHARMACEUTICAL LIMITED	CYPRUS	5787	2013	03
BISOPROLOLUM	BISOPROLOL THESPIS 10 mg	film-coated tablets	10mg	THESPIS PHARMACEUTICAL LIMITED	CYPRUS	5788	2013	03
CANDESARTANUM CILEXETIL	CADEXYL 4 mg	tablets	4mg	NEOLA PHARMA SRL	ROMANIA	5818	2013	04
CANDESARTANUM CILEXETIL	CADEXYL 8 mg	tablets	8mg	NEOLA PHARMA SRL	ROMANIA	5819	2013	04
CANDESARTANUM CILEXETIL	CADEXYL 16 mg	tablets	16mg	NEOLA PHARMA SRL	ROMANIA	5820	2013	04
CANDESARTANUM CILEXETIL	CADEXYL 32 mg	tablets	32mg	NEOLA PHARMA SRL	ROMANIA	5821	2013	04
CETIRIZINUM	REACTIN 10 mg	soft capsules	10mg	MCNEIL PRODUCTS LIMITED	GREAT BRITAIN	5693	2013	01
CHINIDINI SULFAS	CHINIDINA ARENA 200 mg	tablets	200mg	ARENA GROUP S.A.	ROMANIA	5682	2013	03
CHLORQUINALDOLUM	SAPROMED 100 mg (see P01AA04)	lozenges	100mg	ARENA GROUP S.A.	ROMANIA	5722	2013	03
CHLORQUINALDOLUM	SAPROMED 100 mg (see A07AXN1)	lozenges	100mg	ARENA GROUP S.A.	ROMANIA	5722	2013	03

CIPROFLOXACINUM	CIPROFLOXACINA CLARIS 2mg/ml	solution for infusion	2mg/ml	CLARIS LIFESCIENCES LTD.	GREAT BRITAIN	5758	2013	02
COLISTIMETHATE SODIUM	COLISTIMETAT SODIC XELLIA 1 MILION INTERNATIONAL UNITS (IU)	powder for solution for injection or infusion	1 MILLION IU	XELLIA PHARMACEUTICALS APS	DENMARK	5706	2013	01
COMBINATIONS	MAGNEBENE 470 mg/5 mg	lozenges	470mg/5mg	BIOFARM S.A.	ROMANIA	5702	2013	01
COMBINATIONS (CLORAMPHENICOLUM+ BETHAMETASONUM)	BETABIOPTAL 1.3mg/g+2.5 mg/g	eye gel	1.3mg/g+ 2.5mg/g	THEA FARMA S.P.A.	ITALY	5801	2013	01
COMBINATIONS (CLORMADINONA+ ETINILESTRADIOL)	TYARENA 200 micrograms/30 micrograms	film-coated tablets	200micrograms/ 30micrograms	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5764	2013	04
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA DR. REDDY'S 80 mg/12.5 mg	tablets	80mg/12.5mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	5691	2013	03
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA DR. REDDY'S 40 mg/12.5 mg	tablets	40mg/12.5mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	5690	2013	03
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA DR. REDDY'S 80 mg/25 mg	tablets	80mg/25mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	5692	2013	03
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA BILLEV 40 mg/12.5 mg	tablets	40mg/12.5mg	BILLEV PHARMA APS	DENMARK	5708	2013	18
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA BILLEV 80 mg/12.5 mg	tablets	80mg/12.5mg	BILLEV PHARMA APS	DENMARK	5709	2013	18
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA BILLEV 40 mg/25 mg	tablets	80mg/25mg	BILLEV PHARMA APS	DENMARK	5710	2013	18
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA SANDOZ 80 mg/12.5 mg	lozenges	80mg/12.5mg	SANDOZ S.R.L.	ROMANIA	5779	2013	01
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/ HIDROCLOROTIAZIDA SANDOZ 80 mg/25 mg	lozenges	80mg/25mg	SANDOZ S.R.L.	ROMANIA	5780	2013	01
DICLOFENACUM	VIKLAREN 10 mg/g	gel	10mg/g	ICN POLFA RZESZOW S.A.	POLAND	5716	2013	04
DILTIAZEMUM	DILTIAZEM SR ROMPHARM 90 mg	prolonged-release capsules	90mg	ROMPHARM COMPANY S.R.L.	ROMANIA	5680	2013	01
DILTIAZEMUM	DILTIAZEM SR ROMPHARM 180 mg	prolonged-release capsules	180mg	ROMPHARM COMPANY S.R.L.	ROMANIA	5681	2013	01
DONEPEZILUM	DONEPEZIL HAMELN 5 mg	film-coated tablets	5mg	HAMELN RDS A.S.	SLOVACIA	5822	2013	12
DONEPEZILUM	DONEPEZIL HAMELN 10 mg	film-coated tablets	10mg	HAMELN RDS A.S.	SLOVACIA	5823	2013	12
ESCITALOPRAMUM	ELICEA Q-TAB 5 mg	orodispersible tablets	5mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5805	2013	12
ESCITALOPRAMUM	ELICEA Q-TAB 10 mg	orodispersible tablets	10mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5806	2013	12

ESCITALOPRAMUM	ELICEA Q-TAB 15 mg	orodispersible tablets	15mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5807	2013	12
ESCITALOPRAMUM	ELICEA Q-TAB 20 mg	orodispersible tablets	20mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5805	2013	12
FENTANYLUM	FENTANYL PFIZER 12 micrograms/h	transdermal patch	12micrograms/h	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5711	2013	09
FENTANYLUM	FENTANYL PFIZER 25 micrograms/h	transdermal patch	25micrograms/h	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5712	2013	09
FENTANYLUM	FENTANYL PFIZER 50 micrograms/h	transdermal patch	50micrograms/h	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5713	2013	09
FENTANYLUM	FENTANYL PFIZER 75 micrograms/h	transdermal patch	75micrograms/h	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5714	2013	09
FENTANYLUM	FENTANYL PFIZER 100 micrograms/h	transdermal patch	100micrograms/ h	PFIZER EUROPE MA EEIG	GREAT BRITAIN	5715	2013	09
FLUDARABINUM	FLUDARABINA KABI 50 mg	powder for solution for injection or infusion	50mg	FRESENIUS KABI ONCOLOGY PLC.	GREAT BRITAIN	5734	2013	01
FLUDARABINUM	FLUDARABINA ACTAVIS 25 mg/ml	concentrate for solution for injection or infusion	25mg/ml	ACTAVIS GROUP PTC EHF.	ICELAND	5735	2013	02
FLUOROURACILUM	FLUOROURACIL ACCORD 50 mg/ml	solution for injection or infusion	50mg/ml	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	5783	2013	05
GABAPENTINUM	GABAPENTIN ARENA 100 mg	capsules	100mg	ARENA GROUP S.A.	ROMANIA	5719	2013	01
GABAPENTINUM	GABAPENTIN ARENA 300 mg	capsules	300mg	ARENA GROUP S.A.	ROMANIA	5720	2013	01
GABAPENTINUM	GABAPENTIN ARENA 400 mg	capsules	400mg	ARENA GROUP S.A.	ROMANIA	5721	2013	01
GEMCITABINUM	DERCIN 200 mg	powder for solution for infusion	200mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5737	2013	01
GEMCITABINUM	DERCIN 1000 mg	powder for solution for infusion	1000 mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5738	2013	01
IBUPROFENUM	IBUPROFEN CIPLA 600	film-coated tablets	600mg	CIPLA (UK) LIMITED	GREAT BRITAIN	5804	2013	01
IBUPROFENUM	IBUPROFEN CIPLA 400	film-coated tablets	400mg	CIPLA (UK) LIMITED	GREAT BRITAIN	5803	2013	01
IBUPROFENUM	IBUPROFEN CIPLA 200	film-coated tablets	200mg	CIPLA (UK) LIMITED	GREAT BRITAIN	5802	2013	01
ISOSORBIDI MONONITRAS	MONO ROM SR 40 mg	prolonged-release capsules	40mg	ROMPHARM COMPANY S.R.L.	ROMANIA	5747	2013	01
ISOSORBIDI MONONITRAS	MONO ROM SR 60 mg	prolonged-release capsules	60mg	ROMPHARM COMPANY S.R.L.	ROMANIA	5748	2013	01
KETOPROFENUM	KETOPROFEN OZONE 25 mg/g	gel	25mg/g	OZONE LABORATORIES PHARMA S.A.	ROMANIA	5770	2013	01
LATANOPROSTUM	LATANOPROST STADA HF 50 micrograms/ml	eye drops,	50micrograms/	STADA HEMOFARM S.R.L.	ROMANIA	5786	2013	03

		solution	ml					
LETROZOLUM	ETRUZIL 2.5 mg	film-coated tablets	2.5mg	EGIS PHARMACEUTICALS PLC	HUNGARY	5815	2013	09
LEVOCETIRIZINUM	ZENARO 5 mg	film-coated tablets	5mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	5814	2013	15
LIDOCAINUM	VERSATIS 5%	medicinal plaster	5%	GRUNENTHAL GMBH	GERMANY	5736	2013	05
LINEZOLIDUM	DILIZOLEN 2 mg/ml	solution for infusion	2mg/ml	HELM AG	GERMANY	5745	2013	02
LISINOPRILUM	LISIREN 20 mg	tablets	20mg	AC HELCOR S.R.L.	ROMANIA	5751	2013	02
LISINOPRILUM	LISIREN 10 mg	tablets	10mg	AC HELCOR S.R.L.	ROMANIA	5750	2013	02
LOPERAMIDUM	LOPERAMID TERAPIA 2 mg	capsules	2mg	TERAPIA S.A.	ROMANIA	5792	2013	01
MEMANTINUM	MEMIGMIN 10 mg	film-coated tablets	10mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	5688	2013	13
MEMANTINUM	MEMANTINA DR. REDDY'S 10 mg	film-coated tablets	10mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	5689	2013	12
MEMANTINUM	MIRVEDOL 10 mg	film-coated tablets	10mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	5718	2013	04
MEMANTINUM	MEMANTINA ABDI 10 mg	film-coated tablets	10mg	ABDI FARMA, UNIPESSOAL LDA.	PORTUGAL	5790	2013	11
MEMANTINUM	MEMANTINA ABDI 20 mg	film-coated tablets	20mg	ABDI FARMA, UNIPESSOAL LDA.	PORTUGAL	5791	2013	11
MEMANTINUM	MEMANTINA ABDI 5 mg/10 mg/15 mg/20 mg (BOX FOR TREATMENT ONSET)	film-coated tablets	5mg/10mg/ 15mg/20mg	ABDI FARMA, UNIPESSOAL LDA.	PORTUGAL	5789	2013	01
MEMANTINUM	XAPIMANT 10 mg	film-coated tablets	10mg	SANDOZ S.R.L.	ROMANIA	5793	2013	44
MEMANTINUM	XAPIMANT 20 mg	film-coated tablets	20mg	SANDOZ S.R.L.	ROMANIA	5794	2013	44
MEMANTINUM	XAPIMANT 10 mg/ml	oral solution	10mg/ml	SANDOZ S.R.L.	ROMANIA	5795	2013	03
MEROPENEMUM	LODITER 500 mg	powder for solution for injection/infusion	500mg	TERAPIA S.A.	ROMANIA	5756	2013	02
MEROPENEMUM	LODITER 1000 mg	powder for solution for injection/infusion	1000mg	TERAPIA S.A.	ROMANIA	5757	2013	02
MEROPENEMUM	MEROPENEM KABI 500 mg	powder for solution for injection or infusion	500mg	FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	5824	2013	04
MEROPENEMUM	MEROPENEM KABI 1 g	powder for solution for injection or infusion	1g	FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	5825	2013	06
MIFEPRISTONUM	MIFEPRISTONA LINEPHARMA 200 mg	tablets	200mg	LINEPHARMA FRANCE	FRANCE	5698	2013	02
MIRTAZAPINUM	REMERON SOLTAB 30 mg	orodispersible tablets	30mg	NV ORGANON	HOLLAND	5746	2013	05
MONTELUKASTUM	MONTELUKAST UNIMARK 4 mg	chewable tablets	4mg	UNIMARK REMEDIES S.R.O.	THE CZECH REPUBLIC	5742	2013	01

MONTELUKASTUM	MONTELUKAST UNIMARK 5 mg	chewable tablets	5mg	UNIMARK REMEDIES S.R.O.	THE CZECH REPUBLIC	5743	2013	01
MONTELUKASTUM	MONTELUKAST UNIMARK 10 mg	film-coated tablets	10mg	UNIMARK REMEDIES S.R.O.	THE CZECH REPUBLIC	5744	2013	01
MONTELUKASTUM	MONTELUKAST MYLAN 10 mg	film-coated tablets	10mg	GENERICS (UK) LTD.	GREAT BRITAIN	5765	2013	23
MONTELUKASTUM	MONTELUKAST LABORMED 4 mg	chewable tablets	4mg	LABORMED PHARMA S.A.	ROMANIA	5772	2013	15
MONTELUKASTUM	MONTELUKAST LABORMED 5 mg	chewable tablets	5mg	LABORMED PHARMA S.A.	ROMANIA	5773	2013	15
MONTELUKASTUM	MONTELUKAST LABORMED 10 mg	film-coated tablets	10mg	LABORMED PHARMA S.A.	ROMANIA	5774	2013	15
MONTELUKASTUM	ISPYRRA 4 mg	chewable tablets	4mg	ROMASTRU TRADING SRL	ROMANIA	5811	2013	02
MONTELUKASTUM	ISPYRRA 5 mg	chewable tablets	5mg	ROMASTRU TRADING SRL	ROMANIA	5812	2013	02
MONTELUKASTUM	ISPYRRA 10 mg	film-coated tablets	10mg	ROMASTRU TRADING SRL	ROMANIA	5813	2013	02
NAFTIFINUM	NAFTIFINA ATB 10 mg/g	cream	10mg/g	ANTIBIOTICE S.A.	ROMANIA	5752	2013	01
NAPROXENUM	NALGESIN 220 mg	film-coated tablets	220mg	KRKA, D.D., NOVO MESTO	SLOVENIA	5781	2013	03
NATRII CHLORIDUM	SODIUM CHLORIDE 9 mg/ml	solution for injection	9mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	5686	2013	03
NATRII IODIDUM (131I)	SODIUM IODIDE (131I), CAPSULES FOR DIAGNOSIS	capsules	3.7MBq	GE HEALTHCARE LIMITED	GREAT BRITAIN	5723	2013	01
NITROXOLINUM	NITROXOLIN-MIP 250mg	capsules	250mg	MIP PHARMA GMBH	GERMANY	5701	2013	03
OLANZAPINUM	OLANZAPINA POLIPHARMA 5 mg	film-coated tablets	5mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5724	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 10 mg	film-coated tablets	10mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5725	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 15 mg	film-coated tablets	15mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5726	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 20 mg	film-coated tablets	20mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5727	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 5 mg	orodispersible tablets	5mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5728	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 10 mg	orodispersible tablets	10mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5729	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 15 mg	orodispersible tablets	15mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5730	2013	08
OLANZAPINUM	OLANZAPINA POLIPHARMA 20 mg	orodispersible tablets	20mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5731	2013	08
PARACETAMOLUM	SANADOR FOR CHILDREN 150 mg/ml	oral solution	150mg/ml	LAROPHARM S.R.L.	ROMANIA	5700	2013	01
PIOGLITAZONUM	PIOGLITAZONA POLIPHARMA 15 mg	tablets	15mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5759	2013	07
PIOGLITAZONUM	PIOGLITAZONA POLIPHARMA 30 mg	tablets	30mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5760	2013	07
PIOGLITAZONUM	PIOGLITAZONA POLIPHARMA 45 mg	tablets	45mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	5761	2013	07
PRAMIPEXOLUM	PRAMIPEXOL SANDOZ 0.088 mg	tablets	0.088mg	SANDOZ S.R.L.	ROMANIA	5694	2013	08
PRAMIPEXOLUM	PRAMIPEXOL SANDOZ 0.18mg	tablets	0.18mg	SANDOZ S.R.L.	ROMANIA	5695	2013	08
PRAMIPEXOLUM	PRAMIPEXOL SANDOZ0.35 mg	tablets	0.35mg	SANDOZ S.R.L.	ROMANIA	5696	2013	08
PRAMIPEXOLUM	PRAMIPEXOL SANDOZ 0.7 mg	tablets	0.7mg	SANDOZ S.R.L.	ROMANIA	5697	2013	08

PRAMIPEXOLUM	PRAMIPEXOL ARENA 0.18mg	tablets	0.18mg	ARENA GROUP SA	ROMANIA	5809	2013	02
PRAMIPEXOLUM	PRAMIPEXOL ARENA 0.7 mg	tablets	0.7mg	ARENA GROUP SA	ROMANIA	5810	2013	02
PREDNISONUM	LODOTRA 1 mg	modified-release tablets	1mg	MUNDIPHARMA GESELLSCHAFT M.B.H.	AUSTRIA	5703	2013	05
PREDNISONUM	LODOTRA 2 mg	modified-release tablets	2mg	MUNDIPHARMA GESELLSCHAFT M.B.H.	AUSTRIA	5704	2013	05
PREDNISONUM	LODOTRA 5 mg	modified-release tablets	5mg	MUNDIPHARMA GESELLSCHAFT M.B.H.	AUSTRIA	5705	2013	05
PRILOCAINUM	PRILOTEKAL 20 mg/ml	solution for injection	20mg/ml	NORDIC GROUP B.V.	HOLLAND	5717	2013	01
PROGESTERONUM	MASTOPROFEN 10 mg/g	gel	10mg/g	ANTIBIOTICE SA	ROMANIA	5800	2013	01
NITROGEN PROTOXIDE + OXYGEN	ENTONOX 50%/50%	compressed medical gas	50%/50%	AGA AB	SWEDEN	5707	2013	08
PYRAZINAMIDUM	PIRAZINAMIDA ATB 500 mg	tablets	500mg	ANTIBIOTICE S.A.	ROMANIA	5749	2013	02
RAMIPRILUM	RAMIPRIL TEVA 5 mg	tablets	5mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5768	2013	12
RAMIPRILUM	RAMIPRIL TEVA 10 mg	tablets	10mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5769	2013	12
RAMIPRILUM	RAMIRAN 1.25 mg	tablets	1.25mg	TERAPIA SA	ROMANIA	5828	2013	04
RAMIPRILUM	RAMIRAN 2.5 mg	tablets	2.5mg	TERAPIA SA	ROMANIA	5829	2013	08
RAMIPRILUM	RAMIRAN 5 mg	tablets	5mg	TERAPIA SA	ROMANIA	5830	2013	10
RAMIPRILUM	RAMIRAN 10 mg	tablets	10mg	TERAPIA SA	ROMANIA	5831	2013	06
REPAGLINIDUM	REPAGLINIDA LABORMED 0.5 mg	film-coated tablets	0.5mg	LABORMED PHARMA S.A.	ROMANIA	5775	2013	05
REPAGLINIDUM	REPAGLINIDA LABORMED 1 mg	film-coated tablets	1mg	LABORMED PHARMA S.A.	ROMANIA	5776	2013	05
REPAGLINIDUM	REPAGLINIDA LABORMED 2 mg	film-coated tablets	2mg	LABORMED PHARMA S.A.	ROMANIA	5777	2013	05
SALMETEROLUM+ FLUTICASONUM	SERETIDE DISKUS 50 micrograms/100 micrograms	inhalation powder	50micrograms/ 100micrograms	GLAXO WELLCOME UK LIMITED	GREAT BRITAIN	5797	2013	01
SALMETEROLUM+ FLUTICASONUM	SERETIDE DISKUS 50 micrograms/250 micrograms	inhalation powder	50micrograms/ 250micrograms	GLAXOWELLCOME UK LTD.	GREAT BRITAIN	5798	2013	01
SALMETEROLUM+ FLUTICASONUM	SERETIDE DISKUS 50 micrograms/500 micrograms	inhalation powder	50micrograms/ 500micrograms	GLAXOWELLCOME UK LTD.	GREAT BRITAIN	5799	2013	01
SILDENAFILUM	SILDENAFIL SANDOZ 25 mg	orodispersible film	25mg	SANDOZ S.R.L.	ROMANIA	5753	2013	10
SILDENAFILUM	SILDENAFIL SANDOZ 50 mg	orodispersible film	50mg	SANDOZ S.R.L.	ROMANIA	5754	2013	10
SILDENAFILUM	SILDENAFIL SANDOZ 75 mg	orodispersible film	75mg	SANDOZ S.R.L.	ROMANIA	5755	2013	10
SPIRAMYCINUM	ROVAMYCINE 3 Mil. IU	film-coated tablets	3Mil. IU	LABORATOIRES AVENTIS	FRANCE	5741	2013	02
TEICOPLANINUM	TARGOCID 400 mg	powder and solvent for solution for injection	400mg	AVENTIS PHARMA LTD.	GREAT BRITAIN	5796	2013	01
TELMISARTANUM	TELMISRTAN DR. REDDY'S 40 mg	tablets	40mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	5766	2013	03

TELMISARTANUM	TELMISRTAN DR. REDDY'S 80 mg	tablets	80mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	5767	2013	03
TRIMETAZIDINUM	TRIMETAZIDINA TEVA 35 mg	prolonged-release tablets	35mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	5717	2013	03
HEPATITIS B VACCINE	EUVAX B ADULT 20 µg/ml	suspension for injection	20µg/ml	LG LIFE SCIENCES POLAND SP. ZO.O	POLAND	5834	2013	02
HEPATITIS B VACCINE	EUVAX B PEDIATRIC 10 µg/0.5 ml	suspension for injection	10µg/0.5ml	LG LIFE SCIENCES POLAND SP. ZO.O	POLAND	5833	2013	03
VALACYCLOVIRUM	VALACICLOVIR ARENA 500 mg	film-coated tablets	500mg	ARENA GROUP S.A.	ROMANIA	5771	2013	02
VERAPAMILUM	VERAPAMIL ARENA 40 mg	capsules	40mg	ARENA GROUP S.A.	ROMANIA	5832	2013	01
VORICONAZOLUM	VORICONAZOL SANDOZ 50 mg	film-coated tablets	50mg	SANDOZ SRL	ROMANIA	5762	2013	17
VORICONAZOLUM	VORICONAZOL SANDOZ 200 mg	film-coated tablets	200mg	SANDOZ SRL	ROMANIA	5763	2013	17

EMA centrally authorised medicinal products for which a marketing price was established in Romania during the 3rd quarter of 2013

INN	Invented name	Pharm. form	Strength	Manufacturer	Country	MA number		
INFLIXIMABUM	INFLECTRA 100mg	powder for concentrate for solution for infusion	100mg	HOSPIRA UK LIMITED	GREAT BRITAIN	854	10.09.2013	05
INFLIXIMABUM	REMSIMA 100mg	powder for concentrate for solution for infusion	100mg	CELLTRION HEALTHCARE HUNGARY KFT.	HUNGARY	853	10.09.2013	01
VISMODEGIB	ERIVEDGE 150mg	capsules	150mg	ROCHE REGISTRATION LTD	GREAT BRITAIN	848	17.07.2013	01