2014 ANNUAL REPORT
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

INTRODUCTION

The National Agency for Medicines and Medical Devices (NAMMD) is the national competent authority in the field of the medicinal products for human use. Its mission requires awareness of the importance of permanent self-assessment in view of adapting its policy for promotion and safeguard of public health depending on socio-economic issues or any other types of challenges that may occur at a given time.

The continuing effort to handle stakeholders' requests and expectations (healthcare professionals, the pharmaceutical industry, patients, the general public, mass-media) has concerned the NAMMD in 2014 as well, all the more so as the Agency has acquired new and highly important responsibilities during this period.

Current activity of the NAMMD in 2014 meant issuance of 1222 marketing authorisations (MAs) (401 through NP – national procedure for marketing authorisation and 821 MAs through EP – European procedures for marketing authorisation); more MAs can be issued, depending on the strengths and/or pharmaceutical forms approved for the same active substance(s), and the assessment work in itself is performed for each strength and/or pharmaceutical form submitted for authorisation.

New authorisations have been issued for the following therapeutic areas:

A – Alimentary tract and metabolism - 93 MAs
B – Blood and blood forming organs - 65
C - Cardiovascular system - 259
D - Dermatologicals - 23
G - Genito-urinary system and sex hormones - 53
H - Systemic hormonal preparations, excluding sex hormones and insulins - 23
J - Antiinfectives for systemic use - 113
L - Antineoplastic and immunomodulating agents - 71
M - Musculo-skeletal system - 97
N – Nervous system - 311
P - Antiparasitic products, insecticides and repellents - 7
R – Respiratory system - 69
S – Sensory organs - 21
V - Various - 15
X – Plants and homeopathic products – 2.

In 2014, 269 Decisions for MA discontinuation were issued, requested by the Marketing Authorisation Holder (MAH), on commercial grounds.

If in 2011, 2012 and 2013, generics have been on top of entrances on the market, they have preserved their status in 2014 as well.

Of the medicinal products included in the Index of medicinal products for human use in 2014, about 30% are original products authorised through centralised procedure by the European Medicines Agency (EMA), placed on the market upon request of the MAH.

In 2014, 821 marketing authorisations (MAs) were issued for medicinal products for human use authorised through European procedures, of which 425 MAs (51.76%) through DCP, 15 (1.83%) through MRP, 59 (7.2%) through MRP-RU (repeat-use mutual recognition

procedure) and 322 (39.21%) through renewal procedure. The percentage of renewed authorisations through European procedures has doubled since 2013.

It is of particular importance to highlight the fact that Government Decision no. 315 of 23 April 2014 on amendment of Government Decision no. 734/2010 on the organisation and operation of the NAMMD redefines the main duties of the NAMMD in the medicinal product field, among which the elaboration of the List of free and compensated medicinal products. Thus, in 2014, the NAMMD becomes the national competent authority in the medical technology assessment field.

Therefore, a transfer of assessment activities of medical technologies has been performed, from the Ministry of Health to the NAMMD, by setup of the Medical Technology Assessment Department (MTAD). The process of setup of a new Order of the Minister of Health concerning HTA (*"Health Technology Assessment"*) technology has been started, resulting in issuance of Order of the Minister of Health no. 861 of 23 July 2014 for approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products provided in national health insurance programmes, as well as the means for appeal thereof, published in the Official Gazette of Romania, of Romania, Part I, no. 557 of 28 July 2014. This Order has been subsequently amended in 2014 through a legislative document, Order of the Minister of Health no. 1200/16.10.2014 (Official Gazette, no. 755/16.10.2014), amending assessment criteria for compensated INNs from the List, new INNs, INNs which are orphan medicinal products, new curative INNs addressing infectious/contagious diseases, having a major impact upon public health, as well as the criteria for issuance of the decision for maintenance in the List.

Following the activity performed by the Medical Technology Assessment Department (within the NAMMD), Government Decision no. 720/2008 for the approval of the *List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes* was twice amended in 2014:

1. Government Decision no. 389/2014 (Official Gazette, no. 360/15.05.2014),
2. Government Decision no. 996/2014 (Official Gazette, no. 815/7.11.2014).

The activity of the MTAD in 2014 consisted of issuance of decisions referring to unconditional inclusion, inclusion conditioned by signing of a cost-volume or cost-volume-result contract between the MAH and the NHIH, or non-inclusion in the *List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes,* approved through Government Decision no. 720/2008.

By means of the two amendments to Government Decision no. 720/2008, 40 INNs were included as of 2014:

1. Government Decision no. 389/2014 (May) - 17 (sublist C: 2 in section C1 and 15 in section C2)
2. Government Decision no. 996/2014 (November) – 23: 9 (sublist B), 14 (sublist C).

The products included in the List address various therapeutic areas: oncology, cardiology, endocrinology, gastroenterology, haematology, infectious diseases, nephrology, ophthalmology, pneumology, psychiatry, rheumatology, urology, diabetes.

With each passing year, the pharmacovigilance activity performed during past years by the Pharmacovigilance and Risk Management Service becomes more complex, in line with the

alertness of special European regulations and Guidelines. The number of reported spontaneous adverse reactions (ARs) is constantly increasing, thus showing the increasing importance given by physicians and overall health staff to patients. Moreover, this increased involvement in the pharmacovigilance activity must also involve encouragement of patients to report ARs, all the more so as the new European legislation empowers them in this respect. However, training of patients and the general public about the significance of AR reporting for deeper awareness of the effect of medicinal products is the responsibility of competent authorities at national and European level, requiring proper partnership with healthcare professionals. The NAMMD has undertaken its role of referring to AR reporting by various means (on the NAMMD website, within scientific actions, meetings with associations and professional/patient organisations), each time highlighting the importance of the partnership between physician-pharmacist-assistant-patient for optimal knowledge of the safety profile of medicinal products, via these reports. The need for re-assessment of the risk-benefit reform for certain medicinal products or classes of medicinal products can only be manifested by transmission of the largest possible number of ARs into the EudraVigilance European database.

Therefore, if 2012 meant the first steps taken for enforcement of the new pharmacovigilance approach, the following years have shown real progresses in terms of reporting. In 2014, 2054 ARs were signalled, as opposed to 1874 in 2013. Practically, local handling and archiving of spontaneous adverse reaction reports have been performed, received from all sources: physicians, pharmacists, medical assistants, consumers, special literature – 2054 ARs, of which 823 SARs (serious ARs grave) and 1231 NSARs (non-serious adverse reactions).

Activity of the Pharmaceutical Inspection Department (PID) consisted, among others, of 38 inspections for assessment of compliance with Good Manufacturing Practice (GMP) rules for authorisation for manufacturing/import/certification BPF, 5 inspections on Good Laboratory Practice (GLP) for recertification at bioequivalence centres, 5 inspections for assessment of Good Laboratory Practice (GLP) in view of authorisation of independent quality control units, 6 inspections for assessment of compliance with Good Clinical Practice (GCP) rules, 103 inspections for authorisation of wholesale distributors of medicinal products. 1551 thematic inspections were carried out at the sites of wholesale and retail distribution units.

In 2014, because of non-compliance with legislation in the field, the NAMMD has sanctioned 28 distribution/representation units. Total sum of sanctions: 396,570 lei. In 2014, export declarations for 4713 medicinal products were approved, upon request of 40 manufacturers/distributors of medicinal products. There is an obvious increase in the activity of export to third countries, as opposed to 2013.

The year 2014 has witnessed an increase in the number of cases of falsified/suspected of falsification coming from Romania, distributed in various EU states: Pegasys, Mabthera, Avastin, Sutent. All signalled cases have been investigated by the NAMMD for establishment of traceability and forwarded to the General Inspectorate of the Romanian Police in view of finding out the source of falsified medicinal products. As of 01.11.2011, the PID handles the database of distributed medicinal products and updates it with data submitted monthly by manufacturers, importers and authorised wholesale distributors, initially in accordance with provisions of NAMMD Scientific Council Decision (SCD) no. 5/22.02.2011, subsequently amended through SCD no. 17/06.07.2011, repealed through Order of the Minister of Health no. 502/11.04.2013 on approval of mandatory monthly reporting of placement on the market in Romania and of sales of medicinal products for human use, respectively, by authorised wholesale distributors/importers/manufacturers.

In 2014, the Legal Department and the other departments have fought against falsified medicinal products, continuing the previously initiated collaboration through signing of the protocol of March 2010 for cooperation with the General Inspectorate of the Romanian Police, having the main purpose of establishing the framework for bilateral cooperation and exchange of information in the field of counterfeiting of medicinal products for human use, in accordance with specific duties and abilities stipulated by the legislation in force.

Some of the main trends of NAMMD cooperation with the General Inspectorate of the Romanian Police are:

 compliance with the legislation in the field of medicinal products for human use;

 exchange of information for accomplishment of the legal duties of each of the two institutions;

 performance of studies and market analyses, in view of a most exact knowledge of the Romanian medicinal product market, particularly as far as manufacture, import and distribution are concerned;

 monitoring of operation of markets in view of identification of cases of infringement of national and/or community legislation in the field of medicinal products for human use, enabling the two authorities to take the required measures, according to their abilities and their correlation;

 promotion and information of the public and economic agents active on the markets of medicinal products for human use regarding measures taken in cases of infringement of national and/or community legislation related to counterfeiting;

 reciprocal support in view of ensuring efficient functioning and safety of the sector of medicinal products for human use, also concerning required legislative amendments.

The ”SAVEmed Microstructure secured and self-verifying medicines” project was finished in 2014; it has been initiated by the UNICJRI (United Nations Interregional Crime and Justice Research Institute) by signing of a *Protocol on prevention and disproof of counterfeiting and traffic of medicinal products* by the NAMMD and by public and private partners.

Thus is enforced the framework for provisions of Directive 2011/62/EU amending Directive 2001/83/EC, the community code in the field of the medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, transposed into national legislation through EGO no. 91 / December 2012 amending certain healthcare regulations.

As of 13.10.2014, by issuance of Law 132/2014 on approval of Emergency Government Ordinance no. 2/23 January 2014 for amendment of Law 95/2006 on healthcare reform and of certain regulatory acts, the NAMMD is the competent authority dealing with medical devices and has taken over these from the Ministry of Health, as well as the market surveillance activity.

Since its set-up in 2010, through merger of the NMA with the Technical Office for Medical Devices, the NAMMD has been the sole institution authorised and able to assess performance and safety of medical devices in use.

The Nuclear Unit (NU) performs the same type of activities as the Laboratories - Technical Department (LTD), however, it uses ionizing radiations for medical devices. As a consequence, the activity report is the same, apart from formal specifications. Year 2014 has been equally demanding for the Laboratories - Technical Department and for the Nuclear Unit. Just like during previous years, the highest percentage of the 2014 activity of the two units was related to control, by periodic check of medical devices. This activity is conducted for all high-risk fixed and operated medical devices, at the sites of all users of medical devices, both private and public, and consists of assessment of performances and safety of medical devices in use, the assessment bulletin being one of the documents required for

signing the medical service contract, made between health insurance houses and cabinets/hospitals/medical centres.

The Medical Technology Assessment Department has performed its activity until May 2014, in line with Law 176/2000 on medical devices, as amended, and with Order of the Minister of Health no. 1636/2004 for approval of Methodological norms implementing Law 176/2000 on medical devices, as amended, on approval of technical-medical units, as amended, and with Title XIX of Law 95/2006, as amended and of Order of the Minister of Health no. 748/2014. The activity consisted of assessment of the organisations' ability to perform services for which Ministry of Health approval is required. Assessed activities are related to optics, repairing, maintenance and setup/commissioning of medical devices, prosthetics (auditory, orthopaedic, other).

Given its relatively low qualified staff, the department must ensure activity throughout the entire country, performing both initial assessment of organisations in view of obtaining the approval, supervision assessments every 2 years in view of maintaining the approval, as well and acknowledgement and sanctioning of contraventions concerning implementation of laws regulating its activity. A new amendment of Law 95/2006 has led to more responsibilities of the department – issuance of operation approvals for societies granting services in the field of medical devices (medical optics - fixing, glass repairing, fixing, maintenance and installation / commissioning of medical devices, prosthetics) and of Annexes to these operation approvals.

One of the main goals of the Human Resources and Payroll Department (HRPD) in 2014 has been the continuing and systematic process of analysing the institution's required human resources, to elaborate staff strategies and policies, in accordance with the Agency's long-term objectives and efficiency. In this respect, the Department considered the possibility of ensuring the hiring of qualified staff for all structures, the maintenance, development and efficient use of staff, taking into account the requirements to be met in order to ensure harmonious cooperation so as to grant accomplishment of organisational and individual goals of each employee.

Speaking of this aspect of utmost importance for optimal performance of the institution's activity, it is worth mentioning that in 2014, as opposed to previous years, vacant jobs have been opened for recruitment in line with Article 19 of Emergency Government Ordinance no. 103 of 14 November 2013 on remuneration of staff paid from public funds in 2014, as well as other measures related to public expenses, according to which "*in 2014, the maximum number of jobs financed from public funds, for public institutions and authorities, regardless of the manner of financing and subordination, is established so as to ensure full payment of wage-related rights granted in accordance with the law, while respecting the limits of expenses for paid wages approved through the budget. Chief credit officers establish the maximum number of jobs paid jobs in 2014, in line with the provisions of paragraph (1), for their own organisation and for subordinated public authorities coordinated by them.*"

However, the aforementioned legislation text implies that vacant jobs had become available, within the limits of the budget of income and expenses approved for the chapter on wage expenses. Considering this containment, the HRPD couldn't reach its goal consisting of covering the lack of qualified staff within the NAMMD. Only 5 persons have been hired for a determined period, for jobs that had become vacant in 2014, having a budget approved for wage-related expenses.

One major event of 2014 has been the visit of the audit team of the Heads of Medicines Agencies (HMA), in September (22-24.09.2014), with the participation of competent authorities in the field of the medicinal product from Portugal, Great Britain and Italy, in the context of BEMA III - Benchmarking of European Medicines Agencies. The BEMA programme measures the overall performance of an Agency, as a system, by comparison with

standards established within the HMA network, available for all European medicine agencies. This programme also allows exchange of experience in the field of good practices, as well as identification of fields for improvement of activity at both agency and network level.

The second audit visit within this programme has taken place in May 2011, after the one in 2005, these visits being each time considered an opportunity to assess the progress and to identify future development lines. BEMA II has helped the NAMMD to create the framework for correct and realistic self-assessment of abilities and performances, based on performance indicators, and to identify the lines for improvement of the activity and re-establish its priorities, by implementation of appropriate measures for risk management.

The institution started getting ready for the BEMA III audit in 2012. During 6 – 9.05.2014, one of the PID inspectors, appointed in the List of auditors for the BEMA benchmarking programme, has participated in the auditing visit of the quality system of the Danish Medicines Agency (DHMA). The visit was conducted in accordance with the methodology and procedures approved by the BEMA steering group and was carried out by 3 auditors, coordinated by the representative of the Austrian Agency for Health and Food Safety. The experience of this visit, as well as the theoretical training granted by NAMMD representatives in BEMA seminars have been enforced in the context of the training process of the NAMMD for required self-assessment for the BEMA III visit. This extended endeavour has taken an important part of NAMMD's activity, which has made maximum efforts during the first semester of 2014, when all NAMMD structures have been enrolled in participation in sessions preparing the answers for relevant performance indicators as regards the organisation's activity, in view of completing the self-assessment questionnaire, document preparing the BEMA III audit, focusing, in this third stage, on establishing the management system's ability to handle:

- general organisation fields
- the organisation's strategies
- pre- and post-authorisation assessment
- pharmacovigilance
- pharmaceutical inspection
- communication with stakeholders.

In the context of the BEMA III audit, the NAMMD has shown 3 examples of „good practices": stimulation of AR reporting; regulation of advertising; participation in studies assessing ability of quality control laboratories within the OMCL network, coordinated by EDQM.

The Agency's effort has shown in the mark obtained, according to assessment of the risk management activity (identification of the risk on all institution levels), based on demonstration of a transparent conflict of interests, of an adequate procedure for management of crisis situations (with the involvement of the Agency's and staff's infrastructure), by conducting inspections assessing compliance with risk-based Good Practices (GxP), by showing the existence of a significantly improved pharmacovigilance activity, as well as by highlighting public information about data issued from clinical trials, meant to raise the public's level of awareness in this respect. The lines of improvement of the Agency's activity, as seen after the BEMA III audit, refer to IT resources, assignment of additional funds for appropriate staff training, acquisition of additional expertise in the field of clinical trial inspection and also optimisation of activity transparency, particularly as regards accurate establishment of information of public interest.

Other aspects concerning NAMMD activity refer to:

 Active participation in debates, in bimonthly/monthly/quarterly meetings of scientific committees and working groups of coordinating European bodies in the field of the medicinal products for human use (The European Medicines Agency - EMA, Heads of Medicines

Agencies - HMA, The European Directorate for the Quality of Medicines - EDQM, the European Commission).

As in all years starting with 2007, the NAMMD participated, in 2014, through assigned representatives, in meetings of the scientific committees and working groups of European bodies, dealing with various aspects of regularisation and European procedures in the field of the medicinal product; the participation in the following is worth mentioning:

- The CHMP of the EMA (The Scientific Committee for Medicinal Products for Human Use), with appointment as co-rapporteur within re-examination procedures;

- The PDCO of the EMA (The Paediatric Committee) – assessed by a PIP (paediatric investigation plan), participation in the setup of the 2014 Yearly Romanian Paediatric Report, forwarded to the EMA/PDCO for the European Commission and to teleconferences and monthly/bi-monthly meetings of working subgroups (Extrapolation of efficacy and safety in development of the paediatric medicinal product and Pharmaceutical formulation – active participation and setup of assessment reports);

- The Coordination Group for Mutual Recognition and Decentralised Procedures - CMDh. Romania is a Reference Member State in several decentralised procedures;

- The Committee on Herbal Medicinal Products - CHMP, RO being a reporter/assessor of certain community monographs;

- Meetings of the *Pharmacovigilance Risk Assessment Committee* (PRAC) of the EMA;

- The working group for medicinal products and medical devices of the EU Council, where NAMMD representatives have participated in debates on setup and harmonisation of clinical trial legislation in all Member States. The NAMMD was assigned by the Ministry of Health to participate in debates upon the new Clinical trial regulation; the proposal for repeal of Directive 2001/20/EC has been made in July 2012;

- Sessions of the European Pharmacopoeia Commission.

 Regulatory activity and grant of technical support upon Ministry of Health request:

- In 2014, the NAMMD Scientific Council approved 13 Decisions (SCDs) (7 non-regulatory and 6 regulatory); the non-regulatory decisions are published on the website under "Legislation" and in the quarterly "Newsletters"). It is worth mentioning that SCD no. 7/01.07.2014 on approval of the Guideline on assessment of advertising of medicinal products for human use (regulatory) has been approved through Order of the Minister of Health no. 194/23.02.2015 on rules for assessment and approval of advertising of medicinal products for human use.

- As known, the NAMMD has received a new duty in 2013, as seen in Order of the Minister of Health no. 85/07.02.2013 on approval of the Norms for implementation of provisions of Article 699 (1) and (2) of Law 95/2006 on healthcare reform concerning medicinal products for special needs. The Agency has continued this activity in 2014 as well: 57 Authorisations for Special Needs (ASNs) were issued (for 67 medicinal products), of which 17 for each patient, and the rest for certain medicinal products meant for categories of patients with various diseases, upon request of consulting commissions/directions of the Ministry of Health,

- The NAMMD has granted the Ministry of Health technical support for amendment and supplementation of the List in the Annexes to Order of the Minister of Health no. 456/02.04.2013 on approval of the List of International Non-proprietary Names of medicinal products at high unavailability risk, as provided to insurants in the health insurance system and agreement on a measure to secure their market availability in Romania, as amended. The Order of the Minister of Health refers to temporary suspension, according to Law 95/2006, of distribution outside Romania of medicinal products mentioned in the List attached to the Order of the Minister of Health.

- The NAMMD answered to the requests of the Ministry of Health concerning:

a) ensurance of technical support for setup of the Lists for national auctions for the required amount of medicinal products:

- in hospital sections;

- for national programmes (setup of Annexes concerning medicinal products involved in national health programmes).

b) ensurance of technical support for quarterly setup of CANAMED (the national price catalogue), based on update of the Index of medicinal products.

 Strategies – The Organisational Strategy and the Communication Strategy for 2013-2015, as approved through NAMMD Scientific Council Decisions in 2013.

- In 2014, the entire NAMMD personnel has participated both in implementation of the *Organisational strategy* for 2013-2015 and of the NAMMD *Communication Strategy* for the same period. The Policies and Strategies Department has always monitored the adjustment of the communication strategy to the new requirements and legal and socio-economic changes and ensurance of feedback, legal and socio-economic changes and ensurance of feedback upon request of stakeholders, enabling the creation of a real partnership with these, based on dialogue and action.

 Participation in gatherings/workshops/conferences/informal meetings with stakeholders concerning legislation and procedures in 2014

Among others, year 2014 consisted of:

- participation in various meetings of patient associations, with presentations on the importance of adverse reaction reporting for medicinal products, generics and innovative medicinal products, falsified products and importance and significance of clinical trials, off-label use of medicinal products;

- setup of the NAMMD-ARPIM, working group settling legal provisions in the field of clinical trials;

- participation in debates within the Health Forum (February 2014) organised by the APMGR, concerning the issue of generics on the Romanian pharmaceutical market.

 Participation with special papers in various scientific events

The NAMMD mission is to be constantly present in the scientific life in the field of the medicinal products for human use.

The NAMMD displayed openness and transparency in its activity by participation with papers in important scientific events:

- The National Paediatrics Conference, Bucharest, April 2014;

- The "To the point: Medicinal product advertising", organised by the Romanian College of Pharmacists, Bucharest, June 2014;

- The National Pharmacy Congress, Iași, September 2014;

- The European conference organised by the *European Directorate for the Quality of Medicines* & HealthCare (*EDQM*), the European Council, Strasbourg, France, October 2014;

- The National Conference of Family Medicine – Bucharest, October 2014;

- The National Pharmacy Conference, Bucharest, November 2014.

The topics of the special papers presented by NAMMD representatives have been many, in accordance with the activity performed by the Agency in the field of its profile; here are some of the titles of papers written by Agency specialists:

-*"Implementation of European Commission Decisions or of approvals of the Coordination Group for Mutual Recognition and Decentralised Procedures, concerning medicinal products for human use – one of the missions of the National Agency for Medicines and Medical Devices";*

- "*Control of OTC advertising in EU member states"*

- *"EU policy on control of OTC advertising*"

- *„Issuance of decisions for referral procedures at European level"*

- *„Definition of starting materials of the active substance – critical issue for medicinal product quality"*

- *„Adverse reaction reporting – main factor in establishment of the safety profile of medicinal products at European level".*

NAMMD ACTIVITIES IN 2014

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

In 2014, the Scientific Council adopted 13 Scientific Council Decisions (SCDs); out of these, 5 regulatory decisions await approval through Order of the Minister of Health (OMH); the remainder of 8 non-regulatory SCDs have been posted on the NAMMD website under section "Legislation/Scientific Council Decisions" and published in the bilingual NAMMD Newsletters of 2014.

SCD no. 7/01.07.2014 on approval of the Guideline on assessment of advertising of medicinal products for human use, regulatory Decision, has been approved through Order of the Minister of Health no. 194/23.02.2015 on Rules for assessment and approval of advertising of medicinal products for human use.

3 ordinary meetings of the Scientific Council (28.03.2014, 01.07.2014 and 10.09.2014) and an extraordinary meeting (13.02.2014), related to presentation by NAMMD management of a notification on the situation created by the non-compliance identified in flu vaccine batches manufactured by the Cantacuzino Institute for the season of 2013-2014, have taken place in 2014.

Non-regulatory SCDs were related to:

- The Guideline on Good Pharmacovigilance Practice – Annex I – Definitions, Rev. 2
- The abbreviated standard terms used for labelling of oral, oromucosal, dental, cutaneous and transdermal, vaginal, rectal, inhalation and tracheopulmonary, the Romanian version of standard terms approved by the European Pharmacopoeia Commission
- The Good Pharmacovigilance Practice, Module XV – Safety communication
- Authorisation of units performing clinical trials in the field of the medicinal product for human use
- Posting on the NAMMD website information issued from clinical trials authorised by the NAMMD

2. Activity of the NAMMD Administration Council (AC)

In 2014, the Administration Council (AC) adopted 10 Administration Council Decisions (ACDs). Thematically speaking, ACDs have covered various aspects of current activities.

3. Regulatory activity

The Legal Department and other NAMMD professional departments have set up documentation (drafts of regulatory documents, substantiation notes, approval papers) for promotion via the chief credit accountant, namely the Ministry of Health, of the following regulatory documents:

a) three law/ordinance drafts for amendment of Law 95/2006 on healthcare reform, approved through Emergency Ordinance no. 2/2014 on amendment of Law no. 95/2006 on healthcare reform and of certain regulatory acts; Emergency Ordinance no. 23/2014 on amendment of Law 95/2006 on healthcare reform and amendment of certain legislation; Law 132/2014 on approval of Emergency Ordinance no. 2/2014 on amendment of Law 95/2006 on healthcare reform and of certain regulatory acts;

b) two Government Decision drafts, approved through Decision no. 315/2014 on amendment of Government Decision no. 734/2010 on the organisation and operation of Decision no. 1184/2014 on repeal of the Technical Office for Medical Devices - Certification and on amendment of certain regulatory acts;

c) 13 drafts of Orders of the Minister of Health, namely:

- draft *approved through Order no. 861/2014* for approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes, as well as the means for appeal thereof;

- draft approved through Order no. 888/2014 on approval of fees payable to the National Agency for Medicines and Medical Devices for services related to medicinal products for human use;

- project approved through Order no. 1018/2014 on approval of Conditions for authorisation of human medicinal products for compassionate use, in accordance with provisions of Article 83 of Regulation (EC) no. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency;

- draft approved through Order no.1200/2014 on amendment of Order of the Minister of Health no. 861/2014 for approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes, as well as the means for appeal thereof;

- draft for repeal of Order no. 279 of 30 March 2005 on approval of implementation of changes to marketing authorisations approved by the National Medicines Agency;

- draft for repeal of Order no. 399 of 12 April 2006 on approval of European models of package leaflet, summary of product characteristics and label information for medicinal products authorised for marketing in Romania;

- draft for repeal of Order no.1483 of 9 December 2010 on approval of the Norms on administrative procedure of the National Agency for Medicines and Medical Devices on handling of variations;

- draft for approval of implementation of leaflet drafts, Summary of Product Characteristics and leaflet information for medicinal products authorised for marketing in Romania, as well as of declaration formats, authorisations and certificates, in accordance with the European regulations in force;

- draft for amendment of Order no. 85 of 7 February 2013 on approval of the Norms for implementation of provisions of Article 699 (1) and (2) of Law No. 95/2006 on healthcare reform concerning medicinal products for special needs;

- draft for approval of the regulations for manufacturing authorisation of producers, importers of medicinal products for human use, including products for clinical investigation and independent control units and grant of the Good Manufacturing Practice certificate;

- draft for approval of the Good Distribution Practice;

- draft for approval of the procedure on record of manufacturers, importers or distributors of active substances used as starting materials for medicinal products for human use;

- draft for approval of the norms on authorisation of wholesale distribution units for medicinal products for human use, Good Distribution Practice certificate and record of brokers of medicinal products for human use.

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions

In 2014, within meetings of the two commissions for marketing authorisation (Commission for Marketing Authorisation - National procedure, Commission for Marketing Authorisation – European procedures), set up through Decision of the NAMMD Administration Council, as established through President decision, discussion of assessment reports was continued, in view of issuance of the Agency's opinion concerning marketing authorisation of various medicinal products with a request in this respect, as well as other issues related to authorisation for marketing of medicinal products for human use.

In 2014, 24 working sessions took place, divided by commissions (13 for Commission for marketing authorisation - National procedure and 11 for Commission for marketing authorisation - European procedures).

Commissions approved the issuance of 1152 marketing authorisations, of which 673 through European procedures (decentralised, mutual recognition, mutual recognition-repeat use) and 497 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 a structure approved through President Decision, the Commission continued its activity in 2014 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 inspection decisions disputed by the inspected site.

In 2014, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 127 inspection reports, of which:

- 42 inspection reports on compliance with Good Manufacturing Practice rules;
- 75 inspection reports on compliance with Good Distribution Practice rules;
- 1 inspection report on compliance with Good Clinical Practice rules;
- 5 inspection reports on compliance with Good Laboratory Practice rules;
- 4 inspection reports on compliance with Good Analytical Laboratory Practice rules.

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 2014, 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 2014, non-compliance of the flu vaccine manufactured by the Cantacuzino Institute for 2013-2014 has determined three meetings of the Commission.

5. Marketing authorisation and related activities

In 2014, the main activities of the Agency, assessment of the documentation submitted to the NAMMD for marketing authorisation and marketing authorisation renewal, as well as post-authorisation surveillance of a product's safety, have been performed admirably, as imposed by high complexity standards, established through an increasingly severe legislation in the field of the medicinal product for human use, within the European Union. These activities are specific to a competent authority in the field of the medicinal product, carried out in accordance with legal provisions on national procedure and European procedures (mutual recognition/decentralised/repeat-use mutual recognition procedure). Authorisation for marketing and related activities were carried out during the first semester of 2014, according to the organisational structure established in 2010 through an Order of the Minister of Health on reorganisation of the NAMMD and setup of the National Procedure Department and of the European Procedures Department, and during the second semester according to the organisational structure established through Order of the Minister of Health no. 860 of 22 July 2014 on approval of the NAMMD organisational structure, published in: the Official Gazette of Romania, Part I, no. 560 of 29 July 2014.

5.1. Marketing authorisation through national and European procedures

In 2014, 821 marketing authorisations (MAs) were issued for medicinal products for human use authorised through European procedures: 425 (51.76%) through decentralised procedure, 15 (1.83%) through Mutual Recognition Procedure, 59 (7.2%) through repeat-use mutual recognition procedure and 322 (39.2%) through renewal procedure.

The percentage of authorisations renewed through European procedures has doubled as opposed to 2013.

Assessment work performed within the national procedure resulted in grant of 914 MAs (120 authorisations and 281 renewals), a double number as opposed to the previous year, thanks to the effort made in order to recover belated renewals (102 authorisations and 93 renewals in 2013).

As opposed to 2013, when the number of discontinued MAs has risen to 320 (versus 247 in 2012), 269 decisions for MA discontinuation, requested by MAHs on commercial grounds, were issued in 2014.

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

5.2.1. As concerns post-authorisation assessment of variations to terms of marketing authorisation (MA) granted through national procedure, the NAMMD assessed and approved:

- 3426 Type I variations
- 322 Type II variations
- 75 MA transfers
- 316 changes of packaging design and printing
- 784 variations concerning safety and efficacy

5.2.2. In 2014, as regards post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures, for medicinal products for human use authorised through decentralised/mutual recognition/repeated mutual recognition procedure, the NAMMD approved (issued applications for approval):

- 3338 Type IA variations for Romania (as a concerned member state);
- 21 Type IA variations for Romania (as a reference member state);
- 1630 Type IB variations for Romania (as a concerned member state);
- 16 Type IB variations for Romania (as a reference member state);
- 441 Type II variations for Romania (as a concerned member state);
- 1 Type II variations for Romania (as a reference member state);
- 87 MA transfers for Romania (as a reference member state);
- 58 notifications in accordance with Article 61(3) of Directive 2001/83/EC.

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

Part of the National Procedure Department in the first semester of 2014, following approval of the new NAMMD organisational structure, the Pharmacovigilance and Risk Management Service has become a separate structure, under coordination of the NAMMD vice-president.

In 2014, 245 applications were submitted for authorisation of clinical trials, more than in 2013 and less as opposed to previous years (266 applications in 2010, 253 in 2009 and 275 in 2008). Most of these are Phase III clinical trial applications (173 applications in 2014), meaning that the respective medicinal products undergo advanced research and are therefore nearing authorisation. Phase II clinical trials are the second most frequent type of clinical trial applications (43 applications in 2014); these are exploratory studies concerning the most effective dose for medicinal products whose safety and tolerability have been proven.

In Romania, there are few applications for performance of Phase I clinical trials (15 applications in 2014), more than 12 (in 2013), which require special conditions.

In 2014, the NAMMD granted 196 authorisations for conduct of clinical trials, mostly for Phase III (138) and II (41) clinical trials; 8 Phase I and 9 Phase IV studies were authorised.

Moreover, 39 applications for observational clinical trials were received; acknowledgement letters have been issued for 28 observational studies.

In 2014, the Clinical Trial Service approved 615 substantial amendments and 529 important amendments and 220 for new investigational sites; moreover, 117 authorisations for conduct of bioequivalence clinical trials were granted after assessment by the National Procedure Assessment Service of the protocol of bioequivalence clinical trials.

As regards authorisation of clinical units for performance of clinical trials, a new activity was given to the Clinical Trials Service on repeal of Order of the Minister of Health no. 912/2006 and entry into force of SCD 2/April 2014; the following are worth mentioning:

- applications for assessment and authorisation of medical units for performance of clinical trials in the field of received and issued medicinal products: 193

- authorisations issued: 117.

5.4 Assessment of medical technologies

Government Decision no. 315 of 23 April 2014 for amendment of Government Decision no. 734/2010 on organisation and operation of the NAMMD redefines the main responsibilities of the NAMMD in the field of the medicinal products for human use, such as setup of the List of on-prescription compensated and free medicinal products from the Index of medicinal products for human use as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, together with the Ministry of Health and the National Health Insurance House.

In 2014, the NAMMD thus becomes the national competent authority in the field of medical technologies assessment. In order to implement these new responsibilities of the Agency, a new NAMMD department was created - the Medical Technology Assessment

Department (MTAD), by transfer of this assessment activity from the Ministry of Health. Moreover, the new MTAD has been directly involved in elaboration of the new Order of the Minister of Health concerning Health Technology Assessment (HTA), namely Order of the Minister of Health no. 861 of 23 July 2014 for approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes, as well as the means for appeal thereof, published in the Official Gazette of Romania, Part I, no. 557 of 28 July 2014. This Order has been subsequently amended in 2014 through Order of the Minister of Health no. 1200/16.10.2014 (the Official Gazette no. 755/16.10.2014) supplementing assessment criteria for INNs (offering the possibility of inclusion in the Compensation list of new INNs, orphan INNs, new curative INNs for infectious, contagious pathologies, having a major impact upon public health), as well as the criteria for issuance of a decision for maintenance in the List.

Applications submitted – 160

Applications for new INNs or extension of indications - 150

Applications for relocation - 6

Applications for lowering of the number of stars - 4

The MTAD activity in 2014 consisted of issuance of decisions on unconditional inclusion, to inclusion conditioned by signing a cost-volume / cost-volume-outcome agreement between the MAH and the NHIH, or non-inclusion in the *List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes*, as approved through Government decision no. 720/2008.

Following medical technologies assessment, two amendments of Government decision no. 720/2008 on approval of the *List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programmes* were issued in 2014; 40 INNs were introduced, as follows:

Government decision no. 389/2014 (The Official Gazette of Romania no. 360/15.05.2014) - 17 (sublist C: 2 in section C1 and 15 in section C2).

Government decision no. 996/2014 (The Official Gazette of Romania no. 815/7.11.2014) – 23 (sublist B: 9 and sublist C: 14).

Medicinal products introduced on the List address various therapeutic areas: oncology, cardiology, endocrinology, gastroenterology, hematology, infectious diseases, nephrology, ophthalmology, pneumology, psychiatry, rheumatology, urology, diabetes.

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

In 2014, the same importance has been given to supervision and control of advertising of medicinal products for human use, just like during previous years, starting with 2010.

516 advertising materials for OTCs, meant for the general public, were assessed.

572 advertising materials for OTCs, meant for the general public, were assessed for renewal of the approval.

217 advertising materials for educational programs were assessed and approved.

23 notifications for withdrawal were received.

Year 2014 also meant approval through NAMMD SCD, in July, of a revised version of the regulatory Guideline on advertising of medicinal products for human use, submitted for approval through Order of the Minister of Health (Order of the Minister of Health no. 194/23 February 2015 on rules for assessment and approval of advertising of medicinal products for human use, published in the Official Gazette of Romania, no. 168 of 11 March 2015).

5.6. Pharmacovigilance

During the first semester of 2014, the Pharmacovigilance and Risk Management Service has been a part of the European Procedures Department; after approval of the new NAMMD organisational structure through Order of the Minister of Health, this Department would become a separate structure, coordinated by the NAMMD vice-president, and deal with the issue of the medicinal product for human use. This activity is performed in accordance with Law 95/2006 and specific European guidelines, handling the safety of medicinal products authorised in Romania.

The pharmacovigilance activity of the NAMMD is conducted based on European legislation, transposed into national legislation. Pharmacovigilance activity includes, among others, assessment and transmission of adverse reactions within the EudraVigilance (the European network for pharmacovigilance data-processing and management), assessment of Periodic Safety Update Reports (PSURs), as forwarded by pharmacovigilance systems of authorisation holding companies, assessment of Risk Management Plans. Approval of direct communications to healthcare professionals concerning special warnings related to medicinal product safety, translation in view of posting on the NAMMD website of press releases and documents containing EMA questions and answers, representing notifications and recommendations made during monthly meetings of the PRAC, CHMP or CMDh, are all part of the pharmacovigilance activity. The pharmacovigilance field in Romania also covers provision of answers to non-urgent information, as well as to those appearing through the European and international rapid alert system.

In accordance with European regulations in force, all available information concerning the safety of the medicinal product are currently published on the NAMMD website.

Via the Direct Communications for Healthcare Professionals, due to national medical and pharmacy symposia, conferences and congresses, as well as through participation of NAMMD representatives in various meetings of patient organisations, an appeal concerning suspected adverse reaction (AR) reporting is made to physicians, pharmacists, medical and pharmacy assistants and, as of July 2012, to patients. NAMMD's message of encouragement stays the same: It is important to report adverse reactions; that is the only way to obtain complex information about medicinal products after marketing authorisation, through impact with the general public!

During previous years, by means of each activity report, the NAMMD records the progress occurred in AR reporting by a simple presentation of the numbers. In spite of only 280 spontaneous reports submitted in 2004, the following years have brought progressive increases in AR reporting, namely 1847 ARs in 2013 (935 - serious and 912 - non-serious). 295 of these were forwarded by physicians directly to the NAMMD and 1552 by MAHs (of which 100 from consumers, 34 from pharmacists, 59 from medical assistants, and most of the rest from physicians, including from articles from special literature).

Year 2014 brought a new progress, namely the reporting of 2054 ARs (823 – serious ARs and 1231 non-serious ARs). The number of ARs submitted by MAHs (via Eudravigilance, MAHs only report such cases via Eudravigilance), as follows: 949 reported by physicians; 36 by pharmacists; 25 de alt personal medical; 194 consumers; 424 are special literature reports and 3 are reported by a lawyer/the media. The number of ARs received directly by the

NAMMD (professionals/consumers): 408 directly reported by physicians; 7 directly reported by pharmacists and 8 by consumers.

The pharmacovigilance activity performed by the Pharmacovigilance and Risk Management Service in 2014 materialised in the following:

a) management of safety data issued from spontaneous reporting:

- validations/confirmations of adverse reaction (AR) reporting to the European database for adverse reactions, EudraVigilance (EV) (ICSR and SUSAR) – 3006 confirmations (ACK);

– retransmission to EVHUMAN of cases received in the Inbox of NAMMD's EV (in electronic form) – 1371 serious adverse reactions;

– transmission within EV to EVHUMAN and the MAH of serious and non-serious adverse reaction reports received directly from the NAMMD in written form, by fax, post, e-mail – SARs - 142, NSARs - 327, Total - 469;

– local management and archiving of spontaneous adverse reactions reports received from all sources – 2054 ARs, of which 823 SARs and 1231 NSARs;

- electronic retransmissions of adverse reactions to the WHO database (the Uppsala Monitoring Centre) via the VigiFlow electronic channel – 1217 ARs;

– monthly transmission of post-vaccine undesirable adverse reactions (PVUARs) received directly by the NAMMD to the National Institute for Surveillance and Control of Infectious Diseases;

– notification letters to the College of Physicians concerning spontaneous reporting of adverse reactions by physicians in view of grant of Continuing Medical Education (CME) credits - 4;

– notification letters to the College of Pharmacists concerning spontaneous reporting by pharmacists of adverse reactions to medicinal products, in view of grant of Continuing Medical Education (CME) credits – 4;

– notification letters sent to pharmacists concerning grant of Continuing Medical Education (CME) credits by the Romanian College of Pharmacists for transmission of spontaneous adverse reaction reports in Romania and validated by the NAMMD - The National Pharmacovigilance Centre – 17;

– information letters sent to physicians concerning grant of Continuing Medical Education (CME) credits – 754;

– letters of confirmation of receipt of AR reporting sheets from physicians within the network – 172;

– letters of confirmation of receipt of AR reporting sheets from pharmacists within the network– 1;

– responses to MAH requests concerning adverse reactions reported to the NAMMD involving medicinal products authorised in Romania – 90;

– request of additional information on adverse reactions to MAHs concerning pharmacovigilance issues – 395.

b) Collection, validation and archiving of 670 archived Periodic Safety Update Reports (PSURs).

c) Pharmacovigilance activities within the system of national European authorities;

– EMA press releases translated and posted on the website – 48 documents;

– 28 Direct Healthcare Professional Communications (DHPCs) related to safety concerns raised in relation with medicinal products;

– transmission of 17 information letters to the Commissions (the National Health Insurance House, the College of Physicians, the College of Pharmacists);

- Management of "Lines to take" documents (proposed for handling of requests for information concerning the safety of medicinal products) - 40;

d) pharmacovigilance activities in the context of rapid alert/non-urgent information (AR/NUI) action:

– 32 replies (NUI) upon request for information by certain EU national authorities concerning information about individual medicinal products or medicinal products categories.

e) Assessment of pharmacovigilance documentation in the marketing authorisation and renewal procedure:

– 1494 assessment reports of the pharmacovigilance documentation in view of obtaining/renewal of a marketing authorisation through decentralised procedure (DP)/mutual recognition procedure (MRP)/ repeat-use mutual recognition procedure (Repeat-Use)/renewal (R) (Romania as a concerned member state);

– 200 assessment reports of the pharmacovigilance documentation – pharmacovigilance system/summary of the pharmacovigilance system/Risk Management Plan (initial + supplementations) to obtain a marketing authorisation/marketing authorisation renewal through national procedure.

- Romania as a reference member state (RMS) in European procedures: - Assessment report for the pharmacovigilance documentation (PBRER assessment for MA renewal procedures reports, assessment of summary of pharmacovigilance system and Risk management plan in procedure for grant of marketing authorisation): 3 reports.

f) Assessment and approval of educational materials included in the Risk Management Plan (RMP):

- 58 dossiers containing 148 educational materials.

g) Assessment of reports concerning variations to terms of marketing authorisations as regards the pharmacovigilance system for medicinal products authorised through national procedure

– 22 validations of applications for Type IB and II variations (through national procedure);

– Type IA variations/- summary of the pharmacovigilance system (national procedure): 190

– Type IB, II variations – Risk Management Plan, Active surveillance study – Vaccine safety (1) - national procedure – 16

– Type II variations (RMP) through work-sharing procedure (work-sharing – WS) – 3

– Type IB and II variations for medicinal products authorised through mutual recognition/decentralised procedure – 142;

h) Assessment of requirements concerning the holders' pharmacovigilance system for grant of parallel import authorisation

- parallel import procedure: 114 assessments.

5.7. Miscellanea

Handling of the database of the Index of medicinal products for human use, consisting of introduction of the new medicinal products authorised through national procedure, European procedures and centralised procedure, performance of changes to MA for already authorised medicinal products, inclusion of variations to issued MAs, highlighting of medicinal products undergoing MA renewal procedure, MA withdrawal/discontinuation decisions.

Thus, in 2014, the National Procedure Department (with support of IT professionals within the Information Logistics and Electronic Management of Data Department for posting on the Agency's website) ensured:

- Maintenance of the database of authorised medicinal products:

- 1222 products authorised through: national/European/centralised procedure - for those notifying effective placement on the market) – information about the marketing authorisation (MA) are introduced: trade name, MAH, batch release responsible person, packaging;

- variations to MAs approved through national/European/centralised procedure (information on approved MA changes shall be introduced: trade name, MAH, person responsible for batch release, packaging etc.)

- Issuance of 267 decisions for MA withdrawal/discontinuation (withdrawal of national MA when the same product is granted marketing authorisation through European procedure; discontinuation of a valid MA on request by the company);

- 801 notifications for MA withdrawal/discontinuation sent to the Ministry of Health, the National Health Insurance House, the MAH;

- handling of data concerning the tax of maintenance in the Index for: 6121 (products);

- inclusion of „blank spaces" for medicinal products submitted for renewal (R): 433;

- other types of discontinuation (pending/marketing discontinuation: 547+30=577 medicinal products;

- inclusion of 180 discontinued medicinal products into the database of the Index and registry;

- Assessment of the National Brochure of the prices of medicinal products (4 times) authorised for marketing in Romania (quarterly and whenever required by the Ministry of Health) in terms of CIM codes and technical identification data – 6100 occurrences analysed/quarter;

- Transmission of the Index of Medicinal Products to the NHIH in the format agreed (4 times) for reception of SIIS (single integrated information system), quarterly and whenever required by the NHIH, and analysis of non-compliances between SIIS and CANAMED (the national price catalogue), forwarded to the NHIH quarterly and whenever required;

- 8500 pdf files, of which 2900 pdf files (packaging), 3200 (leaflets) and 2400 (SmPCs), as current versions of Annexes I, II and III, for the aforementioned products, have been published on the NAMMD website, via the Index of medicinal products in web format,

- analysis of situations forwarded by the NHIH/Ministry of Health concerning discontinued/suspended/expired MAs – quarterly.

As regards *"parallel import"* activities, 76 parallel import authorisations (PIAs) (assessment of submitted documentation, of supplementations sent by applicants and setup of PIAs and their Annexes).

In this respect, 11 competent authorities of EU member states have received 70 requests for information were issued, needed for PIA release, as well as for changes of issued PIAs (45 variations to PIAs were released).

"Parallel export" activities consisted of:

- issuance of 399 responses to requests for information received from 21 EU competent authorities (plus another about 180 responses for disambiguation and completion of initially forwarded information), for grant of a parallel import authorisation for the respective member states. The correspondence for disambiguation and supplementation of data initially forwarded contains individualised data referring to: the MA number of the medicinal product in Romania; the MAH; the manufacturers involved in the entire manufacturing process; details on the qualitative and quantitative composition of the product; the ATC code, manner of presentation, storage conditions;

- permanent update of the internal database concerning the *„parallel export" activity,* namely inclusion of the following data: export country/Contact name/Product/MA/MAH/MA in Romania/ Applicant/question date/answer date.

The following activities have also been continued:

- management of responses received under application of provisions of Articles 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*");

As regards *"sunset clause"* implementation, assessment of the database set up according

to documents submitted by the MAH is worth mentioning. 259 reports have been submitted from companies/representations (dossiers and electronic formats). 25 Decisions of MA discontinuation have been issued in accordance with provisions of Article 729 of Law 95/2006 on healthcare reform – Title XVII, The medicinal product.

- 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 submission of variation applications (83 cases) for implementation of the EC Decision.

Other activities performed, related to the Index of medicinal products for human use, have been:

- setup of various reports based on data available in the NAMMD Index:

- assessment/reporting of the situation/declarations concerning reimbursement prices for products included in the C2 sublist of Government Decision no. 720/2008 (2);

- participation in meetings of the Commission of appeals for requests for inclusion of the new INN into Government Decision no./720/2008;

6. Activity of Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), Good Laboratory Practice (GLP), Good Analytic Laboratory Practice (GALP), Good Clinical Practice (GCP), pharmacovigilance and market surveillance

During 2014, the PID continued to perform the activities mentioned in the specific legislation (Law 95/2006 - Title XVII – The medicinal product, as amended and secondary legislation), in accordance with the Department's Standard Operating Procedures and according to the deadlines stipulated by the law. Types of 2014 inspections:

GMP, GLP, GALP, GCP, pharmacovigilance

- 30 GMP inspections for grant of manufacturing authorisation

No follow-up inspections at the sites of manufacturers or importers of medicinal products have taken place in 2014:

- 8 inspections for authorisation at the sites of medicinal product importers.

Each authorisation/certification process meant the setup of deficiency lists and setup of the inspection report, following transmission of the corrective measure plan and its assessment.

Manufacturing/import authorisations, namely GMP compliance certificates, have been issued for units whose authorisation/certification process had a favourable outcome.

As regards medicinal products importers, in most cases, the qualified person has managed to correctly release the manufacturing batch, sustaining documents included, which has enabled issuance of import authorisations.

- 15 certification inspections for GMP compliance of pharmaceutical companies from third countries;

In 2014, 11 inspections concerning compliance with GMP Guidelines were carried out upon request of pharmaceutical companies in third countries (India, Moldavia, Macedonia, Serbia, Egypt, Turkey). The certification process is ongoing for the 11th company inspected.

An inspector of the NAMMD-PID and EDQM inspectors have participated in 2 inspections required by the EDQM concerning starting materials for pharmaceutical use at Chinese manufacturing sites (having led the inspection team in an inspection). Inspections resulted in issuance of 1 certificate of GMP compliance, namely a declaration of GMP noncompliance for the other company in China.

In 2014, a NAMMD inspector from the PID department participated, together with other inspectors from the Italian authority in the field of the medicinal product (AIFA) and from the Finnish authority in the field of the medicinal product, in 2 inspections requested by the

European Medicines Agency (EMA), concerning reconfirmation of GMP compliance by a manufacturer in the USA (for centrally authorised medicinal products), namely by a manufacturer in India (for active substance manufacturers).

The 15 inspections resulted in 15 GMP compliance certificates, for both medicinal products for human use and pharmaceutical active substances.

- 5 inspections on Good Laboratory Practice;

- 5 GLP inspections in laboratories performing bioequivalence studies.

5 recertification GLP inspections were carried out at bioequivalence centres (clinical unit and/or bioanalytical laboratory) performing bioequivalence studies.

-5 inspections for authorisation of independent units assessing control of medicinal product quality - GALP.

In 2014, 5 inspections were requested at independent control units for physical/chemical and/or microbiological laboratories for which 4 authorisations and annexes have been issued; one of these units is still in the authorisation process.

Authorisation has involved setup of a List of deficiencies and, after transmission of the corrective measure plan and its assessment, setup of the inspection report, based on which the independent control unit has been authorised, on a case-by-case basis.

- 6 inspections for verification of compliance with Good Clinical Practice

The following were performed in 2014:

- 4 scheduled GCP inspections (in accordance with the NAMMD yearly inspection program) assessing compliance with Good Clinical Practice din care: at the site of the sponsor (1) / CRO (1) / investigator (2);

- 2 GCP inspections concerning decentralised procedure assessing compliance with Good Clinical Practice at the site of the investigator (1) and at the bioanalytical laboratory (1).

Pharmacovigilance inspections

In accordance with PID's yearly inspection plan, 16 inspections for surveillance of the pharmacovigilance activity at the MAH / representative in Romania of a MAH were planned for 2014; the inspection still goes on at the site of a MAH representative.

The activity of consultancy conducted by inspectors of local units at clinics, hospitals, cabinets of family physicians, in view of actuating the activity of reporting local spontaneous adverse reactions, was continued in 2014 as well. 956 reports following local consultancy pharmacovigilance visits were set up in 2014, showing an increase in the number of adverse reaction reports submitted to the NAMMD by MAHs or healthcare professionals.

GDP inspections

In 2014, GDP inspections were as follows:

- authorisation for wholesale distribution of Romanian distribution units in accordance with the legislation and setup of a national database containing information from issued wholesale distribution authorisations;

- management of the database of wholesale distributors and wholesale medicinal products in accordance with monthly reports received from wholesale distributors/manufacturers/importers in line with Order of the Minister of Health no. 502/April 2013;

- coordination of local inspectors concerning local performance of inspections for authorisation of wholesale distributors;

- follow-up inspections to assess wholesale distribution of medicinal products in authorised units;

In 2014, 103 inspections for authorisation have been performed, leading to release of 94 authorisations for wholesale distribution and Annexes; 48 units undergo various stages of the authorisation process. An authorisation for wholesale distribution has not been issued for one unit, because of critical findings.

In 2014, performance of follow-up inspections assessing distribution, at a rate of 1-3 years, depending on risk assessment, was established for all units which have been granted wholesale distribution authorisation.

In 2014, 1 unexpected inspection was performed, for assessment of the distribution activity and of the manner of compliance with provisions of the Guideline for Good Distribution Practice.

Both inspectors from central headquarters and those from the 11 territorial inspection units have been involved in surveillance of quality of products authorised for marketing in Romania. Thus, in 2014, this activity was represented by:

a) Execution of the sampling scheme for medicinal product quality monitoring (sampling, analysis, results):

In accordance with the selection criteria underlying set-up of the yearly sampling plan, 33 products were proposed for assessment of quality. Of the 33 products, 21 were sampled, the rest of the 12 were not found in the distribution network.

The results of laboratory analyses were as follows:

- 10 samples have been declared compliant, the rest undergo analysis.

In addition to the sampling plan, the following have been sampled in 2014:

- 4 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) (tablets containing telmisartan and pramipexole); the 4 samples have been declared appropriate;
- 12 medicinal products sampled for resolution of medicinal product quality complaints; both have been found compliant;
- 4 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, hospital pharmacies, drugstores) conducted by UTI inspectors: storage conditions, documents concerning quality, advertising, compliance of primary/secondary packaging and leaflet with MA, assessment of the manner of performance of withdrawals of medicinal products with quality deficiencies.

To this end, 1551 thematic inspections were conducted in wholesale and retail distribution units.

In case of deficiencies found in the pharmacy activity, which are unrelated to NAMMD's scope, the Ministry of Health has been informed for implementation of required measures.

c) Coordination of activities of the Territorial Inspection Units (TIU) related to resolution of issues related to legislation in the field of the medicinal product and/or to the quality of products marketed into Romania.

The grant of special assistance upon request of bodies and institutions such as: Customs, Police Inspectorates, Offices for Consumer Protection, Public Health Inspectorates, in 2014, consisted of joint actions with local special bodies, performed by local inspectors: 9 (4 in Galaţi, 1 in Cluj, 2 in Timişoara, 1 in Satu Mare, 1 in Târgu Mureş).

d) Inspections of the quality of oxygen used in hospitals:

Considering the risks involved by use of noncompliant medicinal gases in hospitals, particularly in emergency services, the source of medicinal gases was also assessed during inspections monitoring quality from hospital pharmacies, to stop use of unauthorised oxygen. Conclusions:

- liquid oxygen is provided solely by GMP certified producers;

- compressed oxygen for 4 of the inspected hospitals is still provided by 2 unauthorised manufacturers. The Ministry of Health has been informed on the situation.

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

10 complaints were received in 2014. Of 8 resolved, 5 had no follow-up and 3 have been found justified, resulting in recall of the respective medicinal products from the market (these can be found below).

In order to solve complaints, NAMMD inspectors have performed 5 inspections at the sites of distribution units and one product has been sampled for laboratory testing within the NAMMD - MPQCD.

Complaints were filed by territory inspectors (1) or by patients/healthcare professionals (9). 2 could not be solved, on grounds of not receiving relevant information required from the applicant.

f) Recall from the market of quality noncompliant medicinal products:

In 2014, the NAMMD requested recall of medicinal products as follows:

- 44 medicinal products were identified with intrinsic quality nonconformities and have therefore been proposed for destruction (12 by the NAMMD, 7 due to rapid alert and 25 voluntary recalls performed by manufacturers);

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

g) Rapid alert system:

- in 2014, 121 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Of these:

- 74 have envisaged products unauthorised for marketing in Romania;

- 16 alerts have been redirected to other Romanian bodies with relevant abilities;

- 24 have envisaged products authorised for marketing in Romania, but unimportant/undistributed;

- 7 have envisaged products authorised and imported/distributed in Romania.

In 2014, there was an increase of almost 40% in the number of rapid alerts, as well as an increase in their complexity.

- 7 rapid alerts received referred to medicinal products suspected of falsification/falsified.

In 2014, 1 rapid alert was issued by the NAMMD.

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

- 21 reported cases of noncompliance with GMP rules by manufacturers:

* 11 related to active pharmaceutical substances:

* 10 related to medicinal products:

- 9 certificates of compliance with the European Pharmacopoeia suspended/recalled by the EDQM.

- 1 case of noncompliance with GDP

- 1 case of noncompliance with the GMP guideline set up by the competent authority in the USA.

15 notifications for MAHs have been issued for change of active substance manufacturers.

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

In 2014, the quarterly reported TIU activity consisted of:

- transmission and resolution of punctual complaints on medicinal product quality;

- assessment and reporting to the NAMMD of outcomes of recalls performed by MAHs for noncompliant medicinal products;

- assessment and reporting to the NAMMD of outcomes of thematic plans established by the NAMMD – PID;
- sampling as proposed in the yearly plan and their submission to the NAMMD, accompanied by documents specified in the Standard Operating Procedure;
- sanctioning of contraventions in accordance with legislation in force;
- report of quality noncompliances to the NAMMD, identified during local surveillance inspections.

7. Quality control of medicinal products for human use

Quality control of medicinal products for human use is part of the NAMMD general policy for accomplishment of its mission to ensure medicinal product quality, safety and efficacy by laboratory tests.

This activity is performed by two NAMMD departments: the Medicine Product Quality Control Department (MPQCD) and the Biological Product Evaluation and Control Department (BPECD).

Process-based approach is used for activities in both control departments, in line with requirements of standards SR EN ISO 9001/2008 and SR EN ISO 17025/2005.

Both NAMMD control departments are part of 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 tests performed by the MPQCD are as follows: physico-chemical tests, pharmacotoxicological tests, micro-biological tests and radio-pharmaceutics tests.

Main activities conducted in 2014 were aimed at quality control of non-biological (chemical) and biological medicinal products.

In 2014, 56 medicinal products were submitted for MPQCD testing (36 – as part of the Annual Plan for Sampling and Testing, 3 – products subject of quality complaints, 12 – international collaborations (EDQM/FIP), 2 – biological products analysed within official batch release, 2 - counterfeit products, 1 – medicinal product analysed within marketing authorisation procedure).

According to procedures, a set of specific tests (individual parameters) was performed for each medicinal product tested, according to characteristics.

241 analyses were thus conducted:

- 189 pharmaco-chemical/instrumental analyses, of which 3 radiopharmaceutical;
- 52 pharmacological and microbiological tests.

For the 56 medicinal products tested within the MPQCD in 2012, 241 individual parameters were analysed, according to the techniques described in the European Pharmacopoeia or the manufacturer's pharmaceutical files forwarded by the EDQM. These parameters reflect, in an objective manner, laboratory activities conducted within the MPQCD.

Moreover, there were all operations and activities (over 800) preceding or accompanying every analysis: equipment checks and calibration (IR; HPLC; UV, analytical balances); assessment of volume measurement systems (droppers, biurets, measuring bottles, graded cylinders); titre tests - volumetric solutions; preparation and solutions and growth media; preparation of chemical, pharmacological, biological reactives; preparation of pH buffer solutions; scale weighing; monitoring of environment conditions in each laboratory; cleaning and decontamination of tools, equipment, glass, work surfaces, premises etc. All these tasks are performed according to procedures and in accordance with approved work instructions and are included, following performance, in work sheets (equipment cards, environment surveillance cards, temperatures, etc.).

Among frequent and complex analytical techniques used in 2014, in the context of medicinal product quality control, the following are worth mentioning: HPLC, pH-metry, Karl Ficher, spectrophotometry (IR, UV-Vis), pharmaco-technical testing (dissolution, mechanical resistance), volumetric dosing, determination of substance melting points, determination of liquid densities, determination of refractive indices, antibiotic microbiological dosage, sterilities (parenterals) and microbiological contaminations (ophthalmic solutions, syrups and paediatric solutions, certain film-coated tablets and capsules), endotoxin determinations (LAL test).

a) Products included in the Sampling and Testing Plan

36 products sampled by the Pharmaceutical Inspection Department (PID) as included in the Sampling and Testing Plan have been assessed on a case-by-case basis, from a physico-chemical, pharmacological, microbiological or radiopharmaceutical viewpoint.

Laboratory investigations of medicinal products included in this category have not revealed quality deficiencies.

For certain medicinal products, although compliant from in terms of quality, MAHs have been asked to update respective specifications and methods of analysis in accordance with PhEur monographs, by submission of applications for approval of variations to MA terms.

Moreover, several observations on analytical methods have been made for radiopharmaceuticals, requiring their compliance with provisions of the European Pharmacopoeia.

b) Medicinal products - complaints

The Pharmaceutical Inspection Department, following complaints received from patients or health units, has requested performance of laboratory analyses for 3 medicinal products received/sampled from the territory (1 batch) or from the SC Unifarm storehouse (2 batches), suspected for quality deficiencies. As regards the local product, following the complaint of a patient, the complaint wasn't considered just; the product has been declared compliant, while the two batches imported by Unifarm have received non-compliant certificates of analysis on behalf of their mechanical impurities.

c) Testing of medicinal products suspected of falsification

Upon request of the Timişoara Customs, 2 batches of a product named ,,Weight loss capsules''– imported from China, suspected of containing sibutramine – substance whose MA was suspended in EU as of 2010. The analyses conducted, with the help of HPLC and UV techniques described in the USP or specialised literature, have not yet shown the presence of the incriminated substance.

d) Biological products analysed within batch release procedure

Two batches of anti-hepatitis vaccine imported from Korea have been analysed (microbiologically and pharmacologically).

In 2014 as well, the MPQCD has continued its collaboration with European institutions on medicinal product quality control, by participation to studies initiated by the EDQM and the International Pharmaceutical Federation (IPF), as seen below:

- Studies initiated and coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM):

In 2014, the MPQCD has participated in:

- 3 PTS (Proficiency Testing Scheme) studies – Inter-laboratory studies for measurement of professional performance.

Assessment of performances and abilities of laboratories to solve highly difficult issues concerning medicinal product control is based on interpretation of outcomes obtained by each laboratory, depending on several statistic operators (average of determinations, standard deviation, relative standard deviation).

An integrated value results out of processing these operators, namely the „Z score", which represents the professional capacity and ability of each laboratory and is considered a performance indicator, when the Z score ≤ 2.

According to the data communicated by the EDQM, out of the 3 studies conducted for the 3 samples analysed by the MPQCD, the obtained values are compliant with the specified performance criteria, the Z score having a value below 2.

CRS (chemical reference substance) studies:

- 2 studies performed for revision of the PhEur monograph, in accordance with the protocol forwarded by the EDQM
- 1 CRS study (Assessment of the microbiological dosage method for Kanamycin sulphate monohydrate)
- 1 CRS study (Assessment of control methodology for Neohesperidin dihydrochalcone)

Forwarded outcomes have been confirmed by the EDQM and will be taken into consideration when setting up monographs for the two substances.

MSS studies. The purpose of these studies is to assess the quality of medicinal products circulating on the internal market of each participating state, by comparison with a reference product, in accordance with the analytic protocol submitted by the EDQM.

In 2014, in the context of this programme, the MPQCD analysed 3 medicinal products from the internal market.

FIP studies initiated by the International Pharmaceutical Federation (4 studies)

According to the analytic report received from the FIP laboratory, the outcomes of determinations forwarded by the MPQCD have been correct and compliant with the given requirements.

Sampling, analysed through MRP procedure

These are inter-laboratory tests, analysing authorised medicinal products through European procedures, in line with PA/PH/OMCL (06)116 7R – "Co-operation in Post-marketing Surveillance of Mutual Recognition / Decentralised Procedure Products".

By laboratory analysis of critical parameters with pharmacological impact, performed by the MPQCD, it was found that control methodology, underlying the approved documentation, is reproducible and the product is found acceptable, as far as its quality is concerned. The outcomes have been sent to the EDQM and registered, according to procedure, into the electronic database of the European directorate (EDQM-MRP database).

Assessment of chemical-pharmaceutical documentation (DSSA, finished products, clinical trials).

The activity, related to control activities, has been approached by the department starting with 2005.

In 2014, MPQCD performed the following:

- Assessment of active substances (ASMF) through European procedure;
- Quality Assessment – European procedure;
- Assessment of active substances (ASMF) through national procedure;
- Quality assessment – national procedure;
- Assessment of clinical trial documentation.

All these 675 activities are assessment activities for active substances (DMF/ASMF) undergoing assessment and they represent the highest percentage (65.2%).

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

In 2014, the BPECD has issued 8 analysis bulletins (ABs), as follows: 4 ABs for two batches of biological medicinal product for official batch release, 3 Abs for two batches of

biological medicinal product included in PID's sampling plan and 1 for one batch of biological medicinal product for special needs.

For the two batches of biological product, tested batch-to-batch, outcomes monitored by NAMMD laboratories have been checked (4 BPECD analysis bulletins and 4 MPQCD analysis bulletins); 2 official batch release certificates were issued.

There were 268 marketing intentions accompanied by the appropriate/final batch release certificate for biological products whose official batch release has been performed in the EU.

In 2014, the Laboratory for Physical-Chemical Determinations and Immunochemistry (LPCDI) has started taking the necessary steps for introduction of *in vitro potency assay* through the ELISA method (the manufacturer uses the ECLIA method in order to assess this parameter) into batch release testing for an antihepatitis B vaccine. The potency test is a critical parameter for the antihepatitis B vaccine. The LPCDI usually uses the ELISA method for potency assay of antihepatitis B vaccines. Validation of this testing method and drafting of the rating note for this parameter are envisaged for year 2015.

In accordance with the requirements for quality insurance and recommendations of external audits, in order to maintain manuality of operators in the context of applications for testing, manuality exercises have been planned and performed. Thus, the performance of a manuality exercise for the LPCDI staff as regards vaccine control, and particularly, anti-hepatitis B vaccine control (including in the sampling plan for 2014, conducted by the PID) was deemed necessary, and manuality exercises have been performed for the ELISA testing method, in accordance with LPCDI's specific SOP.

As of 2012, the BPECD also performs the validation of applications for variations of MA terms (type IB and II) for biological products.

During 2014, this activity mainly consisted of:

- 173 validations of applications for Type IB and II variations;
- 13 invalidations of applications for Type IB and II variations;
- 23 notifications for harmonisation of the fee for Type I variations (A, B) and II.

In 2014, the BPECD assessed the quality documentation for national and imported biological products, submitted for:

- authorisation through national procedure: 5 reports have been issued, containing applications for supplementation and 11 assessment reports for supplementation to final chemical-pharmaceutical documentation;
- MA renewal through national procedure, generating 56 reports: 25 reports with request for supplementation, 30 reports with proposal for approval of MA renewal, 1 assessment report for post-approval supplementations.

Moreover, in 2014, the BPECD has assessed and issued 2 periodic update reports.

The BPECD has also assessed support dossiers for variations / changes of design / MA transfer, submitted through national procedure, and:

 230 assessment reports were issued for Type II variations (simple and grouped), as follows:

- 45 assessment reports with requests and 77 assessment reports with proposal for approval of simple Type II variations;
- 40 assessment reports with requests and 66 assessment reports approved/finished for grouped Type II variations;
- 2 post-approval assessment reports for Type II variations.

 297 notifications to the manufacturer were issued after assessment of documentation for Type IA and IB variations / changes of design/MA transfer/ Braille imprinting:

- 14 applications for supplementation of the documentation for simple Type IA variations;
- 82 applications for simple Type IA variations;

- 3 applications for supplementation of the documentation for grouped Type IA variations;
- 47 applications for grouped Type IA variations;
- 10 applications for supplementation of the documentation for simple Type IB variations;
- 90 applications for simple Type IB variations;
- 40 applications for grouped Type IB variations;
- 5 applications for modification of design;
- 6 applications for MA transfer.

 18 reports have been issued for Type IA, IB and II variations, following assessment of post-approval documentation.

In 2014 as well, quality documentation has been assessed as related to products submitted through mutual recognition and decentralised procedures, concluding in submission of assessment reports according to deadline, as follows:

Mutual recognition procedure

19 reports have been issued for 15 products:
- 7 reports with proposal for authorisation;
- 9 reports with proposal for MA renewal;
- 3 reports with request for supplementation of quality documentation;

The BPECD also assessed support dossiers for variations submitted through Mutual Recognition Procedure, for which 46 reports and Annexes for (simple and grouped) Type II variations and 82 Annexes for (simple and grouped) Type IB variations have been issued:
- 12 reports with request for simple Type II variations;
- 18 reports with proposal for approval of simple Type II variations;
- 7 reports with request for grouped Type II variations;
- 9 reports with proposal for approval of grouped Type II variations;
- 6 Annexes with request for supplementation for simple Type IB variations;
- 56 Annexes with proposal for approval of simple Type IB variations;
- 7 Annexes with request for supplementation for grouped Type IB variations;
- 13 Annexes with proposal for approval of grouped Type IB variations.

Decentralised procedure

10 reports have been issued for 6 products pending authorisation:
- 5 assessment reports for authorisation, with request for supplementation;
- 4 reports with request for authorisation;
- 1 report with request for recall.

In 2014, the BPECD also assessed quality documentation submitted for approval of applications for performance of clinical trials for 19 biological products; 32 assessment reports have been issued, of which:
- 16 final (positive) reports for assessment of quality documentation;
- 1 final (negative) reports for assessment of quality documentation;
- 14 reports containing requests for supplementation of quality documentation;
- 1 assessment report of post-approval supplementations.

As regards amendment of marketing authorisation terms for biological medicinal products for human use, following approval of Type I or II variations or following proofreading, the BPECD has performed 42 changes to MAs in 2014.

8. Ensuring communication and transparency

The NAMMD pays particular attention to ensuring better information and communication with all stakeholders, in accordance with Law no. 544/2001 on free access to public information and Law 95/2006 - Title XVII - The medicinal product, as amended, relating to transparency in the work of EU drug competent authorities.

8.1. External communication

In line with provisions of its Communication Strategy 2013-2015, in 2014 the Agency has provided for:

- Internal and external communication, i.e. official statements, communication with print and TV media (by phone, e-mail, television interviews, participation in TV programmes), relations with other Romanian and foreign institutions specialised in this area;
- Free access to public information in accordance with Law 544/2001, by rule and/or request for both media representatives and anyone interested, providing information on NAMMD work or the safety of medicinal products for human use;
- Collaboration of all departments for proactive communication and reactive response on request, i.e. ensuring transparency/accessibility/public availability of information on medicinal products for human use.

The Department for Policies and Strategies (DPS) has provided:

- Collection of data from scientific departments and organisation of information required for development and draft of responses requested by stakeholders;
- Notification of media representatives and/or other stakeholders within the timeframes allowed by existing rules, when the information requested has already been transmitted by rule as one communication form as mentioned in art. 5 of Law no. 544/2001, also indicating the location of the requested information;
- Notification of the enquirer, within time limits provided in current rules, when the information requested is found exempt from free access;
- Dissemination to the media of official NAMMD press releases and statements.

The Agency las constantly pursued accurate information of institutional partner on activities conducted in all domains within its scope.

The NAMMD has published quarterly bilingual newsletters (BI) on its website, mirroring Agency's regulatory work in the medicinal product field, in line with European legislation, as well as other priority activities of its own. The Agency's Newsletter includes:

- Laws, Ordinances, Government Decisions in the field of human medicines or other areas of NAMMD interest;
- Orders of the Minister of Health for approval of decisions of the NAMMD Scientific Council and Orders of the Minister of Health concerning other areas of NAMMD interest;
- Decisions of the NAMMD Scientific Council;
- Decisions of the NAMMD Administration Council;
- Quarterly list of applications for marketing authorisation/ marketing authorisation renewal;
- Quarterly list of medicinal products authorised through centralised procedure by the EMA, for which a price has been established for marketing in Romania;
- Quarterly list of medicinal products authorised for marketing by the NAMMD;
- Quarterly list of medicinal product batches recalled on NAMMD request for quality defects.

The NAMMD has assured regular update on its website of the Index of medicinal products for human use, containing all medicines authorised for the pharmaceutical market in Romania, providing data on trade name, international non-proprietary name (INN), marketing authorisation holder, pharmaceutical form, strength, route of administration, type of

packaging, manner of administration etc. In 2014, implementation was continued of individual electronic versions of Summaries of Product Characteristics (SPC), Leaflet and Labelling.

The NAMMD develops and constantly updates information on the Agency's bilingual website. Accordingly, the following information and documents have been posted and updated:

- EMA and NAMMD Press release on medicinal product safety;
- Direct healthcare professional communications;
- Notifications to marketing authorisations holders (MAH) or other stakeholders on issues of interest;
- Information on medicinal products authorised under the centralised procedure;
- SPCs for medicinal products authorised in Romania through mutual recognition procedure and the decentralised procedure;
- SPCs for medicinal products authorised in Romania through national procedure;
- List of employees assigned as NAMMD full/alternate representatives to the EMA Management Board and EMA Scientific Committees and working groups;
- List of EMA experts nominated by the NAMMD.

Under the heading "Pharmaceutical Inspection" the following information is published and constantly updated:

- List of Romanian manufacturers of medicinal products and active pharmaceutical substances;
- List of NAMMD certified manufacturers in third countries;
- List of Romanian medicinal product importers;
- List of Romanian medicinal product distributors;
- List of medicinal product control laboratories;
- List of medicinal product batches recalled;
- List of NAMMD certified qualified persons and contact details for submission of medicinal product quality complaints.

It is the Agency’s permanent aim that external NAMMD website users can benefit from update of sections related to medicinal product legislation, structured by type of regulatory provision:

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

Proof of stakeholders’ manifest interest in information posted on the NAMMD website has been the large number of visitors, over 100,000 visitors/year.

In 2014, the NAMMD has continued to inform stakeholders on its work by means of other publications than its own newsletter as well, i.e. in articles by Agency experts published in such magazines as “Practica farmaceutica”, “Medical Business”, “Politici de sănătate”, “Pharma Business”).

NAMMD representatives made presentations in numerous scientific/professional events organised in Romania and abroad.

8.2. Internal communication

In 2014, for better and prompter information on professional and/or organisational issues, data available to Agency employees on the intranet was further supplemented and updated.

Thus, the following information can be found on the NAMMD intranet:

- Instructions of the NAMMD President;
- NAMMD quality policies;

- NAMMD regulations;
- Glossary of quality assurance terms;
- Work plans of NAMMD departments;
- Useful forms;
- Information from the Pharmacopoeia Service;
- Reports by staff attending training sessions both at home and abroad;
- Useful information;
- Useful addresses etc.

9. Quality Management

Work of the Quality Assurance Bureau (BAC) aims to establish, document, implement, maintain and constantly improve the effectiveness of the NAMMD quality management system (QMS).

Given the *quality policy* and *quality objectives* set by the top management as well as processes identified and applied, in addition to NAMMD size and structure and ISO 9001 and 9004 principles in force, in 2014, together with other organisational structures, the BAC participated in implementation, development and improvement of the QMS on full organisation level.

Thus, the following have been developed:

• BAC Activity Report 2013;
• Individual 2013 activity reports;
• Internal Quality Audit program in 2014;
• BAC Work Plan for 2014;
• BAC Training Program in 2014;
• Individual training programs for 2014;
• Set up of individual evaluation sheets 2013;
• *The process of internal quality audit was conducted in accordance with the Internal quality audit program for 2014, approved by the NAMMD President.*

Other processes conducted at BAC level:

• Provision of consulting on quality management system (QMS) to the various NAMMD organisational structures, in preparation of objective evidence relating to the BEMA audit conducted by an external team in September 2014.

• Set up of *documents* requested by the BAI on implementation of the internal control /management system.

• Set up of *documents* requested by the BAI on the BAC Risk Register.

• Update of *declarations of interest /undertakings of confidentiality/non-individual and individual job descriptions*.

• Update of specific BAC (electronic) databases (*SOP registers* - organisational structures NAMMD/*Quality assurance Glossary, NAMMD SOPs, QM-NAMMD, KPI - NAMMD* organisational structures etc.)

NAMMD top management is involved in activities related to the QMS and implementation of the process-based approach.

10. Medical devices

10.1 Control by periodic check of medical devices

Since its establishment in 2010 by merger of the NMA with the Technical Office for Medical Devices, the NAMMD has been the only institution assigned and able to assess performance and safety of medical devices in use.

The Nuclear Unit (UN) carries out the same type of activities as the Technical Department-Laboratory (DTL), on medical devices with ionizing radiation. For this reason, work is reported in a joint report and necessary specifications are made.

As previous years, 2014 was busy for the Technical Department - Laboratories and Nuclear Unit, and the largest share in their work was periodic control of medical devices. This is performed for all medical devices in use, of significant risk to all users in both the public and the private sectors. This consists of assessing the performance and safety of medical devices in use, the periodic check bulletin being one of the necessary documents for medical service contracts between the health insurance funds and individual practices/hospitals/medical centres. A test report is prepared for each medical device checked, which is kept in the respective file and only provided to the customer on request, for a fee, together with the periodic verification report.

Given the large number of hospitals using medical devices and the limited number of specialists and appropriate measuring tools, careful scheduling of control is needed.

Great part of applications for check was submitted by public healthcare units, which are exempt from fees. Such requests concerned most medical devices.

Therefore, works completed in 2014 are as follows:

- Total applications registered: 957 (of which 591 in the private sector)
- Total periodic check bulletins issued: 1,442
- Total user opinions issued: 224
- Total medical devices checked: 6,370
- Total mobile intervention units checked: 1,066
- Total test reports issued: 3,500
- Total negative test reports (medical devices rejected): 207

The Medical Device Verification and Testing Laboratory in the DTL and the UN constantly supervise the manner of SR EN 17025 implementation for accredited tests.

Following repeal of Law no. 176/2000 on medical devices, republished, and entry into force of Title XIX of Law 95/2006, as amended, for harmonisation with legislation in force, a proposal was submitted for amendment of Order of the Minister of Health no. 44/2013 on control through regular checks.

Given the need to maintain medical devices in use at an acceptable level of performance and security, the DTL and the UN have made great efforts to avoid gaps in their work, despite financial and staff difficulties encountered.

10.2 Inspection of technical and medical assessment units

The Medical Assessment Unit Technical Department carried out its work until May 2014 under Law no.176/2000 on medical devices as amended and supplemented, and Order the Minister of Health no.1636/2004 approving Implementation Rules regarding Law no. 176/2000 on medical devices, as amended, relating to approval of medical technology units, as subsequently amended, and afterwards under Title XIX of Law no.95/2006, as amended, and Order the Minister of Health no.748/2014. The work consisted of evaluating the capability of organisations to provide services for which approval of the Ministry of Health had been sought. Activities under evaluation had been optical related, repair, maintenance and installation/commissioning of medical devices, prosthetic (hearing, orthopaedic, other).

With relatively few qualified personnel, the department must cover work throughout the country, performing both initial assessment of organisations for authorisation purposes, and surveillance assessments every two years for continued authorisation, and finding and sanctioning contraventions on the application laws that govern their activity. A new amendment to the Law no.95/2006 has resulted in assignment of new tasks to the department-grant of authorisation to companies providing medical device-related services (medical-

optical – eyeglass mounting, repair; maintenance and installation/commissioning of medical devices and prosthetics) and annexes to respective authorisations.

Services have been provided as follows:

- Number of registered new applications for evaluation: 154
- Number of evaluations carried out and reports issued: 89
- Number of unfavourable evaluation reports: 6
- Number of surveillance-evaluation works carried out, resulting in reports: 195
- Number of unfavourable surveillance-evaluation reports: 7
- Number of applications cancelled (no dossier submitted for assessment, the organisation is only involved in trading activity, conditions for surveillance not met): 62
- Number of works completed: 346
- Number of assessment and evaluation-surveillance works in progress at the end of the year: 268.

Three control actions were carried out, resulting in one penalisation.

Given the latest amendment to Law no.95/2006 and the new duties assigned to the Medical Devices Department, personnel structure has changed by employment of 1 IA engineer, 1 junior engineer and 1 IA referent; also, at the end of the year, the archive of operation authorisations was transferred from the Ministry of Health to the NAMMD.

The draft for amendment to Order of the Minister of Health No. 748/2014 was submitted to the Ministry of Health in November 2014, for harmonisation with updated Title XIX of Law no.95/2006.

Performance of personnel in the department was as expected, and works were also carried out in the country, for 5 consecutive day's travels, undertaking several works in the same locality, so as to increase travel efficiency.

11. International relations

In 2014, NAMMD specialists continued participation in activities of various institutions and bodies in its scope, involved in cooperation:

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

Since as early 2003, when, at the initiative of the European Medicines Agency, the NAMMD was invited as active observer in EMA working groups, scientific committees and groups dedicated to implementing information technology human medicines, representatives of the Romanian Agency have taken active part in EMA initiatives.

This participation has been and continues to be the most effective way to maintain the NAMMD connection with medicinal product activities on EU level.

Full members since 2007 in EMA scientific committees and working groups, NAMMD experts took part in over 100 meetings of their respective committees and working groups:

- Committee for Medicinal Products for Human Use - CHMP;
- Committee for Orphan Medicinal Products - COMP;
- Committee for Herbal Medicinal Products - HMPC;
- Paediatric Committee - PDCO;
- Committee for Advanced Therapies - CAT;
- CHMP Safety Working Party;
- Pharmacovigilance Risk Assessment Committee - PRAC;
- CHMP Blood Products Working Party;
- CHMP Biologics Working Party;
- CHMP Vaccines Working Party;
- CHMP/CVMP Quality Working Party;
- GMP/GDP Inspectors Working Group;

- EudraGMP database Sub-Working group;
- GCP Inspectors Working Group;
- GLP Inspectors Working Group;
- Pharmacovigilance Inspectors Working Group;
- EudraPharm TIG;
- EudraVigilance TIG;
- EudraCT Clinical trials TIG;
- EudraNet TIG;
- e-Submission TIG;
- European Union Telematics Controlled Terms - EUTCT;
- Product Information Management = PIM;
- Quality Review Documents = QRD;
- Invented Name Review Group.

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

NAMMD representatives also actively participate in meetings of the European body the Heads of Medicines Agencies - HMA, and in meetings of its working groups, i.e. :

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

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

In 2014, NAMMD experts attended meetings of the EU Council and the European Commission (EC), including the Working Group on medicines and medical devices of the EU Council, debating on proposals for the new Regulation on clinical trials for repeal of Directive 20/2001/EC on clinical trials in the EU.

11.4. Participation in activities of the World Health Organisation (WHO)

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

In 2014, the Agency granted the drug certificate in WHO format, for a total of 472 Romanian medicinal products producers seeking their authorisation in other countries.

11.5. Participation in activities of the Council of Europe

In 2014, the NAMMD representative attended the meeting of the Committee of Experts on the Classification of Medicines as regards their Supply (CD-P-PH/PHO).

Also, the NAMMD nominee attended the meeting 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 Council of Europe (CoE), organised by the European Directorate for the Quality of Medicines (EDQM).

11.6. Participation in the activities of the European Pharmacopoeia Commission

NAMMD designated representative, member of the European Pharmacopoeia Commission, participated in the commission’s 2014 working sessions and the annual meeting

of the secretariats of the national pharmacopoeia of states members of the European Pharmacopoeia Convention.

At the same time, cooperation was continued with the European Directorate for the Quality of Medicines (EDQM) in the development and re-update of Standard Terms (ST) in Romanian, as a translation of ST adopted by the European Pharmacopoeia.

11.7. Participation in activities of the European Network of Official Medicines Control Laboratories (OMCL)

These activities are detailed under pts. 7.1 and 7.2.

12. Logistics, information and electronic data management-related activity

The Department for logistics, information and electronic management of data (DLIGED) also met its assignments in 2014 related to achievement of effective communication with the EMA and provision of real time exchange of information between the Agency and its external collaborators (MAHs, distributors, healthcare professionals, patient organisations and associations).

Maintenance, change and update of the Medicinal Product Index database were continued in 2014 as well. On request by the Ministry of Health, the National Health Insurance House, the NAMMD President or the various Agency departments, data were extracted from the Index statistic reports.

The DLIGED also ensured maintenance of the NAMMD website (www.anm.ro) and other software applications (website maintenance, change and update of search engines (Medicinal Product Index, search by specific keywords, management of recalled medicinal products, management of GMP sites), of the section "Counterfeiting" section (ongoing project - *www.crimemedicine.ro*, involving: website development, participation in specialised training, conducting internet investigations, set up of investigation dossiers); numerous activities were also conducted relating to update of the different website sections (Newsletters, Forms, Decisions of the NAMMD Scientific Council, Laws and ordinances, Orders of the Minister of Health, Press releases, Questions and answers, Important notifications, Direct communications to healthcare professionals etc.), as well as activities for maintenance, change and update of the NAMMD intranet website.

The DLIGED has ensured maintenance and administration of NAMMD servers (file server, web-intranet server, internet server with several services, accounting server).

Workstations have been configured to be used in webinars using the Adobe Connect service - 35.

Servicing of both NAMMD software and hardware has been provided, together with installation and configuration of employees' computers; the NOD32 antivirus software and security programs have been maintained and administered on NAMMD servers.

The Data and Documents Management Service provides entry of documents into the Agency and their distribution to respective departments and offices, release of all Agency documents to external collaborators and facilitates prompt inter-departmental flow of documents.

In 2014, The Data and Documents Management Service has been involved in several types of activities, for instance:

- Issuing Marketing Authorisations and their Annexes 1, 2, 3, 4 and 5 - for 1222 medicines, authorised through both European (821) and the national procedure (401);
- Issuing the Marketing Authorisation lists - 332 lists (for 1222 MAs);
- Entry into the 'Registry' database of information on medicinal products authorised - 1222 medicinal products;

- Update of marketing authorisations and 5 annexes on the server (Patient Leaflet, SmPC, Packaging, data on qualitative and quantitative composition of the product, data on drug manufacture - 1222 medicinal products;

- Draft of notification to manufacturers on MA issue as instructed by the NAMMD President and archiving of a copy in the product dossier - 652 notifications.

- Draft of manufacturer undertakings on MA issue and archiving in the authorisation dossier - 250 notifications;

- Entry into the "Registry" Database of the receipt notifications and its archiving in the authorisation dossier - 652 notifications;

- MA release to applicants/holders - 652 Marketing Authorisations;

- Participation in meetings of the Marketing Authorisation Commission - 23 meetings deliberating on 1224 medicinal products;

- Draft of medicinal product certificates in WHO format: 472 certificates;

- Draft of confirmations of product undergoing Marketing Authorisation renewal, stating "selling allowed" – 94 conformations for 471 for medicinal products;

- Draft of Authorisations for special needs – 57 authorisations concerning 67 medicinal products;

- Preparation of minutes for Authorisations for special needs - 15 minutes.

- Evaluation of advertising materials for approval.

- 516 novel approvals;

- 572 re-approvals;

- 217 educational materials.

Other activities:

- Transmission of Annexes in electronic format (daily);
- Record of WHO format certificates issued by the NAMMD.

13. Ensuring implementation of NAMMD policies and strategies

- In 2014, the Department for Policies and Strategies (DPS) conducted the following activities:

- Participation, together with other departments, in implementation of the *2013-2015 NAMMD organisational strategy*, in pursuit of, according to its own main scope, communication, consolidation of the Agency's role as an expert source for accurate information in the field, provided to healthcare professionals in a timely fashion, to the pharmaceutical industry, patients, the general public, the media;

- *Continued active and priority participation in implementation of the 2013-2015 NAMMD Communication Strategy*, continually pursuing to improve its strategy and find ways for its adjustment to new demands and changes in the legislative and socio-economic area.

As promoter of the *2013-2015 NAMMD Communication Strategy*, the DPS contributed as follows in 2014:

- Preparation of responses to media queries and NAMMD top management positions in various issues and their communication by:

- TV interviews, including live broadcasts;

- Written responses for TV and print media;

- Telephone interviews for print, TV and radio media;

- Press releases and important announcements posted on the NAMMD site;

- Participation in scientific meetings, making presentations expressing the NAMMD stand on various issues related to medicinal products for human use;

- Communication with other institutions specialised in this field in both Romania and abroad.

- Ensuring free access to public information in accordance with Law 544/2001, by default and/or request for both media representatives and interested members of the public, providing information on NAMMD work or on safety of human medicines;

- Providing information to media representatives and/or other members of the public, on request, within the time allowed by existing rules, when information requested has already been provided by default in one of the forms mentioned in art. 5 of Law no. 544/2001, also indicating the location where the requested information can be found;

- Notification of applicants within the time limits provided by current rules, if the requested information has been found as exempt from free access;

- Work with all departments to collect and organise NAMMD information requested by the media in formulating and drafting the requested responses.

Together with other professional departments, the DPC took part in insuring proper NAMMD operations in the European network of drug competent authorities, acting as an interface between the NAMMD and European and international authorities, by:

- Managing and monitoring participation of Agency employee appointed as full or alternate members in scientific committees and working groups of the EMA, the HMA, the EDQM, the Council of Europe, the EU Council, European Commission;

- Update of the List of employees assigned as NAMMD representatives or substitutes in scientific committees and working groups, in accordance with decisions of the President and posting on the NAMMD website;

- Ensuring communication with the EMA for approval of nominations for Agency experts;

- Checking/Centralising forms completed by NAMMD experts;

- Communication with the secretariats of respective working groups/committees of scientific bodies for submission of forms;

- Electronic record of WHO, EDQM, OMCL etc. paper documents received and their distribution to departments for information or expression of opinion; the DPS has prepared the NAMMD annual activity report for 2013 by corroborating data from activity reports of NAMMD departments.

The DPS has also provided:

- Centralising and managing in folders dedicated to meetings of the NAMMD Scientific Council of the electronic versions of 27 Scientific Council decisions (HCS), from initial design to their publication on the site (under "Legislation" and "Newsletters") in accordance with interdepartmental SOP;

- Preparation of meetings of the Scientific Council, of the SC agenda, electronic/paper submission of meeting documents to Scientific Council members sending;

- Secretarial work for the Scientific Council and preparation of minutes of meetings.

Work for preparation of the NAMMD newsletter and its posting on the Agency website has continued thus:

- 4 Newsletter issues in Romanian (4/2013, 1/2014, 2/2014, 3/2014) and

- 4 Newsletter issues in English (3/2013, 4/2013, 1/2014, 2/2014).

The DPS also contributed as part of the interface between NAMMD and its stakeholders by updating and improving information on the NAMMD website in collaboration with other departments of the institution, by managing the posting of the following:

- Legislative documents, notifications in Romanian and English;

- NAMMD Newsletters in Romanian and English;

- Updated list of NAMMD employees assigned as representatives or substitutes in scientific committees and working groups of the European Medicines Agency (EMA) and the "Heads of Medicines Agencies", the European Directorate for the Quality of Medicines (EDQM), the Council of Europe, the EU Council, of the Pharmaceutical Inspections Cooperation Scheme (PIC/S) and the European Commission.

The DPS also provided:

- Translation into English of the NAMMD quarterly;
- Check of the translation of EMA press releases, EMA question and answer documents, direct communications to healthcare professionals, educational material etc.
- Monitoring of terminology to ensure compliance with European terminology, especially in relation to the EMA and Eudra websites;
- Advice for translation of SPC and package leaflet, of mail exchanges and communication in English with European bodies;
- Check of the translation of assessment reports and documents in English, under the mutual recognition procedure;
- Ensuring on request by the various NAMMD structures of advice/translation of specific mail and communications with various international bodies and/or representatives of pharmaceutical companies;
- Update of the English version of the website NAMMD by translating legal documents, NAMMD announcements and press releases.

Ensuring communication with the Permanent Representative of Romania to the EU/Brussels was achieved by:

- Monitoring/Managing electronic records of all e-mails (over 600 e-mails) received from the Permanent Representation of Romania to the EU and/or the Ministry of Health regarding participation of assigned NAMMD employees as representatives or substitutes in Boards, scientific committees and working groups of the EMA, the HMA, the EDQM, Council of Europe, Council of the European Union, the PIC/S and the European Commission and redirection towards NAMMD appointed experts;
- Coordinating and monitoring the participation of appointed NAMMD experts in meetings of working groups/committees and ensuring exchanges with the aforementioned Representative, on this issue, as applicable;
- Monitoring/managing Electronic records Decisions European Commission (EC), received by the Registry of External EU/RP Romania's EU relating to: medicinal products authorised conditionally, marketing authorisation maintenance/suspension/withdrawal/ amendment following completion of arbitration procedures on safety, quality, and efficacy issues, and redirect them to specialists NAMMD nominated for their implementation in Romania.

The DPS also ensured conduct of Pharmacopoeia-related activities through technical and scientific coordination of activities resulting from Romania's accession to the "Convention for the elaboration of the European Pharmacopoeia" of the Council of Europe, namely by:

- Participation by the designated representative in annual sessions of the European Pharmacopoeia Commission, as a member of its annual meeting and secretariats of national competent authorities Pharmacopoeias;
- Centralisation and review of electronic documentation provided by the Commission of the European Pharmacopoeia/EDQM;
- Maintenance and update of the intranet "INFO-Service Pharmacopoeia" NAMMD database containing electronic versions of records of documentation provided, of Standard Terms in Romanian and other useful information;
- File/Folder records of national and international pharmacopoeias and other documents of the Commission of the European Pharmacopoeia,the Pharmacopoeia of the United States (USP), journals (Pharmeuropa, Pharmeuropa-Bio, Pharmeuropa Scientific Notes) etc. .

14. NAMMD legal issues

One of the main tasks of the NAMMD Legal Department is Agency representation in court, comprising in 2014 to a total of 19 litigations related to insolvency proceedings,

complaints, orders of payment, request for annulment, review, contractual liability, evacuation.

Regarding areas addressed, these have focused on activities and actions related to most branches of the law (labour law, civil law, civil procedure, administrative law, contentious proceeding etc.).

In pursuit of its second object, the Legal Department together with professional departments NAMMD have prepared documentation (draft legislation, substantiation notes, memoranda for approval) to promote through the Ministry of Health as main credit officer of the following rules and regulations:

a) three draft laws/ordinances amending Law no.95/2006 on healthcare reform, approved by Emergency Ordinance no. 2/2014 amending and supplementing Law no. 95/2006 on healthcare reform, and amending and supplementing certain acts; Emergency Ordinance no. 23/2014 amending and supplementing Law no. 95/2006 on healthcare reform and amendment of certain healthcare laws; Law no. 132/2014 approving Government Emergency Ordinance no. 2/2014 amending and supplementing Law no. 95/2006 on healthcare reform, and amending and supplementing certain acts;

b) two draft government decision, approved by Resolution no. 315/2014 amending and supplementing Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices and Decision nr.1184/2014 on the discontinuation of the Technical Office for Medical Devices Certification and amending certain healthcare legislative acts;

c) 13 draft ministerial orders covering:

- Approval of approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof, draft approved by Order no. 861/2014 for approval of criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof;

- Approval of fees for operations of the National Agency for Medicines and Medical Devices for human medicines, draft approved by Order no. 888/2014 on approval of fees payable to the National Agency for Medicines and Medical Devices for operations related to medicinal products for human use;

- Approval of terms for authorisation of for authorisation of human medicinal products for human use, in accordance with provisions of Article 83 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, the project approved by Order no. 1018/2014 approving the Terms for authorisation of human medicinal products for human use, in accordance with provisions of Article Art. 83 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency;

- Amendment of the order on criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof approved by Order No.1200/2014 amending the Order of the Minister of Health no. 861/2014 for criteria and methodology for assessment of health technologies, of documentation to be submitted by applicants, methodological means used in the assessment for inclusion, extension of indications, non-inclusion into or exclusion from the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs, as well as the means for appeal thereof;

- Repeal of Order no. 279 of 30 March 2005 for approval of the manner of implementation of amendments to marketing authorisations approved by the National Medicines Agency;

- Repeal of Order no. 399 of 12 April 2006 on approval of the European template of the leaflet, summary of product characteristics and labelling information for medicinal products authorised for marketing in Romania;

- Repeal of Order no. 1483 of 9 December 2010 on approval of the Regulation on Administrative Procedure of the National Agency for Medicines and Medical Devices of for handling variations;

- Approval of implementation of the template of the leaflet, summary of product characteristics and labelling information for medicinal products authorised for marketing in Romania and templates for declarations, authorisations and certificates in accordance with European standards in force;

- Amendment of Order no. 85 of 7 February 2013 on approval of the Implementation rules for art. 699 par. (1) and (2) of Law no. 95/2006 on healthcare reform on the medicinal products used for special needs;

- Approval of regulations for authorising the manufacturing authorisation of manufacturers, importers of medicinal products for human use, investigational medicinal products included, as well as of independent control sites and grant of the good manufacturing practice certificate;

- Approval of the Guideline on good wholesale distribution practice;

- Approval of the procedure for authorisation of manufacturers, importers or distributors of active substances to be used as raw/starting materials for medicines for human use;

- Approval of the rules on authorisation of wholesale sites for medicines for human use, good distribution practice certification and registration of brokers of human medicinal products.

Professional activities of the Legal Department mainly focused on ensuring accomplishment of duties included in Chapter IV, Section 13 of the Rules of organisation and functioning of NAMMD Rules of Procedure, (hereinafter NAMMD- ROF), approved by Order the Minister of Health no. 1031/2011, as well as other activities.
To give an accurate statistic array of activities conducted in 2014, the following should be mentioned:

- Endorsement of the legal character of measures to be taken and any documents liable to engage NAMMD patrimonial liability - 14 936 visas;

- Endorsement of lawful interpretation of legislation applicable to the NAMMD scope;

- Draft of the minutes of the 3 meetings of the NAMMD Administration Council held in and its 10 rulings;

- Other works related to ensuring the secretarial activities of the NAMMD Administration Council;

- Draft and endorsement of 213 decisions of the NAMMD President.

Also, together with the other NAMMD departments, the Legal Department has contributed if fight off of counterfeiting of medicines, which is why in 2014 the collaboration initiated with conclusion of the previous Collaboration Protocol 5/03.03.2010 with the General Inspectorate of the Romanian Police has been continued in 2014 as well, mainly aiming to establish a general framework for bilateral cooperation and exchange of information on counterfeiting of medicinal products in accordance with the duties and powers provided by the law.

The NAMMD main directions of cooperation with the General Inspectorate of the Romanian Police are as follows:

• marketing, manufacture, import, distribution and use of medicinal products for human use;

• compliance with legislation on medicinal products for human use;

• exchange of information for fulfilment of respective legal obligations;

• conduct of studies and market analyses seeking more accurate information on the Romania market for human medicines, particularly as regards manufacture, import and distribution;

• surveillance of market operation in order to identify cases of violation of national and/or Community legal provisions on counterfeiting and other legal stipulation on medicinal products for human use, for necessary steps by the two authorities, according to their specific functions and their correlation;

• action for awareness raising and information of the public and economic agents operating on the markets for human medicinal products relating to measures taken in cases of breach of national legislation and/or Community counterfeiting laws;

• mutual support to ensure efficient operation and safety in the human medicinal product sector, including necessary legislative changes.

At the same time, 2014 was the deadline for completion of the "SAVEmed Microstructure secured and self-verifying medicines", initiated by UNICRI (the United Nations Interregional Crime and Justice Research Institute), by NAMMD and its public and private partners co-signing of the *Protocol on prevention and combating of medicinal product counterfeiting and trafficking*. Therefore, a frame has been created for implementing provisions of Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 establishing a Community code on human medicinal products with regard to preventing falsified medicines in the legal supply chain published in the Official Journal of the European Communities (OJEC) no. L174/86 of 01.07.2011, as transposed into national legislation by Ordinance no.91/2012 amending and supplementing certain healthcare bills.

15. Management of human resources

15.1. Human resources policy

The Agency's Department of human resources, payroll (DRUS) has maintained its main objectives in 2014 as well, from among which the following may be specified:

- Providing human resources for NAMMD structures undergoing shortage of highly qualified personnel, particularly medical and pharmaceutical, able to provide capacity to achieve the Agency's object of work;

- Human resource development through training and retraining of employees, namely by:
- Specialist staff training and development, to ensure a highly qualified personnel, designed to ensure NAMMD capacity to solve specific tasks;

- Planning, implementation and evaluation of NAMMD staff training and development; in this context, it should be noted that the training activity is planned annually at departmental level, based on each employee's specific activity and qualification. Personnel receives training on employment, aiming to continue systematic professional training, both internally and, depending on NAMMD funding opportunities, from external sources, provided by institutions specializing in fields in areas such as management of quality assurance (ISO 9001 and 9004), pharmaceutical inspection activity specific training, pharmacovigilance, clinical evaluation and authorisation, accounting, financial legislation etc.;

- Active participation with presentations in various symposia, congresses on medicinal product issues and sustained participation of NAMMD competent specialists in working groups of European and international bodies in the field of medicines and medical devices.

15.2. Ensurance of human resources to NAMMD structures

In result of Government Emergency Ordinance no. 2/2014 amending and supplementing Law no. 95/2006 on healthcare reform, and amending and supplementing certain bills for NAMMD operation as competent authority in medical devices as well, requiring extensive work for surveillance of the medical devices market in accordance with European directives 93/42/EEC, 98/79/EC and 90/385/EEC transposed into Romanian legislation by Government Decision no. 54/2009 on conditions for medical devices marketing, Government Decision no. 798/2003 establishing conditions for marketing and use of *in vitro* diagnostic medical devices and Government Decision no. 55/2009 on active implantable medical devices, the NAMMD requested the Ministry of Health and received express approval for hiring competition involving 12 vacancies as engineer, in order to pursue new NAMMD activities for market surveillance of medical devices. Following Ministry of Health approval, 12 engineers were hired to work in the Technical Medical Evaluation Unit, reporting directly to the NAMMD Vice-President for medical devices.

In conclusion, shortages of qualified staff could not be covered in 2014 either, as positions open for competition and employment were solely intended to cover new activities for medical devices, whereas other specialised departments, whose activities address medicinal products for human use, are still faced with lack of specialised medical and pharmaceutical personnel.

15.3. Development of human resource through employee training and retraining

Participation in decision making at European level, active involvement in the work of scientific committees and working groups of European organisations in the field of medicinal products for human use requires NAMMD specialists' high levels of competence. It is certainly a prime objective of the Agency, which cannot be achieved in the absence of a program of continuous training, specific professional development in this area, in the Agency, particularly without participation in training organised nationally or internationally by various authorities and similar bodies.

Within the limits of funding available from European bodies and the Agency, part of NAMMD professionals could benefit from training. Training has improved administrative validation of applications and documentation for authorisation, management of medicinal product information, scientific assessment of the documentation. It also enabled initiation and appropriate conduct of activities, matching the standard of the other European national competent authorities as regards European authorisation procedures (mutual recognition procedure, mutual recognition procedure "repeat use" and the decentralised procedure).

In 2014, numerous NAMMD staff took part in scientific events and professional training sessions, some with presentations:

• in Romania:

- Poster paper presented at the XV edition of the National Congress of Pharmacy in Romania, which took place in September in Iasi. Moreover, several articles were published in journals for biologic medicines.

- The National Conference of Paediatrics, April 2014;

- "Control of advertising for OTC medicines in EU Member States", at the Conference "Advertising of medicinal products", organised by the Romanian College of Pharmacists, Bucharest, June 2014;

- Participation in the training course "Single Use System Benefits & Solutions" and "Single Use Systems Qualification & Validation" and Pre-Use/Post-Sterilization Integrity Testing in Single-use Systems", organised by *Pall Austria Filter GmbH*. and *Life Science* at the National Agency for Medicines and Medical Devices, Bucharest;

- Symposium dedicated to innovations in mass spectrometry (involving the company Shimadzu - Japan) and electron transmission microscopy (involving the JEOL company - Japan);

- Paediatrics National Conference, organised by the Romanian College of Physicians, held in Bucharest April 2-5, 2014;

- Participation in the National Congress of Pharmacy, 24 -27 September 2014, Iaşi;

- The National Conference of Pharmacy, Interdisciplinary Conference Pharmacist – Physician, organised by the Romanian College of Pharmacists, held in Bucharest, 12-15 November 2014;

- The 5th Gemotherapy National Conference , May 23 - 25, 2014, Bucharest;

- The National Conference of Clinical Homeopathy: Homeopathic medicine intake in paediatric practice, Sighisoara, Romania, June 20 - 22, 2014;

- The Conference on "Implications of the immune system in human pathology", organised by the Bucharest Ilfov County College of Physicians, 17-18 September 2014;

- The Conference "Novelties in paediatric practice, organised by the Ilfov County College of Physicians, 19-20 September 2014;

- Symposium "Novelties in vasodilator therapy", organised by Alvogen, Bucharest October 8, 2014;

-The Annual Congress of the Romanian Association for the Study of Pain on "Orofacial Pain", Bucharest, November 14, 2014;

- Participation in the conference "Advertising of medicinal products", Bucharest, 5 - 6 June 2014;

- The Symposium "Emergencies in chronic diseases", organised by the Society of Family Physicians in collaboration with the Romanian College of Physicians, Bucharest, March 19-20, 2014;

- Participation in the Workshop Pharmacovigilance (topic: new information about management of Risk Management, Electronic Reporting, XEVMPD aspects), Bucharest, 09-10.09.2014;

- The International Virtual Conference on Toxicology (Seminars in general toxicology and clinical toxicology), Bucharest, October, 2014;

- The Annual National Meeting of the Romanian Society for the History of Pharmacy, Braila, June 2014;

- Participation 4 GMP inspectors in the training course on "Single use technology: features, benefits and validation", organised by Pall Filter Austria GmbH, NAMMD headquarters, May 2014;

- Participation of a NAMMD inspector in the second meeting of PIC/S experts on Good Distribution practice, organised by PIC/S, March 2014;

- Participation of several NAMMD inspectors in the Interdisciplinary Pharmacy Conference, Bucharest, October 2014;

- Participation of several NAMMD inspectors in the Pharma Forum, Bucharest, October 2014.

• abroad:

- Training for auditors of the MJA/MJV OMCL Network, organised by the European Directorate for the Quality of Medicines (EDQM);

- Workshop on regulatory requirements in assessing live attenuated and inactivated human influenza vaccines, organised by the World Health Organisation (WHO), as well as in two further webinars organised by the EMA for assessment of biological medicinal products;

- Meeting of the Communication Professionals Working Party, under the aegis of the Heads of Medicines Agencies, Rome, Italy, December 2014;

- The 148th Session of the European Pharmacopoeia Commission - participation as a member of the PhEur, Strasbourg, France, March 2014;

- Annual meeting of Secretaries of National Pharmacopoeia Competent Authorities, London , UK, April 2014;

- HPMC Training for assessors of herbal monographs on and related european Union documents - development and usage, EMA London, UK, November 25, 2014;

- Participation in the European Conference organised by the European Directorate for the Quality of Medicines and health protection (EDQM), the Council of Europe, Strasbourg, France, 6–8 October 2014:

- Workshop on Experience with European Pharmacopoeia monographs and expectations for the future;

- Workshop on European Pharmacopoeia monographs for finished products;

- Workshop on impurities.

- Participation via teleconference (Adobe Connect) to webinars organised by the EMA/CHMP on practical information related to Patient Leaflet and Summary of Product Characteristics (SmPC), obtained after scientific assessment and information on efficacy and safety: 6;

- Electronic Reporting of ICSRs in the EEA, during 17.02.2014-21.02.2014, London, UK;

- Participation of two inspectors in the training course for pharmacovigilance inspectors, Rome, Italy, October 2014.

• Participation in on-line training:

- On-line Webinar SmPC Instructions and background documents - 02/13/2014;

- On-line Webinar Particiption VigiLyze 3 - MedDRA and WHO-ART, April 7, 2014;

- On-line Webinar The NCA Webinar for contact points on the new pre-submission phase for source & PSUSAs and on referral procedures, 14 May 2014;

- On-line Webinar VigiFlow Monthly Webinar November 2014 - Reactions and medicinal products in VigiFlow Coding (MedDRA version) - 05/11/2014;

- On-line Webinar VigiFlow December 2014 Monthly Webinar - Causality assessment and analysis in VigiFlow - 12/03/2014;

- On-line Webinar EPITT Using Adobe Training - 10/12/2014;

In 2014 as well. Training has been supplemented with internal training, as follows:

Ongoing training related to professional development was carried out at the NAMMD offices.

Specific training was provided to inspectors at the headquarters:

- Information on topics and issues discussed at EMA working groups (GMP, GDP, GCP and PhV) – based on reports drafted by NAMMD representatives;

- Training on revised general and specific SOPs;
- In June, the NAMMD organised a session of joint training reuniting inspectors working both in Bucharest and in the country, on GDP, Pharmacovigilance and Advertising legislation topics as well as current aspects of quality surveillance work;

Pursuant to the annual training plan, all the staff in the Inspection department received training in labour health and safety and management of emergencies;

16. Economic activity

In 2014, the Economic Department developed and managed an income and expenses budget worth 17,697 million RON, of which expenditures were in amount of 17,550,665 RON.

The structure of expenses can be detailed as follows: personnel expenses, amounting to 14,530,220 RON, goods and services-related expenditures - 2,989,123 RON and capital expenditures - 22.506 RON.

All costs were within the 2014 budget approved, in line with legal provisions on economic and financial control.

The 2014 approved budget was under NAMMD requirements, which has determined inconsistencies against the real needs of the institution.

17. General administration

As in previous years, the General Administration Department (DGA) has made efforts to meet the proposed objectives, at the same time responding, to the extent possible, requests from NAMMD structures.

The Public Procurement Service organised and completed the entire procurement process necessary for development of NAMMD activity, consistent with the needs and objectives of its approved budget, responding to a 520 requests (purchase requisitions).

Management of goods was developed through records and management of fixed assets, inventory items and related paperwork.

The activity of the administrative, maintenance, repair, safety and PSI materialised mainly in 2014, the following activities:

- Development of the *Annual Public Procurement Plan* for 2014;
- Centralisation of purchase requisitions drawn up by the NAMMD organisational structures for set up of the Annual Public Procurement Plan for 2015;
- Implementation of changes in and further additions to the Annual Public Procurement Plan by development of sheets related to the Annual Public Procurement Plan;
- Provision of information and publication of data on preparation and organisation of public procurement procedures, their object and timeframes as well as other information in line with the principles underlying award of public contracts;
- Preparation of files for procurement of goods, services and works and their keeping within the Service;
- Fulfilment of obligations relating to advertising (publication in the Public Purchases Electronic System – SEAP – of information related to the initiation of direct purchases from the of SEAP electronic catalogue, notifications of award);
- Preparation and monitoring of the conduct of public procurement contracts for goods/services/works - 38 pcs.;
- Resolution of 520 purchase requisitions for public procurement of products/services/ works;
- Conduct of 342 purchases by direct purchase from the SEAP catalogue;

The SAP prepared the following documents:

- Global budget commitments (ABG's) - 18 pcs.;
- Individual budgetary commitments (ABI's) related to contracts - 86 pcs;
- Proposal for engagement of expenses (PACs) - 457 pcs.;
- Authorisation of payment (OP) - 609 pcs.;

- Preparation and constant update of the database for procurement of goods/services/works and related payment documents (ABG, ABI, PAC, OP etc.);
- Preparation of documents (reports, letters) needed for service operation;
- Preparation of the Public procurement annual report for 2013 and its submission to the National Authority for Regulation and Monitoring of Public Procurement;
- Monitoring of contracts for utilities (electricity, water, sanitation, natural gas) and preparation of documents for payment;
- Monitoring of rental contracts/addenda for territorial inspection units (utilities included) and preparation of payment documents.

18. Internal audit

IAC established at NAMMD is subject NAMMD President. Is an independent, objective assessment purposes faults found in Agency departments, audited and making appropriate recommendations address them.

In April 2014 it was conducted internal audits, namely:

- Assessment of conduct of operations of the Pharmaceutical Inspection Department;
- Assessment of conduct of operations of the Human Resources, Payroll Department;
- Assessment of conduct of operations of the Pharmaceutical Inspection Department;
- Assessment of conduct of operations of the Legal Department;
- Assessment of conduct of operations of the Pharmaceutical Inspection Department;
- Assessment of conduct of operations of the Department for Logistics, IT and Electronic Data Management;

Objectives set out in the audit missions carried out have been:

- Organisation and operation of work conducted in audited structures.
- Compliance with tasks, duties and specific legislation in the audited structures.
- Record and reporting of activities within the audited structures.
- Document archiving.

Among risks potentially impacting NAMMD work during the period under review, the following may be mentioned: organisational risks, operational risks, legal risks and financial risks.

Main recommendations can be summarised as compliance with current legislation and compliance with the Rules of NAMMD Organisation and Operation.

19. Challenges

Since 2009, the NAMMD has been faced with increasing difficulties in conduct of its mission, among which the following should be outlined: fore and foremost, the difficulty of hiring specialised personnel and their retaining in the Agency, lack of the financial capacity to ensure permanent training of staff and their update with the latest generally scientific and specialised developments, the limited capacities of databases.

20. Priorities/Projects for 2015

Priorities are related to projects for which the Agency would require:

• Greater number of highly qualified specialists in the field of the medicinal products for human use and medical devices, to ensure fulfilment of all obligations incumbent on the

Agency within the established timeframes, and, respectively, to recuperate delays caused by acute shortage of staff basically perpetuated since 2009;

• more flexibility in hiring;

• a budget that would allow direct competition with other competent authorities in the field of human medicinal products in the European Union by:

- Ensuring an adequate number of specialists in all NAMMD departments, especially for assessment of authorisation-related dossiers, for proper management of the national authorisation procedure and the predominant European DCP/MRP procedures, as well as of the centralised procedure; ensuring appropriate expertise of NAMMD specialists could allow Romania's active participation in the activities of EMA structures (Committee for Medicinal Products for Human Use, CHMP Paediatric Committee- PDCO, Committee on Herbal Medicinal Products-HPMC, Pharmacovigilance Risk Assessment Committee -PRAC etc.) since medicinal product authorisation through the centralised procedure is done with existing expertise at national level in EU Member States;

- Increasing NAMMD involvement in decision-making at European level, through active participation in European working groups, proposal of viable solutions for amendment of current legislation in the field of medicinal products for human use, enhanced NAMMD integration in medicines related issues at European level by means of work conducted by rapporteurs, pharmacovigilance assessments, DOSSIER assessment activities at elevated scientific competence when acting as a Reference Member State in the decentralised procedure for marketing authorisation;

- Training of doctors employed in the Pharmacovigilance Service in matters of electronic transmission of adverse reactions to the EudraVigilance – training provided by the EMA and the WHO - Uppsala Monitoring Centre, compulsory for competent authority members but incurring transport and accommodation costs;

- Development of an integrated software that is versatile and multi-tasking, for the management of information about medicines throughout their lifecycle and provision of robust NAMMD databases, aiding conduct of NAMMD activities, also providing technical support to the Ministry of Health, the Health Insurance House etc.;

- Study of the technical feasibility for implementation of a data storage system and management of servers through the virtualisation technology, important to ensure long-term operation of NAMMD IT services.

- Increased participation of personnel in national and international congresses and symposia in the field, for training and update of information in the field.

Other priorities/proposals/projects for 2015:

- Strengthening of the NAMMD role in development of medicinal product-related policy from the perspective of amendments to national legislation brought about by Government Ordinance no. 2/29 January 2014, amending and supplementing Law no. 95/2006 on healthcare reform, and amending and supplementing certain acts, for establishing the public service obligation public, of medicinal product manufacturer and distributor's accountability to citizens *(... to permanently ensure an adequate range of medicinal products to meet the needs of a geographic location and deliver throughout the area quantities requested as soon as possible after order receipt*) and the Agency's role in enforcement in cases of breach of this obligation;

- Participation at a higher level than in previous years, of the NAMMD management representatives in working meetings with representatives of different groups of stakeholders (drug manufacturers, distributors, medical and pharmaceutical professionals, patients);

- Compliance with mandatory reporting of inputs/outputs by all manufacturers/ importers/distributors to ensure of medicinal product traceability throughout the chain, from

manufacturing and/or distribution to the level of community pharmacy, hospital pharmacy, drugstore, will allow the NAMMD to:

- detect falsified medicinal products;
- prevent falsified medicinal products from entering the authorised distribution network;
- counteract illegal parallel circuits selling respectively medicinal products;
- ensure the rapid withdrawal of batches of noncompliant medicinal products or in health emergencies.
- further activities for assessment of medical technologies in order to lie the foundation for patient access to most recent medicinal products in various therapeutic areas;
- become actively involved in debates on delegated acts concerning the single identifier for medicinal products, to be approved by the European Commission under the European Directive of 2011 on measures to be taken by the European Union to avoid entry of falsified medicines into the authorised distribution chain;
- further activities for regulation of advertising even after approval of NAMMD Scientific Council Decision no. 7/07.01.2014 by ministerial order approving implementation rules for assessment and endorsement of advertising to medicinal products for human use.
- timely develop secondary legislation for ensuring national implementation as of 2016 of the Clinical trials Regulation in collaboration with the ARPIM within the working group constituted for this purpose;
- strengthen pharmacovigilance work, meant to provide, through enhanced national and global reporting of adverse effects, as thorough as possible knowledge of the risk-benefit ratio for a drug or a medicinal product class;

In the medical devices (DM) area:

- For 2015, revision is envisaged of assessment of technical and medical units, including assessment questionnaires pursuant to the new Order the Minister of Health no. 748/2014, meant to achieve expected technical and quality level of services in medical devices.
- Review of the order of the minister of health on finding and sanctioning contraventions in the field will allow for control activities, for better discipline and conduct of service providers and enforcement of legality.
- In area related to grant of approval for operation and their annexes, in addition to ordinary activities, the 2015 plan envisages conversion of about 1980 of approvals for operation granted based on the Order of the Minister of Health no. 1636/2004 as amended.
- A project for the coming year as well as a priority is to obtain a clear picture of market problems and deficits. The initiation of activities among MD distributors and users has become a pressing necessity for promotion and awareness of legislation as well as for identification of serious breaches, against which measures have to be taken.

In 2015, the NAMMD will consistently pursue raising market awareness of mandatory compliance with specific regulations.

Next, a top priority will be related to thorough audits and assessments (not only of accompanying documents, but also of the quality of marketed products).

- If, in recent years, advertising of medicinal products for human use has been a constant concern and a challenge for the Agency the same efforts are required in the future regarding advertising of medical devices.
- Also, an additional aspect for NAMMD focus of future work is falsification of medical devices.

To strengthen and improve the internal audit activity, the following are proposed:

- Organising training courses in internal audit by the Ministry of Health, for NAMMD accessing European of funds;
- Preparation and publication of procedural guidelines by Ministry of Health experts on public internal audit activities in the healthcare system.

CONCLUSIONS

The National Agency for Medicines and Medical Devices (NAMMD) is the competent national authority in the field of medicinal products for human use, whose entire activity is conducted for the purposes of promoting and protecting public health by ensuring compliance with European standards of quality, effectiveness and safety of medicines authorised for marketing in Romania, and ensuring the maintenance of a high level of performance and security of medical devices in use in health networks across the country.

The NAMMD aims to constantly strengthen its partnership with healthcare professionals, the pharmaceutical industry, with the media as an opinion former and, last but not least, with the patient in order to promote a proper policy for the authorisation, regulation and control under its scope: human medicines and medical devices.

In 2014, the NAMMD current activity represented issuance of 1222 marketing authorisations (MA) in (401 MAs granted following the National Marketing Authorisation Procedure and 821 MAs granted in line with the European Marketing Authorisation Procedure).

In 2014 as in previous years, foremost among entries on the market have been generics.

From among human medicines listed in the Index of medicinal products registered in 2014, about a third are original medicinal product, authorised through the centralised procedure (i.e. by the European Medicines Agency European – EMA), marketed in Romania on request of the MA Holder.

In 2014, a new reference task has been allocated to the NAMMD and it is essential to emphasize that Government Decision no.315 of 23 April 2014 amending Government Decision no. 734/2010 on NAMMD organisation and operation has redefined NAMMD main duties related to medicinal products for human use, including set up of the List of compensated and free of charge medicines. Thus, in 2014, the NAMMD has also become the competent national authority in the field of health technology assessment; accordingly, the Agency's Department of Health Technology Assessment (DETM) has been created, by transfer of respective operations from the Ministry of Health.

The work involves implementation of a mechanism for rapid assessment of health technologies, based on reviews and evaluation reports of other EU Member States underlying the Ministry of Health decision. The legal basis of the new activity is *Order of the Minister Health no. 861 of 23 July 2014 approving NAMMD criteria and methodology for assessment of medical technologies including INNs of prescription medicinal products provided to insurants, with or without personal contribution, in the frame of the healthcare insurance system and INNs of medicinal products granted under national healthcare programs and means of appeal thereof*, published in the Official Gazette of Romania, Part I, no. 557 of 28 July 2014. Subsequently, in 2014, Order of the Minister of Health no.861 of July 2014 was amended by Order of the Minister of Health No.1200/16.10.2014 (Official Gazette no. 755/10.16.2014), which added to INN the evaluation criteria and providing for the possibility for inclusion into the compensation List of new INNs, orphan drug INNs, of new curative INNs for infectious, transmissible pathologies of major impact on public health as well as criteria for grant of decision on continuation of the listed status.

Following evaluation of health technologies were developed in 2014, two amendments to Government Decision no. 720/2008 approving the List of INNs of prescription medicinal products provided to insurants, with or without personal contribution, in the frame of the healthcare insurance system and INNs of medicinal products granted under national healthcare programs have been operated, allowing for entry into the List of 40 INNs addressing different therapeutic areas: oncology, cardiology, endocrinology, gastroenterology, haematology, infectious diseases, nephrology, ophthalmology,

pulmonology, psychiatry, rheumatology, urology, diabetes. This is an achievement worth outlining as of utmost importance for the Romanian healthcare system.

Pharmacovigilance work conducted in recent years by the Pharmacovigilance and Risk Management Service has become increasingly complex. Such aspects have been present in extensive detail in NAMMD activity reports for previous years. The important issue to note here is the steady increase of the number of spontaneous adverse drug reactions reported, which speaks for the ever growing awareness of physicians and medical staff in general concerning patient safety. However, compared to other EU countries, increased involvement of healthcare professionals in safety issues is still necessary.

Implementation of new pharmacovigilance regulations has created the legal frame for patient direct reporting to authorities or MAHs of spontaneous suspected adverse reactions. The Agency's message on the importance of adverse reaction reporting, as the main factor to increase knowledge of medicinal product safety profile, therefore addresses all those (nurses-physicians-pharmacists-consumers) who, by joint efforts, are able to contribute to this fulfilment of this goal.

In 2014 as well, the NAMMD has undoubtedly pursued to ensure surveillance of the safety of human medicines already in the therapeutic chain, not only by means of pharmacovigilance, but also by pharmaceutical inspection.

The year 2014 witnessed an increase in the number of cases of counterfeit/suspected medicinal products originating from Romania and distributed to various EU Member States: Pegasys, MabThera, Avastin, Sutent. All cases reported have been investigated the NAMMD to establish traceability and communicated to the Romanian General Police Inspectorate for identification of the origin of counterfeit products.

The failure in 2014 to market the influenza vaccine manufactured by the Cantacuzino Institute for the 2013-2014 season, resulting from noncompliant bacterial endotoxin content, has had consequences for healthcare in 2014.

Among events marking 2014, the BEMA audit of the Heads of Medicines Agencies (HMA) conducted in 22-24.09.2014 was a noteworthy occasion. The auditing team consisted of representatives of drug competent authorities in Portugal, the United Kingdom and Italy, under the BEMA III Programme for Benchmarking of European Medicines Agencies. NAMMD preparations for the BEMA III visit started as early as 2012. It should be noted that experience gained by one of DIF inspectors, nominated among auditors in the BEMA benchmarking program for participation in the quality system audit of the Denmark Medicines Agency (DHMA) of 6 - 05.09.2014 and theoretical training received by the NAMMD representative in BEMA training sessions have been successfully applied in the preparation of NAMMD self-evaluation required for the BEMA III audit. This comprehensive approach has focused a large part of the Agency's work, eliciting maximum efforts in the first half of 2014, when all NAMMD structures were involved in meetings for preparation of responses to relevant performance indicators for the Agency's operation, in order to fill in the requested self-assessment questionnaire, the preparatory document for the BEMA III audit, its third stage now focusing on determination of the level of maturity of the management system's capability mainly regarding: areas of general organisation, organisation's strategies, of pre - and post-marketing evaluation, pharmacovigilance, pharmaceutical inspection, communicating with stakeholders.

The commendable score obtained from review of the self-assessment questionnaire and discussions with the auditing team in the BEMA III programme was due to appreciation of the business risk management (identification of risks at all organisational levels), to demonstration of transparent management of conflicts of interest, to appropriate procedure for management of crisis situations (involving both the Agency's infrastructure and personnel), to standard risk based implementation of good practice (GxP) inspections, to demonstration

of significant improvements in pharmacovigilance following the BEMA II audit, and to highlight of actions for public awareness concerning clinical trials data, intended to raise public awareness in this regard.

The BEMA Programme allows not only realistic self-assessment based on standards defined at the level of the HMA network and applicable to all European drug agencies, but also exchange of experiences on good practices and identification of areas for improvement in both the Agency and across the network itself. Directions for Agency improvement emerging from the BEMA III audit concerned use of IT resources, allocating more funds for adequate staff training, determined and constant pursuit of acquisition of further expertise in inspection of clinical trials and, last but not least, improvement of transparency, in particular in relation with clarity regarding information of public interest.

For the NAMMD, similar to all years following 2007, the year 2014 has meant:

- Active participation in discussions in fortnightly/monthly/semi-annual meetings of scientific committees and working groups set up in the various coordinating European bodies in the field of medicinal products for human use (the European Medicines Agency, the Heads of Agencies, the European Directorate for the Quality of Medicines, the European Commission);
- Support to regulatory work through preparation of new NAMMD Scientific Council decisions and provision of technical support at the request of the Ministry of Health;
- Implementing NAMMD strategies in both the organisational and communication areas as established for 2013-2015;
- Continued communication and participation in meetings/workshops/ conferences/informal meetings with the various categories of stakeholders (representatives of the pharmaceutical industry, of patient associations, of media organisations, healthcare professionals), debating on specific medicinal product aspects;
- Participation of Agency representatives with specialist presentations in various scientific events, once again proving the Agency's openness to communication and transparency.

In 2014 as well, the NAMMD top management, together with all Agency structures have continued implementation, development and improvement of the NAMMD quality management system, based on principles set out in *SR EN ISO 9001* and *9004*, in force.

The same difficulties have been identified in 2014 as well related to conduct of operations, perpetuated from previous years and resulting from underfunding, insufficient human resources (despite the slightly higher responsiveness at the end of 2013 as shown by Government Emergency Ordinance no. 77/2013 lifting the ban on employment by competitive examinations to cover vacancies), notwithstanding the decision to allow competitions for vacancies based on art. 19 of Government Emergency Ordinance no. 103 of November 14, 2013 on remuneration of personnel paid from public funds in 2014 as well as other measures for public spending. According to such legal provisions, "*In 2014, the maximum number of posts for institutions and public authorities, to be financed from public funds, regardless of the manner of funding and subordination, shall be such as to ensure full payment of salary rights granted under the law without exceeding the wage funds approved in the budget. Main credit officers shall determine the maximum number of posts to be financed in 2014 under par. (1), for their own staff and public institutions and authorities under their respective subordination/coordination*".

Given this restriction, the NAMMD was unable to achieve its objective to cover its deficit of qualified staff. Thus, only 5 hirings have been possible, for determined periods of time and for posts vacated in 2014, for which there existed approved budgetary funding for wage costs.

Publication on 13.10.2014 of Law no.132/2014 approving Government Emergency Ordinance no. 2/23 January 2014 amending and supplementing Law no. 95/2006 on healthcare reform, and amending and supplementing certain acts has turned the NAMMD into

the competent authority for medical devices as well, taking over specific functions, market surveillance included, from the Ministry of Health. By May 2014, NAMMD assessment of medical equipment in technical-medical units was conducted under Law no.176/2000 on medical devices as amended and supplemented, and Order of the Minister of Health no.1636/2004 approving the Implementation Rules for Law no. 176/2000 on medical devices, as amended, relating to approval of medical technology units, as amended, and afterwards under Title XIX of Law no.95/2006, as amended, and Order of the Minister of Health no.748/2014. Respective work consisted of assessment of units' capability to provide services requesting Ministry of Health approval. Activities assessed are related to services for optical devices, repair, maintenance and installation/commissioning of medical devices, prosthetic devices (hearing, orthopaedic, other).

A further amendment to Law no.95/2006 has resulted in new assignments to the Medical Devices Department, such as grant of licenses for companies providing services in medical devices (medical-optical repair, maintenance and installation/commissioning of medical devices and prosthetic devices) as and Annexes thereof.

From the Agency's perspective, appropriate funding in a favourable regulatory framework would mean the possibility to provide adequately motivated human resources necessary for all specific processes, ensuring a high degree of specialisation only acquirable and maintainable by provision of appropriate continued professional training.

Priorities/Projects for 2015:

Competitions to cover vacancies and adequate training of specialised staff are a necessity imposed by both the complexity of NAMMD functions and the dynamic legislative changes.

Listed randomly and not in order of their importance, which is in fact the same throughout in terms of impact on NAMMD work, other priorities are as follows:

In the field of medicinal products for human use:

- Continued work for health technology assessment, the only means able to lay the foundations for patient access to next-generation medicinal products in various therapeutic areas;
- Active involvement of NAMMD representatives in debate of delegated acts on the single identifier for medicinal products, to be approved by the European Commission under provisions of the 2011 European Directive on EU measures to avoid entry into the authorised distribution chain of falsified medicines;
- Further regulation of advertising even after approval by order of the Minister of Health of NAMMD Scientific Council Decision No. 7/01.07.2015 approving Implementation Rules for assessment and approval of advertising to medicinal products for human use;
- Timely preparation in the dedicated working group together with the ARPIM of secondary legislation ensuring national implementation as of 2016 of the Clinical Trials Regulation;
- Strengthening pharmacovigilance work to provide, through enhanced national and global reporting of adverse effects, in-depth knowledge of the risk-benefit ration for a medicine or class of medicinal products;
- Strengthening the NAMMD role in development of the drug policy in the light of amendments to national legislation by Emergency Government Ordinance No. 2/29 January 2014 amending and supplementing Law no. 95/2006 on healthcare reform, and amending and supplementing certain acts, in terms of establishing the public service obligation, of medicinal product manufacturer and distributor's public accountability to citizen *(... to permanently ensure an adequate range of medicinal products to meet the needs of a geographic location and deliver throughout the area quantities requested as soon as possible after order receipt*) as well as of the Agency's role in enforcement in breach cases thereof;

- Continued strengthening of NAMMD involvement and contribution in preventing entry of falsified medicines into the authorised distribution, in fight against parallel circuits for illegal medicinal product sales, in ensuring prompt withdrawal of noncompliant medicinal product batches or for emergency health reasons by monitoring of mandatory reporting of entries/exits by all manufacturers/importers/distributors for tracing medicinal products throughout the chain, from manufacturing and/or distribution to the level of community pharmacy, hospital pharmacy, drugstore;

- Adoption of a communication strategy tailored to the requirements of all stakeholders. More active participation of NAMMD representatives is needed than previously in terms of presentations of papers at scientific events of professional associations of doctors and pharmacists, pharmaceutical manufacturers and medical societies and, last but not least, meetings of the various patient associations and organisations.

For the medical devices (MD) area:

- Revision, in line with Order of the Minister of Health no. 748/2014, of the procedure for assessment of technical and medical units, evaluation questionnaires included, to ensure provision of services in medical devices to achieve the technical level and quality expected;

- Revision of the order of the Minister of Health on finding and sanctioning of contraventions in the field, to allow for control activities, improvement of discipline and conduct of service providers and enforcement of legality;

- Conversion of about 1980 operation approvals issued based on Order of the Minister of Health no. 1636/2004, as amended.

- Detailed overview of market issues and deficits;

- Promotion and awareness-raising among MD distributors and users in relation to legislation and identification and enforcement of necessary measures in cases of serious infringement of respective regulations;

- Information of the market on mandatory compliance with industry-specific regulations;

- Conduct of detailed checks and assessments (not merely of accompanying documents, but of marketed product quality as well);

- Taking measures in respect of MD advertising;

- Future focus work on falsified MDs.