2015 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 product for human use, medical devices and medical technologies.

The NAMMD mission is to help protect and promote public health by:

- Evaluation at the highest scientific competence of documentation for authorisation in view of marketing high quality, safe and effective medicinal products for human use;
- Evaluation of dossiers for authorisation of clinical trials in Romania and clinical units for performance of clinical trials;
- Medical technologies assessment, according to scientific criteria adopted through legislation in force, 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;
- Surveillance of the safety of medicinal products for human use in therapeutic use by means of inspection and pharmacovigilance activities;
- Ensuring access for the pharmaceutical industry, patients and healthcare professionals to useful and accurate information on medicinal products for human use authorised for marketing in Romania;
- Maintenance of a high level of performance and safety of medical devices in use by healthcare networks throughout the country, irrespective of ownership;
- Most demanding assessment of service providing medical-technical units in the area of medical devices, for optimum delivery of competent and quality prosthetic and repair – maintenance services;
- Issuing specific technical procedures in the field of medical devices;
- Ensuring institutional administrative effectiveness, efficiency and transparency of practices and procedures in use.

This is a mission imposing continual self-assessment, a permanent accommodation of the strategy proposed for social-economic issues or for any other type of challenges which may occur at a given time, meaning sustained efforts to meet the requirements of stakeholders (healthcare professionals, pharmaceutical industry, patients, public, mass-media). In this respect, it is worth mentioning that the NAMMD has continued in 2015 as well the same policy of being an equal partner of all representatives of the pharmaceutical industry (manufacturers, Marketing Authorisation Holders - MAHs, importers), wholesale manufacturers, healthcare professionals (physicians and pharmacists), partners without whom it could not have fulfilled its mission as warrant of quality, efficacy and safety of medicinal products authorised for marketing in Romania. This year as well, communication with all parties involved in the pharmaceutical market represented a major and constant preoccupation, trying, not always successfully, to find viable solutions setting up a regulatory framework for support of the Ministry of Health policy for ensurance of patient access to prescribed treatments, particularly to treatments with new, modern medicinal products available in other European Union (EU) member states within the health ensurance system.

Throughout the last years, the NAMMD dealt with a significant increase in the value chain of the entire pharmaceutical industry. Since innovation is one of the main objectives of the Europa 2020 Strategy, the NAMMD considered and supported the fact that, in 2015, the pharmaceutical industry must display proactive involvement, capitalizing the public agenda of encouragement and support of innovation and high-technology products. The pharmaceutical industry, as a provider of high-end technology and knowledge, should continue to play an important role in supporting specialised authorities in promotion of a health policy adequate for an EU member state, truly interested in the patients' wellbeing.

The NAMMD, as an observer involved in the field of the pharmaceutical market, is able to see that permanent adaptation to pharmaceutical legislation, undergoing an alert dynamics of its evolution, requires special efforts from all stakeholders and all links in this chain. To that effect, it should be highlighted that year 2015 marks the anniversary of 50 years of pharmaceutical legislation in the EU, which has started with Directive 65/65. The current EU legal framework in the field of the medicinal product for human use grants high quality and safety standards, also promoting good operation of the internal market through measures which encourage innovation and competitiveness. Directive 83/2001 of the European Commission (EC), continually amended throughout the years, has set up a community code in the field of the medicinal product for human use. Obviously, the main objective of the norms regulating manufacturing, distribution and use of medicinal products is to safeguard public health. The legal act states: „However, this objective must be met through means which do not impede the development of the pharmaceutical industry/commerce with medicinal products within the Community". The two European Directives, namely 84/2010/EU and 62/2011/EU amending Directive 83/2001/EC, the first, related to a new pharmacovigilance approach, and the second, to avoidance of entry of falsified medicinal products into the authorised supply chain, with direct implication upon the pharma industry and the MAH, are of major importance for the evolution of the EU legislation in this field. Submission of the system for handling of risks, the pharmacovigilance system and the standard dossier of the pharmacovigilance system, represent obligations which have been imposed since 2012, ever since implementation of the new pharmacovigilance Directive. The Directive related to counterfeiting imposes, among others:

- Written confirmation attesting that the product's manufacturer managed to assess compliance of the manufacturer of the active substance and excipients with GMP principles and guidelines by performance of audits;
- Immediate notification of the competent authority and of the MAH in case the medicinal products subject to the respective manufacturing authorisation are found to be suspected or falsified;
- Assessment of registration of manufacturers, importers or distributors who provide the active substances, performed by the competent authority in their member state of residence;
- Assessment of the authenticity and quality of active substances and excipients;
- Enforcement of unique identifiers of safety elements shall be another requirement attributed to the pharmaceutical industry.

In 2015, 1,179 Marketing Authorisations (MAs) were issued (387 through NP – national procedure for marketing authorisation and 792 through EPs – European procedures for marketing authorisations); more MAs can be issued for the same active substance(s) depending on the approved strengths and/or pharmaceutical forms, and the assessment itself is performed for each strength and/or pharmaceutical form submitted for authorisation.

Performed in accordance with specific provisions related to national and European procedures (mutual recognition procedure, decentralised procedure, repeat-use mutual recognition procedure), marketing authorisation and related activities have been performed

starting with August 2014 according to the organisational formula represented by the Evaluation-Authorisation Department, which coordinates the activity of the National Procedure Department (NPD) and of the European Procedures (EPs) Department, as well as the activity of the Information Logistics and Electronic Management of Data Department (DLIGED). This organisation facilitated an overall approach of the two procedures, ensuring integration of existing EPs and NP related data at informational level, thus leading to an overall streamlining of the process.

The numbers (below) confirm a decrease in the number of MAs released by the NAMMD through NP during the past years. This can be explained by reduction of the Agency's ability to process the documentation on behalf of the decrease in the number of employed specialists and staff fluctuation, and on behalf of the relative decrease in the number of requests, in favour of EPs. This is absolutely normal for Romania, an EU member state having a pharmaceutical market faced with an ongoing process of harmonisation with European requirements. A comparative analysis of MAs (authorisations and renewals) issued by the Agency through NP and EPs, during the past years:

- 2013: APP through NP and EPs → 773 (PN= 195 and PE=578)
- 2014: APP through NP and EPs → 1222 (PN= 401 and PE=821)
- 2015: APP through NP and EPs → 1179 (PN= 387 and PE 792)

320 MA withdrawal/discontinuation decisions were issued (withdrawal of a national MA when another MA is released through a European procedure for the same product; discontinuation of a valid MA upon request of the company).

It is particularly important to highlight again that, this year, Government Decision no. 315 of 23 April 2014 for amendment and supplementation of Government Decision no. 734/2010 on NAMMD organisation and operation redefines the main duties of the NAMMD in the field of the medicinal product for human use, including setup of the List of free and compensated medicinal products. Thus, starting with 2014, the NAMMD has become the national competent authority in the field of medical technologies assessment.

The activity of the Medical Technologies Assessment Department (MTAD) in 2015 consisted of 45 applications for assessment of 42 new International Non-proprietary Names (INNs), thus continuing an activity which, in 2015, resulted in a triple update of Government Decision no. 720 of 9 July 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.

During the past years, the NAMMD focused on implementation of a communication strategy with all stakeholders (among which patient organisations, which have always had an important status). The NAMMD observed with increased interest, through the efforts of the National Alliance for Rare Diseases, that the objectives of maximum importance have been reached, from facilitation of the dialogue to participation and involvement of all stakeholders in the field (patients, specialist physicians, authorities, pharmaceutical industry, mass-media) in taking measures required for implementation and update of the National Plan for Rare Diseases. However, effective involvement of the NAMMD in treatment for patients with rare diseases has become possible through the new responsibility of the medical technologies assessment (MTA) institution. In May 2014, Government Decision no. 720/2008 introduced 17 new orphan medicinal products in the List, for *P6: The national programme for diagnosis and treatment of rare diseases and severe sepsis*. The NAMMD got effectively involved in both setup and implementation of Order of the Minister of Health no. 861/July 2014 on 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. While the first version of this Order did not contain criteria facilitating unconditional entry into the List of new orphan medicinal products, the amendment and supplementation of Order of the Minister of Health no. 861/July 2014 through Order of the Minister of Health no. 387/March 2015, with introduction of Table no. 5. - Criteria for assessment of new INNs approved by the European Medicines Agency as orphan medicinal products, have made possible the rapid inclusion of other three orphan medical products into the List.

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. In 2015 as well, the NAMMD promoted, by various actions, the importance of an increased involvement of the healthcare staff into pharmacovigilance activities, involving better training of patients in AR reporting, all the more so as the new European legislation empowers them in this respect. 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. In 2015, the NAMMD continued to appeal to AR reporting by various means (on the NAMMD website, in scientific events, meetings with professional and patient associations and 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 which, after thorough assessment, can generate new medicinal product information. 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 to the EudraVigilance European database.

Therefore, while year 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. In 2015, there were 2401 ARs, of which 926 SARs (serious ARs) and 1475 NSARs (nonserious adverse reactions).

The activity of the Pharmaceutical Inspection Department (PID) consisted, among others, of 43 inspections for assessment of compliance with Good Manufacturing Practice (GMP) rules for authorisation for GMP manufacturing/import/certification, 3 inspections on Good Laboratory Practice (GLP) for recertification at bioequivalence centres, 3 inspections on Good Analytical Laboratory Practice (GALP) for authorisation of independent quality control units, 7 inspections for assessment of compliance with Good Clinical Practice (GCP) rules, 96 inspections for authorisation of wholesale distributors of medicinal products. 1451 thematic inspections were carried out at the sites of wholesale and retail distribution units.

In 2015, the NAMMD fined 24 distribution units/representative units (total value of the fines: 280,000 lei) for noncompliance with the legislation in the field.

In 2015, 4475 export declarations for medicinal products were approved, so the activity was comparable to the one of 2014.

As opposed to year 2014 (which has witnessed an increase in the number of cases of medicinal products falsified/suspected of falsification coming from Romania, distributed in various EU states), there were no such cases encountered in 2015.

As already specified, 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, in accordance with the provisions of 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 2015, the Legal Department continued its previously initiated collaboration, by signing the Protocol of March 2010 for cooperation with the General Inspectorate of the Romanian Police, whose main objective was to establish a general framework for bilateral cooperation and exchange of information in the field of medicinal products counterfeiting, in line with the specific attributions and competences stipulated by the legislation in force.

As regards counterfeiting of medicinal products, continuation of institutional collaboration based on the Protocol on prevention and control of counterfeit and traffic of medicinal products, signed by the NAMMD with public and private partners in 2014, within the SAVEMED project, is worth mentioning. The protocol's main objectives are:

a) Prevention and control of marketing, manufacturing, import, export, holding, storage, transit, distribution and use of counterfeit medicinal products;

b) Compliance with the medicinal product legislation;

c) Reciprocal notification about data and information held by each stakeholder, which are useful for fulfilment of the attributions specific to the other stakeholder;

d) Presentation of substantiation notes to legal factors with attributions in the field, for improvement of national legislation, implementation of community regulations into national legislation, namely signing of international conventions allowing an efficient action to control medicinal product counterfeiting;

e) Use of information resulting from market studies and analyses conducted by special companies in view of a most precise knowledge of the market of medicinal products;

f) Surveillance of functioning of markets in view of identifying cases of breach of national/community and international legislation in the field of medicinal product counterfeiting, enabling partners to take the required measures, in accordance with each person's abilities and their correlation;

g) Reciprocal support to ensure security of medicinal products, by collaboration of all stakeholders, according to their given competences, to identify counterfeit medicinal products, source of counterfeiting and their withdrawal from the market.

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 remained the same, apart from formal specifications. Year 2015 has been equally demanding for the Laboratories - Technical Department and for the Nuclear Unit. Just like during previous years, the highest percentage of the 2015 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

etc. 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. A test report is issued for noncompliant medical devices, prohibiting the use until resolution of noncompliances and procurement of a periodic assessment bulletin or of an approval for use. This type of report is forwarded to the user of the medical device. As far as the NU is concerned, the test report is provided to the customer together with the periodic verification bulletin and, quarterly, a list containing an abridged inventory of checked installations is sent to the National Commission for Nuclear Activities Control (CNCAN).

Until March 2015, the Technical-Medical Units Assessment Department performed its activity in line with Title XIX of Law 95/2006, as amended, and with Order of the Minister of Health no.748/2014 for approval of Methodological norms implementing Title XIX of Law 95/2006, as amended, on approval of medical-technical units. Order of the Minister of Health no. 309/2015 on approval of Methodological norms for enforcement of Title XIX of Law 95/2006 on healthcare reform entered into force in March 2015, and Law no. 95/2006, leading to a new numbering of Titles and Articles, was republished in August 2015. Thus, medical devices are dealt with in Title XX of the republished Law. The activity of the Technical-Medical Units Assessment Department consisted of assessment of the organisations' ability to perform services related to medical devices (optics, prosthetics, repairing, maintenance, setup/commissioning) for which operation approval and issuance of operation approvals and their Annexes is required (for both assessed activities and for import and/or distribution of medical devices). At the same time, changes of authorisations for operation issued before entry into force of Order of the Minister of Health no. 748/2014 were performed in accordance with provisions of Minister of Health Orders governing the Department's activity. The department should be able to cover work throughout the country, performing both initial assessment of organisations for authorisation purposes, surveillance assessments every two years for continued authorisation, issuing new authorisations for functioning and their Annexes and operating the required changes given the deadlines mentioned in the Order of the Minister of Health.

One of the main goals of the Human Resources and Payroll Department (HRPD) in 2015 has been the continuing process of analysing the institution's required human resources, the elaboration of 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. Speaking of this aspect of utmost importance for optimal performance of the institution's activity, it is worth mentioning that in 2015, as in 2014, vacant jobs have been opened for recruitment in line with Article 31 of Emergency Government Ordinance no. 83 of 12 December 2014 on remuneration of staff paid from public funds in 2015, as well as other measures related to public expenses, according to which *"In 2015 and 2016, 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 paid jobs in 2015 and 2016"*.

However, the aforementioned legislation text implies that vacant jobs had become available, within the limits of the budget of income and expenses approved for wage expenses. Considering this containment, the HRPD couldn't reach its goal consisting of covering the lack of qualified staff within the NAMMD. Moreover, the NAMMD could not fully capitalize the possibility of organising contests for the vacant jobs, following the notification received from the Ministry of Health, according to which 30 vacant jobs have been erased from the job list,

thus leaving the NAMMD with only 354 jobs from 384. Only 15 persons have been hired, for jobs that had become vacant in 2015, having a budget approved for wage-related expenses.

To conclude, the lack of qualified staff continued in 2015 as well, facing the institution's departments with a lack of special medical-pharmaceutical staff.

Changes at organisational level in 2015 are worth mentioning. Therefore, considering that the NAMMD has been, since 2014, the competent authority in the field of medical devices as well, a new organisational chart has brought more changes, such as the setup of the Medical Devices Department which coordinates the Technical Laboratory Department and the Technical-Medical Units Assessment Department, already existing, and the setup of the Department for Medical Device Market Regulation, Authorisation and Supervision, as approved through Order of the Minister of Health no. 65/2015.

Moreover, another issue considered for establishment of the new organisational structure was narrowing of the control of management staff within the National Procedure Department, the European Procedures Department, the Medicinal Product Quality Control Department and the Biological Product Evaluation and Control Department, by setting up several substructures (bureaus and laboratories).

It is also worth mentioning that recently founded structures, in 2015, have been included in the institution's organisational chart until 01.08.2013 when, through NAMMD president decision, they have been disbanded, following entry into force of Emergency Government Ordinance no. 77/2013 mentioning that the number of management jobs should represent 12% of the total number of approved jobs. Implementation of this regulatory act meant reduction of the number of management jobs from 80 la 43, fact leading to demotivation of demoted employees, as well as to constrained widening of the control area. Subsequently, Emergency Government Ordinance no. 77/2013 was declared fully unconstitutional and the mentioned substructures were setup.

In 2015, the NAMMD took on a new duty. Thus, starting with February, the Agency handled *lipsamedicament@anm.ro*, an e-mail address setup upon request of the Ministry of Health. It is worth mentioning that the report of the European Medicines Agency (EMA) for 2015 analyses the initiatives of the institution coordinating the EU network of competent authorities in order to prevent discontinuation in supply of medicinal products to the people, which represents a significant public health risk. It is equally true that the past 10 years have seen the global tendency according to which discontinuation in supply of medicinal products has become a serious issue, increasing in the EU, having a negative impact upon the healthcare provided to European patients, because of multiple causes (manufacturing issues, price policy for medicinal products, parallel export etc.). The NAMMD affirms, entirely agreeing with the EMA, that this situation requires efficient collaboration between various stakeholders and regulatory authorities, including an international collaboration combined with an improved planning of the pharma affair and a good communication between manufacturers, distributors and authorities. This is a viewpoint affirmed by the NAMMD within working meetings with representatives of MAHs/manufacturers, wholesale distributors, patient associations.

The mission of the Department for Policies and Strategies (DPS), given its new duty, consisted of cooperation with other NAMMD departments in order to solve the complaints coming from patients, physicians or pharmacists concerning discontinuation of supply of the pharma market with certain products or with MA discontinuation upon MAH request. In addition to formulating answers to those who have e-mailed the NAMMD, the DPS centralised these notices to ensure a correct assessment of this deficit, while informing the NAMMD management about the lack of other medicinal products, on an ongoing basis, in order to forward the respective information to the Ministry of Health and find a viable solution ensuring

the required amount of products for a large spectrum of therapeutic areas, many of these being scarce since the second half of year 2015.

Together with the Legal Department, the DPS contributed to issuance of the Memorandum of understanding signed on 19 August 2015 between the NAMMD and the National Agency for Medicines and Medical Devices of Serbia (ALIMS). According to this Memorandum, two NAMMD representatives have participated, in November 2015, in the 11th ALIMS symposium, leading to an efficient delineation between the two homologous authorities, the main objective of the Memorandum being the support given to the Serbian Agency, for its future EU accession, based on the expertise of Romanian experts in implementation of corresponding EU legislation.

For the Agency, the regulation of advertising of medicinal products for human use represented a constant preoccupation throughout the past years, materialised in 2015 through entry into force of Order of the Minister of Health no. 194 of 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. Apart from supplementations and clarifications, brought to the chapter dealing with advertising of Law 95/2006, extremely useful to both assessors and applicants, Order of the Minister of Health no.194/2015 contains provisions related to rendering transparent sponsorships in the field. Thus, the Order stipulates: „*It is mandatory that manufacturers, MAH or their representatives to Romania as well as wholesale and retail distributors notify the NAMMD, before 31 March of the current year, all sponsoring activities as well as any other expenses undertaken the previous year, provided to healthcare professionals, patient organisations and any other type of organisations conducting healthcare activities, medical or pharmaceutical care",* stating that: „ *in 2015, notifications hall be submitted before 30 June, and the information provided in templates under (5) is posted on NAMMD's, the reporting entity's and the recipient's website, as appropriate, before 30 September 2015".* Consequently, the NAMMD posted on its website, in due time, the register of receipt of 4550 sponsorship forms from beneficiaries and 142 forms from sponsors.

Noteworthy for year 2015 is NAMMD's active participation, via representatives of the DPS and the General Administration Department (GAD), in the organisation in Bucharest of a training, supported by the team of the European Directorate for the Quality of Medicines (EDQM), concerning the European Pharmacopoeia, with the participation of a large number of Agency assessors. In the opening of the training session presentations, two NAMMD representatives have presented papers such as: „Romanian Pharmacopoeia: tradition, use and development" and „Role of the National Agency for Medicines and Medical Devices of Romania at national and European level".

Other aspects concerning NAMMD activity in 2015 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 7/52 Agencies - HMA, The European Directorate for the Quality of Medicines - EDQM, the European Commission).

Year 2015, as well as all years starting with 2007, meant participation of the NAMMD, via its assigned representatives, in meetings of scientific committees and working groups of European bodies, dealing with various aspects of regularisation and European procedures in the field of the medicinal product, such as participation in the following:

- EMA's CHMP (The Committee for Medicinal Products for Human Use) with appointment as co-rapporteur within re-examination procedures;
- EMA's PDCO (The Paediatric Committee) – assessment of PIP (Paediatric Investigation Plan), participation in setup of the 2015 Annual Paediatric Report for Romania, forwarded to the EMA/PDCO for the European Commission and participation in monthly/bimonthly teleconferences and 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 2015, the NAMMD Scientific Council approved 35 Decisions (SCDs) (32 non-regulatory and 3 regulatory); the non-regulatory decisions are published on the website under "Legislation" and in the quarterly "Newsletters";
- In line with the new NAMMD duty received in 2013, as defined and implemented through provisions of 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 2015 as well: 68 authorisations for special needs (ASNs) for 72 medicinal products, of which a small part for each patient, upon request of the specialist physician, and the majority for certain medicinal products meant for categories of patients with various diseases, upon request of consulting commissions/directions of the Ministry of Health. ASNs have become, in 2015, a manner of temporary resolution of the discontinuation (*shortage*) of supply of the pharma market with certain medicinal products, phenomenon acutely manifested during the second part of 2015, following manufacturing issues, but particularly because of the changing of the legal framework, as regards the price of medicinal products. This issue managed to persuade certain MAHs to temporarily discontinue marketing of the respective products or even to give up on their MAs.
- 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. Order of the Minister of Health no. 811/2015 for amendment and supplementation of Order of the Minister of Health no. 456/2013 refers to temporary suspension until 31.12.2015, in line with Law 95/2006, of distribution outside Romania of the medicinal products mentioned in the List attached to the Order.

- 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. Order of the Minister of Health no. 811/2015 for amendment and supplementation of Order of the Minister of Health no. 456/2013 refers to temporary suspension until 31.12.2015, in line with Law 95/2006, of distribution outside Romania of the medicinal products specified in the List attached to the Order.

- The NAMMD replies to the Ministry of Health's requests concerning:
  a) ensurance of technical support for setup of 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 has been updated in 2015 for another 3 years (2015-2017) by adoption of a new SCD;
  - The communication strategy for 2013-2015 has been approved in 2013.

In 2015, the entire NAMMD staff has participated in both implementation of the Organisational Strategy (updated in 2015) and of the Communication Strategy for the same period. The Department for Policies and Strategies 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, based on dialogue and action.

- Participation in gatherings/workshops/conferences/informal meetings with stakeholders on legislation and procedure-related issues in the period of reference (2015)

Moreover, year 2015 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;

- organisation, at the NAMMD headquarters, of round tables on themes of interest with participation of representatives of patient associations;

- participation in "International Health Forum: Changing the paradigm: reducing healthcare costs through patient centred strategies"- event organised by the APMGR (September 2015).

- 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:

- participation with *„The NAMMD –media relationship between actual partnership and desideratum"*, at the Summer School for Journalists – Pharmaceutical Journalism, second edition, Sighișoara, June 2015;

- participation with „*Monitoring of "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"* at the National Toxicology Congress, October 2015;

- participation with „*EU legislation, guarantor of quality, efficacy and safety of vaccines authorised for marketing*" at the meeting of the PSD Group from the Senate, for signing of the resolution for notification and education concerning children vaccination;

- participation with *„Update of the Database of Romanian Standard Terms, ongoing procedure at the NAMMD"* at the National Pharmacy Conference, November 2015;

- participation in the Health Excellence Awards, April 2015;

- participation in the event related to the Indian economic mission in the pharma field, February 2015;

- participation in the Pharmacists' Gala, event which awards excellency shown in conduct of the pharmacist profession, December 2015;

- participation in the workshop „*Improvement of communication for immunisation programmes and public health",* organised by the Romanian Microbiology Society in collaboration with the Association of Medical Journalists (September 2015);

- Participation with exposure of pharmacovigilance issues and NAMMD contribution to fighting against medicinal product counterfeiting:

- National Congress of Allergology and Clinical Immunology – May 2015, Poiana Brasov
- Multidisciplinary Approach of Tuberculosis – September 2015, Constanta
- The National Conference of Clinical Hematology and Transfusional Medicine – October 2015, Sinaia
- National Congress of Dermatology – October 2015.

Difficulties in meeting the proposed objectives were encountered by all NAMMD structures in 2015, when the Agency, just like during past years, was faced with a lack of staff with high professional competence, as well as with the permanent threat of migration of already trained specialists in the field.

It is highly important that NAMMD specialists become more involved in the EU network of national competent authorities, coordinated by the European Medicines Agency (EMA); several improvement measures of the 2015 situation can be formulated in the future, in this respect:

- Increase in the number of specialists with appropriate professional background, motivated in line with their position within a national competent authority in the EU network (current lack of an appropriate financial stimulus);
- Ensuring modern gear, in line with requirements imposed by EU legislation in force (outworn gear, lack of funds at a given moment);
- Staff training in order to meet the increasingly strict requirements in the field (such as the current lack of funds);
- Appropriation of funds for purchase of appropriate informational systems, allowing setup of a performant database for the Index of medicinal products for human use, for reported adverse reactions, for clinical trials.

NAMMD ACTIVITIES IN 2015

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

In 2015, the Scientific Council adopted 35 Scientific Council Decisions (SCDs); out of these, 3 regulatory decisions were sent to the Ministry of Health and await approval through Order of the Minister of Health (OMH); the other 32 non-regulatory SCDs have been posted on the NAMMD website under section "Legislation/Scientific Council Decisions" and published in the bilingual NAMMD Newsletters of 2015.

3 ordinary meetings of the Scientific Council (26.02.2015, 03.07.2015 and 30.09.2015) have taken place in 2015.

Non-regulatory SCDs were related to:

- The Organisational Strategy of the National Agency for Medicines and Medical Devices (2015 – 2017)
- Adoption of certain European Guidelines and procedures related to the pharmaceutical inspection activity
- Adoption of the Guideline on Good Pharmacovigilance Practice, Module II – Pharmacovigilance Master File
- Adoption of the Form for Patient report of adverse reactions occurred in last resort treatments
- Adoption of the Romanian version of Standard Terms, as approved by the European Pharmacopoeia Commission
- Approval of criteria governing NAMMD's approval of supply of free samples, of establishment of conditions for grant of approval for supply of free samples of medicinal products for human use authorised for marketing in Romania and approval of the procedure for supply of free samples of medicinal products for human use authorised for marketing in Romania

2. Activity of the NAMMD Administration Council (AC)

In 2015, the Administration Council (AC) adopted 6 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:

I) one law/ordinance draft for amendment of Law 95/2006 on healthcare reform;

II) 10 drafts of Orders of the Minister of Health, namely:

a) amendment and supplementation of 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;

b) approval of the Norms for assessment and approval of medicinal product advertising;

c) approval of the Good Distribution Practice;

d) amendment and supplementation of Order no. 1173/2010 on setup and operation of the expert group responsible for issuance of technical viewpoints on documents undergoing debate at community level and ensurance of representation within meetings of working structures of EU institutions;

e) amendment and supplementation of Order no. 861/2014 on 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;

f) approval of the Norms for enforcement of Articles 695 point 17 and 792 point (2) of Law no. 95/2006 on healthcare reform (prior to republication of the Law in August 2015);

g) setup of a Commission for resolution of complaints against decisions for assessment of medical technologies concerning inclusion, extension of indications, non-inclusion 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;

h) approval of the Guideline on Good Distribution Practice principles for active substances of medicinal products for human use;

i) amendment and supplementation of the Order on setup of the Administration Council;

j) amendment and supplementation of the Order on setup of the Scientific Council.

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions

In 2015, within meetings of the two commissions for marketing authorisation (Commission for Marketing Authorisation), setup 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 2015, 21 working sessions took place, divided by commissions (9 for Commission for marketing authorisation - National procedure and 12 for Commission for marketing authorisation - European procedures).

The 2015 activity of the Commission for Marketing Authorisation (CMA) mainly consisted of:

- preparation of dossiers meant to be discussed in CMA sessions: 1135 NP and EPs dossiers;
- setup of the minutes of CMA meetings:
  - for National Procedure: 9 meetings, where 364 dossiers were discussed, of which 54 for authorisation, 267 for MA renewal, 43 in view of MA discontinuation/cancellation;
  - for European Procedures: 12 meetings, where 771 dossiers were discussed, of which 447 through DCP, 14 through MRP, 33 through MRP - repeat use, 272 for MA renewal with Romania as a Concerned Member State and 5 dossiers for MA renewal with Romania as a Reference Member State.

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 2015 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 2015, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 142 inspection reports, of which:

- 34 inspection reports on compliance with Good Manufacturing Practice rules;
- 8 inspection reports on compliance with Good Manufacturing Practice rules at the importer's site;
- 87 inspection reports on compliance with Good Distribution Practice rules;
- 6 inspection report on compliance with Good Clinical Practice rules;
- 3 inspection reports on compliance with Good Laboratory Practice rules;
- 1 inspection report on compliance with Good Analytical Laboratory Practice rules;
- 3 inspection reports on compliance with the duties of MAHs in Romania, other than pharmacovigilance-related.

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 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 and deontology, as approved through Order of the Minister of Health no. 160/2004.

In 2015, 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 2015, there were no situations requiring summons of the Commission.

5. Marketing authorisation and related activities

In 2015, 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).

5.1. Marketing authorisation through national and European procedures

In 2015, 771 marketing authorisations (MAs) were issued for medicinal products for human use authorised through European procedures: 447 through decentralised procedure, 14 through Mutual Recognition Procedure, 33 through repeat-use mutual recognition procedure and 272 through renewal procedure with Romania as a Concerned Member State (CMF) and 5 for renewal with Romania as a Reference Member State (RMS).

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:

4329 Type I variations
322 Type II variations
77 MA transfers
190 changes of packaging design and imprinting
1425 clinical variations

5.2.2. In 2015, as regards **post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures**, the NAMMD approved:

3359 Type IA variations for Romania (as a CMS);
3019 Type IB variations for Romania (as a CMS);
633 Type II variations for Romania (as a CMS);
81 MA transfers for Romania (as a RMS);
47 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 and of units where clinical trials can be performed

In 2015, 220 applications were submitted for authorisation of clinical trials, more than in 2014 (245). Most of these are Phase III clinical trial applications (134), 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 (64); these are exploratory studies concerning the most effective dose for medicinal products whose safety and tolerability have been proven, as well as 7 applications for approval of Phase IV clinical trials, post-authorisation.

In Romania, there are few applications for performance of Phase I clinical trials (15 applications in 2015, just as many as in 2014), which require special conditions.

In 2015, the NAMMD granted 192 authorisations for conduct of clinical trials.

Moreover, 33 applications for observational clinical trials were received; acknowledgement letters have been issued for 32 observational studies.

In 2015, the Clinical Trial Service approved 876 substantial amendments.

As regards authorisation of clinical units for performance of clinical trials, the following are worth mentioning:

- applications for assessment and authorisation of medical units for performance of clinical trials in the field of medicinal products, received and assessed: 193
- authorisations issued: 117

5.4 Assessment of medical technologies

In 2014, the NAMMD became the national competent authority in the field of medical technologies assessment, in accordance with Government Decision no. 315 of 23 April 2014 on amendment of Government Decision no. 734/2010 on organisation and operation of the NAMMD, which redefines the main responsibilities of the NAMMD.

Applications submitted in 2015: 45 (42 International Non-proprietary Names – INNs)

- Oncology – 18 applications submitted, 15 New INNs
- Cardiology – 4 applications submitted, 4 New INNs
- Diabetes and metabolic diseases – 1 application submitted, 1 INN
- Endocrinology - 1 application submitted, 1 INN
- Gastroenterology/Contagious diseases – 9 applications submitted, 9 INNs
- Ophthalmology - 3 applications submitted, 3 INNs
- Pneumology – 6 applications submitted, 6 INNs
- Rheumatology – 2 applications submitted, 2 INNs
- Psychiatry – 1 application submitted, 1 INN

The MTAD activity in 2015 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, or change of the position within the List. The table below shows the situation of issued decisions, by:

Specialty	Unconditioned	Conditioned	Non-inclusion	Change
Oncology	10 INNs	3 INNs	2 INNs	
Cardiology	2 INNs	2 INNs		
Diabetes and metabolic diseases		1 INN		
Endocrinology			1 INN	
Gastroenterology/ Infectious diseases	1 INN	7 INNs	1 INN	
Ophthalmology		1 INN	2 INNs	
Pneumology	5 INNs	1 INN		
Psychiatry			1 INN	
Rheumatology			1 INN	1 INN
Total	**18 INNs**	**15 INNs**	**8 INNs**	**1 INN**

Following assessment of medical technologies, 3 amendments of Government Decision no. 720/2008 were performed in 2015: Government Decision no. 741/2015, no. 799/2015 and no. 877/2015.

Another duty of the Technical-Medical Units Assessment Department is critical assessment of therapeutic protocols, as stipulated in Common Order of the Ministry of health and of the National Health Insurance House no. 1301/500/2008. In 2015, this activity consisted of 4 amendments of Order of the Minister of Health/NHIH no. 1301/2008:

1. Order of the Minister of Health/NHIH no. 275/2015 published on 12.03.2015 - 28 therapeutic protocols;
2. Order of the Minister of Health/NHIH no. 968/2015 published on 03.08.2015 - 9 protocols;
3. Order of the Minister of Health/NHIH no. 1317/2015 published on 27.10.2015 - 1 protocol;
4. Order of the Minister of Health/NHIH no. 1379/2015 published on 04.11.2015 - 24 protocols.

To conclude, the Technical-Medical Units Assessment Department ensured assessment of 62 therapeutic protocols in 2015.

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

In 2015, 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.

1171 new advertising visas, 1223 extensions of advertising visas and 248 approvals of advertising materials were issued.

Year 2015 also meant entry into force of 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, stipulating that „ *It is mandatory that manufacturers, MAHs or their representatives in Romania as well as wholesale and retail distributors notify the NAMMD, before 31 March of the current year, all sponsoring activities as well as any other expenses undertaken the previous year, provided to healthcare professionals, patient organisations and any other type of organisations conducting healthcare activities, medical or pharmaceutical care.",* mentioning that: „*in 2015, notifications shall be submitted before 30 June, and information provided in templates under (5) is posted on the NAMMD, the reporting entity's and their recipient's website, as appropriate, before 30 September 2015."* Therefore, the NAMMD has posted on its website the register resulted after receipt of 4550 sponsorship forms from recipients and 142 from sponsors.

Another important activity, conducted by a group appointed in this respect, was the assessment of 648 dossiers on consultation with target patient groups for the package leaflet for medicinal products for human use, of which 266 have been approved within the authorisation procedure, 312 have been approved within the procedure for approval of variations to MA and 70 represented completion of the documentation, in accordance with NAMMD requests.

5.6. Pharmacovigilance

During the past years, each Agency activity report analysed the progress met with AR reporting by simple presentation of numbers. Only 280 spontaneous reports were sent in 2004, yet the following years have brought progressively more reports, namely 2401 ARs, of which 1475 NSARs (non-serious adverse reactions) and 926 serious adverse reactions (SARs). Please find the source of reports below; the results show that, for the time being, safety signals sent directly to the Agency by patients are still few, since patients rather report them to physicians than to pharmacists/assistants:

ARs coming from an assistant – 1 NSAR
ARs coming from a consumer – 7 NSARs
ARs coming from a pharmacist – 12 NSARs and 1 SAR
ARs coming from a physician – 201 NSARs and 136 SARs
ARs coming from a MAH/other medical staff – 25 NSARs and 6 SARs
ARs coming from a MAH/pharmacy assistant – 3 NSARs
ARs coming from a MAH/consumer – 228 NSARs and 74 SARs
ARs coming from a MAH/pharmacist – 26 NSARs and 6 SARs
ARs coming from a MAH/physician – 789 NSARs and 496 SARs
ARs coming from a MAH/literature – 180 NSARs and 204 SARs
ARs coming from a MAH/media – 3 NSARs and 3 SARs.

a) Management of safety data issued from spontaneous reporting:

- validations/confirmations of adverse reaction (AR) reporting to EudraVigilance (EV) (ICSR and SUSAR) – 3375 confirmations (ACK);
- retransmission to EVHUMAN of cases received from the MAH in the Inbox of NAMMD's EV (in E2B electronic form) – 1471 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 - 148, NSARs - 205, Total – 353.
- local management and archiving of spontaneous adverse reactions reports received from all sources – 2401 ARs (except for duplicates encountered in literature);
- electronic retransmission of adverse reactions to the WHO database (the Uppsala Monitoring Centre) via the VigiFlow electronic channel – 1419 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 – 33 ARs;
- 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 - 3;
- notification letters to the College of Pharmacists concerning spontaneous reporting by pharmacists of adverse reactions to medicinal products, in view of grant of Continuing Pharmaceutical Education (CPE) credits – 3;
- 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 – 23;
- information letters sent to physicians concerning grant of Continuing Medical Education (CME) credits – 655;
- letters of confirmation of receipt of AR reporting sheets from physicians within the network – 205;
- letters of confirmation of receipt of AR reporting sheets from pharmacists within the network – 5;
- responses to MAH requests concerning adverse reactions reported to the NAMMD involving medicinal products authorised in Romania – 17;
- responses to MAH requests concerning adverse reactions reported to the NAMMD (in E2B format, using the Eudravigilance system) – 447;

– request of additional information on adverse reactions to rapporteurs (physicians/pharmacists/consumers) - 4.

b) Collection, validation and archiving of 666 archived Periodic Safety Update Reports (PSURs).

c) Pharmacovigilance activities in the context of the system of European national authorities under EMA coordination:

– EMA press releases translated and posted on the website – 28 documents;
– 23 Direct Healthcare Professional Communications (DHPCs) related to safety concerns raised in relation with medicinal products (translated/posted on the website);
– transmission of 20 information letters to the National Health Insurance House, the Ministry of Health, 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) – 26 documents.

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

– 25 replies (NUI) upon request for information by certain EU national authorities concerning information about individual medicinal products or medicinal products categories;
– Transmission of a non-urgent information (NUI) to the other EU member states concerning certain products or classes of products - 1 NUI.

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

– 900 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) (Romania as a concerned member state);
– 240 assessment reports of the pharmacovigilance documentation (summary of the pharmacovigilance system/Risk Management Plan (module 1.8) and *addendum to clinical overview* (module 2.5) in view of MA renewal for medicinal products authorised through DCP/MRP/ repeat-use MRP/renewal (R) (Romania as a concerned member state);
– 250 assessment reports of the pharmacovigilance documentation – pharmacovigilance system/summary of the pharmacovigilance system/Risk Management Plan (initial + supplementations) to obtain a marketing authorisation through national procedure;
– 146 checks of the pharmacovigilance documentation submitted by the MAH in view of MA renewal for medicinal products authorised through NP;
– 18 assessment reports of the pharmacovigilance documentation – the Periodic Safety Update Report (PSUR) (module 5)/*addendum to clinical overview* (module 2.5), in view of MA renewal for medicinal products authorised through NP;
– Participation in setup of Lists of medicinal products which meet the criteria for inclusion into the unique European procedure for assessment of Periodic Safety Update Reports (PSURs) – 242 feedbacks.

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

- 109 educational materials.

g) Assessment of requests concerning variations to terms of marketing authorisations as regards the pharmacovigilance system for medicinal products authorised through national procedure (NP) and European procedures (EPs)

- 3 validations of Type IB and II variations (through national procedure);
- Type IA variations - summary of the pharmacovigilance system (national procedure): 101;
- Type IB and II variations (RMP) authorised through NP or through work-sharing procedure (work-sharing – WS) – 26;
- Type IB and II variations for medicinal products authorised through European procedure – 77.

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

- Parallel import procedure: 13 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.

In 2015, the National Procedure Department - NPD (with support of IT professionals within the Information Logistics and Electronic Management of Data Department for posting on the Agency's website) ensured:

a) Maintenance of the database of authorised medicinal products:

- 1149 products authorised through: national/European/centralised procedure(s) - 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 320 decisions for MA withdrawal/discontinuation (withdrawal of national MA when the same product is granted a marketing authorisation through European procedure; discontinuation of a valid MA on request by the company);
- 960 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: 6272 products;
- Inclusion of "blanks" for medicinal products submitted for MA renewal: 414;
- Other types of discontinuation (pending/marketing discontinuation: 107 medicinal products;

- Inclusion of 154 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 per quarter;
- Transmission of the Index of Medicinal Products to the NHIH in the format agreed (12 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;
- Analysis of situations forwarded by the NHIH/Ministry of Health concerning discontinued/suspended/expired MAs – quarterly.

Other activities related to the Index of Medicinal Products:

- setup of a database in xls. In view of handling compliance with provisions of Articles 729 and 730 of Law 95/2006 on healthcare reform - Title XVII, The medicinal product and Articles 737 and 738 of Law 95/2006, republished in 28.08.2015, on healthcare reform - Title XVIII - The medicinal product;
- issuance of 25 decisions for MA discontinuation in accordance with provisions of Articles 729 and 730 of Law 95/2006 and Article 738 of Law 95/2006, republished in 28.08.2015;
- introduction of the documentation (received in written and/or electronic form) submitted (concerning marketing) by the MAH into the „SUNSET CLAUSE" database: 527 addresses/e-mails;
- introduction of data on temporary marketing discontinuation into the „SUNSET CLAUSE" database: 135 addresses;
- introduction of information on permanent marketing discontinuation into the „SUNSET CLAUSE" database: 116 addresses;
- introduction of data on applications for waver from MA discontinuation terms into the „SUNSET CLAUSE" database: 23 applications/9 waivers;
- handling of 17775 entries into the „SUNSET CLAUSE" database.

As regards "*parallel import*" activities, 60 parallel import authorisations (PIAs) were released (assessment of submitted documentation, of supplementations sent by applicants and setup of PIAs and their Annexes).

"Parallel export" activities consisted of:

- issuance of 461 responses to requests for information received from 20 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.

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 2015, the PID continued to perform the activities mentioned in the specific legislation (Law 95/2006 - Title XVIII – The medicinal product, republished and secondary legislation), in accordance with the Department's Standard Operating Procedures and according to the deadlines stipulated by the law. Types of 2015 inspections:

- **GMP, GLP, GALP, GCP, pharmacovigilance inspections**

- 43 GMP inspections for grant of manufacturing/import/certification authorisation

The following types of GMP inspections have been conducted, in accordance with the provisions of the legislation in force:

- 27 GMP inspections for release of a manufacturing authorisation;
- 11 inspections for authorisation at the sites of medicinal product importers.

No follow-up inspections were conducted in 2015 at the sites of manufacturers/importers.

- 5 certification inspections for GMP compliance of pharmaceutical companies from third countries (India, Egypt, Belarus). The 5 inspections concluded with 4 GMP certificates for finished medicinal products and active pharmaceutical substances.

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 one of the two inspections). Inspections resulted in issuance of 1 certificate of GMP compliance, namely a declaration of GMP noncompliance for the other company in China.

In 2015, a NAMMD inspector from the PID department participated, together with other inspectors from the Italian authority in the field of the medicinal product (AIFA), in 1 inspection at the site of a manufacturer in a third country (USA), within the inspection programme addressing centrally authorised products, coordinated by the European Medicines Agency (EMA); the inspection was concluded by issue of a GMP compliance certificate by AIFA.

- **GLP inspections (3)**

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

The main findings discovered during GLP recertification inspections have consisted of:

- Issues concerning record traceability;
- Documents attesting the quality and origin of blank plasma;
- noncompliant aspects concerning the quality control documentation;
- noncompliances concerning the centre's Standard Operating Procedures (SOPs), as opposed to the legislation in force on conduct of bioequivalence studies;
- design deficiencies of the informed consent form, protocol and final report of the bioequivalence study;
- deficiencies of monitoring the bioequivalence study;
- insufficient training of the centre's staff.

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

In 2015, 3 inspections were requested at independent control units for physical/chemical and/or microbiological laboratories for which 2 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.

- **Pharmacovigilance inspections (3)**

In accordance with PID's yearly inspection plan, 14 inspections for surveillance of the pharmacovigilance activity at the MAH / representative in Romania of a MAH were planned for 2015; however, none has been conducted, due to various reasons.

3 unexpected inspections were conducted in 2015, assessing compliance with MAH obligations, in accordance with the legislation in force (Article 799 (6) of Law 95/2006, republished).

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 2015 as well. 910 reports following local consultancy pharmacovigilance visits were set up in 2015, showing an increase in the number of adverse reaction reports submitted to the NAMMD by healthcare professionals.

- **GDP inspections (96)**

In 2015, GDP inspections were as follows:

- authorisation for wholesale distribution of Romanian distribution units in accordance with the legislation in force;
- management of the national database containing information about wholesale distribution authorisations issued;
- 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;
- adaptation of information from monthly reporting sent by wholesale distributors/manufacturers/importers in accordance with Order of the Minister of Health no. 502 of 2013 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;
- coordination of local inspectors concerning local performance of inspections for authorisation of wholesale distributors;

As regards authorisation of wholesale distributors of medicinal products from Romania, the activity performed in accordance with the provisions of Order of the Minister of Public Health no. 1964/2008 consisted of:

- Assessment of the documentation forwarded by applicants to the NAMMD;
- Scheduling and conduct of inspections;
- Setup and release of wholesale distribution authorisations;
- Setup and handling of inspection dossiers for each inspected unit;
- Introduction of wholesale distribution authorisations issued by the NAMMD into the database.

In 2015, 96 inspections for authorisation have been performed, leading to release of 84 authorisations for wholesale distribution and Annexes; 46 units undergo various stages of the authorisation process. An authorisation for wholesale distribution has not been issued for 5 units, because of critical findings.

In 2015, 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 2015, no unexpected/follow-up inspections were performed, for assessment of the distribution activity and of the manner of compliance with provisions of the Guideline for Good Distribution Practice.

175 applications for issuance of updated authorisations and/or Annexes to wholesale distribution authorisations were received and assessed.

27 GDP authorisations were withdrawn upon holder request.

8 GDP authorisations were suspended following noncompliance with the Guideline on Good Wholesale Distribution Practice concerning acquisitions, as well as following noncompliance with the conditions underlying authorisation, and the fine has been lifted only for one unit which has proven appropriate resolution of the findings.

18 GDP authorisations were suspended upon request, of which only 2 units have restarted their activity.

Inspections for authorisation of wholesale distribution were conducted by PID inspectors (from the main headquarters) and by some of the inspectors from local inspection units who, in order to implement the legislation specific to wholesale distribution during inspections, have received the required documentation and information and have forwarded the issued documents to the headquarters.

- **Inspections for assessment of compliance with GCP rules (4 clinical trials/7 centres)**

The following were conducted in 2015:

- GCP inspections (programmed in accordance with the yearly inspection schedule of the NAMMD - 7) of which: at the sponsors' site (1), at Contract Research Organisations - CROs (2), at the investigator's site (4).

One of the inspections conducted at the investigator's site, programmed by request of the Clinical Trials Service, was unattended and aimed at checking the noncompliance information received from the CRO. Cancelled inspections involved: assessment of documents requested from sponsors/CRO for their acceptance for preparation of inspections, setup of inspection plans, deficiency lists, inspection reports and the inspection-related correspondence.

The most important findings identified during GCP inspections have been:

- Insufficiently detailed documentation of shipping and handling of Investigational Medicinal Products (IMPs) at the investigation site, depending on particular issues of IMP packaging during the trial;
- Inadequate handling and questionable authenticity of essential documents of the clinical trial into the electronic dossier containing essential documents, handled by an external provider contracted by the study's sponsor;
- Improper assessment and reporting of AEs/ARs by the sponsor and investigator, delays in sending investigators data on IMP safety;
- Improper procedure for obtaining the informed consent of the child patient's parents in view of participation in clinical trials;

- deficiencies of the quality management system implemented at investigation centres: lack of Standard Operating Procedures (SOPs) from the minimal SOP list specified in Annex 2 to Scientific Council Decision no. 2/2014, procedures of investigation centres not set up in line with GCP legislation in force;

- deficiencies of source documents: lack of a document which defines source documents specifically used in a study at the investigation centre, incorrectly drafted source documents.

Following GCP inspections, the PID has taken the following measures:

- requested sponsors (CRO/investigators) to adopt preventive measures to avoid repetition of findings of future clinical trials conducted at that organisation/investigator site;

- informed NAMMD's Clinical Trials Service about taking required measures for authorisation of clinical trials conducted by a certain organisation/institution and for invalidation of data collected during the study at an investigation centre, for which the GCP inspection report was concluded as noncompliant with the GCP Guideline and with the clinical trial legislation;

- informed the Medicines and Healthcare products Regulatory Agency (MHRA) about the findings of one of the CROs, whose coordinating headquarters is located in Great Britain.

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 2015, 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, 32 products were proposed for assessment of quality. Sampling has been performed by PID inspectors, in accordance with this department's SOP.

Of the 32 products, 18 were sampled, the rest of the 14 were not found in the distribution network.

The results of laboratory analyses were as follows:

- 14 samples have been declared compliant, the rest of 4 undergo analysis.

In addition to the sampling plan, the following have been sampled in 2015:

- 3 medicinal products sampled on request of the Medicinal Product Quality Control Department, for participation in market surveillance studies, proposed by the OMCL network (Official Medicines Control Laboratories); the 3 samples have been declared noncompliant;
- 5 medicinal products sampled for resolution of complaints on the quality of certain medicinal products; their quality was declared noncompliant;
- 4 medicinal products sampled from distribution units within the programme coordinated by EMA/EDQM for surveillance of centrally authorised medicinal products; testing of these products has been conducted by laboratories of other EU competent authorities; results were compliant.

b) Follow-up inspections of the quality of medicinal products in the distribution network (warehouse, pharmacies, hospital pharmacies, drugstores) conducted by TIU 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, 1451 thematic inspections were conducted in wholesale and retail distribution units.

Inappropriate storage of medicinal products, especially as regards temperature and relative humidity (not all retail distribution units have equipment to ensure correct storage conditions; in some units, although possessing the required tools, storage conditions are not monitored in all the compartments of a pharmacy; likewise, the presence of tools measuring the temperature and relative humidity which were not calibrated or uncertified has been detected, as well as the lack of records/formal records of the conditions for storage of medicinal products);

- Improper storage of expired products;
- Marketing of a product coming from an unauthorised source, not imprinted in Romanian;
- noncompliance with MA provisions in force as regards packaging imprinting;
- units operating in the absence of the pharmacist;
- improper storage spaces of lacking sanitation.

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) Collaboration of TIU with other bodies, in view of resolution of issues related to legislation in the field of medicinal products and/or quality of medicinal products marketed in 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 2015, consisted of joint actions with local special bodies, performed by local inspectors: 8 inspections (4 in Galaţi, 1 in Satu Mare, 3 in Piteşti).

d) Resolution of findings concerning potential quality noncompliances of medicinal products for human use.

16 complaints were received in 2015, of which 2 from territorial inspectors and 14 from consumers/healthcare professionals.

Out of the 16 complaints, 11 had no follow-up, 2 were forwarded to competent authorities, 1 could not be solved on account of lack of relevant information required from the complainant, 2 have been found justified, resulting in recall of the respective medicinal products from the market**.**

In order to solve the complaints, NAMMD inspectors have performed 5 samplings, for laboratory testing within the NAMMD - MPQCD.

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

In 2015, the NAMMD requested recall of 35 medicinal products as follows:

- 14 medicinal products identified with intrinsic quality noncompliances or potentially uncertain;
- 3 medicinal products had packaging inscription nonconformities;
- 18 recalled following MA discontinuation, MA variations or MA transfers.

f) Rapid alert system:

In 2015, 138 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Of these:

- 93 have envisaged products unauthorised for marketing in Romania;
- 7 alerts were forwarded;
- 30 have envisaged products authorised for marketing in Romania, but not imported/not distributed;
- 8 have envisaged products authorised and imported/distributed 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 2015, there was an increase in the number of rapid alerts, as well as an increase in their complexity.

Of the 138 rapid alerts received, 18 referred to medicinal products suspected of falsification/falsified.

In 2015, 1 follow-up alert was issued by the NAMMD for a rapid alert issued in 2014.

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

- 26 reported cases of noncompliance with GMP rules by manufacturers:
* 19 related to active pharmaceutical substances:
* 7 related to medicinal products:
- 7 certificates of compliance with the European Pharmacopoeia suspended/recalled by the EDQM
- 15 case of noncompliance with GDP
- 3 cases of noncompliance with the GMP guideline set up by the competent authority in the USA
- 1 EMA notification

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

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

In 2015, 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 PID 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: physical-chemical tests, pharmacotoxicological tests, micro-biological tests and radio-pharmaceutics tests

Main activities conducted in 2015 were aimed at:

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

In 2015, 59 medicinal products were submitted for MPQCD testing (25 – as part of the Annual Plan for Sampling and Testing, 9 – products subject of quality complaints, 21 – international collaborations (EDQM/FIP), 2 – biological products analysed within official batch release, 2 - medicinal products 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.

For the 59 medicinal products, 283 separate analyses were performed, in line with the techniques described in the European Pharmacopoeia or the manufacturer's pharmaceutical files/analytical protocols forwarded by the EDQM/FIP. The number of these analyses reflects, in an objective manner, laboratory activities conducted within the MPQCD, in 2015, representing the main criteria for quantitative assessment.

In addition to the 283 analyses, there were all the operations and activities (over 800) preceding or accompanying every analysis: equipment checks and calibration (IR; HPLC; UV, analytical balances, pH-metre); assessment of volume measurement systems (droppers, biurets, measuring bottles, graded cylinders); titre tests - volumetric solutions; preparation of solutions and growth media; preparation of chemical, pharmacological, biological, radiopharmaceutical reactives; preparation of pH buffer solutions; 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 SOPs in force and are included, following performance, in work sheets (equipment cards, environment surveillance cards, temperatures, etc.).

Among frequent and complex analytical techniques used in 2015, in the context of medicinal product quality control, the following are worth mentioning: HPLC, pH-metry, Karl Fischer, spectrophotometry (IR, UV-Vis), pharmaco-technical testing (dissolution, mechanical resistance, viability), 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 tablets and capsules), endotoxin determinations (LAL test), radionuclidic purity, radiopharmaceutical activity (isotopes), tests on laboratory animals (pyrogenicity, abnormal toxicity).

a) Products included in the Sampling and Testing Plan

The 25 medicinal products sampled and tested, have generally been compliant with the quality conditions approved and accepted by the NAMMD, a set of observations has been made for 9 of these, related to their name, packaging imprinting, change of leaflet or observations on analytical methods described. These observations have been forwarded as requests to MAHs or manufacturers in view of amendment/supplementation of medicinal product documentation, by

submitting to the NAMMD, as required, applications for approval of variations to the respective MA terms.

b) Medicinal products - complaints

Another class of medicinal products analysed in 2015 consisted of 9 products which have received complaints for quality deficiencies, following complaints received from patients or from some local health units. Of 9 products analysed, one was declared non-compliant (with mechanical impurities into the solution). As regards the other products analysed, quality suspicions invoked by applicants were not confirmed. Extended investigations have been conducted for each medicinal product, considering critical physical-chemical or biological parameters, correlated with the object of complaint.

c) Biological products analysed within batch release procedure

Two batches of anti-hepatitis vaccine – Euvax B – recombinant paediatric vaccine, suspension, imported from Korea, have been analysed (microbiologically and pharmacologically).

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

In 2015 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):

- PTS studies;
- MSS studies;
- CAP studies.

In 2015, the MPQCD has participated in 3 study categories:

- **4 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, for the 4 studies conducted by the MPQCD, the obtained values are above the specified performance criteria, the Z score having a value between ± 0.05 and ± 0.73.

- **Marketing Surveillance Studies (MSS) organised by the EDQM**

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 analytical protocol submitted by the EDQM.

In 2015, in the context of this programme, the MPQCD analysed 7 medicinal products (2 from the EDQM and 5 from the Romanian distribution network, sampled by the PID). The analysed products, with right of circulation within Romania, have been compliant, from a

quality viewpoint, having obtained values similar to those obtained for the 2 medicinal products from the EDQM.

- **CAP studies – centrally authorised medicinal products**

The study, included into the EMA surveillance plan of the European market, consisted of analysis of a product sampled from 3 countries: Austria, Ireland and Luxembourg, compared with a reference product. In accordance with the analytical protocol, each of the 4 medicinal products has been investigated according to 3 parameters, by using the HPLC technique.

e) IFP studies initiated by the International Pharmaceutical Federation (3 studies**)**

Study outcomes are on their way to the FIP.

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

In 2015, 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.

In the context of these activities, assessment of the documentation for active substances (DMF/ASMF) represents the highest average (86 %).

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

In 2015, the BPECD has issued 15 analysis bulletins (ABs), as follows: 4 ABs for two batches of biological medicinal product for official batch release, 5 ABs for four batches of biological medicinal product included in PID's sampling plan and 3 for one batch of biological medicinal product reported, 2 for 2 medicinal products undergoing authorisation procedure and 1 for 1 batch of a biological medicinal product authorised 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 321 marketing intentions accompanied by the appropriate/final batch release certificate for biological products whose official batch release has been performed in the EU.

In 2015, the Laboratory for Physical-Chemical Determinations and Immunochemistry (LPCDI) has continued 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 ELISA method for determination of the "identity" parameter, continuing the streamlining of implementation of the potency assay.

Finalisation of implementation of the ELISA method for determination of the "potency" parameter, by validation of this method, and drafting of the rating note for this parameter are envisaged for year 2016.

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, antihepatitis B vaccine control (including in the sampling plan for 2015, 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 2015, this activity mainly consisted of:

- 178 validations of applications for 92 Type IB and 86 Type II variations;
- 9 invalidations of applications for 1 Type IB variation and 8 Type II variations.

In 2015, the BPECD **assessed the quality documentation for national and imported biological products, submitted for:**

- **National procedure**:

18 reports have been issued for 16 products:

- authorisation through national procedure:
  - 3 reports with request for supplementation of the documentation;
  - 1 report with proposal for authorisation.
- Renewal through national procedure:
  - 10 reports with request for supplementation of the documentation;
  - 4 reports with proposal for approval of MA renewal.

Moreover, in 2015, within the MPQCD, the reports on post-marketing experience were analysed (periodic safety update reports and shortened cumulative report, if needed) and 4 assessment reports were issued, together with the Pharmacovigilance and Risk Management Service.

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

318 notifications/annexes to the applicant were issued after assessment of documentation (notifications accompanied by Annexes were forwarded in electronic format **for Type IA and IB variations/changes of design/MA transfer/Braille imprinting**:

- 21 notifications with annexes with request for supplementation of the documentation for simple Type IA variations;
- 109 notifications (to the National Procedure Department and applicants) with proposal for approval of simple Type IA variations;
- 10 notifications with annexes with request for supplementation of the documentation for Type IA grouped variations;
- 25 notifications with proposal for approval of Type IA grouped variations;
- 25 notifications with annexes with request for supplementation of the documentation for simple Type IB variations;
- 3 notifications with annexes with request for supplementation of the documentation for simple Type IB variations - *worksharing* procedure;
- 50 notifications (to the National Procedure Department and applicants) with proposal for approval of simple Type IB variations;
- 17 notifications (to the National Procedure Department and applicants) with proposal for approval of simple Type IB variations - *worksharing* procedure;
- 6 notifications with annexes with request for supplementation of the documentation for grouped Type IIB variations;
- 1 notification and Annex with request for supplementation of the documentation for grouped Type IIB variations - *worksharing* procedure;

- 15 notifications (to the National Procedure Department and applicants) with proposal for approval of grouped Type IIB variations;
- 9 notifications (to the National Procedure Department and applicants) with proposal for approval of grouped Type IIB variations - *worksharing* procedure;
- 1 notification and Annex with request for supplementation of the documentation for 1 application for change of design;
- 19 notifications with proposal for approval of applications for change of design;
- 7 notifications with proposal for approval of applications for MA transfer.

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

- 26 reports with request for supplementation of the documentation for simple Type II variations;
- 34 reports with proposal for approval of simple Type II variations;
- 5 reports with request for supplementation of the documentation for simple Type II variations - *worksharing* procedure;
- 13 reports with proposal for approval of simple Type II variations - *worksharing* procedure;
- 22 reports with request for supplementation of the documentation for grouped Type II variations;
- 26 reports with proposal for approval of grouped Type II variations;
- 11 reports with request for supplementation of the documentation for grouped Type II variations - *worksharing* procedure;
- 21 reports with proposal for approval of grouped Type II variations - *worksharing* procedure.

2 reports have been issued for 2 Type II variations, following assessment of post-approval documentation.

In 2015 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**

15 reports for MA authorisation/renewal have been issued for 17 products:

- 8 reports with proposal for authorisation;
- 6 reports with proposal for MA renewal;
- 1 report with request for supplementation of the documentation.

The BPECD also assessed support dossiers for variations submitted through Mutual Recognition Procedure, for which 102 Annexes for Type IB variations (annexes forwarded to the European Procedures Department) and 62 assessment reports and their corresponding Annexes for Type II variations (forwarded to the European Procedures Department) have been issued, as follows:

- 4 annexes with request for supplementation of the documentation for simple Type IB variations;
- 33 annexes with proposal for approval of simple Type IB variations;
- 3 annexes with request for supplementation of the documentation for simple Type IB variations - *worksharing* procedure;
- 18 annexes with proposal for approval of simple Type IB variations – *worksharing* procedure;

- 4 annexes with request for supplementation of the documentation for grouped Type IIB variations;
- 35 annexes with proposal for approval of grouped Type IIB variations;
- 5 annexes with proposal for approval of grouped Type IIB variations – *worksharing* procedure;
- 4 reports with request for supplementation of the documentation for simple Type II variations;
- 22 reports with proposal for approval of simple Type II variations;
- 3 reports with proposal for approval of simple Type II variations - *worksharing* procedure;
- 12 reports with request for supplementation of the documentation for grouped Type II variations;
- 11 reports with proposal for approval of grouped Type II variations;
- 4 reports with request for supplementation of the documentation for grouped Type II variations –*worksharing* procedure;
- 6 reports with proposal for approval of grouped Type II variations –*worksharing* procedure.

- **Decentralised procedure**

10 reports have been issued for 7 products pending authorisation:

- 5 assessment reports for authorisation, with request for supplementation;
- 3 reports with request for authorisation;
- 2 report with request for recall.

In 2015, the BPECD also **assessed quality documentation submitted for approval of applications for performance of clinical trials** for 10 investigational biological products; 15 assessment reports have been issued, of which:

- 6 final (positive) reports;
- 8 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 59 changes to MAs in 2015.

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 XVIII - 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 2015 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 Article 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 has constantly pursued accurate information of institutional partner on activities conducted in all domains within its scope.

The NAMMD has published quarterly bilingual newsletters (IB) on its website, mirroring the 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, packaging type, manner of administration etc. In 2015, implementation of individual electronic versions of Summaries of Product Characteristics (SPC), Leaflet and Labelling was continued.

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

- EMA and NAMMD Press releases on medicinal product safety;

- Direct healthcare professional communications;

- Notifications sent to marketing authorisation holders (MAHs) or other stakeholders on issues of interest;

- Information on medicinal products authorised under the centralised procedure;

- SmPCs for medicinal products authorised in Romania through mutual recognition procedure and decentralised procedure;

- SmPCs for medicinal products authorised in Romania through national procedure;
- List of 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 2015, 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", and "Politici de sănătate".

NAMMD representatives made presentations in numerous scientific/professional events organised in Romania and abroad, as shown in section 15.3, **Development of human resource through employee training and retraining.**

8.2. Internal communication

In 2015, 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 2015, 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:

- The internal quality audit programme 2015;
- The BAC activity programme for 2015;
- The BAC training programme for 2015;
- Individual training programmes for 2015.

The process of internal quality audit was conducted in accordance with the internal quality audit program for 2015, approved by the NAMMD President.

In the context of the liability mentioned in Article 827 (2) of Law 95/006 on healthcare reform, republished - Title XVIII – The medicinal product, chapter X - Pharmacovigilance, according to which „ the NAMMD shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter", the **„Report to the European Commission referring to the pharmacovigilance audit conducted on behalf of the National Agency for Medicines and Medical Devices - Romania"** has been forwarded to the European Commission on 10.09.2015.

Other processes conducted at BAC level:

• Provision of consulting on quality management system (QMS) to the various NAMMD organisational structures;

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

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. For DTL and UN, year 2015 has been as busy as the previous years. The largest share in their work was represented by periodic control of medical devices. This activity 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 demand, for a fee, together with the periodic verification report.

Given the fact that the number of medical devices from an order varies from 1 to scores of hospitals, and the limited number of specialists and adequate measuring tools, the activity has thus been conducted by careful scheduling.

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 2015 are as follows:

- Total applications registered: 1,300
- Total periodic check bulletins issued: 1,631
- Total user opinions issued: 259
- Total medical devices checked: 6,779
- Total mobile intervention units checked: 746
- Total test reports issued: 4,521
- Total negative test reports (medical devices rejected): 84

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

2 internal audits have been conducted in 2015 by a NAMMD employee trained for this purpose.

Fees required by the ANMDM - DTL and UN, are in line with provisions of Order of the Minister of Health no.1356/13.11.2013.

In 2015, the institution purchased equipment for measuring and control of medical devices required for performance of the required activity within the test laboratory as well.

At the working point of Bd. N. Titulescu, repairing of the institution's heating installation (older than 30 years) and related sanitation and furnishing of affected spaces, were performed from appropriated funds.

In 2015, in order to ensure optimal working conditions, 12 air conditioning devices and one thermal power station burning gas, made of 2 connected boilers of 150 KW, were purchased and installed.

10.2 Inspection of technical and medical-assessment units

The Medical Technology Assessment Department has performed its activity in line with Title XIX of Law 95/2006, as amended, and with Order of the Minister of Health no. 748/2014 for approval of Methodological norms implementing Title XIX of Law 95/2006, as amended, on approval of medical-technical units, until March 2015. In March 2015, Order of the Minister of Health no. 309/2015 on approval of Methodological rules for implementation of Title XIX of Law 95/2006 on healthcare reform, as well as Law 95/2006, entered into force, thus leading to a new numbering of Titles and Articles (republished in August 2015). Title XX of the republished Law deals with medical devices.

The activity consisted of assessment of the organisation's ability to perform services in the field of medical devices (optics, prosthetics, repairing, maintenance, setup/commissioning) requiring issuance of approvals for operation and their Annexes, for both assessment activities and activities related to import and/or supply of medical devices. Simultaneously, in accordance with provisions of the Order of the Minister of Health ordering the department's activity, changes in the approvals for operation issued prior to entry into force of Order of the Minister of Health no. 748/2014 were performed.

The Department has to cover the activity within the entire country, thus performing the initial assessment of organisations for obtaining an approval, assessment of every two-year surveillance in view of maintenance of the approval, issuance of new approvals for functioning

and their Annexes and required changes, given the deadlines mentioned in the Order of the Minister of Health.

Medical Assessment Unit Technical Department services have been provided as follows:

- Total number of works in 2015: 881,
  of which:
- Number of ongoing evaluation and evaluation-surveillance works in the beginning of the year: 26
- Number of registered new applications for evaluation: 236
- Number of allocated surveillance works: 377
- Number of initial evaluations performed: 180
- Evaluation reports issued: 170
- Number of unfavourable evaluation reports: 4
- Number of surveillance-evaluation works carried out, resulting in reports: 342
- Number of unfavourable surveillance-evaluation reports: 11
- Number of assessment – surveillance reports with domain restraint: 27
- Number of applications cancelled (no dossier submitted for assessment, the organisation is only involved in trading activity, conditions for surveillance not met): 133
- Number of works completed: 655
- Number of assessment and evaluation-surveillance works in progress at the end of the year: 226

Internal training and discussions concerning the situations encountered on the field have taken place on a weekly basis, encouraging the entire staff to take uniform action and to improve performed activities.

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. There were no delays in issuance of approvals/Annexes to approvals for functioning, and required changes were performed in line with legal deadlines.

A first draft for amendment of Order of the Minister of Health no. 309/2015, for harmonisation with republished Law 95/2006, was submitted to the Ministry of Health in October 2015.

11. International relations

In 2015, 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 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 for medicinal products for human use.

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:

- The Committee for Medicinal Products for Human Use - CHMP;

- The Committee for Orphan Medicinal Products - COMP;
- The Committee for Herbal Medicinal Products - HMPC;
- The Paediatric Committee - PDCO;
- The Committee for Advanced Therapies - CAT;
- The CHMP Safety Working Party;
- The Pharmacovigilance Risk Assessment Committee - PRAC;
- The 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" (HMA)

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 2015, NAMMD experts attended meetings of the EU Council and the European Commission (EC), including the Working Group on medicines and medical devices, the Standing Committee, the Pharmaceutical Committee, Notice to Applicants.

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 2015, the Agency granted the drug certificate in WHO format, for a total of 466 Romanian medicinal products producers seeking their authorisation in other countries.

11.5. Participation in activities of the Council of Europe

The representative assigned by the NAMMD, member of the European Pharmacopoeia Commission, attended the PhEur Commission's meetings of 2015, as well as the annual meeting of the secretariats of National Pharmacopoeias of member states of the Convention for issuance of the European Pharmacopoeia.

Also, collaboration with the EDQM for issuance and update of Romanian Standard Terms (translation of the standard terms adopted by the European Pharmacopoeia Commission) was continued.

11.6. Participation in the activities of the 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 2015 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 2015 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 "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 different website sections (Newsletters, Forms, Decisions of the NAMMD Scientific Council, Legislation, 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 2015, 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 1179 medicines, authorised through both European (792) and the national procedure (387);
- Issuing the Marketing Authorisation lists - 238 lists (for 1179 MAs);
- Entry into the 'Registry' database of information on medicinal products authorised - 1179 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 - 1179 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 - 642 notifications;
- Draft of manufacturer undertakings on MA issue and archiving in the authorisation dossier - 383 notifications;
- Entry into the "Registry" Database of the receipt notifications and its archiving in the authorisation dossier - 1214 notifications;
- Participation in meetings of the Marketing Authorisation Commission - 21 meetings;
- Draft of medicinal product certificates in WHO format: 466 certificates;
- Draft of confirmations of products undergoing Marketing Authorisation renewal, stating "selling allowed" – 16 conformations for 36 medicinal products;
- Preparation of minutes for Authorisations for special needs - 28 minutes;
- Draft of Authorisations for special needs – 68 authorisations concerning 72 medicinal products.

13. Ensuring implementation of NAMMD policies and strategies

In 2015, the Department for Policies and Strategies (DPS) conducted the following activities:

- has issued, via interdepartmental collaboration, under coordination of the NAMMD management, *the NAMMD Organisational Strategy for 2015-2017*, contributing to its implementation particularly by:

  - consolidation of the Agency's status of national reference authority in the field of the medicinal product for human use, for the field of activity it fulfils;
  - consolidation of the Agency's role as a trustworthy and expert source for accurate information in the field, provided to healthcare professionals in a timely fashion, through active and priority participation in implementation of the *2013-2015 NAMMD Communication Strategy*, internally and externally, 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 2015:

- 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 viewpoint 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 Article 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 DPS 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 employees 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, the European Commission;

- Periodic 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 appointed as representatives in meetings of scientific committees and working groups at European level;

- 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 2014 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 32 Scientific Council decisions (SCDs), from initial design to their publication on the site (under "Legislation" and "Newsletters") in accordance with interdepartmental SOP (3 regulatory SCDs have not yet been approved through Order of the Minister of Health in 2015);

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

- 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 was continued:

- 4 Newsletter issues in Romanian (4/2014, 1/2015, 2/2015, 3/2015) and
- 4 Newsletter issues in English (3/2014, 4/2014, 1/2015, 2/2015).

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 newsletters;
- Translation of EMA press releases, EMA question and answer documents, direct communications to healthcare professionals, „Lines to take", educational materials etc.
- Monitoring of terminology to ensure compliance with European terminology, especially in relation to the EMA and Eudra websites;
- Advice for translation of SmPC and package leaflets, 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 of 14 Decisions of the European Commission (EC) and 2 CMDh consensus agreements received from the External Registry of EU/RP of Romania to the EU, concerning: medicinal products authorised conditionally, MA maintenance/suspension/withdrawal/amendment following completion of referral procedures on safety, quality and efficacy issues, and their redirection to NAMMD specialists nominated for their implementation in Romania (for the 10 EC decisions and the 2 consensus agreements of the CMDh referring to medicinal products which are authorised in Romania as well);

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 of the appointed 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.

- maintenance and update of the database with contact coordinates for state institutions, European and international organisations, corresponding agencies in the EU, personalities, collaborators etc.

In 2015, the DPS received new attributions. Thus, starting with February, the DPS handled the e-mail address lipsamedicament@anm.ro, established upon request of the Ministry of Health. DPS mission in handling this new task consists in collaboration with other NAMMD departments in order to address patient/physician/pharmacist complaints related to discontinuation in supply of the pharmaceutical market with medicinal products or termination of MAs upon MAH request. Moreover, apart from the feedbacks given to those who have e-mailed the NAMMD, the DPS centralised these findings and permanently informed the NAMMD management on lack of certain medicinal products, in order to determine the Ministry of Health to find appropriate solutions.

In 2015, it was also the DPS who coordinated the participation of NAMMD representatives' lecturers in scientific manifestations of several medical societies:

- The National Congress of Allergy and Clinical Immunology – May 2015, Poiana Braşov
- Multidisciplinary approach of tuberculosis – September 2015, Constanţa
- National Conference of Clinical Hematology and Transfusiology – October 2015, Sinaia
- National Dermatology Congress – October, Bucharest.

As of April 2015, the DPS also administered the NAMMD Facebook page (setup of notifications and NAMMD releases, posting EMA press releases on review of the safety profile of certain products/classes of medicinal products, replying to messages sent via this social network site).

In 2015, the DPS also organised two round tables with patient associations. The first round table was organised on 25.03.2015 and dealt with *The Patient File for spontaneous reporting of adverse reactions to medicinal products*. The second round table took place on 20.05.2015 and referred to the pharmacovigilance activity at EU level, namely to monitoring and review of the safety profile of certain medicinal products/classes of medicinal products. During this manifestation, a representative of the DPS presented a paper on "Implementation of EC decisions or of the agreement by consensus of the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh), referring to medicinal products for human use – one of NAMMD's missions".

Starting with 2015, the NAMMD permanently handled a section in the monthly review "Health policies", by issuing articles related to the NAMMD activity and the related EU legislation, written by representatives of the management and of other structures of the institution, including the DPS. The discussed themes were as follows: parallel export, medical technologies assessment, medicinal product counterfeiting, Patient file for spontaneous reporting of adverse reactions to medicinal products, administration of codeine in children – restricted in the EU, medicinal products for special needs, last instance treatment, control of advertising of medicinal products in various EU member states.

Together with the Legal Department, the DPS contributed to issuance of the Memorandum of agreement signed on 19 August between the NAMMD and the Medicines and Medical Devices Agency of Serbia (ALIMS). According to this Memorandum, a NAMMD detachment, containing one DPS representative, participated, in November 2015, in the 11th symposium organised by ALIMS in Kragujevac, Serbia.

The DPS and the GAD, supporting the EDQM, were involved in organising in Bucharest a training related to the European Pharmacopoeia. In the opening of the training session, the DPS representative presented a paper on „The Romanian Pharmacopoeia: tradition, use and development".

14. NAMMD legal issues

The main tasks of the NAMMD Legal Department (LD) is Agency representation in court, comprising in 2015 of 47 litigations related to insolvency proceedings, complaints, orders of payment, request for annulment, review, contractual liability, evacuation, presidential ordinance.

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.).

It is also worth mentioning that year 2015 saw an increase in the number of litigations in which the authority was involved, particularly following extension of NAMMD attributions in the field of medical technologies and medical devices, through Government Decision (GD) no. 315/2014 on amendment and supplementation of Government Decision no. 734/2010 on organisation and operation of the National Agency for Medicines and Medical Devices and through Government Decision no. 1184/2014 on repeal of the Technical Office for Medical Devices and on amendment of certain regulatory acts, also referring to the latter, to the amendment and supplementation of Government Decision no. 734/2010.

Moreover, more than 20% of the litigations recorded in 2015 were related to the obligation of the National Agency for Medicines and Medical Devices, the National Health Insurance House, the Ministry of Health and the Romanian Government to issue a decision for inclusion of certain medicinal products 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 programs, as well as the means for appeal thereof*, as approved through Government Decision no.720/2008.

In pursuit of its second object, the Legal Department together with professional NAMMD departments have prepared the documentation (draft legislation, substantiation notes, memoranda for approval) to promote through the Ministry of Health as main credit ordinator of certain regulation drafts, as described in section 3 "**Regulation**".

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 of the Minister of Health no. 1031/2011, as well as other activities, such as:

- Endorsement of the legal character of measures to be taken and any documents liable to engage NAMMD patrimonial liability;
- Endorsement of lawful interpretation of legislation applicable to the NAMMD scope;
- Draft of the minutes of the 2 meetings of the NAMMD Administration Council and its 6 rulings;
- Other works related to ensuring secretarial activities of the NAMMD Administration Council;

- Approval of decisions of the NAMMD President;
- Handling of the institution's security activities;
- Participation as members in the commissions for assessment of procedures for acquisition of assets and services;
- participation in annual commissions for patrimony inventory;
- participation in counselling activities upon request of other departments;
- ensurance of the preventive financial control approval for the institution's financial-accounting documents;
- setup of requirements for external travels of NAMMD staff to meetings of EMA scientific committees and working groups or to other working groups of competent authorities in the field of the medicinal product.

Also, together with the other NAMMD departments, the Legal Department has contributed to fighting off counterfeiting of medicines, which is why in 2015 the collaboration initiated with conclusion of the previous Collaboration Protocol with the General Inspectorate of the Romanian Police has been continued 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 specific duties and powers provided by the law.

As far as counterfeiting is concerned, the interinstitutional collaboration according to the Protocol on prevention and control of counterfeiting and traffic of medicinal products signed within the SAVEMED Project is worth mentioning; its main objectives are:

a) prevention and control of marketing, manufacturing, import, export, holding, storage, transit and distribution, as well as use of counterfeit medicinal products;
b) compliance with the legislation in the field of medicinal products;
c) reciprocal information with data and information held by each party, which are useful in view of attaining the specific goals of the other party;
d) presentation of substantiation notes to legal factors with attributions in the field, for improvement of national legislation, inclusion of community regulations into the national legislation, namely signing of international conventions allowing an efficient control of medicinal product falsification;
e) use of information resulting from market studies and analyses performed by special companies for most accurate knowledge on the medicinal product market;
f) surveillance of market operation in view of identifying breaches of national/community and international legislation related to counterfeiting, in order to take the measures imposed by partners, according to each one's abilities and their correlation;
g) reciprocal support for ensurance of medicinal product safety, by cooperation of all stakeholders involved, according to their abilities and duties, to identify falsified medicinal products, their recall and identification of the source of counterfeit.

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 amending Directive 2001/83/EC 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 Emergency Government Ordinance no. 91/2012 amending and supplementing certain healthcare regulations.

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 2015 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. The staff 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 trial assessment 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

Speaking of this aspect of utmost importance for optimal performance of the institution's activity, it is worth mentioning that in 2015, as opposed to previous years, vacant jobs have been opened for recruitment in line with Article 19 of Emergency Government Ordinance no. 83 of 12 December 2014 on remuneration of staff paid from public funds in 2015, as well as other measures related to public expenses, according to which "in 2015 and 2016, 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 in 2015 and 2016…"

However, the aforementioned legislation text implies that vacant jobs had become available, within the limits of the budget of income and expenses approved for wage expenses. Considering this containment, the HRPD couldn't reach its goal consisting of covering the lack of qualified staff within the NAMMD. Moreover, the NAMMD could not fully capitalize the possibility of making available vacant jobs, following the notification received from the Ministry of Health stating that 30 vacant jobs have been erased from the job title list (from 384 jobs, the NAMMD only remained with 354).

15 jobs were occupied, replacing the vacant jobs available in 2015, having a budget approved for wage-related expenses.

In conclusion, shortages of qualified staff could not be covered in 2015 either, as the Agency's specialised departments 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, considered highly competent and exigent, as regards European authorisation procedures (mutual recognition procedure, mutual recognition procedure "repeat use" and the decentralised procedure).

In 2015, many NAMMD employees took part in scientific events and professional training sessions, some with presentations:

- **in Romania**:

- participation with *„Relationship between the NAMMD and the media: between a real partnership and an utopian desideratum"*, at the Summer School for Journalists – Pharmaceutical journalism, second edition, organised by the Romanian College of Pharmacists, Sighişoara, June 2015;
- participation with „*Monitoring of implementation of European Commission decisions and opinions adopted by consensus by the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) – one of the NAMMD missions"*- in the National Toxicology Congress, October 2015;
- participation with „*EU legislation, warrantor of quality, efficacy and safety of vaccines authorised for marketing*" in the meeting of the PSD group of the Senate, for signing the resolution for notification and training related to child vaccination;
- participation with *„Update of the Database of Romanian Standard Terms, ongoing procedure at the NAMMD"*, at the National Pharmacy Conference, November 2015;
- participation in Prizes for Excellence in Health, April 2015;
- participation in the event related to „The Indian economic mission in the pharma field", February 2015;
- participation in the Pharmacists' Gala, awarding excellency in the pharmacist profession, December 2015;
- participation in „*Improvement of communication related to immunisation and public health programmes",* workshop organised by the Romanian Microbiology Society in association with the Association of Medical Journalists, September 2015;
- participation in "*International Health Forum: Changing the paradigm: reducing healthcare costs through patient centred strategies*" - event organised by the Association for Generic Medicine Producers (APMGR) - September 2015;
- participation in "*From Science to Guidance and Practice. Industrial Manufacturing and Control of Pharmaceutical Products*" – symposium organised by O.F. SYSTEMS – Romania, October 2015;

- participation in the international congress *"From Science to Guidance and Practice"*, dedicated to the pharmaceutical field, organised by O.F. Systems and the Teaching Staff Association of the Faculty of Pharmacy of Bucharest, October 2015;
- participation in ***„Solutions and innovations for the pharmaceutical industry",*** **organised by** SARTOROM and the Teaching Staff Association of the Faculty of Pharmacy of Bucharest, October 2015;
- participation in the international exposition for measuring and control devices, ROMCONTROLA 2015, the 22nd edition, March 2015, Bucharest, Romexpo;
- Symposium dedicated to innovations in mass spectrometry (involving the company Shimadzu - Japan) and electron transmission microscopy (involving the JEOL company - Japan), organized by VIOLA-SHIMADZU, Romania, April 2015;
- participation in "*Inorganics standards and reagents in Quality Control for Pharmaceutical labs"* organised by Merck Romania, September 2015;
- participation in *„OCTOBER SARTOFEST"*, organised by TEKNOLEB – Romania, September 2015;
- participation in a pharmacovigilance conference on *"Pharmacovigilance Conference on risk management, electronic reporting, XEVMPD updates, audits, inspections and periodic reporting"*, May 2015;
- participation in the interdisciplinary pharmacy conference, September 2015;
- participation in the Annual National Conference on „*Ensurance of healthcare quality"*, organised by the OAMGMAMR (The Order of Medical Assistants, Bucharest), May 2015;
- participation in the Annual National Conference on „***Medical assistants and midwives – a vital resource ensuring quality in the healthcare field,*** *quality care and patient safety"*, organised by the OAMGMAMR (The Order of Medical Assistants, Bucharest), May 2015.

- **abroad:**

- participation in "*Fundamentals of cGMP Influenza Vaccine Manufacturing"*, organised by the Biomedical Advanced Research and Development Authority (BARDA), USA, at the Golden LEAF Bio-manufacturing Training and Education Center (BTEC), Raleigh, North Carolina, USA, June 2015;
- participation in the assessment process of the national competent authority in Azerbaijan, organised by the World Health Organisation, WHO [*WHO National Regulatory Authority (NRA) assessment in Azerbaijan*], Baku, September 2015;
- The 151th Session of the European Pharmacopoeia Commission - participation as a member of the PhEur Commission, Strasbourg, France, March 2015;
- Annual meeting of Secretaries of National Pharmacopoeia Competent Authorities, Utrecht, Holland, June 2015;
- Meeting of the Communication Professionals Working Party, under the aegis of the Heads of Medicines Agencies, Edinburgh, Great Britain, December 2015;
- participation in the annual meeting of the Official Medicines Control Laboratories network, Bruxelles - Belgium, June 2015;
- participation in the Annual Meeting related to medicinal products authorised through mutual/decentralised procedure (MRP/DCP) and centrally authorised medicinal products (CAPs)", Zagreb, November 2015;
- participation in the *8th EGA Pharmacovigilance Discussion Conference*, London, January 2015;
- participation in the meeting related to *Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) Joint Action*, London, September 2015;

- participation in the Signal Detection Workshop, European Medicines Agency (workshop), London, December 2015;
- participation in the training course for pharmacovigilance inspectors, London, November 2015;
- participation in the meeting related to market surveillance and handling of reports on quality noncompliances found in medicinal products, organised by the EMA, London, October 2015;
- participation in *„Global Learning Opportunities for Vaccine Quality (GLO/VQ) Good Clinical Practices Inspection training course, Cape Town"*, South Africa, July 2015.

- **on-line participation (training):**

- webinar – "*Article 57 Publication Dashboard Report support webinar"* - December 2015;
- webinar – „*Application of fundamental statistical principles in Scientific Advice assessment"* – December 2015;
- webinar EMA "*The revised Risk Management Plan assessment process for new marketing authorisations"* – May 2015;
- webinar *"EMA Pharmacovigilance training"*- April 2015;
- webinar on key elements related to the new process of the PhV referral procedures - April 2015;
- webinar *"How to Prepare a Successful CEP Application"*, organised by the EDQM - November 2015;
- webinar *"Regulatory Awareness Session on ATMPs"*, organised by the EMA, March 2015, via Adobe Connect;
- webinar «*Biologicals of the twenty-PhEur-st century*», organised by the EDQM, March 2015, via global.gotowebinar.com ;
- webinar «*Certification and EDQM inspections*» organised by the EDQM, November 2015, via Adobe Connect com;
- webinar «*Glass containers for pharmaceutical use*», organised by the EDQM, December 2015, via global.gotowebinar.com;
- webinar «*CAT webinar on ATMPs classification*», organised by the EMA, December 2015, via Adobe Connect com.

In 2015 as well, training has been supplemented with **internal training**, as follows:

- trainings on the basis of materials and papers issued by staff with higher education within special departments, in accordance with the training plan;
- work-related trainings of staff with secondary education – handling of specific SOPs;
- training for occupational health and safety, both for staff with higher education and staff with secondary education and auxiliary staff;
- training for emergency situations, for both staff with higher education, staff with secondary education and auxiliary staff;
- specific training for professional development has been performed for inspectors from the headquarters, as follows:

  - 2 GMP training sessions, organised by the representatives of Klarwin and Pall from Romania, related to *Sterilising filtration and single use technologies* (May 2015), namely to *Validation of sterile manufacturing processes* (October 2015);
  - notification on issues discussed in EMA working groups (GMP, GDP, GCP and Pharmacovigilance inspections) – based on reports setup by PID representatives;

- in June, the NAMMD organised a common training session for both inspectors from the headquarters and local inspectors, related to GDP legislation, in the field of inspection techniques and related to other current issues concerning quality surveillance as well.

16. Economic activity

In 2015, the approved expenses budget was worth **21,962,000 million lei.**

Given the lack of specialised staff, the NAMMD has encashed this year, from activities performed for third parties, tariffs and taxes amounting to **70,698,580,03 lei**, sum fully transferred to the state budget.

17. General administration

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

NAMMD public procurement activities were performed within the Public Procurement Service:

- Development of the Annual Public Procurement Plan for 2015;
- Centralisation of purchase requisitions drawn up by the NAMMD organisational structures for set up of the Annual Public Procurement Plan for 2016;
- Setup of *the Annual Public Procurement Report* for transmission to the National Authority for Regulating and Monitoring Public Procurement, until 31 March of each year for the previous year;
- Change and subsequent supplementation of the annual public procurement plan by preparation of files related to the annual public procurement plan;
- Preparation of substantiation notes required in order to obtain funds for investments within the department;
- Performance and finalisation of the public procurement procedure – *Offers for* final stage of the online auction for procurement of *"Measurement and control equipment"* - 9 batches*;*
- Acquisition of investments included in the 2015 Investment List:
  - 11 equipment positions - valuing 636.000 lei;
  - Software / licenses valuing 56.000 lei;
- Resolution of 57 purchase requisitions for public procurement of products/services/ works;
- Preparation and monitoring of the conduct of public procurement contracts for goods/services/works;
- Conduct of purchases by direct purchase from the SEAP catalogue;
- Resolution of 824 purchase requisitions for public procurement of products/services/ works;
- Conduct of 374 purchases by direct purchase from the SEAP catalogue;
- The SAP prepared the following documents:
  - Global budget commitments (ABGs) - 27 pcs.;
  - Individual budgetary commitments (ABIs) related to contracts - 415 pcs;
  - Proposal for engagement of expenses (PACs) - 652 pcs.;
  - Authorisation of payment (OP) - 841 pcs.;
- Ensurance of setup and maintenance within the *public acquisition files* for products, services and papers;
- Fulfilment of obligations relating to advertising (publication in the Public Purchases Electronic System – SEAP – notifications of award);

- Reception and analysis of requisitions for public procurement contracts for goods/services/works;
- Setup of explanatory notes concerning choice of the public purchase procedure;
- 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.

18. Internal audit

Internal public audit, in accordance with Law no. 672/2002 on internal public audit, is defined as a functionally independent and objective activity, which ensures and counsels the top management with regard to the good administration of public incomes and expenditures, and improves the activities of the public entity. It helps the public entity fulfil its objectives through a systematic and methodical approach, which assesses and improves the efficiency and efficacy of the management system, based on management of risk, control and administration processes. Generally speaking, an audit mission can have three main objectives:
- ensurance of compliance of procedures and operations with legal regulations - regularity audit;
- assessment of results concerning the followed objectives and examination of the effective impact – performance audit;
- assessment of management and internal control systems – system audit.

The internal audit structure (BAI) established at NAMMD is subordinated to the NAMMD President. It is an independent, objective assessment purposes faults found in Agency departments, audited and making appropriate recommendations in order to solve these.

The Internal Audit Plan was conducted in 2015; 5 audit missions have been approved:

- ✓ Assessment of conduct of operations of the Prevention and Protection Service for Safety and Health at Work;
- ✓ Assessment of conduct of operations of the General Administration Department;
- ✓ Assessment of conduct of operations of the Department for Assessment of Medical Technologies;
- ✓ Assessment of conduct of operations of the Clinical Trials Service;
- ✓ Assessment of conduct of operations of the Pharmacovigilance and Risk Management Service.

Audit tasks for 2015 have been 100% fulfilled.

Objectives set out in the conducted audit missions 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 legislation in force, compliance with the NAMMD Regulation for Organisation and Operation and implementation of Order no. 400/12.06.2015 on the Code of internal/management control of public institutions.

A mission for counselling the National Procedure Department in its relation with the Economic Department has been performed upon recommendation of the NAMMD president.

19. Challenges

Since 2009, the NAMMD has been faced with increasing difficulties in conduct of its mission, among which the following should be outlined: the difficulty of hiring specialised staff and their retaining in the Agency, lack of the financial capacity (approved income budget much smaller than the Agency's real requirements) to ensure adequate training of staff and lack of laboratory gear imposed by the Official Medicines Control Laboratory (OMCL) and the limited capacities of databases.

20. Priorities/projects for 2016

The NAMMD shall focus on:

- Scientific assessment of the documentation related to the quality, efficacy and safety of medicinal products authorised for marketing;
- Supplementation of Law 95/2006 as regards regulation of advertising of medical devices and subsequent establishment of assessment norms;
- Prevention, within competence limits, of medicinal product and medical device counterfeiting, and timely preparation of the national system for implementation of delegated acts concerning the single code for medicinal products, as approved by the European Commission, in accordance with the European directive on falsified medicinal products;
- Internal reorganization of the Agency by best optimisation of its activity;
- Adequate training of the existing and recently hired specialised staff (please note that a good assessor can be trained in minimum 5 years, assessment expertise being a warrant for marketing of medicinal products corresponding to the current requirements at EU level);
- Continuation and improvement of the activity of assessment of medical technologies;
- Improvement of assessment criteria for medical technologies in view of grant of a score allowing decision on inclusion/non-inclusion into the List of compensated and free medicinal products, approved through Government Decision no. 720/2008. Establishment of general criteria for performance of *„real-life" studies* for new medicinal products, for which recognized authorities in the field of medical technologies in France (HAS), Germany (IQWIG), Great Britain (NICE) have not yet drafted a report;
- Timely preparation of secondary legislation ensuring implementation, at national level, of the Clinical Trial Regulation, once the EMA portal for clinical trials (envisaged for 2018) becomes functional;
- Strengthening of the pharmacovigilance and pharmaceutical inspection activity, in line with the efforts made in this respect at EMA level. Adverse reaction reporting at national level underlies the decision on the opportunity of review of the benefit-risk report for a medicinal product or a class of medicinal products. Pharmaceutical inspection's role is to assess compliance with GMP, GDP, GLP, GALP rules, in the context of the pharmacovigilance activity and, last but not least, in the context of the activity conducted within units where clinical trials are performed;
- Establishing an adequate policy for NAMMD intervention in order to avoid the risk of discontinuation of supply of the pharma market with certain medicinal products. In this respect, the following shall be considered:

  - Finding a reliable solution for fulfilling the obligation related to public service;
  - Increasing the number of medicinal products included in the annual testing plan, for a more efficient surveillance of the quality of medicinal products within the therapeutic circuit;
  - A growing number of unexpected inspections for assessment of compliance with Good Distribution Practice Rules.

- 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.
- Elaboration of a project for security of the NAMMD network, internet access and USB mobile storage devices.

For such projects, the Agency would require:

- more specialists in the field of the medicinal product for human use and medical devices, to ensure that all attributions given to the Agency, according to legal terms, are met;
- more flexibility in hiring;
- a budget allowing direct competition with the other competent authorities in the field of the medicinal product for human use from the EU for all performed activities;
- increasing involvement of the Agency in the decision-making process at European level, by improvement of rapporteur activity, pharmacovigilance assessment, assessment of the authorisation dossier at a high scientific level in case of receiving the status of Reference Member State in the context of the decentralised procedure for marketing authorisation, by involvement in the centralised authorisation procedure, which is performed by using the existing expertise at national level within the EU.

In the medical devices (DM) area: - For 2016, revision is envisaged of assessment of technical and medical units, including assessment questionnaires pursuant to the new Order on enforcement of Law 95/2006, republished, meant to achieve expected technical and quality level of services in medical devices.

Moreover, the NAMMD intends to catalogue the works of the department and to implement a new type of electronic record for surveillance of the market of medical devices.

In the field related to grant of approval for operation and their annexes, in addition to ordinary activities, the 2015 plan envisages conversion of about 977 of approvals for operation, granted based on the Order of the Minister of Health no. 1636/2004 as amended, prior to 1 October 2016.

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

- Participation in training in fields related to public internal audit, organised by the Ministry of Health and/or The Ministry of Finance or other empowered institutions;
- Preparation and publication of procedural guidelines by Ministry of Health experts, concerning public internal audit activities in the healthcare system.
- Preparation and publication of procedural guidelines by Ministry of Health experts, concerning risks in the healthcare system;
- Organising training courses by the Ministry of Health, for access of European funds – implementation methods – procedures - risks.

CONCLUSIONS

The National Agency for Medicines and Medical Devices (NAMMD) is the competent national authority in the field of medicinal products for human use, assessment of medical technologies and medical devices, whose entire activity is conducted for the purposes of promoting and protection of 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. This mission imposes ongoing self-assessment,

permanent adaptation of the strategy proposed for social and economic issues or any other type of challenges which may occur at a given moment and which require sustained efforts.

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: medicinal products for human use, health technologies assessment and medical devices.

In 2015 as well, the NAMMD has proven its ability as an equidistant partner of all representatives of the pharmaceutical industry (manufacturers, MAHs, importers), wholesale distributors, healthcare professionals (physicians and pharmacists). This year as well, communication with all stakeholders interested in the pharma market represented a major, constant preoccupation, aiming, not always successfully, to find viable solutions to enforce a regulatory framework for support of the Ministry of Health's policy of ensuring patient access to prescribed medicinal products, particularly to treatment with new, modern products, available in other EU member states within the health insurance system.

In 2015, the NAMMD current activity represented issuance of 1179 marketing authorisations (MA) (387 MAs granted following the National Marketing Authorisation Procedure and 792 MAs granted in line with the European Marketing Authorisation Procedure).

As opposed to previous years, a decline in the number of MAs released by the NAMMD through NP was detected. This can be explained by lowering the Agency's ability of processing the documentation on account of the reduced number of hired specialists and of staff fluctuation, but also of the relative decrease of the number of applications received, favouring European procedures (EPs), which is absolutely normal, considering the fact that Romania is an EU member state with a pharmaceutical market undergoing the process of harmonisation with European requirements.

In 2015 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 2015, 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, and the other two thirds are generics.

In 2015, the Medical Technology Assessment Department (DETM) recorded 45 applications for assessment of 42 new International Non-proprietary Names (INNs), following an activity whose result, in 2015, was the triple update of Government Decision no. 720 of 9 July 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.

During the last years, the NAMMD focused on implementing a strategy for communication with all stakeholders (including patient organisations, which were and are of particular importance). This is also proven by round tables organised at the NAMMD headquarters, presenting themes of interest for patients, and by participation of NAMMD representatives in these meetings with presentations and answers provided to the questions asked by participants.

Pharmacovigilance work conducted in recent years by the Pharmacovigilance and Risk Management Service has become increasingly complex, in line with the dynamics of specialised European regulations and guidelines. The number of spontaneous adverse reactions (ARs) continues to grow, which speaks for the ever growing awareness of physicians and medical staff in general concerning patient safety. In 2015 as well, the NAMMD has continued to appeal for AR reporting through various means (via the website, during scientific meetings / meetings with associations and organisations of professionals and patients), each time

highlighting the importance of equally empowering professionals and patients, as regards contribution to knowledge of the safety profile of medicinal products via these reports, which, following thorough assessment, can generate new product information.

In 2015 as well, the NAMMD has undoubtedly pursued to ensure surveillance of the safety of human medicinal products already in the therapeutic chain, not only by means of pharmacovigilance, but also by pharmaceutical inspection, by inflicting sanctions upon discovery of noncompliance with regulations in force.

After 2007, the NAMMD has become the national competent authority in the field of medicinal products for human use, leading to:

- 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;
- 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 2015 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.

As of 2014, the NAMMD is the national competent authority in the medical technology assessment field, by transfer of this duty from the Ministry of Health to the NAMMD, as well as of the market surveillance activity. This has led to more responsibilities of the NAMMD – 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.

Special departments of the NAMMD have also benefitted in 2015 from constant and efficient support of all supporting structures (the Legal Department, the Economic Department, the General Administration Department, the Human Resources and Payroll Department, the Information Logistics and Electronic Management of Data Department, the Quality Insurance Bureau, the Internal Audit Bureau, the Prevention and Protection Service for Safety and Health at Work).

In 2015, the Agency faced certain difficulties which have perpetuated over the last years, caused by underfunding, insufficient human resources (although, starting with 2013, there was a certain openness manifested in this respect). Vacant jobs within the institution were made available, provided that they are compliant with the existing income and expense budget approved for the wage expenses sector. This containment has led to partial fulfilment of NAMMD's objective of covering the lack of qualified staff.

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, as well as the possibility of ensuring laboratory and IT gear compliant with the status of national competent

authority within the EU network as regards the medicinal product for human use, medical technologies assessment and medical devices.

The report contains priorities/projects for 2016 to cover all NAMMD fields of activity, all being equally important in order to fulfil Agency attribution at peak standards, able to ensure competitive performance at EU level.