**Activity report**
**of the National Agency for Medicines and Medical Devices**
**2016**

## Introduction

The National Agency for Medicines and Medical Devices, The National Agency for Medicines and Medical Devices (NAMMD) is the national competent authority in the field of medicinal products for human use, medical devices and in the field of medical technology assessment.

NAMMD's mission is to contribute to protecting and promoting public health by:

- Assessment at highest scientific competence level of documentation for authorisation for marketing of high quality, safe and effective medicinal products for human use;
- Assessment of documentation for clinical trial conduct in Romania as well as of their sites;
- Assessment of health technologies based on scientific criteria adopted by legislation in force for inclusion/non-inclusion/maintenance in/exclusion from the List attached to Government Decision 720/2008 on 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 of healthcare professionals, the pharmaceutical industry, of patients and the general public to useful and accurate information on medicinal products for human use authorised for marketing in Romania;
- Development of legal provisions and implementation rules in the fields of medicinal products for human use, medical devices and health technologies, submitted for approval to the minister of health;
- Maintaining 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;
- Development of specific technical procedures on medical devices
- Ensuring institutional administrative effectiveness, efficiency and transparency of practices and procedures in use.

The NAMMD pursues recalibration, through constant self-assessment, in line with current socio-economic problems or any other type of challenge potentially arising at any given time. The process involves steadfast endeavour to meet stakeholders' expectations (healthcare professionals, the pharmaceutical industry, patients, the general public, the media). And it is precisely along these lines that we need to highlight NAMMD further steps in 2016 in its consistent policy as unbiased partner for all representatives of the pharmaceutical industry (manufacturers, marketing authorisation holders - MAHs, importers), wholesalers, healthcare professionals (doctors and pharmacists), key for the Agency's efforts to fulfil its mandate as a guarantor of the quality, efficacy and safety of medicines it authorises for marketing in Romania.

This year as well, communication with all parties involved in the pharmaceutical market has represented a major and constant preoccupation, in the Agency's not always successful attempts, to find effective solutions for establishing a regulatory framework in support of the Ministry of Health policy to insure patient access to prescribed treatments, particularly treatments with new, cutting edge medicinal products available in other European Union (EU) member states within the healthcare insurance system.

A hallmark of the Romanian Agency's work in 2016 has been the high-level visit of Prof. Guido Rasi, Executive Director of the European Medicines Agency (EMA). The purpose of the official visit of the EMA delegation to Romania was to develop the cooperation of the coordinating agency of the European Network with the Ministry of Health (MS) and the NAMMD in the field of human medicines. This has been an opportunity for talks conducted to focus on potential support to the NAMMD for increased administrative capacity, its role at national and European levels, achievements and challenges currently facing the NAMMD. The event has signified recognition of NAMMD efforts to meet requirements imposed on national competent authorities in the field of human medicines, a member of the European network, as well as finding issues able to lead to more active involvement, with the commitment to additional responsibilities in the centralised EMA procedures. This has also been an was evidenced results obtained by te NAMMD specialists work carried out within working groups established at European level, namely preparation of monographs of plant products, assessment of applications for orphan designation, set up of lists of medicinal products meeting criteria for inclusion in the procedure for Single European Assessment of Periodic Safety Reports (PSUSA), development of advanced therapies classification reports etc. Several issues have been identified in debates, among worth emphasising are those relating to the need to:

- Set out complex programs in line with the EMA strategy;
- Increase the number of staff specialised in assessment;
- Adopt measures to ensure staff motivation to be assigned and become involved, respectively, in additional tasks at European level;
- Provide suitable NAMMD budget for purchases related to needs of scientific activity support activities;
- Provide adequate training to existing and newly employed personnel;
- Develop clinical trials;
- Involve patients in the Agency's decision-making process, according to the EMA already implemented model;
- Increasingly involve the NAMMD in achieving the objectives of the Medicines Agency Network's Strategy for the European Union by 2020, "Cooperation for Health Improvement".

In NAMMD view, the visit of the EMA highest level delegation has fully accomplished its envisaged goal to initiate the steps for achievement of objectives to develop the cooperation between the participating authorities: the EMA, Ministry of Health and the NAMMD.

Noteworthy for the year 2016 as well is the appointment of the NAMMD president as a member of a new Heads of Medicines Agencies (HMA) sub-group on early access of patients to new drugs (Timely Access sub-group) and designation of a NMMD representative in the EMA - Big Data Taskforce working group.

The same "2016 Achievements" chapter comprises progress noted in pharmacovigilance. The number of adverse reactions (ADRs) received by the NAMMD together with their processing, has been on steady rise since 2012. Notice must also be made that, from 7 to 11 November 2016, the NAMMD conducted a media campaign for promotion of reporting of suspected drug Ras,

organised in the framework of a European campaign developed under the coordination of the UK Agency. The NAMMD campaign was a component of the Joint Action Project "Strengthening Collaboration for Operational Pharmacovigilance in Europe" (SCOPE), one of the objectives of which was to raise public awareness of national reporting systems for suspected adverse reactions.

The campaign consisted of a video telling the story of a patient experiencing a suspected drug reaction. Details are further given on the prescribed medicinal product, on the occurrence of a suspected adverse reaction, and finally, the manner of reporting and report submission to the competent authority, by patients or health professionals.

Competent authorities rely on suspected RA reporting, awareness of which contributes to the safe administration of marketed medicines. Patients, the general public, were reminded that reporting of adverse reactions has enable such decisions as the following:

- withdrawal from the market of fusafungin-containing sprays used in the treatment of airways infections, because of serious allergic reactions and insufficient evidence of benefit to the patient;
- restricted use of codeine-containing medicines in both cough and colds, as well as in the treatment of pain in children, given the risk of serious side effects, including respiratory disorders;
- suspension of marketing authorisation for oral of ketoconazole containing medicines, as a result of the review of available data leading to the conclusion that their efficacy in treating fungal infections no more outweigh the risk of liver injury.

According to the statement of Dr. Nicolae Fotin, President of the Agency:

"The most important goal of our work is to ensure patients that the medicines they use meet high quality and efficacy standards and can be used safely.

Our campaign seeks to assist the general public, patients and healthcare professionals to report on possible side effects and reassure them on the importance of their reports.

By reporting suspected adverse reactions using the *Form for spontaneous reporting of adverse drug reactions*, they may help improve drug safety."

The impact of the campaign has resulted in a significant feedback on the Agency's Facebook page, from professionals, many patients, various patient associations, the public in general, as well as from the media promoting the NAMMD campaign.

In relation to this topic, it is necessary to underline that staff of the Pharmacovigilance and Risk Management Service (SFMR) team was involved in the development of the European SCOPE project conducted with NAMMD participation, one of the outcomes of which has been availability to professionals/patients of the RA electronic reporting system.

Government Decision no. 315/2014 has redefined main NAMMD responsibilities in the field of human medicines, including joint set up with the Ministry of Health (MS) and the National Health Insurance House (CNAS) of the List of compensated and medicines provided free of charge. As already shown in previous annual reports, since 2014, the NAMMD has also been the competent national authority in health technology assessment (HTA). Further conduct of this activity in 2015 and 2016, actually involving Romanian patients' access to new, modern treatments, has resulted by the end of 2016 in 6 updates of Government Decision no. 720/2008 approving the List of compensated and free medicines. Assessment of medical technologies is a, ongoing process, which has allowed listing of many medicines used in various therapeutic areas. Particularly noteworthy progress in this period has been the treatment of hepatitis C and rare diseases.

| Number of dossiers submitted for HTA | 2014 | 2015 | 2016 |
|---|---|---|---|
| completed | 156 | 40 | 39 |

| | | | |
|---|---|---|---|
| of which scoring for inclusion into the List | 75 | 33 | 34 |

The NAMMD has been actively involved in both proposal 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. Not providing in its initial version of July 2014 for criteria to facilitate unconditional entry into the list of new orphan drugs, subsequent amendments to the order (Order of the Minister of Health no. 387/March 2015, introducing Table no. 5. – Assessment criteria for new INNs approved by the European Medicines Agency as Orphan Medicinal Products) have allowed for other rare diseases drugs to be included in the List. Improving the criteria for assessing medical technologies to be included in the List of compensated and free medicines, as annex to Order of the Minister of Health no. 720/2008, has been a constant concern of NAMMD since 2015. In 2016, new proposals for amendment of the original Order have been made, which will basically involve increased patients' access to drugs, primarily in rare diseases and infectious, transmissible diseases. The aim is to establish general criteria for the development of "real life" studies for new drugs, for which well-known authorities in medical technology assessment, HAS (France), IQWIG (Germany) and NICE (UK) have not yet reported on. The newly proposed criteria will be a complementary manner of assessment of the benefits of treatment and their budgetary impact. In actuality, this new methodology for listing based on the "real life" studies for very new drugs, replaces the scoring system provided for HTA reports from well-established institutions and can help healthcare decision-makers both in choosing a more effective therapeutic strategy for a particular pathology, and in targeting the spending of public funds to the most effective and safe therapeutic scheme. The state does not pay treatment for one year, following which results obtained are assessed and the Health Insurance House or decides on treatment payment, as the case may be.

On countless occasions, NAMMD representatives have emphasised improvement of access to medicines for rare diseases and rare cancers as a concern of the Agency. It is the NAMMD goal to continue to make important, viable proposals in this respect as well. Currently, a national register is being developed jointly with the National Committee for Rare Diseases of comprising patients with rare diseases and their appropriate treatment, with an aim to ascertaining whether the respective medicines are authorised for marketing in Romania. Accurate assessment of the incidence and prevalence of rare diseases in Romania as well as of locally available vs. yet unavailable treatments is an absolute requisite at this stage and therefore accomplishment of this approach will bring forth further progress in this recent European priority area. Achievements in treating rare diseases have been made since May 2014, with the addition into the List annexed to Government Decision no 720/2008 of 17 new orphan drugs addressing rare diseases in Romania. Since then, the Decision has undergone six further amendment and additions, each time resulting in supplementation with new molecules for the treatment of other rare diseases, added into the Compensated and Free Medicines List, following assessment carried out by the specialised NAMMD department. Thus, the next amendment to the Annex List will provide new therapeutic alternatives for the treatment of other rare diseases such as the Gaucher disease, immune

thrombocytopenic purpura, Duchenne muscular dystrophy, hereditary angioedema, idiopathic pulmonary fibrosis.

An additional important NAMMD role is to critically assess and endorse therapeutic protocols developed and/or amended by Ministry of Health specialised committees. In October 2016, the NAMMD concluded assessment of 17 therapeutic protocols corresponding to the medicines entered into the Compensated and Free Medicines List, approved by Government Decision no 720/2008, amended by Government Decisions no. 877/2015 and 552/2016. This ensures access to new therapeutic alternatives in:

- Oncology - for renal neoplasm, colorectal neoplasm, lung cancer, ovarian cancer, leukaemia, multiple myeloma
- Neurology - for multiple sclerosis
- Cardiology - for angina pectoris, prevention of venous thromboembolism and hypercholesterolemia
- Pneumology - for chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis.

The NAMMD has submitted to the Ministry of Health the status of approved protocols, for further initiation of the procedure for approval by order of the minister of health for amendment of Order of the Minister of Health/CNAS no. 1301/2008.

In 2015, the NAMMD undertook a new task, i.e. management, since February, of the lipsamedicament@anm.ro e-mail address, established on request of the Ministry of Health; since September 2016, the Ministry of health has provided technical support required to manage the www.medicamente.lipsa.ro website.

Notice is important to make that the European Medicines Agency's report for 2015 provides an examination of initiatives of the coordinating body of the EU Competent Authorities Network to prevent disruptions in medicinal product supply, currently a significant risk to public health. It is no less true that for the past 10 years, for multiple causes (manufacturing issues, drug pricing policy, parallel export etc.), a tendency has become manifest for global medicines supply discontinuity to become a major problem, with EU at greater risk with potential negative impact on healthcare in Europe. Medicinal product shortages have been a constant topic of press at national, European and international level. Patients should obviously be the first consideration in debates on drug market deficits and their impact on health. Rights of European patients are enshrined in provisions of Article 81 of Directive 2001/83/EC (transposed into Member States' national laws), according to which "The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply Medicinal products so that the needs of patients in the Member State in question are covered". However, there are difficulties in supplying medicines to the public in many EU countries, Romania included, for causes from manufacturing problems, raw material shortages, price reductions as a means diminishing costs, unexpected demand, parallel export, minimum stocks etc.

As in other EU member states, in Romania as well there is a legislative leverage applicable in drug shortage situations allowing for marketing authorisation of certain drugs under special conditions. According to the task the NAMMD undertook in 2013, as defined and implemented by provisions of Order of the Minister of Health no. 85 / 07.02.2013 for approval of the Rules for application of provisions of Article 703(1) and (2) 703 of Law 95/2006 on healthcare reform as republished, concerning medicinal products for special needs, the competent authority issues special needs authorisations (ANS) for various medicines, a small part of which only regarding a

single patient, on specialist prescription, whereas most authorisations concern certain medications addressing categories of patients with various pathologies, on request by Ministry of Health advisory commissions/directorates. Thus, since 2015 and in 2016 as well, special needs authorisations have served as a temporary solution for drug market shortages.

In full agreement with the EMA, the NAMMD advocates effective collaboration among the various stakeholders and regulators, including international collaboration combined with improved business planning in the pharmaceutical industry, and good communication among manufacturers, distributors and authorities as viable solution for this national and global deficit. This is a viewpoint the NAMMD has voiced in working meetings with representatives of MAH/ manufacturers, wholesale distribution, patient associations. The mentioned legislative provisions (Medical Technology Assessment, Special Needs Authorisations), in conjunction with compliance with MAH, importer and wholesaler public service obligation and better information and communication among all parties involved in the pharmaceutical market, are able to reduce and even settle drug shortages.

In recent years, the NAMMD has witnessed significant increase in the value chain of the pharmaceutical industry across all its segments. Bearing in mind that innovation is one of the main goals of the Europe 2020 Strategy, in 2016 as well, the NAMMD has also considered and has maintained that the pharmaceutical industry as a provider of high-end technology and knowledge should play an important role as support to relevant authorities involved in promoting health policies appropriate to an EU Member State that truly serves the patient.

In 2016, work of the Pharmaceutical Inspection Department (DIF) was audited in the frame of the Heads of Medicines Agencies / EMA Joint Audit Program (JAP); the audit took place from 17 to 21 October 2016, at the same time with the planned audit of the competent authority of Canada, as a state of the Mutual Recognition Arrangement (MRA) EU agreement, for assessment of legislation implemented by Romania and the NAMMD GMP inspection system, as a competent authority in the field of the medicinal products for human use. Two auditors representing the US Competent Authority (FDA) have also attended as observers, whose goal has been to pursue the specific objectives set for the pharmaceutical sector in the framework of the Transatlantic Trade and Investment Partnership. The assessment aimed to establish the equivalence between GMP national and Canadian/ US legislation together with inspection systems in this field, with a view to mutual recognition of GMP inspections. The audit final conclusions have been positive on NAMMD-DIF compliance with JAP audit requirements in terms of legislation, quality management system and GMP inspection techniques. The report has also highlighted aspects of DIF work that require improvement.

The HMA / EMA JAP Audit also aimed at the work of the Department of Drug Quality Control (DECCM). The preparation of this audit involved the preparation of questionnaires, materials, presentations, situations. DECCM specialists have successfully collaborated with the audit team through interviews, clarifications, document presentations, but also by reviewing the audit report and developing proposals to solve identified nonconformities.

The Audit of the European Directorate for Product Quality (EDQM), carried out in the frame of the EDQM Mutual Joint Audits (MJA) has been the main 2016 event for the NAMMD Medicinal Product Quality Control Department (DECCM). This audit took place from November 15 to 17, 2016, and involved an important effort in preparing questionnaires, materials, presentations, and reports by DECCM staff. During the audit, DECCM personnel provided the audit team with all the necessary information and documents, subsequently involving and reviewing the audit report and formulating proposals for resolution of nonconformities found. It is

worth noting that, in the preparation of the EDQM audit in November 2016, works were carried out to renovate some laboratories, as well as to develop programmes, transfers and staff training. The same preparations and in result of reorganisation of the control departments, the Sample Collection Compartment has also been rearranged and relocated to a new area, appropriately furnished for specialised activities, specific test sample reception and verification, recording and storage in adequate conditions. The opportunity for this relocation was confirmed by EDQM auditors' positive audit feedback. It is very important to note that the 31 nonconformities finally reported by the EDQM audit team (of which 10 were QMS-related and 21 were technical) have been classified typical for MJAs performed within the OMCL official laboratory control network; in addition, the number of findings also being at averages identified in network audits. The audit team's report has highlighted the good quality of work performed in the laboratories. Moreover, the audit team has drawn attention to the particular potential of the OMCL in Romania, considering the qualified laboratory staff and the constantly improving facilities and top management during the audit. The audit team also expressed its opinion that combination and harmonisation of standard operating procedures (by simplifying the quality system after merger of the two former control departments, the DCCM and the Department for Evaluation and Control of Biological products - DECPB), constant investment in staff training and update of laboratory equipment, the OMCL in Romania represents a valuable contribution to the European network of official control laboratories.

The NAMMD is fully aware of the importance of efficient communication and sharing of information within the European network in the field, an integral part of priorities of the Multiannual Work Plan (MAWP) of the Heads of Medicines Agencies (HMA) drafted following completion of the HMA/EMA High Level Strategy to 2020 (HMA-EMA HLS).

The Working Group of Communication Professionals (WGCP) coordinated by the HMA was established in 2008, mainly for the purpose of building a network and sharing of best practices among communication professionals within national competent authorities (NCA) and the European Medicines Agency (EMA). The group is composed of representatives of all Member States (including the NAMMD) and, according to the MAWP, one of its tasks is to develop a method for information exchange on important issues throughout the entire communication network. The MAWP comprises five strategic communication actions to be carried out by the WGCP (activities 48, 49, 50, 51, 52), an action to be undertaken together with the HMA Management Group (47) and an additional action (8) to be carried out jointly with the HMA Timely Access sub-group.

HMA MAWP communication activities to be developed by the HMA WGCP and Timely Access sub-group became a priority in December 2016, as shown in the following table:

| Priority | Action | Lead |
|---|---|---|
| International collaboration | 8. HMA will work in the following years to explore how to improve the involvement of patients/users, Health Care professionals and academic community in those regulatory activities which have an impact on them or on which they can influence.<br>Moreover, the collaboration with other key bodies (such as HTAs, pricing and reimbursement authorities and payers) | WGCP for patient input<br><br>HMA Timely Access subgroup for work with HTA, payers and P&R authorities HCP and academic community |

| | | |
|---|---|---|
| | has to be reinforced to enable appropriate decision making and exchange of information to allow optimal market access. | |
| Optimisation of the regulatory operations: | 47. Increase transparency and proactivity in communicating the remit of HMA and NCAs in relation to our role in protecting public and animal health whilst ensuring a joined-up communications approach with EMA | HMA Management Group<br>HMA WGCP |
| Optimisation of the regulatory operations: | 48. Develop a strategic narrative for the work of HMA, its alignments with the objectives of the HLS and its practical implementation through the MAWP as part of a five-year communication plan. Enhance regular communication from HMA to stakeholders, including exploring new ways to communicate as appropriate. | HMA WGCP |
| Optimisation of the regulatory operations: | 49. Evaluate current mechanisms for sharing information between national communication teams and strengthen if necessary. | HMA WGCP |
| Optimisation of the regulatory operations: | 51. Map key stakeholders at EU level. Agree key strategic areas of interactions. Plan for proactive engagement with such stakeholders. Agree plan of action with such stakeholders.<br>National competent authorities should strengthen national level links to agencies including pricing and reimbursement and health technology assessment and to patients and the public. | HMA WGCP |
| Optimisation of the regulatory operations: | 52. Develop more streamlined mechanisms to obtain regular feedback from key stakeholders on the operation of HMA activities and the quality of the output. | HMA WGCP |
| Support for better use of medicines | 50. Improved communication tools for patients and HCP's to improve use of medicines including embracing new approaches to optimise communication in | HMA WGCP |

| | | |
|---|---|---|
| | different media mediums, tailoring guidance on prescriptions and improving information to patients. | |

**NAMMD ACTIVITIES IN 2016**

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

No meetings of the NAMMD Scientific Council have taken place in 2016.

**2. Activity of the NAMMD Administration Council (AC)**

In 2016, the Administration Council (AC) adopted 2 Administration Council Decisions (ACDs), leading to adoption of 4 Decisions. As regards the areas concerned, respective 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) 3 law/ordinance/government decision drafts;

a) the draft of emergency ordinance on establishment of reorganisation measures, as well as on amendment of certain regulatory acts;

b) the draft of emergency ordinance on amendment of Law 95/2006 on healthcare reform, republished as amended;

c) the draft of Decision on amendment of Decision no. 720/2008 on approval of the List of International Non-proprietary Names of on-prescription medicinal products as provided to insurants, irrespective of personal contribution, in the frame of the health insurance system, as well as of International Non-proprietary Names of medicinal products provided in national health insurance programs;

II) 9 Minister of Health Order drafts:

a) the draft of Order on approval of the Rules for authorisation of sites for conduct of clinical trials on medicinal product for human use;

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

proprietary Names of medicinal products provided in national health insurance programmes, as well as the means for appeal thereof;

c) the draft of Order on setup of the commission for resolution of complaints related to Decisions for 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;

d) the draft for amendment of Order of the Minister of Public Health and of the National Health Insurance House President no. 1301/500/2008 on approval of therapeutic protocols on prescription of medicinal products with International Non-proprietary Names included 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;

e) the draft of Order on amendment of Order of the Minister of Health 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;

f) the draft of Order on amendment of Order no. 502/2013 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 wholesalers/importers/manufacturers;

g) the draft of Order on amendment of Annex 1 to Order of the Minister of Public Health and of the NHIH President no. 1301/500/2008 on approval of therapeutic protocols for prescription of medicinal products with International Non-proprietary Names specified 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;

h) the draft of Order on setup of the NAMMD Scientific Council;

i) the draft of Order on setup of the NAMMD Administration Council.

## 4. Activity of NAMMD commissions

### 4.1. NAMMD Marketing authorisation commissions

In 2016, within meetings of the Commission for Marketing Authorisation, established through Decision of the NAMMD Administration Council, as established through President decision, discussion of assessment reports was continued, for grant of the Agency's opinion concerning marketing authorisation of various medicinal products applied for in this respect, as well as other issues related to marketing authorisation of medicinal products for human use.

In 2016, 23 working sessions took place, separated by authorisation procedure type (12 for National procedure - NP and 11 for European procedures - EPs).

In 2016, work of the Commission for Marketing Authorisation (CMA) mainly consisted of:

- for national procedure: 12 meetings, involving discussion of 524 dossiers, of which 36 for authorisation, 409 for MA renewal, 56 for MA discontinuation/cancellation and 23 for grant of parallel import authorisation.
- for European procedures: 11 meetings, involving discussion of 652 dossiers, of which:

- 331 for medicines authorised through DCP, of which 3 with Romania as a reference member state - 9 authorised through MRP, of which 2 with Romania as a reference member state
- 35 authorised through MRP - repeat use,
- 277 for MA renewal, of which 4 for medicinal products, 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 structure approved through President Decision, the Commission continued its activity in 2016 as well. The Commission reviews inspection reports issued by Agency inspectors, concerning the manner of compliance by inspected sites 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 2016, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 152 inspection reports, of which:

- 33 inspection reports on compliance with Good Manufacturing Practice rules;
- 5 inspection reports on compliance with Good Manufacturing Practice rules at the importer's site;
- 97 inspection reports on compliance with Good Distribution Practice rules (of which 37 for unexpected inspections);
- 12 inspection report on compliance with Good Clinical Practice rules (of which 9 for unplanned inspections);
- 3 inspection reports on compliance with Good Laboratory Practice rules;
- 1 inspection report on compliance with Good Analytical Laboratory Practice rules;
- 1 inspection report on MAH compliance with respective obligations 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 2016, there were no requests for summons of the Commission.

### 4.4 Commission for management of crisis situations caused by medicinal product quality, safety and/or efficacy concerns

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 2016, the Commission was summoned in May, imposed by certain media information on the quality of medicinal products included in the therapeutic circuit in Romania. The commission agreed upon issuing a press release specifying the NAMMD activity as a national competent authority in the field of the medicinal product for human use, a member of the network of related authorities in the EU, under the coordination of the European Medicines Agency. It was deemed important to highlight that the NAMMD has a balanced policy as regards original versus generic medicinal products. The same assessment standards for the authorisation dossier are applied with the same strictness to both original (innovative, reference medicinal products) and generic medicinal products.

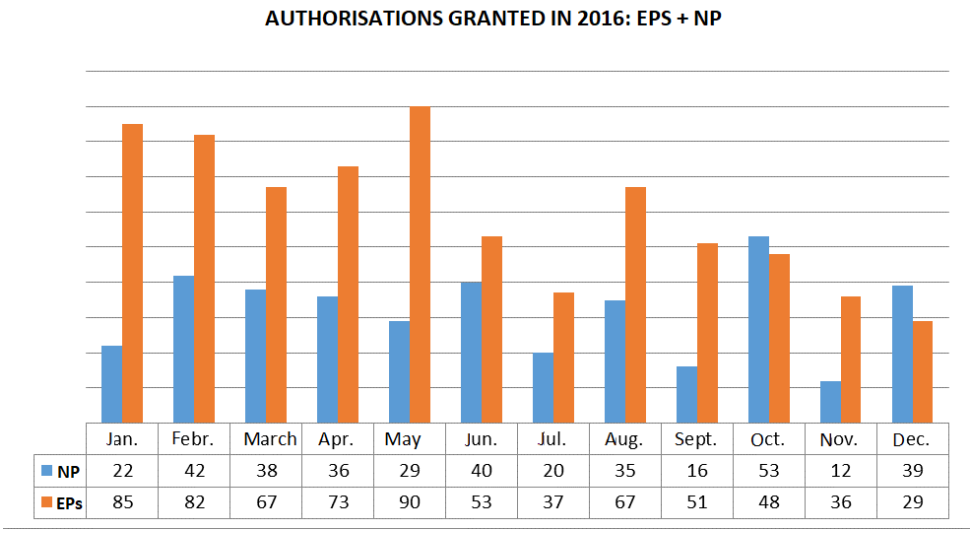
The same balanced policy characterises the NAMMD in relation with internal/external manufacturers from the EU or outside the EU.

## 5. Marketing authorisation and related activities

In 2016, 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 commendably performed, as imposed by high complexity standards, established through an increasingly severe European Union legislation in the field of the medicinal product for human use. 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 2016, 1100 marketing authorisations (MAs) were issued for medicinal products for human use authorised through European procedures: 718 through European procedures (65.27%), (343 through decentralised procedure, 5 through Mutual Recognition Procedure, 49 through repeat-use mutual recognition procedure and 382 (34.7%) through national procedure (33 new APPs and 349 MA renewals).




| | Jan. | Febr. | March | Apr. | May | Jun. | Jul. | Aug. | Sept. | Oct. | Nov. | Dec. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NP | 22 | 42 | 38 | 36 | 29 | 40 | 20 | 35 | 16 | 53 | 12 | 39 |
| EPs | 85 | 82 | 67 | 73 | 90 | 53 | 37 | 67 | 51 | 48 | 36 | 29 |

**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:

5806 Type I variations
432 Type II variations
63 MA transfers
156 changes of packaging design and imprinting
1336 clinical variations

**5.2.2.** In 2016, as regards **post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures**, the NAMMD approved:

2084 Type IA variations for Romania (as a CMS);
1795 Type IB variations for Romania (as a CMS);
455 Type II variations for Romania (as a CMS);
59 MA transfers for Romania (as a RMS);
40 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 clinical trial sites**

In 2016, 229 applications were submitted for authorisation of clinical trials, more than in 2015 (220). Most of these are Phase III clinical trial applications (142), 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 (61); these are exploratory studies concerning the most effective dose for medicinal products with proven safety and tolerability, as well as 16 applications for approval of Phase IV clinical trials, post-authorisation.

In Romania, there are few applications for conduct of Phase I clinical trials (10 applications in 2016, as compared to 15 in 2015), which require special conditions.

In 2016, the NAMMD granted 200 authorisations for conduct of clinical trials.

Moreover, 23 applications for conduct of observational clinical trials were received; acknowledgement letters have been issued for 19 observational studies.

In 2016, the Clinical Trial Service approved 576 substantial amendments.

As regards authorisation of clinical trial sites, there were 181 authorisations issued and 8 applications withdrawn, assessment still underway for 9 dossiers by the end of 2016.

### 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 NAMMD organisation and operation, which redefines main NAMMD responsibilities.

Applications submitted in 2016: 81 applications for 47 new International Non-proprietary Names (INNs), of which 16 for **orphan medicinal products**.

Work in 2016 of the Department for Health Technology Assessment consisted of issue of decisions on unconditional inclusion, conditional inclusion requiring MAH signing of a cost-volume / cost-volume-outcome contract with the National Health Insurance House, 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 status of decisions issued, grouped by speciality:

| Speciality | Unconditional | Conditional | Non-inclusion | Change |
|---|---|---|---|---|
| Oncology | 3 INNs | 11 INNs | 2 INNs | 16 INNs |
| Internal diseases | | | 1 INN | |
| Diabetes and metabolic diseases | 3 INNs | 1 INN | 1 INN | |
| Endocrinology | 2 INNs | | | |
| Infectious diseases | 1 INN | 6 INNs | | |
| Gastroenterology | | 2 INNs | 2 INNs | |
| Ophthalmology | 1 INN | | | |
| Pneumology | 4 INNs | 1 INN | | |
| Rheumatology | 2 INNs | | 1 INN | |
| Dermatology | | 1 INN | | |
| Neurology | 2 INNs | | 1 INN | 5 INNs |
| Haematology-oncology | 2 INNs | | | 1 INN |
| Allergology | 1 INN | | | |
| **Total** | **21 INNs** | **22 INNs** | **8 INNs** | **22 INNs** |

The table below indicates the status of decisions issued, by speciality, for orphan medicinal products:

| Speciality | Unconditional | Conditional |
|---|---|---|
| Allergology | 1 INN | |
| Infectious diseases | 1 INN | |
| Endocrinology | 2 INNs | |
| Haematology-oncology | 2 INNs | |
| Neurology, paediatrics | 2 INNs | |
| Ophthalmology | 1 INN | |
| Oncology | 2 INNs | 2 INNs |
| Pneumology | 2 INNs | |
| **Total** | **13 INNs** | **2 INNs** |

Following assessment of medical technologies, Government Decision no. 720/2008 was amended in 2016: Government Decision no. 522 of 27 July 2016, published in the Official Gazette of Romania, no. 607 of 9 August 2016, also introducing 3 orphan INNs.

Moreover, in 2016, the HTA department participated in assessment of therapeutic protocols published in Order no. 1463/1036/2016 of 16 December 2016 issued by the Minister of Health and by the NHIH President, on amendment of Annex 1 to Order no. 1301/500/2008 of the Minister of Health and of the National Health Insurance House on approval of therapeutic protocols for prescription of medicinal products with International Non-proprietary Names specified 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, irrespective of personal contribution, in the frame of the health insurance system, as approved by Government Decision no. 720/2008.

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

In 2016, the same importance has been given to supervision and control of advertising of medicinal products for human use, just as during previous years, starting with 2010.

In this context, 541 new advertising visas, 525 extensions of advertising visas and 199 approvals of advertising materials were issued.

Year 2015 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:

„ (3) *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.",*

*(4)* The obligation under (3) also lies with recipients of sponsoring activities, i.e. physicians, nurses, professional organisations, patient organisations, and any other type of organisations *conducting healthcare activities, medical or pharmaceutical care".*

The NAMMD obligation of also mentioned:

„ (6) Information notified in templates specified in par. (5) is posted in the second term of the year for the previous year, on the NAMMD, the reporting entity's and their recipient's website, as appropriate.

Therefore, in 2016, the NAMMD posted the register resulted from receipt of 24975 sponsorship forms from recipients (of which 1648 on paper and 23327 online) and 125 from sponsors.

An additional important activity, conducted by a group appointed in this respect, was assessment of 215 dossiers on consultation with target patient groups for the package leaflet for medicinal products for human use, of which 19 have been approved within the authorisation procedure, 152 have been approved within the procedure for approval of variations to MA terms and 44 represented dossier supplementation, in accordance with NAMMD requests.

### 5.6. Pharmacovigilance

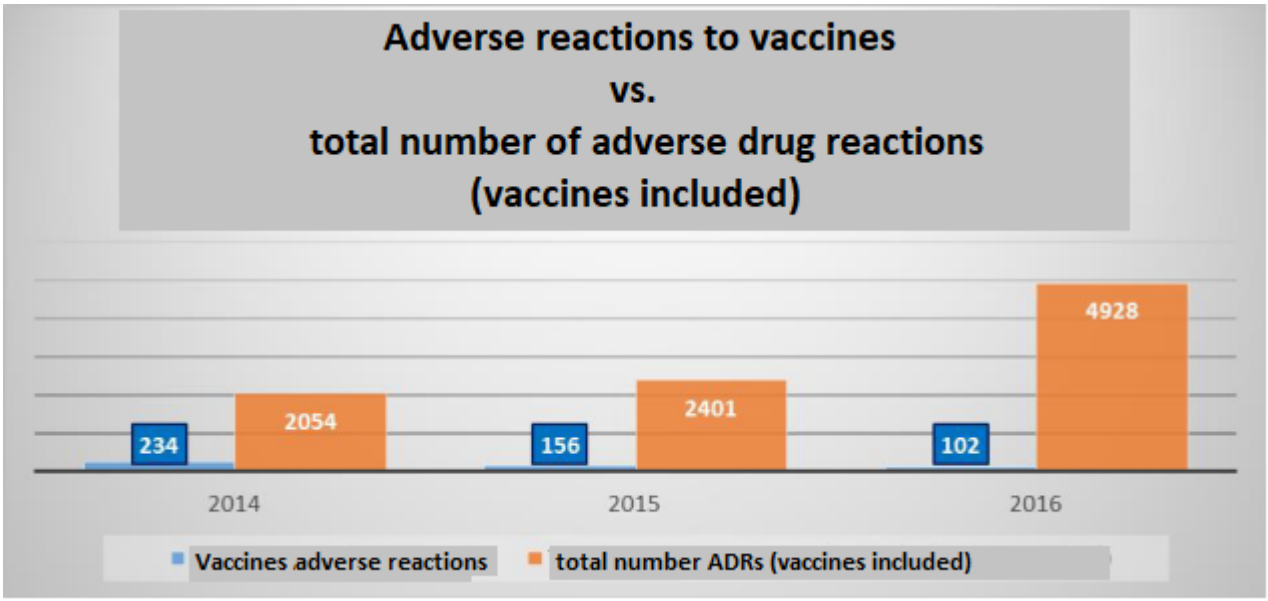
Via its pharmacovigilance system, the NAMMD receives adverse reactions directly from healthcare professionals and patients, which it registers, collects, validates, medically assesses and forwards to the Eudravigilance (the European database for adverse reactions), to the World Health Organisation Database and to the Marketing Authorisation Holders (MAHs) database.

Adverse reactions can also be reported by the MAH. Adverse reactions received by the MAH are subsequently forwarded to the NAMMD, electronically. MAH electronically submitted adverse reactions are entered into the European adverse reaction database.

All EU member states, Romania included, forward suspected adverse reactions reported nationally to the Eudravigilance European database. The collection of adverse reactions from the entire EU territory in a single point facilitates monitoring of medicinal product safety profile at European level, making possible an early detection of potential safety signals.

The number of adverse reactions received by the NAMMD and their processing witnessed a constant increase, particularly as of 2012, on entry into force of the new pharmacovigilance legislation; the specific operational procedures were amended in order to meet the new requirements.

Thus, in 2008, the Agency received and registered 363 spontaneous reports papers, forwarded by healthcare professionals, patients and MAHs. In 2015, the NAMMD received 2401 spontaneous reports forms and 4928 in 2016, of which 2609 SARs (serious adverse reactions).




**Adverse reactions to vaccines**

As of 2012, a collaboration protocol has been in force between the National Agency for Medicines and Medical Devices /The Pharmacovigilance and Risk Management Service and the National Institute for Public Health/The National Centre for Surveillance and Control of Communicable Diseases (INSP/CNSCBT), whose objective is parties' collaboration for mutual notification on post-immunisation adverse reactions reported to the two institutions. The NAMMD received 234 adverse reaction papers for vaccines in 2014, 156 in 2015 and 103 in 2016. Thus, adverse reactions to vaccines represented 11.4% in 2014, 6.5% in 2015 and 2% in 2016 out of the total number of adverse reactions received.

**Directly submitted adverse reactions reports by healthcare professionals and patients**

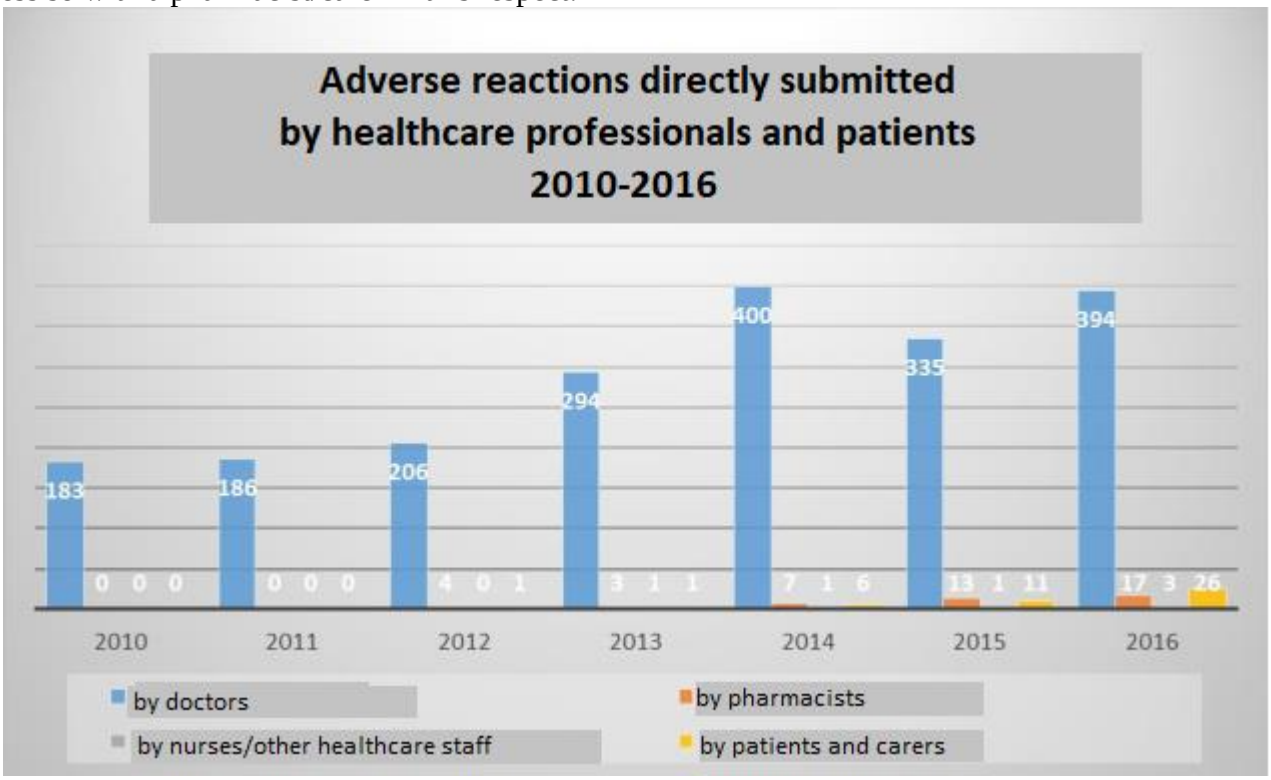
Healthcare professionals and patients submit suspected adverse reaction reports to the NAMMD, using the templates available on the NAMMD website (www.anm.ro) under the section *Medicines for human use/Forward an adverse reaction*. These are filled in and forwarded via regular post, fax, e-mail. In order to facilitate reporting of suspected adverse reactions, the NAMMD has issued an electronic reporting form for professionals and patients, available on the NAMMD website (www.anm.ro) under section *Medicines for human use/Forward an adverse reaction*.

Pharmacovigilance activity mainly aims to reduce the number of adverse reactions and prevent their occurrence by better medicinal product data collection and their safety, through rapid and consistent assessment of issues related to medicinal product safety, through efficient regulatory actions taken in order to assure medicinal product safety and efficacy, through patient involvement and active participation and facilitation of adverse reaction reporting, through increase in the level of transparency and assuring optimal communication.

Adverse reaction reporting by physicians directly to the NAMMD had the best evolution (in the healthcare professionals category), reaching 335 reported adverse reactions in 2015 and 394 in 2016.

The number of adverse reactions reported by pharmacists directly to the NAMMD has increased from 7 adverse reactions reported in 2014 to 17 adverse reactions in 2016.

Patients reported 6 adverse reactions in 2014, 11 adverse reactions in 2015 and 26 adverse reactions in 2016. These numbers show that, for the time being, safety signals sent directly to the NAMMD by patients are still very few, since patients prefer communication with their physician and less so with a pharmacist/carer in this respect.




The activity of the Pharmacovigilance and Risk Management Service in 2016 was as follows:

**a) Management of safety data issued from spontaneous reporting:**

- local management and archiving of spontaneous adverse reaction reports from all sources – 4928 ARs (except for duplicates encountered in literature);
- validations/confirmations of adverse reaction (AR) reporting to EudraVigilance – 6382 confirmations;
- retransmission to EMA of SAR reports from the MAH in the Inbox of NAMMD's EV– 2609 serious adverse reactions;
- electronic transmission to EMA and the MAH of SAR and NSAR (non-serious adverse reactions) reports received by the NAMMD on paper, via fax, post, e-mail – 256 SAR reports, 215 NSAR reports, Total = 471 adverse reaction reports.
- local management and archiving of spontaneous adverse reactions reports from all sources – 4928 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 – 6918 ARs;
- monthly transmission of post-vaccine undesirable adverse reactions (PVUARs) received directly from the National Institute for Surveillance and Control of Infectious Diseases, in accordance with the protocol – 63 ARs;

- notification letters to the College of Physicians concerning spontaneous reporting of adverse reactions by physicians for 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, for grant of Continuing Pharmaceutical Education (CPE) credits – 3;
- notification letters 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 – 25;
- information letters to physicians concerning grant of Continuing Medical Education (CME) credits – 1165;
- letters of confirmation of receipt of AR reporting forms from physicians within the network – 363;
- letters of confirmation of receipt of AR reporting forms from pharmacists within the network – 7;
- responses to MAH requests concerning adverse reactions reported to the NAMMD involving medicinal products authorised in Romania – 70;
- responses to MAH requests concerning adverse reactions reported to the NAMMD (in E2B format, using the Eudravigilance system) – 194;
- request for additional information on adverse reactions to rapporteurs (physicians/pharmacists/consumers) - 70.

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

- EMA press releases translated and posted on the website – 45 documents;
- 32 Direct Healthcare Professional Communications (DHPCs) related to safety concerns raised in relation with medicinal products (translated/posted on the website);
- transmission of 28 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) – 27 documents.

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

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

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

- 838 assessment reports of the pharmacovigilance documentation (the summary of the pharmacovigilance system, the Risk Management Plan – RMP) for grant /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);

– 268 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) for MA renewal for medicinal products authorised through DCP/MRP/ repeat-use MRP/renewal (R) (Romania as a concerned member state);

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

– 3 assessment reports of the pharmacovigilance documentation – the Periodic Safety Update Report (PSUR) (module 5)/addendum to clinical overview (module 2.5), for MA renewal for medicinal products authorised through NP;

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

- 143 educational materials.

**f) Assessment of applications concerning variations to marketing authorisation terms as regards the pharmacovigilance system for medicinal products authorised through national procedure (NP) and European procedures (EPs)**

– Type IA variations - summary of the pharmacovigilance system: 92;
– Type IB and II variations (RMP) authorised through NP or through work-sharing procedure (work-sharing – WS) – 33;
– Type IB and II variations for medicinal products authorised through European procedure – 131.

**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 variations to MA terms for already authorised medicinal products, inclusion of variations to issued MAs, highlighting of medicinal products undergoing MA renewal procedure, MA withdrawal/discontinuation decisions.**

In 2016, 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) assured:

a) **Maintenance of the database of authorised medicinal products:**

- 1178 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.)
- Issue of 361 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);
- 1083 notifications for MA withdrawal/discontinuation sent to the Ministry of Health, the National Health Insurance House, the MAH;
- Handling and presentation of the status of medicinal products/MAs recorded in the Index of medicinal products for human use, valid for the current year, to the Economic Department, concerning the tax of maintenance in and update of the Index";
- Inclusion of "blanks" for medicinal products submitted for MA renewal: 286;
- Inclusion of 662 medicinal products into the database of the Index, as "temporary marketing discontinuation";
- Inclusion of 702 medicinal products with discontinued/suspended MA (113 – MA discontinuation and 589 – MA suspension) into the database of the Index and registry;
- Assessment of the National Brochure of the prices of medicinal products (24 times) authorised for marketing in Romania (quarterly and whenever required by the Ministry of Health) in terms of CIM codes and technical identification data;
- Transmission of the Index of Medicinal Products to the NHIH in the format agreed (4 times) for reception of SIIS (single integrated information system), quarterly and whenever required by the NHIH, and analysis of non-compliances between SIIS and CANAMED (the national price catalogue), forwarded to the NHIH quarterly and whenever required.

Other activities related to the Index of Medicinal Products:
- setup of an .xls database, for 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;
- entry of data on temporary/permanent marketing discontinuation into the „SUNSET CLAUSE" database: 662 medicinal products;
- entry into the "SUNSET CLAUSE" database of information concerning recall of MAs/renewal procedure for 570 medicinal products;
- entry into the "SUNSET CLAUSE" database of information concerning medicinal products suspended through President Decision: 589 medicinal products;
- entry into the "Notifications – temporary marketing discontinuation" of the NAMMD website: 253 medicinal products;
- entry of information on permanent marketing discontinuation on the NAMMD server under the „SUNSET CLAUSE" section: 507 medicinal products.

As regards "*parallel import*" activities, 25 parallel import authorisations (PIAs) were granted (assessment of submitted documentation, of supplementations submitted by applicants and setup of PIAs and their Annexes).

*"Parallel export"* activities consisted of:

- 574 applications received and solved as parallel export papers have been forwarded to 20 European agencies. 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 2016, the Pharmaceutical Inspection Department continued activities mentioned in 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 deadlines stipulated by the law. Types of inspections in 2016:

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

**- 36 GMP inspections for grant of manufacturing/import/certification authorisation**

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

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

No follow-up inspections were conducted in 2016 at the sites of manufacturers/importers.

- 11 certification inspections for GMP compliance of pharmaceutical companies from third countries (India, Egypt, Belarus). The 11 inspections concluded with 7 GMP certificates for finished medicinal products, of which 1 for active pharmaceutical substances.

One NAMMD inspector and EDQM inspectors have participated in 2 inspections required by the EDQM concerning starting materials for pharmaceutical use at Chinese manufacturing sites (as lead inspectors in one of the two inspections). Inspections are being completed, following receipt/assessment of corrective measure plans.

In 2016, a NAMMD inspector from the inspections department participated, together with other inspectors from the Italian authority in the field of the medicinal product (AIFA), in 2 inspections 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 inspections were part of the same application dossier and were concluded by issue of GMP compliance certificates by the AIFA.

- **GLP inspections** (2)

2 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 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.

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

In 2016, 2 inspections were requested at independent control sites for physical/chemical and/or microbiological laboratories for which 2 authorisations (and annexes) have been issued; for one of these sites, authorisation is still pending.

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

- **Pharmacovigilance inspections (0)**

In accordance with yearly inspection plan of the Pharmaceutical Inspection Department, 16 inspections for surveillance of the pharmacovigilance activity at the MAH / MAH representative in Romania were planned for 2016; however, none has been conducted, because of various reasons.

Advisory work conducted by inspectors of local units at clinics, hospitals, practices of family physicians, for boosting of local reporting of spontaneous adverse reactions, was continued in 2016 as well. 671 reports following local advisory pharmacovigilance visits were made in 2016. Decreased pharmacovigilance consultancy can be explained by the priority given quality surveillance and GDP inspections by territorial inspectors.

- **GDP inspections** (74)

In 2016, GDP inspections were as follows:

- authorisation for wholesale distribution of Romanian distribution sites in accordance with legislation in force and handling of the national database of information related to wholesale distribution authorisations granted;

- assessment of applications concerning amendments to Annexes to wholesale distribution authorisations;

- management of databases containing wholesalers and wholesale distributed products in accordance with monthly reports submitted by wholesalers/manufacturers/importers in accordance with provisions of Order of the Minister of Health no. 502/2013;

- processing of information derived from monthly reports submitted by wholesalers/manufacturers/importers in accordance with provisions of Order of the Minister of Health no. 502/2013 concerning wholesale distribution of medicinal products and provision of answers to interested institutions;

- coordination of local inspectors concerning local performance of inspections for authorisation of wholesalers;

- verification by unplanned inspections of medicinal product wholesale at authorised sites.

As regards authorisation of medicinal product wholesalers in Romania, the activity performed in accordance with provisions of Order of the Minister of Health no. 131/2016 on approval of Rules on authorisation of human medicinal product wholesalers, Good Distribution Practice certification and registration of brokers of medicinal products for human use consisted of:

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

In 2016, 74 inspections for authorisation were performed, leading to grant of 57 authorisations for wholesale distribution and Annexes; 57 units undergo various stages of the authorisation process. Because of critical findings, authorisation was refused for 2 wholesale distribution sites.

Conduct of routine inspections for assessment of performance of the distribution activity compliant with deadlines established depending on quality risk assessment, according to internal procedures of the Inspections department was established for all sites authorised for wholesale distribution in 2016.

In 2016, 42 unplanned inspections were performed for assessment of distribution activity and compliance with provisions of the Guideline for Good Distribution Practice (wholesale). Following these inspections, 17 units were fined and the wholesale distribution activity of 12 units was suspended.

123 applications for issue 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 recalled by the NAMMD following transfer of the wholesale distribution activity to new companies, authorised for wholesale distribution of medicinal products. 21 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.

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

Inspections for authorisation of wholesale distribution were conducted by NAMMD inspectors (from the main headquarters) and by some of the inspectors in 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 (7 clinical trials/7 sites)**

The following were conducted in 2016:

- GCP inspections (scheduled in accordance with the NAMMD yearly inspection plan - 8) of which: at the sponsors' site (1), at Contract Research Organisations - CROs (2), at the investigator's site (4), centralised procedure related inspection at the investigator's site (1).

- Unannounced GCP inspections: 9, of which: unannounced inspections at the investigator's site (7), unannounced inspections at CROs (2).

Announced 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 exchanges.

The most important findings identified during GCP inspections have been:

- on the date of inspection, the Phase I unit did not operate in accordance with the description of the area specially designed and equipment for performance of phase I clinical trials, based on which the NAMMD had issued an authorisation for conduct of Phase I clinical trials with medicinal products for human use; not all mandatory equipment was present on site to carry out emergency services specific to centres performing Phase I clinical trials;

- deficiencies of trial documents: suspicions concerning document authenticity, presence of several versions of source documents for a single subject;

- in the electronic dossier containing essential documents from the sponsor /CRO, verified during the inspection, not all essential documents specified in the GCP Guideline were accessible to the inspector and to the personnel of the sponsor/CRO involved in the conduct of the clinical trial;

- the sponsor's/CRO's personnel involved in conducting the trial in Romania does not have access to analysis and batch release certificates of Investigational Medicinal Products (IMPs) received at the site of investigation centres in Romania;

- the sponsor's/CRO's personnel involved in conducting the trial in Romania has not been delegated duties related to check of IMP quality documents received at the site of investigation centres in Romania;

- the electronic dossier containing essential sponsor /CRO documents verified during inspection was not organised in line with GCP Guidelines and was not provided with audit trail function;

- handling of the study medication and attachment of additional labelling for extension of the IMP shelf life at investigation centres had not been delegated by the main investigator to a competent pharmacist in this respect (GMP trained);

- deficiencies of the quality management system implemented at investigation centres: the implemented quality system was not compliant with ISO standards, absence of certain Standard Operating Procedures (SOPs) from the minimal SOP list specified in the legislation, SOPs not set up in line with legislation in force;

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

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

- inform the Commission for assessment and authorisation of clinical trials sites about its findings, for necessary measures regarding authorisation of such sites;

- inform the NAMMD Clinical Trials Service about respective findings, for measures necessary in relation to clinical trials conducted by a certain organisation/institution.

Inspectors from both the central headquarters and the 10 territorial inspection units have been involved in **surveillance of quality of products authorised for marketing in Romania.**

Thus, in 2016, this activity consisted of:

**a) Execution of the sampling plan for medicinal product quality monitoring** (sampling, testing, results):

In accordance with selection criteria underlying set-up of the yearly sampling plan, 53 products were proposed for quality assessment. Sampling has been performed by NAMMD inspectors, in accordance with this department's SOP.

Of the 53 products, 39 were sampled, 12 were not found in the distribution network and 2 radiopharmaceuticals were not sampled upon request of the Control Department, following laboratory refurbishment.

The results of laboratory tests were as follows:

-1 product has been declared noncompliant (recalled in February 2017);
-18 sampled products have been declared compliant;
- 19 products undergo analysis.
- 1 product not tested (expired batch).

Supplementary to the sampling plan, the following samples were taken in 2016:

- 2 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);
- 6 medicinal products sampled for laboratory testing for resolution of complaints on their quality; 3 samples have been declared noncompliant, 2 compliant in terms of quality, and 1 still undergoes laboratory analysis;
- 5 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.
- 5 medicinal products sampled for quality surveillance – one product, quality surveillance in imported products for special needs supply – 4; these were found compliant in terms of quality).

**b) Follow-up inspections of the quality of medicinal products in the distribution network** (warehouses, pharmacies, hospital pharmacies, drugstores) conducted by area inspectors: storage conditions, documents concerning quality, advertising, compliance of primary/secondary packaging and leaflet with MA, assessment of performance of withdrawals of medicinal products with quality deficiencies.

To this end, 1587 targeted inspections were conducted at wholesale and retail distribution sites. The following deficiencies were found:

- Inappropriate storage of medicinal products, especially as regards temperature and relative humidity (not all retail distribution sites have equipment to assure correct storage conditions; at some sites, although adequately equipped, storage conditions are not monitored in all the compartments of a pharmacy; likewise, uncalibrated/uncertified

temperature and relative humidity tools have been detected, as well as lack of records/formal records of medicinal product storage conditions);
- Improper storage of expired products;
- noncompliance with MA provisions in force as regards packaging imprinting;
- identification of advertising materials with an expired advertising approval or lacking an advertising approval;
- transfer of medicinal products among pharmacies of the same company in the absence of invoices;
- units operating in the absence of the pharmacist;
- improper/unsanitized storage spaces.
- Use of technical oxygen manufactured by an unauthorised manufacturer instead of medicinal oxygen.

The NAMMD has informed the Ministry of Health on its findings for decision of required legal measures for compliance by retailers with legal provisions in force, underlying their authorisation, as well as with Good Pharmaceutical Practice requirements.

**c) Collaboration of territorial units with other bodies, for resolution of issues related to legislation in the field of medicinal products and/or quality of medicinal products marketed in Romania**

In 2016, grant of specialist assistance upon request to bodies and institutions such as the Customs, Police Inspectorates, Offices for Consumer Protection, Public Health Inspectorates, consisted of joint actions with local specialised bodies, performed by local inspectors: 4 inspections in Galaţi.

**d) Resolution of findings concerning potential quality nonconformities in medicinal products for human use.**

Sixteen complaints were received in 2016, out of which 9 had no follow-up, 2 could not be solved on account of lack of relevant information required from the complainant, 4 have been found justified, resulting in recall of the respective medicinal products from the market; in order to report one of these products, the batch in question was blocked until resolution of the complaint.

To answer the respective complaints, NAMMD inspectors have performed 6 samplings, for laboratory testing within the NAMMD – Medicinal Product Quality Control Department.

The complaints were forwarded from NAMMD territorial inspectors (3) or submitted by healthcare professionals (5) and patients (8).

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

In 2016, the NAMMD requested recall of 68 medicinal products as follows:

- 14 medicinal products found with intrinsic quality nonconformities were proposed for recall and destruction (4 by the NAMMD, 10 manufacturer/MAH voluntary recalls); 8 medicinal products had labelling nonconformities, leading to their recall and destruction;
- 37 medicinal products were recalled in result of expiry of the legal period for implementation of changes to MA/MA transfer in accordance with provisions of Order of the Minister of Health no. 279/2005 or Order of the Minister of Health no. 1810/2006;
- 9 medicinal products were recalled by the MAH following expiry of MA validity or for marketing reasons.

**f) Rapid alert system:**

In 2016, 127 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S), of which:

- 88 have envisaged products unauthorised for marketing in Romania;
- 10 alerts were forwarded;
- 20 envisaged products authorised for marketing in Romania, but not imported/not distributed;
- 9 envisaged products authorised and imported/distributed in Romania;

Of the 127 rapid alerts received, 12 were related to medicinal products suspected of falsification/falsified.

In 2016, the NAMMD initiated no rapid alerts.

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

- 26 reported cases of noncompliance with GMP rules by manufacturers:
- 9 cases of noncompliance with the GMP guideline set up by the US competent authority

Of the 35 cases:

* 23 are related to active pharmaceutical substances:
* 12 are related to medicinal products:
    - 9 cases of GDP noncompliance.

24 notifications to MAHs have been communicated for change of active substance manufacturers.

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

In 2016, the quarterly reported TIU activity consisted of:

- transmission and resolution of medicinal product quality specific complaints;
- assessment and reporting to the NAMMD of outcomes of MAH recalls 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 sample submission to the NAMMD, accompanied by documents specified in the Pharmaceutical Inspection Department Standard Operating Procedure;
- sanction of contraventions in accordance with legislation in force;
- report of quality noncompliances to the NAMMD, found 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 assure medicinal product quality, safety and efficacy by laboratory testing.

This activity is performed by two NAMMD departments: the Medicinal Product Quality Control Department (MPQCD) and the Biological Product Evaluation and Control Department (BPECD). As of 1 June 2016, MPCQD management duties were taken over by the head of the BPECD, leading to setup of the Medicinal Product Quality Assessment and Control Department (MPQACD) through Order of the Minister of Health no. 1407/17.11.2016. 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. Main types of tests performed by the MPQCD** are as follows: instrumental tests, micro-biological tests and radio-pharmaceutics tests.

Main activities conducted in 2016 were aimed at:

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

In 2016, 38 medicinal products were submitted for Instrumental Analysis Laboratory testing - 25 as part of the Annual Plan for Sampling and Testing of medicinal product quality, 12 subject to quality complaints (4 noncompliant under the "Appearance" parameter), and 1 authorised through centralised procedure was analysed upon request of the Ministry for Internal Affairs and found noncompliant.

The Microbiology Laboratory has tested 21 medicinal products sampled within the Annual Sampling and Testing Plan, 5 products authorised for special needs and 1 required by the "Grigore Alexandrescu" Emergency Hospital.

The Radiopharmaceutical Product Control Laboratory has tested 3 samples (2 – market surveillance, 1 – authorisation).

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

For the 62 (38+21+3) medicinal products, about 300 separate analyses were performed, in line with techniques described in the European Pharmacopoeia or the manufacturer's pharmaceutical files/analytical protocols provided by the EDQM/FIP. It is important to note that One should mention that testing performed also included all test preceding or related operations and activities (over 550): equipment checks and calibration (IR; HPLC; UV, analytical balances, pH-meter); 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 reagents; 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 SOPs in force and their performance is followed by their entry into work sheets (equipment sheets, environment and temperature surveillance sheets etc.).

Among frequent and complex analytical techniques used in 2016, 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 NAMMD approved and accepted quality conditions, 4 of these being noncompliant under the "Appearance" parameter.

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

In 2016 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):

In 2016, the MPQCD has participated in 3 study categories:

- PTS studies (5);
- MSS studies (1);
- CAP studies (1).

➢ **5 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 from processing such 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 $\leq 2$.

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

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

In 2016, in the context of this programme, the MPQCD analysed 5 medicinal products sampled from the internal market as opposed to a CTS (Common testing sample) product. According to the protocol, the parameter "Tablet subdivision" was assessed; the results for the assessed products were found compliant.

➢ **Interlaboratory studies for standardization of reference substances**

Participation in interlaboratory studies for standardization of reference substances, organised by the EDQM – CRS (Certified Reference Standard):

- Nicotine Tartrate CRS 5, the test consisting of determination of water content through the KF potentiometric method.

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

In 2016, the 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.

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

In 2016, the BPECD issued 12 test bulletins (ABs), as follows: 4 ABs for two batches of biological medicinal product included in sampling plan of the Pharmaceutical Inspection Department, 3 ABs for biological medicinal products tested for authorisation (in accordance with Article 11 (2) of Order of the Minister of Health no. 1448/2010), 5 ABs for 3 batches of biological medicinal product for special needs.

No demands for official batch release were received in 2016.

There were 423 marketing intentions accompanied by the appropriate/final batch release certificate for biological products whose official batch release has been performed in the EU.

Implementation of the ELISA method for determination of the "Potency" parameter, by validation/revalidation of this method, and drafting of the rating note for this parameter were envisaged for completion in 2016.

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

In 2016, this activity mainly consisted of:

- 119 validations of applications for 70 Type IB and 49 Type II variations;
- 3 invalidations of applications for 1 Type IB variation and 3 Type II variations.

In 2016, the BPECD assessed the quality documentation for national and imported biological products, submitted for:

**National procedure**:

18 reports have been issued for 11 products:

- authorisation through national procedure:
  - 4 reports with request for dossier supplementation.
- MA renewal through national procedure:
  - 4 reports with request for dossier supplementation;
  - 7 reports proposed for approval of MA renewal.

Moreover, in 2016, within the MPQCD, **the reports on post-marketing experience were reviewed** (periodic safety update reports and cumulative summary report, if needed) and 3 assessment reports were issued, together with the Pharmacovigilance and Risk Management Service.

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

243 applicant notifications/annexes 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**:

- 95 notifications (to the National Procedure Department and proponents) proposed for approval/ Annexes with requests for dossier supplementation for simple Type IA variations;
- 26 notifications (to the National Procedure Department and proponents) proposed for approval/ Annexes with requests for dossier supplementation for Type IA grouped variations;
- 54 notifications (to the National Procedure Department and proponents) proposed for approval/ Annexes with requests for dossier supplementation for simple Type IB variations;
- 22 notifications (to the National Procedure Department and proponents) proposed for approval/ Annexes with requests for dossier supplementation for Type IB grouped variations;
- 32 notifications (to the National Procedure Department and proponents) proposed for approval /Annexes with requests for dossier supplementation for simple/grouped Type IB variations – worksharing procedure;
- 4 notifications proposed for approval of change of design;
- 9 notifications proposed for approval of applications for MA transfer.
- 1 notification accompanied by an Annex with requests for dossier supplementation for 1 MA transfer application.

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

- 32 reports with request for dossier supplementation for grouped Type II variations;
- 14 reports with request for dossier supplementation proposed for approval for simple/grouped Type II variations - worksharing procedure.

In 2016 as well, **quality documentation was assessed as related to products submitted through mutual recognition and decentralised procedures**, resulting in submission of assessment reports according to deadline, as follows:

- **Mutual Recognition Procedure (MRP)**

12 reports for MA authorisation/renewal have been issued for 7 products:

- 11 reports proposed for MA renewal;
- 1 report with request for dossier supplementation.

The BPECD also assessed dossiers for variations submitted through Mutual Recognition Procedure, for which 124 Annexes for Type IB variations (annexes forwarded to the European Procedures Department) and 44 assessment reports and their corresponding Annexes for Type II variations (forwarded to the European Procedures Department) have been issued, as follows:

- 94 annexes with request for dossier supplementation/proposal for approval of simple Type IB variations;
- 27 annexes with request for dossier supplementation/proposal for approval of grouped Type IIB variations;
- 3 annexes proposed for approval of grouped Type IB variations – worksharing procedure;
- 38 reports with request for dossier supplementation/reports for proposal for approval for simple Type II variations;
- 6 reports with request for dossier supplementation/reports for proposal for approval of grouped Type II variations.

- **Decentralised Procedure (DCP)**

  12 reports have been issued for 8 products pending authorisation:

  - 1 assessment report for authorisation, with request for supplementation;
  - 8 reports with request for authorisation;
  - 3 reports with request for recall.

In 2016, the BPECD also assessed quality documentation submitted for approval of applications for performance of clinical trials for 9 investigational biological products; 12 assessment reports have been issued, of which 7 (positive) final reports:

- 6 reports containing requests for supplementation of quality documentation;
- 2 assessment reports for assessment of post-approval supplementations.

As regards **change to marketing authorisation terms for biological medicinal products for human use**, following approval of Type I or II variations or following editing corrections, the BPECD performed 48 changes to MA terms in 2016.

## 8. Assuring communication and transparency

The NAMMD pays particular attention to assuring 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, republished as amended, relating to transparency in the work of EU drug competent authorities.

### 8.1. External communication

The NAMMD Communication Strategy has the following specific objectives:

- improvement of the institution's specialists' ability to assess, debate, propose, update and forward the regulations in the field of the medicinal product for human use fully in line with European legislation and standards in force;

- development of the communication activity through improvement and development of the infrastructure responsible for this activity;

- consolidation of procedures and processes in order to clarify the roles and responsibilities within the NAMMD mission;

- highlighting in relation to other bodies, namely recognition of the NAMMD status as an expert and trustworthy source of accurate information in the field of the medicinal product for human use;

- consolidation of the impact of the communication upon NAMMD partners by assuring a wide availability of information and of its immediate availability;

- assuring a quality bilateral communication with various stakeholders (through exchange of messages and questions); stakeholder analysis represents a key issue in establishing objectives specific to the communication strategy. To assure an efficient communication, the NAMMD shall clearly identify what and to whom it should forward and what results it aims to obtain through such communication. It is vital that the NAMMD becomes aware of the differences between various stakeholders and that it adapts its communication style to each stakeholder;

- exchange of information/"good practices" with other EU authorities regarding the timing and manner of communication about:

- proactive communication;
- current, routine communication;
- communication in crisis situations;
- confidentiality / embargo agreements;
- maintenance of trust in the NAMMD, by continuing to constantly meet all proposed objectives, regardless of challenges encountered is resolution of arising concerns.

Given shortage of medicinal products on the market observed since 2015, a constant topic for the media both nationally and internationally, the NAMMD handles the e-mail address lipsamedicament@anm.ro, established upon Ministry of Health request in February 2015. Daily coordination of the activity consisting of providing answers to complaints received on lipsamedicament@anm.ro, directly from patients, carers, hospitals, open circuit pharmacies and hospital pharmacies, patient associations, pharmaceutical warehouses, medical associations, physicians, as well as those redirected by the Ministry of Health from the website signalling medicinal product shortages, is based upon interdepartmental collaboration within the Agency, as well as, in certain cases, on contact of C.N. Unifarm S.A. representatives and/or wholesalers of medicinal products, in order to effectively help patients with updated information.

The NAMMD has permanently updated the website section set up on 01.06.2016 for posting information about notifications received from marketing authorisation holders concerning temporary or permanent discontinuation of medicinal product availability in the Romanian supply chain.

Administration of 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) was integrated into the institution's communication activity in 2016.

The NAMMD has continued to organise meetings, round tables with associations of patients, healthcare professionals and pharmaceutical industry on topics of interest.

The NAMMD has posted its quarterly bilingual newsletter (IB), 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.

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/withdrawn;
- List of NAMMD certified qualified persons and contact details for submission of medicinal product quality complaints.

The NAMMD has continued issue and posting of the Index of medicinal products for human use, containing all medicines authorised for the Romanian pharmaceutical market, 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. Also, implementation of individual electronic versions of Summaries of Product Characteristics (SmPCs), Leaflet and Labelling was continued.

The NAMMD has constantly updated and developed its website information. Accordingly, the following information and documents have been constantly posted and updated:

- EMA and NAMMD Press releases on medicinal product safety;
- NAMMD important notifications, opinions about certain issues from the written press/TV on the Agency's medicinal product policy, to the attention of interested persons;
- Direct healthcare professional communications;
- Notifications to marketing authorisation holders (MAHs) or other stakeholders on issues of interest;
- List of employees assigned as NAMMD full/alternate representatives to the EMA Management Board, EMA Scientific Committees and working groups, Heads of Medicines Agencies – HMA, the European Directorate for the Quality of Medicines & HealthCare – EDQM, the Council of Europe, the Council of the European Union, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and of the European Commission.
- information on marketing authorisation procedures (centralised procedure, European and national procedure (s)): information on contact persons, special warnings, SmPCs, leaflet and labelling information; the „National procedure" section will continue to make available the *List of parallel import authorisations*, issued by the Agency since 2009.

As of particular interest to external NAMMD website users, the following sections have been updated:

- Medicinal product legislation, structured according to the type of regulatory act:
    - Laws, Ordinances, Government Decisions;

- Orders of the Minister of Health;
- Decisions of the NAMMD Scientific Council;
- Decisions of the NAMMD Administration Council.
- The Index of medicinal products for human use authorised for marketing in Romania;
- forms,
- useful information.

Information related to:

- Clinical trials,
- pharmacovigilance,
- pharmaceutical inspection,
- medical technologies assessment
- advertising
- falsified medicinal products

have been continually posted, as vital for NAMMD partners.

Moreover, the section referring to NAMMD activity as a national competent authority in the field of medical devices has been periodically developed and updated.

The NAMMD has continued to inform stakeholders about its activity via other publications, apart from its own Newsletter. Thus, posting of the NAMMD Activity report for the previous year (also available in English) has been continued.

NAMMD specialists have continued to publish articles related to various Agency aspects, in special Romanian magazines ("Politici de sanatate", "Univers farmaceutic – Revista online a Farmacistilor", "Farmacist.ro", "Medical Business", "Viaţa Medicală, "Pharma Business", "Medica Academica", "Practica farmacetica" etc.).

In 2016, 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. assuring 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 enquirers, 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.

NAMMD representatives made presentations in numerous scientific 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 2016, 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 (QAB) 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 *SR EN ISO 9001 and 9004* principles in force, in 2016, together with other organisational structures, the QAB participated in implementation, development and improvement of the QMS on full organisation level.

Thus, the following have been developed:

- The internal quality audit programme 2016;
- The QAB activity programme for 2016;
- The QAB training programme for 2016;
- Individual training programmes for 2016.

The process of internal quality audit was conducted in accordance with the internal quality audit program for 2016, approved by the NAMMD President.

Other processes conducted at QAB level:

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

• Set up of documents requested by the Internal Audit Bureau (IAB) on implementation of the internal control /management system;

• Set up of documents requested by the IAB on the QAB Risk Register.

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

The NAMMD's quality management system (QMS) is well establish, documented, implemented, maintained and constantly improved, according to *international standards 9000, 9001, 9004, 17025, 19011* in force.

The NAMMD top management is involved in QMS-related activities, implementing a process-based approach.

## 10. Medical devices

### 10.1 Control by periodic check of medical devices

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

The Nuclear Unit (UN) carries out the same type of activities as the Technical Department-Laboratory (DTL), on medical devices with ionizing radiation. For this reason, work is reported in a joint report and necessary specifications are made. In 2016, activity in the DTL and UN has been as demanding as in previous years, both units being mostly involved in 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, as the periodic check bulletin is one of the documents mandatory for medical service contracts between 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 that the number of medical devices included in a service order varies from 1 to scores situated in hospitals, and that there is only a limited number of specialists and adequate measuring tools, careful scheduling has been mandatory for conduct of activities.

Most applications for check were submitted by public healthcare units, which are exempt from fees.

Works completed in 2016 are as follows:

Total applications registered: 645 (UN) + 852 (DTL)=1497
Total periodic check bulletins issued: 575 (UN) +1261 (DTL) = 1836
Total user opinions issued: 28 (UN) +256 (DTL) = 284
Total medical devices checked: 2112 (UN) +4974 (DTL) = 7086
Total mobile intervention units checked: 0+348 (DTL) = 348
Total test reports issued: 1335 (UN) +2842 (DTL) = 4177
Total negative test reports (medical devices rejected): 77 (UN) +117 (DTL) = 194

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.

An internal audit of the Nuclear Unit was conducted in 2016 by a NAMMD commission.

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

### 10.2 Inspection of technical and medical-assessment units

Work of the Medical Technology Assessment Department has been in line with provisions of Title XX of Law 95/2006, republished as amended, and with Order of the Minister of Health no.

309/2015 for approval of Rules implementing Title XIX of Law 95/2006, as amended, on approval of medical-technical units, until September 2016. In September 2016, Order of the Minister of Health no. 1008/2016 on approval of Rules for implementation of Title XX of Law 95/2006 on healthcare reform, republished as amended, entered into force.

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 issue of approvals for operation and their Annexes, for both assessment activities and activities related to import and/or supply of medical devices.

Following entry into force of Order of the Minister of Health no. 1008/2016, import and distribution/storage activities have also required assessment for grant of approvals for operation and their Annexes.

The Department has national coverage, performing:

- both initial assessment of organisations for grant of operation approval and their respective annexes, and biennial surveillance assessment for continuation of operation approval,
- changes applied for, in compliance with timeframes stipulated in the Order of the Minister of Health.

In 2016, the Department's activities were as follows:

- **Technical-medical units assessment**

- Number of registered new applications for evaluation in 2016: 524
- Number of initial evaluations performed: 211
- Number of allocated surveillance works: 197
- Number of initial evaluation reports: 211,
- Number of initial unfavourable evaluation reports: 3,
- Number of surveillance reports issued: 197,
  of which: Number of unfavourable surveillance-evaluation reports: 7
- Number of applications cancelled (no dossier submitted for assessment, the organisation is only involved in trading activity, conditions for surveillance not met, no operation approvals changed, in accordance with Order of the Minister of Health no. 309/2015): 86
- Number of initial evaluation and evaluation-surveillance works in progress at the end of the year: 298.

In the context of an application for grant of an approval for operation / Annex to the approval for operation, in some instances, technical-medical units applied for assessment of one or several working stations, sometimes as many as 30. As such work stations were included in the same application, assessments were performed at every required station, however, as stipulated by the department's working procedure, only one assessment report was issued, registered under the same number as the number of the applicant's request. This was also the case for surveillance assessments, when one unit requested assessment of 42 working stations. Actually, multiple assessment has only resulted in one application registered for several working stations, one assessment report and one approval for operation and one assessment dossier was established for each assessed working station. Thus, the number of assessment dossiers issued is greater than the number of applications submitted.

- **Issue of operation approvals/Annexes to operation approvals**

- Operation approvals: 340

- Number of Annexes to operation approvals: 797
- Number of changed operation approvals: 399.

Bimonthly internal training and discussions concerning on-site situations encountered have been conducted, encouraging the entire staff for harmonised action and improvement.

Staff have accomplished their duties and tasks at the anticipated level, and increased business trip efficiency by conducting interventions even for 5 consecutive days and responding to several orders in the same locality or nearby localities during the same trip.

The procedure for assessment of medical-technical units was revised, considering requirements of the new Order no 1008/2016 on enforcement of Law 95/2006, republished, which also includes activities related to import, distribution/storage of medicinal products; the questionnaire for import, distribution and storage of medical devices was issued in accordance with this Order. Changes were introduced to assure that provision of medical devices services meet the expected quality and technical level.

Related to grant of operation approvals and their Annexes, apart from current activities, 399 operation approvals had been changed by 1 October 2016, as stipulated in Order of the Minister of Health no. 309/2015.

The Department aims to setup a public database, allowing for interested persons' access to a list of operation approvals issued/suspended/revoked.

### 10.3 Regulation, authorisation and market surveillance of medical devices

The Department for Regulation, authorisation and market surveillance of medical devices (DRASP) performs its activity as:

- A national market surveillance authority, through its Market Surveillance Service, as well as
- a competent authority in the field of medical devices, through its Regulation-Authorisation Service.

Through its market surveillance activity, the DRASP controls compliance by medical devices with requirements of applicable technical regulations as well as actual action by economic operators in accordance with their duties, to restore compliance with requirements of applicable technical regulations of noncompliant products.

As regards market surveillance work, the DRASP undertakes:

a) monitoring of medical devices introduced on the market and/or commissioned as well as of medical devices presented at fairs, exhibitions, other events;

b) establishment of measures to be taken by the economic operator, as required, to assure product compliance;

c) follow-up of the implementation of established measures.

As regards market surveillance, the dedicated NAMMD unit conducts the following:

- formal assays;
- background assays.

Formal assays focus on the presence and manner of implementation of the EC marking and/or other specific markings mentioned in applicable legislation, availability of the declaration of compliance, technical documentation, the information accompanying the medical device and/or proper manufacturer choice of procedures for assessment of medical device conformity.

Background assays focus on check of medical device conformity with key requirements established by applicable technical regulations.

While DRASP focus in 2015 was market education and knowledgeability of legal provisions in the field, in 2016 it concentrated on measuring the extent of implementation of the proposed measures. Whereas, in 2015, 4 breach measures had been applied, in 2016, there were 87 finding reports and imposition of penalties and 4 warnings. Activities in this respect started the previous year were continued throughout the country in 2016 as well, mainly targeting online supply of medical devices or in ad-hoc presentations organised in hotels as known means of marketing medical devices of uncertain origin and quality. In this respect, the NAMMD has required for support from the National Authority for Consumer Protection (ANPC) and of the Police.

In accordance with Order of the Minister of Health no. 1009/2016 on record of medical devices into the national database, the NAMMD grants a customs approval for medical devices with absent EC mark, under the conditions specified in this Order. Moreover, it also grants an out-of-scope notice when requested by customs authorities (for products already at the border, or which may be used as medical devices but which have not been declared as such by the manufacturer and are thus not in use as medical devices). In 2016, the DRASP received 13 such requests. The products subject to these requests involved lenses, gloves, surgical instruments, needles and dental instruments coming from non-EU countries.

In accordance with Article 8(3) of Directive 93/42/EEC and 98/79/EC and Article 7 (3) of Directive 90/385/EEC, DRASP specialists permanently exchange information on product compliance with other Member States authorities. There is active participation in meetings of the Compliance and Enforcement Group (COEN) – about 300 such consultations / information were reviewed.

As regards regulatory work related to medical devices, the following have been issued:

- Order no. 1009/2016 on record of medical devices into the national database;
- Order no. 1008 /06.09.2016 on approval of Implementation Rules relating to provisions of Title XX – Medical Devices of Law no. 95/2006 on healthcare reform, as republished, regarding approval of medical device-related activities;

Draft of regulatory acts for medical devices:

- draft for amendment of Law 95/2006 on health care reform, on medical device advertising.
- draft for amendment of Government Decision no. 734/2010, on regulatory harmonisation and supplementation of fee paying activities.

As regards implementation of legislation in force in this field, 927 medical devices manufactured by Romanian manufacturers were recorded into the database and corresponding record certificates were issued in line with Orders of the Minister of Health no. 372/2015 and no. 1009/2016 on record of medical devices. The registration of 5 medical devices not meeting requirements set for placement on the market was refused (product outside the scope of the "medical device" definition, no procedures performed for compliance assessment and insufficient proof of meeting key conditions).

**Summary of market surveillance activities in 2016**

| No. | CONTENTS | 2016 |
|---|---|---|
| 1. | Number of products triggering accidents/reported by users | 7 |
| 2. | Number of complaints concerning unfair competition | 2 |
| 3 | Total number of controls | 300 |
| 3.1 | Number of reactive inspections | 10 |
| 3.2 | Number of unexpected inspections | 285 |
| 3.3 | Number of inspections promoted by customs authorities | 5 |
| 4 | Number of inspections based on: | |
| 4.1 | Tests performed in laboratories | 1 |
| 4.2 | Product physical controls | 299 |
| 5 | Number of inspections resulting in: | |
| 5.1 | Noncompliance findings | 32 |
| 5.2 | Corrective measures taken by economic operators (voluntary measures) | 0 |
| 5.3 | Restrictive measures (temporary/permanent discontinuation from marketing) | 37 |
| 5.4 | Enforcement of regulations/sanctions/fines | 16 |
| 6 | Number of inspections conducted in collaboration with other member states | 5 |

**Other DRASP activities:**

- participation in the National Subcommission for Assessment of Medical Devices Suppliers for recovery of organic and functional deficiencies within the National Health Insurance House (NHIH) – whenever required;
- participation in setup of the List of harmonised European standards, planned for translation in 2017;
- feedback to requests to the NAMMD related to medical devices by other ministries, public authorities, natural and legal entities or in the context of medical device working groups – whenever required;
- introduction of data from the national database into the Eudamed (the European centralised database) – whenever required;
- record, centralisation and transmission to then Ministry of Health of the centralised situation of declarations collected through sponsorship forms, in accordance with Order of the Minister of Health no. 874/2015;
- participation in the translation/verification of translation of the two EU Regulations on medical devices.

## 11. International relations

An aspect worth mentioning is that, starting with 2016, NAMMD specialists have shown an increased involvement in the activities of scientific committees and working groups, particularly those organised by the EMA and the Heads of Medicines Agencies – HMA. In 2016, NAMMD specialists continued participation in activities of various institutions and bodies in its scope, involved in cooperation:

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

Since 2003, first as active observer, NAMMD representatives have been involved in work of EMA working groups, scientific committees and groups for implementation of information technology for medicinal products for human use, always the most effective way to maintain the NAMMD updated with medicinal product activities on EU level.

Active members since 2007 in EMA scientific committees and working groups, NAMMD experts have taken 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 Heads of Medicines Agencies - HMA European body, 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 2016, 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 Certification scheme on the quality of pharmaceutical products moving in international commerce.

In 2015, the Agency granted the drug certificate in WHO format to a total of 544 Romanian medicinal product manufacturers seeking authorisation in other countries.

### 11.5. Participation in activities of the Council of Europe

In 2016, NAMMD assigned representatives as a member of the European Pharmacopoeia Commission, continued participation in meetings of the PhEur Commission as well as in the annual meeting of the secretariats of National Pharmacopoeias of member states of the European Pharmacopoeia Convention.

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

### 11.6. Participation in Official Medicines Control Laboratories (OMCL) activities

Respective 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 2016 related to achievement of effective communication with the EMA and provision of real time information exchange 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 2016 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.

Throughout the year, the DLIGED has assured maintenance of the NAMMD website (*www.anm.ro*), of 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, 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 provided 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 - 20.

Servicing of NAMMD both 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 2016, The Data and Documents Management Service has been involved in several types of activities, for instance:

- release of Mas and Annexes 1, 2, 3 4 and 5 - for 1100 medicinal products, of which 718 through EPs and 382 through NP;
- release of MA lists – 212 lists (for 1100 MAs);
- Entry into the 'Registry' database of information on medicinal products authorised - 1100 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) - 1100 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 - 558 notifications;
- Draft of manufacturer undertakings on MA issue and archiving in the authorisation dossier - 162 notifications;
- Entry into the "Registry" Database of the receipt notifications and its archiving in the authorisation dossier - 1058 notifications;
- Participation in meetings of the Marketing Authorisation Commission - 23 meetings;
- Draft of medicinal product certificates in WHO format: 544 certificates;
- Draft of confirmations of products undergoing Marketing Authorisation renewal, stating "selling allowed" – 22 conformations for 29 medicinal products;
- Preparation of minutes for Authorisations for special needs - 45 minutes;
- Draft of Authorisations for special needs – 80 authorisations concerning 87 medicinal products.

## 13. Assuring implementation of NAMMD policies and strategies

In 2016, the Department for Policies and Strategies (DPS) conducted the following activities:

- development by interdepartmental collaboration and under coordination of the NAMMD management, of *the NAMMD Organisational Strategy 2015-2017*, contributing to its implementation particularly by:

- Strengthening of Agency's status as reference national authority in the field of medicinal products for human use in its specific sector.
- Strengthening of Agency's status as expert and reliable source of accurate and timely information in the field of medicinal products for human use, provided to stakeholders, by active and priority participation in implementation of the *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.

In 2016, the DPS provided:

- 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, presentations of the NAMMD perspective on various issues related to medicinal products for human use;
- Communication with other institutions specialised in this field in both Romania and abroad.
- Assuring 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;
- Information to media representatives and/or other members of the public, on request, within the timeframe set by existing rules, when information requested has already been provided by default under 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 assuring 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;
- Assuring communication with the EMA for approval of nominations for Agency experts;
- Checking/Centralising forms completed by NAMMD experts;
- Communication with the secretariats of respective working groups/committees of scientific bodies for submission of forms;

- Monitoring of the Community Register/handling on paper and electronically (within the DPS and on the Romsys/anm/Decizii CE Server) of 25 European Commission (EC) Decisions and of 1 consensus agreement of the CMDh (the Co-ordination Group for Mutual Recognition and Decentralised procedures – Human), periodically received from Romania's permanent representation in the EU, on paper, referring to: medicinal products authorised conditionally, MA maintenance/suspension/recall/amendment following completion of referral procedures concerning safety, quality, efficacy issues and their redirection toward NAMMD specialists assigned for their implementation in Romania (in the case of the 21 EC Decisions and of the 1 consensus agreement of the CMDh, referring to medicinal products authorised in Romania as well, and the other 4 EC decisions referring to medicinal products unauthorised in Romania);

- Electronic record of paper documents received from the Ministry of External Affairs via the Ministry of Health concerning issue of European Commission Decisions for medicinal products authorised in Romania.

The DPS has prepared the NAMMD annual activity report for 2015 by corroborating data from activity reports of NAMMD departments.

The DPS has assured preparation of the NAMMD newsletter and its posting on the Agency website:

- 4 Newsletter issues in Romanian (4/2015, 1/2016, 2/2016, 3/2016) and
- 4 Newsletter issues in English (3/2015, 4/2015, 1/2016, 2/2016).

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

- Legislative documents, notifications in Romanian and English;
- NAMMD Newsletters in Romanian and English;
- The NAMMD Annual Activity Report (2015);

- The List of NAMMD employees assigned as representatives or substitutes in the administration council, 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 terms to assure 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;
- Assuring 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.

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

- Monitoring/Managing electronic records of all e-mails (over 1000 e-mails) received from the Permanent Representation of Romania to the EU and/or the Ministry of Health regarding:
- participation of NAMMD employees assigned as representatives or alternates in the various 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;
- regulatory papers/documents concerning NAMMD's field of competence, in various debate stages/approved at EU level.

The DPS has also assured 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 (head of the DPS) in one of the 3 annual sessions of the European Pharmacopoeia Commission, as a member (at the EDQM headquarters in Strasbourg – 22-23 November 2016);
- Participation of the appointed representative (head of the DPS) in the annual meeting of the national competent authorities pharmacopoeias secretariats – Prague, the Czech Republic – 26-27 April 2016;
- Centralisation and review of electronic documentation provided by the Commission of the European Pharmacopoeia/EDQM;
- Translation into Romanian of the Standard Terms approved by the European Pharmacopoeia Commission (the head of the DPS was assigned „authorised translator" for Standard Terms by the EDQM, since entry into force of the new database of Standard Terms on the EDQM website in November 2014);

- Maintenance and update of the intranet "INFO-Service Pharmacopoeia" NAMMD database containing electronic versions of records of documentation provided, of issued FR X Supplements, of Standard Terms in Romanian (including the section dedicated to Standard Terms on the Agency's website) 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.

In 2016, the DPS has continued:

- Administration of the NAMMD Facebook page, started in 2015 (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).
- Coordination of the organisation and setup of the dossiers for a round table (2 March 2016) held with the representatives of patient associations, dealing with clinical trials, participation in discussions and feedback follow-up;
- Handling of the lipsamedicament@anm.ro e-mail, setup upon request of the Ministry of Health in February 2015. The daily coordination of answers to complaints received on lipsamedicament@anm.ro is based on interdepartmental cooperation (DPS-PID-NPD-BPECD/MPQACD). In some cases, this activity has also involved contacting (by e-mail or telephone) the representatives of C.N. Unifarm S.A. and/or wholesalers of medicinal products, in order to be able to help the patient with updated information.

As regards documenting, setup and transmission of feedback to complaints received on NAMMD's e-mail address, lipsamedicament@anm.ro, these refer to 439 complaints received from patients, kin, hospitals, open circuit and hospital pharmacies, patient associations, pharmaceutical storehouses, medical societies, physicians. Apart from lipsamedicament@anm.ro, the Ministry of Health has developed and applied another manner of signalling the lack of certain medicinal products from the market, namely posting them on http://medicamentelipsa.ms.ro/ in September 2016. Thus, the complaints sent on lipsamedicament@anm.ro were also handled by the DPS. In such cases as well, the employed documentation/assessment was the one used for complaints received directly by the NAMMD on its already functional address.

**Other DPS activities:**

- brief overviews on progress of the Romanian pharmaceutical market were provided upon request of the NAMMD top management or of other Agency units, according to information provided by the CEGEDIM (monitoring of the Romanian medicinal product market, of the share of pharmaceutical companies, of the share of the main therapeutic groups on the pharmaceutical market); in the scientific event organised by the Romanian Society for Allergology and Clinical Immunology together with the Romanian Network for Hereditary Angioedema, under the title « Progresses in Allergology – interdisciplinary approaches».
- In 2016, the DPS continued to publish articles in specialised magazines:
    - "Health Policies" (monthly), about issues related to the NAMMD activity and to specific EU legislation:
        - April 2016: "EU legislation, warranty for the efficacy and safety of vaccines on the market";
        - May 2016: "The NAMMD monitors implementation of European legislation in the pharmaceutical field";
        - June 2016: "The NAMMD, directly involved in increased access to treatments of rare diseases and rare carcinomas in Romania";
        - October 2016: "Various considerations on the global medicinal product shortage".

Year 2016 also meant involvement of the DPS in preparing the NAMMD to receive, on May 16 - 18, of the delegation of the Serbian Agency for Medicines and Medical Devices (ALIMS), co-signatory of a Memorandum of agreement with the NAMMD in August 2015. Its scope consisted of sharing NAMMD specialists' expertise, given Serbia's intention of accession to the EU. The domain of interest for the first work visit consisted in approach of EU legislation on medicinal products for human use, marketing authorisation, advertising and specific communication, as well as transposition of EU legislation into national legislation. In the opening meeting, the NAMMD representatives presented "The NAMMD role at national and European level – the Romanian NAMMD role at national and European level" and subsequently answered, point-by-point, to related questions of the ALIMS spokesperson.

According to this Memorandum, a NAMMD delegation consisting of the NAMMD President, a DPS representative and a Legal Department representative, participated, in the 12$^{th}$ symposium organised by the ALIMS in Kragujevac, Serbia in November 2016.

In May 2016, the DPS representative was invited as a lecturer to the Spiru Haret University – the Social and Human Sciences Faculty of Bucharest, to present "The NAMMD-media relationship: between real partnership and utopian desideratum" within the "Medical-pharmaceutical journalism" workshop.

It is also important to highlight DPS involvement in development of NAMMD communication with both patient organisations and professional/industry associations through:

- participation in the 5th Edition of the Journalism School for Rare Diseases – 10-11 October 2016, presenting "The NAMMD-media relationship: between real partnership and utopian desideratum", 11.10.2016;
- participation in the Conference of the Association of Patients with Autoimmune Diseases (APAA), 14 October 2016, presenting "The medicinal product – useful patient information";
- draft of the address "The NAMMD message for the international ASCO Clinical Trial Workshop", delivered by organisers in the opening session in Cluj, on 23 September 2016.
- participation in the Joint Conference of the Association of the European Self-Medication Industry (AESGP) & the Romanian Association of the Self-Care Industry (RASCI) "The role of self-care in healthcare", 19 October 2016, presenting "Global overview on control of OTC advertising in the EU".

## 14. NAMMD legal issues

The main tasks of the NAMMD Legal Department (LD) is Agency representation in court, comprising in 2016 of 56 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 proceedings etc.).

It is also worth mentioning in 2016 there was an increase in the number of litigations involving the authority, particularly following extension of NAMMD assignments in assessment of medical technologies and in medical devices, through Government Decision (GD) no. 315/2014 on amendment 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 discontinuation of the Technical Office for Medical Devices and on amendment of certain regulatory acts, the latter included, to amendment of Government Decision no. 734/2010 on organisation and operation of the National Agency for Medicines and Medical Devices.

Moreover, over 40% of the litigations in 2016 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, and over 30% were related to complaints against NAMMD penalties.

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 officer, certain regulatory drafts, as described in section 3 "**Regulatory activity**".

Professional activities of the Legal Department mainly focused on assuring 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 liability;
- Endorsement of accurate interpretation of legislation applicable to the NAMMD scope;
- Draft of the minutes of the 2 meetings of the NAMMD Administration Council and its 4 rulings;
- Other works related to assuring secretarial activities of the NAMMD Administration Council;
- Approval of decisions of the NAMMD President;
- Handling of the NAMMD security activities;
- Participation as members in the commissions for assessment of procedures for acquisition of assets and services;
- participation in annual commissions for asset inventory;
- participation in counselling activities upon request of other departments;
- assuring preventive financial control approval for NAMMD financial-accounting documents;
- setup of requirements for external travels of NAMMD staff to meetings of EMA scientific committees and working groups or other working groups of competent authorities in the medicinal product field.

Also, together with the other NAMMD departments, the Legal Department has contributed to fighting off counterfeiting of medicines, which is why in 2016 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 information exchange 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 medicinal product legislation;

c) mutual information about data and information held by each party, useful for attaining the specific goals of the other party;

d) presentation of substantiation notes to legal factors with powers in the field, for improvement of national legislation, inclusion of community regulations into national rule, namely signing of international conventions allowing for effective control of medicinal product falsification;

e) use of information resulting from market studies and reviews by specialist companies for most accurate knowledge on the medicinal product market;

f) surveillance of market operations to detect 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) mutual support for assuring 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/December 2012 amending certain healthcare regulations.

## 15. Management of human resources

### 15.1. Human resources policy

The Agency's Department of human resources, payroll (DRUS) has the following main objectives:

- Providing human resources for NAMMD structures undergoing shortage (in 2016 as well) of highly qualified personnel, particularly medical and pharmaceutical, able to provide the required 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 assure high qualification designed to assure NAMMD capacity to solve specific tasks;
- Planning, implementation and evaluation of NAMMD staff training and development; in this context, it should be noted that training is planned annually at departmental level, based on each employee's specific work and qualification. 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. Assuring human resources to NAMMD structures

As regards this main DRUS objective, the department has performed ongoing analysis of human resource NAMMD requirements, developing staff strategies and policies, in line with the organisation's long-term objectives and the efficiency it seeks. The aim in this respect has been to

find ways and means to provide NAMMD units with specialist qualified staff and efficient maintenance and use of existing staff. With regard to this aspect of utmost importance for optimal NAMMD performance, it is worth mentioning that, in 2016, vacancies have been opened for recruitment in line with Article 31 of Emergency Government Ordinance no. 83 of 12 December 2014 on payment of staff 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 assure full payment of wage-related rights granted in accordance with the law, within limits of expenses for paid wages approved through the budget. Chief credit officers establish the maximum number of jobs paid in 2015 and 2016…"

This regulatory text implies that, though vacancies had become available for hiring by contest, the condition remained to preserve payments within the approved limits of wage expenses in the frame of budget of income and expenses. Considering this limitation, the DRUS was not able to attain its goal of covering lack of qualified staff within the NAMMD. In addition, given the downsizing of the number of staff by decision of the Ministry of Health the NAMMD could not fully capitalize on this opportunity to fill vacancies.

However, 21 vacancies were occupied, replacing the vacancies made available in 2016, of which 7 consisted of administrative and 14 of healthcare specialist positions, within the budget approved for wage-related expenses.

In conclusion, the qualified staff shortage could not be covered in 2016 either, as the Agency's specialised departments are still confronted 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 require NAMMD specialists' high levels of competence. It is certainly a prime objective of the Agency, requiring, on one hand, mandatory ongoing training programs and specific professional development in this area conducted at Agency site, as well as, on the other hand particularly, participation in training organised nationally or internationally by various authorities and similar bodies.

Within the limits of funding provided by 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 has also enabled initiation and appropriate conduct of activities, meeting the standards of the other European national competent authorities, considered highly competent and demanding, related to European authorisation procedures (mutual recognition procedure, mutual recognition "repeat use" procedure and the decentralised procedure).

In 2016, many NAMMD employees took part in scientific events and professional training sessions, some of them as speakers:

- **participation in events held in Romania**:

- the ColaboRARE Conference – Collaboration for Management of Rare Diseases, 29-30 January 2016;
- the National Day of India, 26 January 2016;
- the Conference organised by the Romanian College of Pharmacists – February 2016, Bucharest;
- the "Fascinating by Analytics - reliable and reproducible HPLC analysis with Merck-Millipore" symposium, organised by Merck Millipore Romania SRL – 09 February 2016;
- the National Pharmacy Conference of Family Medicine, Bucharest, 24-27 March 2016;
- the level 2 course ″Radiological safety when dealing with ionising radiation sources″- initial module, 04-08 April 2016 – 08 April 2016, closed sources module, 18.04.2016 – 21.04.2016 and opened sources module, 21.04.2016 - 22.04.2016, IFIN-HH, Măgurele;
- the Medic.ro Conference: "News in treatment of diabetes. Care for diabetic persons in Romania", organised by Versa Media in collaboration with the College of Physicians, Bucharest, 8-9 April 2016;
- the training on qualification and validation in the light of the new Annex 15 to the GMP Guideline, organised by D.O.C. S.r.l. at the NAMMD offices, 11 May 2016;
- the "Qualification and validation in light of new Annex 15 and USP Chapters Update 2016" training organised by Klarwi at the NAMMD offices, 11 May 2016;
- the Pharmacovigilance Conference of 12-13 May 2016 - 3rd Romanian Pharmacovigilance Workshop, Bucharest;
- the "Qualification and validation in light of new Annex 15 and USP Chapters: Update 2016" seminar, organised by DOC Masco Group, Bucharest, 11 May 2016
- the yearly meeting of the Official Medicines Control Laboratories (OMCL), organised by the European Directorate for the Quality of Medicines (EDQM), Paris, France, 23-27 May 2016;
- the National Congress for Clinical Research, Bucharest, 20-21 May 2016;
- the Workshop on mass spectrometry – organised by VIOLA – SHIMADZU, Bucharest, 02 June 2016, Bucharest;
- the "From Science to Guidance and Practice" conference, organised by OFF Systems Romania, 06 – 07 June 2016;
- "The future of today - xenobiotics, neurocomportamental safety and cognitive sciences – lines and perspectives, 17-18 June 2016, Bucharest;
- the First conference of clinical pharmacy, 18 June 2016;
- the Workshop on "Access to orphan medicinal products and other therapies for patients with rare diseases", 29 June 2016, with: "The NAMMD – directly involved in the progress of the access to treatment of patients with rare diseases and carcinomas in Romania";
- the "Agilent techniques for medicinal product assessment" - seminar organised by SC Agilrom SRL together with Agilent Technologies, on 05 July 2016, Bucharest;
- the yearly PIC/S seminar: "Inspectorates of the future" – July 2016, Manchester; GMP inspector
- the National Pharmacy Congress, the 16th edition, 28 September -1 October 2016, with several papers:
    - "The NAMMD – directly involved in the progress of the access to treatment of patients with rare diseases and carcinomas in Romania"
    - "Monitoring of implementation in Romania of the EU legislation in the pharmaceutical field – one of the missions of the National Agency for Medicines and Medical Devices";
    - "Scientific assessment of medicinal product quality – identification of border specific issues"

- "Herbal medicinal products in the context of the current European legislation"
- "Role of the National Agency for Medicines and Medical Devices in handling parallel import/export of medicinal products in Romania"
- "Public Health protection through implementation of the referral procedure in special cases where EU interests are involved. The GVK case"
- "Safe and efficient use of antibiotics – a common objective of the NAMMD-pharmacist partnership"

- the Teknoleb "October Anniversary Fest" symposium, 05 October 2016, Hotel Sheraton, Bucharest;
- the launch of the Pharma Group for Dialogue, 10 October 2016;
- the 5th Edition of the Rare Diseases school for journalists – 10-11 October 2016, with: "The NAMMD-media relationship: between real partnership and utopian desideratum", 11 October 2016;
- the "Merck Steritest Seminar" Conference, organised by Merck Romania in 13 October 2016, Bucharest;
- the Conference of the Association of Patients with Autoimmune Diseases (APAA), 14 October 2016, with: "The medicinal product – useful information for patients";
- the National Conference of the Romanian Society for Radiological Protection, "Radioprotection in professional exposure to ionizing radiations, in accordance with EC Directive no. 2013/59/EURATOM", MB Telecom Ltd., 14 October 2016, Bucharest-Otopeni;
- the National Conference: "Antibiotics: between use and abuse", Bucharest, 14-15 October 2016;
- the Joint Conference of the Association of the European Self-Medication Industry (AESGP) & the Romanian Association of the Self-Care Industry (RASCI) "The role of self-care in healthcare", 19 October 2016, with: "Global overview on control of OTC advertising in the EU";
- the national interdisciplinary conference on "How to diagnose and treat kidney and urinary diseases in children", 20-22 October 2016, with: "Off-label use of medicinal products – call for adoption of strict Good Practice rules for off-label use in the medical practice at European level;
- the DISSO EUROPE 2016 - ADVANCES AND APPLICATIONS IN DISSOLUTION SCIENCE, 20-21 October 2016, Bucharest;
- the Conference MedAcademy Paediatrics, Bucharest, 4 November 2016;
- SFMR staff took part in organisation in Romania of a campaign for acknowledgement of adverse reaction reporting, within the SCOPE project, conducted between 7-11 November 2016, under the coordination of the British Agency. Setup of an analysis report of the campaign for promotion of adverse reaction reporting in Romania;
- the 12th National Conference of the Order of Biologists, Biochemists and Chemists from the Romanian Health System (OBBCSSR), 12 November 2016;
- the "Validation of try-out/analysis methods" course, 21-22 November 2016;
- training on "Legal aspects related to assuring analysis quality: Control of outcomes of try-outs in physical-chemical analysis laboratories", 24-25 November 2016, Braşov;
- the "Synevo Clinical Research Symposium- 8th Edition" seminar, 25 November 2016;
- the National Pharmacy Conference, 24-26 November 2016, with:
    - "Off-label use – need for adoption of strict Good Practice rules in off-label use in medical practice, at European level"
    - Infections associated to the medical performance - are healthcare professionals to blame?

- "Role of the National Agency for Medicines and Medical Devices in handling parallel import/export of medicinal products in Romania"
- "Overview of clinical trials performed in Romania"
- "Serialisation in EU member states – implementation of safety issues".

- **Participation in events organised abroad:**

- the workshop organised by the EURORDIS in Brussels at the initiative of the European Commission in 24-25 February, in order to celebrate the International Rare Diseases Day;
- the training "Counterfeit/Illegal Medicines Testing", 24-25 February, Bern;
- the training course on vaccine assessment, organised by the World Health Organisation in Antalya, Turkey, 29 February – 5 March 2016;
- the course for assessors on practical description and use of PK/PD population models with mixed non-linear effects, useful in drafting and assessment of clinical trials in the paediatric population, which was held at the Biomedical Centre of Uppsala, Sweden, 1-3 March 2016;
- the meeting of the Working Group for legislation, under the coordination of HMA, European Medicines Agencies Co-operation of Legal and Legislative Issues (EMACOLEX), Utrecht, Holland, 17 – 18 March 2016;
- courses organised and reimbursed by COMP-EMA on "Introductory training for COMP Members" which were held in London in 23 March 2016 and 19 May 2016;
- SCOPE workshop "The Strengthening Collaboration For Operating Pharmacovigilance In Europe" for development of the electronic form for adverse reaction reporting, 15 April 2016, MHRA, London;
- the meeting of the Secretariats of the Pharmacopoeia of National Competent Authorities, 26-27 April 2016, Prague, the Czech Republic;
- the workshop for detection of safety signals - signal detection, 23 May 2016, Bratislava, Slovakia;
- the course organised and reimbursed by the EMA on „Update on the new guideline on the assessment of pharmacokinetic studies investigating the effect of renal impairment and the draft guideline on reporting physiologically based pharmacokinetic (PBPK) modelling and simulation" , Madrid, Spain, 25 May 2016;
- the PRACTICAL COURSE ON BCS AND ADDITIONAL STRENGHT BIOWAVER ASSESSMENT" 26 May 2016, the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid;
- the yearly meeting of the Official Medicines Control Laboratory (OMCL), organised by the European Directorate for the Quality of Medicines (EDQM), Paris, France, 23-27 May 2016;
- the meeting of the Working Group Communication Professionals, under the aegis of the Heads of Medicines Agencies (HMA) – 9-10 June 2016, Utrecht, Holland;
- the work meeting on communication issues in risk situations concerning the medicinal product ('Risk Communication Workshop'), Madrid, 16-17 June 2016, organised by the Spanish Medicinal Product Agency (AEMPS) within the SCOPE (Strengthening Collaboration for Operating Pharmacovigilance in Europe) project, as part of ending WP 6 (Work Package 6), coordinated by the AEMPS;
- the yearly PIC/S seminar, with "Inspectorates of the future" – July 2016, Manchester, Great Britain;

- the training course on potency assay in viral vaccines (measles, rubella, mumps), organised by the OMCL Belgium, co-financed by the EDQM, in Brussels, Belgium, between 05 September – 09 September 2016;
- the training session within the SCOPE project: "The Strengthening Collaboration For Operating Pharmacovigilance In Europe" - Work Package 8, referring to assessment of risk management plans (RMP), post-authorisation safety study (PASS) protocols, the PSUSA (the European Unique Assessment Procedure), organised at the site of the INFARMED, I.P. (the Portuguese Agency), Lisbon, between 20-21 September 2016;
- the meeting organised in Strasbourg on 22 September 2016 and transmission to the EDQM of comments on the updated guideline by the NAMMD representative assigned as full member in the Working Group for revision of the Guideline on validation of computer systems;
- the EU NTC Safety & Benefit/risk training & workshop, Dublin 28-29 September 2016
- the work meeting within the project "The Strengthening Collaboration for Operating Pharmacovigilance in Europe- SCOPE", Work Package 7 - Quality Management and Work Package 5 - Signal Management, Budapest, 04-05 October 2016;
- the training of environmental risk assessors (Training for ERA) phase II, 12-13 October, EMA, London, organised by the EU NTC;
- the work meeting within the SCOPE project "The Strengthening Collaboration for Operating Pharmacovigilance in Europe" - Work Package 4 - ADR Collection, London, 13-14 October 2016;
- the Conference organised by the COMP – the EMA Committee for Orphan Medicinal Products, named "COMP strategy review and learning presidency meeting", Rome, 17-18 October 2016;
- the 12$^{th}$ Symposium of ALIMS Serbia, Kragujevac 27-30 October 2016 with "Control of OTC Advertising in the European Union - An Overview";
- the training of assessors from the EMA Committee for Herbal Medicinal Products: "HMPC Assessors Training", 3-4 November 2016, London;
- the training course on "EU Batch Release for Human Vaccines: A Practical Overview for Newcomers", organised by the EDQM, Strasbourg, France, 08 – 09 November 2016;
- the training of assessors of the Committee for Assessment of Pharmacovigilance Risks: "PRAC Assessors Training", London 17-18. November 2016;
- the course for assessors referring to: "The assessment of biosimilar medicinal products„ organised by (EMA, 17-19 November 2016;
- the EU NTC Clinical trials workshop on clinical assessment organised by the Italian authority, AIFA, 21-22 November 2016
- the 156$^{th}$ Session of the European Pharmacopoeia Commission, 22-23 November 2016, Strasbourg, France, at the EDQM site;
- the „ Sub-regional integrated training workshop on AEFI surveillance, causality assessment and communication", Budva, Montenegro, 21-25 November 2016;
- the International Workshop CBRNe 2016 – Univ. of Rome "Tor Vergata'' (approached themes: nuclear, chemical and bacteriological defence, explosives, informatics safety), 25 November 2016, Rome, Italia;
- the training on computer systems, organised by the EDQM, 29-30 November 2016, Strasbourg, France;
- following request of WHO representatives, in preparation and coordination of the "Marketing authorization and licensing of medicinal products (vaccines)" workshop, held at the site of the Competent Authority in Chisinau, Moldova, between 05 – 09 December 2016.

- the „Training on quality assessment of specific types of products", Rome, Italia, 6-7 December 2016;
- the workshop organised by the COMP-EMA, „Defining orphan conditions", London, 9 December 2016
- the "Electronic Reporting of Individual Case Safety Reports (ICSRs) in the EEA", London, 12-14 December 2016;
- the meeting of the Group of Experts for setup of delegated documents referring to „the safety issues" for medicinal products for human use, Brussels, 12-13 December 2016;

- **online participation in training:**

- 2 pharmacovigilance inspectors in the online training course on access to the EVDAS database;
- the „Important issues in the justification of a control treatment in paediatric drug trials"– webinar EU NTC;
- the "Paediatric training for newcomers" – EU NTC webinar;
- the online training session TRREE (Training and Resources in Research Ethics Evaluation) – "Introduction to Research Ethics", January 2016;
- the online training session TRREE (Training and Resources in Research Ethics Evaluation) – "Informed Consent", January 2016;
- the „PSUR Repository – Training of member state users on the new functionality" – 19 January 2016;
- the online training session TRREE (Training and Resources in Research Ethics Evaluation) – "Good Clinical Practice (GCP)", February 2016
- the online training session TRREE (Training and Resources in Research Ethics Evaluation) – "HIV Vaccine Trials", February 2016;
- the webinar: "Finished products monographs containing chemically defined active substances in the European Pharmacopoeia" – EDQM, 04 February 2016;

- the webinar EMA/Cancer Drug Development Forum (CDDF) workshop, on 4-5 February 2016 on cancer immunotherapy: "Challenges for the approval of anti-cancer immunotherapeutic drugs";
- the training organised by the EMA – "Clinical Trials Regulation EU No. 536/2014 Training", 3-4 March 2016, London;
- the webinar EMA - "Pharmacovigilance Training", 22 April 2016;
- the webinar EMA - "Progressing Ethics of Paediatric Trials - Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors", 12 May 2016;
- the SmPC Advisory Group webinar – „SmPC information in subpopulation; from data to labelling" – 24 June 2016;
- presentation of Derek Nexus and Sarah Nexus, programmes used in the pharmaceutical field for assessment of toxicity and prediction of genotoxicity, mutagenicity, carcinogenicity (and online demonstration) held by Dr. Crina Heghes, Business Development Manager la Lhasa Limited – 01 July 2017;
- the webinar: "The use of ICH M7 guidance. Learning from recent submissions at AstraZeneca" (Dr. Andrew Teasdale) – 05 august 2016;
- the webinar EMA - "Validation of Analytical Methods", 2 September 2016;
- the webinar EMA - "Benefit/Risk Training", 19 September 2016;

- the "10th Stakeholders Forum on the operation of the Pharmacovigilance Legislation" – 21 September 2016;
- the Webinar: "Rapid and cost-efficient analysis of pharmaceutical and clinical samples by TXRF" – (Bruker Nano Analytics)- 21 September 2016;
- the SmPC Advisory Group webinar: „Warnings and precautions for use" – 22 September 2016;
- the eRMR training webinar – 18 October 2016;
- the webinar: "Advanced Materials for Single-use Systems"- (Entegris-KNect 365 Life Sciences)- 03 November 2016;
- the webinar: "Screening of Restricted Elements including Sample Thickness Correction with the M1 MISTRAL Micro-XRF Spectrometer" (Bruker Nano Analytics) – 03 November 2016;
- the webinar EMA- EU and international assessor training on Biosimilars, 17-18 November 2016;
- the EMA webinar – "Clinical trials workshop on clinical assessment", 21-22 November 2016;
- the SmPC webinar – 24 November 2016;
- the webinar: "Rapid Analysis of Nutrients and Toxic Elements in Food and Beverages by TXRF"- (Bruker Nano Analytics)- 08 December 2016;

NAMMD specialists in the field of medical devices participated in the following meetings of special working groups of:

- **the European Commission**

- the Notified Body Operational Group –NBOG (1 participation),
- the Medical Devices Expert Group – MDEG (1 participation),
- the Medical Devices Vigilance Expert Group - (2 participations),
- the IVD Technical Group (2 participations),
- the Working Group on Clinical Investigation & Evaluation (2 participations)
- the COEN – group for compliance and enforcement (2 participations),
- the Eudamed WG (1 participation),
- the Classification & Borderline WG (1 participation),
- the UDI WG (1 participation).

- **The European Union Council**

- The working group on medicinal products and medical devices (5 participations)

Training in 2016 was supplemented with **internal training**:

- Based on materials and papers issued by university graduates working for the various NAMMD departments, according to the training plan;
- Training of middle education staff – adaptation of specific SOPs;
- Safety and occupational training for university graduates and middle education staff and auxiliary staff;
- Training on emergency situations for university graduates and middle education staff and auxiliary staff;

- Periodic training of university graduates working in the Variations service, concerning the new Guidelines adopted by the CHMP, for ongoing improvement of assessment quality; inspectors from the main headquarters received specific training, as follows:
  - GMP training session, organised in May 2016 by representatives of Klarwin (Romania) and DOC (Italia), on: the new Annex 15 to the GMP Guideline (qualification and validation) and aseptic processing issues, from the perspective of the pharmaceutical industry;
  - notification on issues discussed in EMA working groups (GMP, GDP, GCP and Pharmacovigilance inspections) – based on reports setup by representatives of the Pharmaceutical Inspection Department;
  - training on revised general and specific Standard Operating Procedures.
- In February and September 2016, the NAMMD organised joint training sessions, for inspectors from the main headquarters as well as for territorial inspectors, on GDP legislation, as well as to current issues on GDP activity and quality surveillance.

### 16. Economic activity

In 2016, the approved expenses budget was **26,394,000 million lei.**

The NAMMD has encashed this year's tariffs and fees amounting to **62,636,803,43 lei**, a sum fully transferred to the state budget; the difference of 3,099,708,39 lei was encashed from remainders registered before 2016 and from creditors.

### 17. General administration

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

The Public Procurement Service performed **NAMMD public procurement activities**:

- Development of the Annual Public Procurement Plan for 2016;
- Centralising purchase requests submitted by NAMMD organisational structures for set up of the Annual Public Procurement Plan for 2017;
- Setup of the Annual Public Procurement Report for submission to the National Authority for Regulating and Monitoring Public Procurement, 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 for investment funds;
- Performance and finalisation of the public procurement procedure – The online simplified procedure dealing with provision of "PC systems with monitors, software, scanners" – 6 batches, amounting to 451,421,10 lei (VAT excluded);
- Purchase of equipment as "medical equipment/machines/means of transportation/ miscellanea and independent facilities" included in the 2016 Investment List;
- Resolution of 66 purchase requests for public procurement of products/services/ works;
- Monitoring of the conduct of public procurement contracts for goods/services/works;
- Setup of documents upon completion of public procurement contracts and their publishing in the SEAP catalogue;
- Resolution of 884 purchase requests for public procurement of products/services/ works;

- Conduct of 681 purchases from the SEAP catalogue amounting to 1,264,432.22 lei (VAT excluded);
- Preparation of the following documents related to budget expenses:
  - Global budget commitments (ABGs) and Individual budgetary commitments (ABIs) - 818 pcs.;
  - Proposal for engagement of expenses (PACs) - 786 pcs.;
  - Authorisation of payment (OP) - 956 pcs.;
- Assuring setup and maintenance within the public acquisition files for products, services and papers;
- Compliance with advertising obligations (publication in the Public Purchases Electronic System –SEAP – notifications of award);
- Reception and review of requests 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, providing assurance and counsel to the top management with regard to effective management of public incomes and expenditures, and improvement of public entity activities. It helps the public entity fulfil its objectives through systematic and methodical approach, assessing and improving efficiency and efficacy of the management system, based on risk management, control and administration processes. Generally speaking, an audit mission can have three main objectives:

- assuring compliance of procedures and operations with legal regulations - regularity audit;

- assessment of results concerning the objectives pursued and examination of impact – performance audit;

- assessment of management and internal control systems – system audit.

The internal audit structure (BAI) established at the NAMMD is subordinated to the NAMMD President. It performs objective evaluation of nonconformities found in audited Agency departments and makes appropriate recommendations for resolution.

The Internal Audit Plan for 2016 consisted of performance of 6 approved audit missions, as follows:

- Assessment of work in the Policies and Strategies Department;
- Assessment of work in the National Procedure Department;
- Assessment of work in the Technical Laboratory Department;
- Assessment of work in the Department for M.D. Market Regulation, Authorisation and Surveillance;
- Assessment work in the Technical-Medical Units Assessment Department;
- Assessment of work in the Nuclear Unit.

Audit tasks for 2016 have been fully met.

Objectives set out in audit missions conducted have been:

- Work organisation and actual operation of audited structures;
- Compliance with tasks, duties and specific legislation in audited structures;
- Record and reporting of activities within 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.

## 19. Challenges in 2016

As of 2009, the NAMMD has been faced with several overcoming several challenges in its work to accomplish its mission, of which special note should be made of the difficulty of recruiting and retaining staff in the Agency, lack of financial resources (in the context of much lower approved expenditure budget than real needs) to ensure adequate training of staff and laboratory equipment to an appropriate level in line with requirements of the OMCL network of which the NAMMD are part, as well as limited databases.

## 20. Priorities/Projects envisaged for 2017

At the end of each year, the NAMMD undertakes a self-assessment of work over the past year, designing projects and setting priorities for the next period, which involves open and direct communication between management and subordinate structures, a certain manner of collaboration with people, which demands total availability and motivation for work and dedication throughout the Agency.

Fulfilment of the current NAMMD mission, the national authority competent for human medicinal products, medical devices and medical technology assessment, is confirmed as the Agency's primary goal.

Presented on several occasions by the NAMMD management, future projects target both medicines and medical devices and mainly consist of:

- Establishing an appropriate NAMMD intervention policy to avoid the medicinal product shortage risk. In that respect, the following are envisaged:

o implementing a viable solution for compliance with the public service obligation;

o increase in the number of unannounced inspections to verify compliance with Good Practice of Distribution Rules.

- Strengthening pharmacovigilance and pharmaceutical inspection activity;
- Strengthening NAMMD capacity to contribute to prevention of medicines counterfeiting and early preparation of the national system for implementation, by 9 February 2019 at the latest, of the delegated acts approved by the European Commission regarding the unique identifier for medicines;
- Improving health technology assessment by amendment of legal assessment criteria;
- Contributing to preparation of secondary national legislation to ensure implementation of the Clinical Trial Regulation once the EMA portal for clinical trials has become operational (expected for 2018);

- Ensuring adequate and ongoing training of specialised personnel;
- Implementing an IT strategy that relates, among others, to the following:
  o development of a new Medicinal Product Index, in line with the latest national and European requirements;
  o creation of the Public Register of operating medical devices;
  o creation of a web portal for submission and approval of advertising material;
  o developing a data management application resulting from manufacturers and wholesalers' reports pursuant to Order of the Minister of Health no. 502/2013.

The NAMMD will further focus on:

- scientific assessment of documentation on the quality, efficacy and safety of medicinal products submitted for marketing authorisation;
- amendment of Law 95/2006 regarding regulation of advertising of medical devices and subsequent establishment of assessment rules;
- preventing counterfeiting of medicines and medical devices to the extent of the Agency's competence, plus preparation of the national system for implementation of delegated acts on a single code for medicinal products approved by the European Commission in accordance with the European Directive on falsified medicinal products;
- internal Agency reorganisation to maximise its efficiency;
- appropriate training of existing and newly hired personnel (taking into account that high quality assessment skills and knowledge take at least 5 years to acquire, evaluation expertise being a guarantor of placing on the market of medicines meeting current EU requirements);
- continuing and improving medical technology assessment work;
- timely preparation of secondary legislation to ensure implementation of the Clinical Trial Regulation at national level once the EMA portal for clinical trials has become operational (expected for 2018);
- strengthening pharmacovigilance and pharmaceutical inspection activity, in line with EMA efforts in the same respect. Reporting of adverse reactions at national level is the foundation of decision-making related to re-evaluation of the benefit-risk ratio for a medicinal product or a class of medicines. Pharmaceutical inspection checks compliance with the rules of good manufacturing practice, good distribution practice, laboratory, analytical laboratory, pharmacovigilance and, last but not least, work undertaken at clinical trials sites.
- establishing an appropriate NAMMD intervention policy to avoid the medicinal product shortage risk.

Currently, the European Medicines Agency is reviewing the legislative framework describing the objectives of and strengthening EMA methodology for interaction with patients and consumers. The revised work framework is based on establishing regular interaction with the European network of patient organisations in order to:

- support EMA access to real-life experience of diseases and how they can be treated, to obtain information on current use of medicines;
- contribute to more effective communication, aimed at increasing patients' role in reasonable and safe use of medicines;
- as much as possible improve patients and their organisations' understanding of the role of the European Network of Regulatory and Control Authorities (of which the NAMMD is part).

All the above are goals that the NAMMD has undertaken and whose achievement it will pursue in the future.

Improvement of the Quality Management System) requires provision of adequate financial resources for:

• training (knowledge improvement) regarding requirements of SR EN ISO 9000: 2015; 9001: 2015 in the field of quality and improvement of communication among the various NAMMD organisational structures.

• ensuring human resources necessary to carry out specific QA processes, resources, requiring ongoing training and motivation.

• preparing an auditor in pharmacovigilance system quality management system (SMCFV) (physician/ pharmacist), as recommended by the EMA.

As regards medical devices, the NAMMD aims at achieving several objectives, including:

- Amendment of Law 95/2006 on regulation of advertising for medical devices and subsequent establishment of evaluation rules;
- Preparation, based on the model of the Medicinal Product Index, of a Public Register of medical devices available on the Romanian market;
- Creation of a Vigilance Bureau with responsibilities in registering and evaluating information on incidents and creating a related database, including communication with the European Commission;
- Establishment of a Compliance and Communication Bureau for medical devices, with responsibilities in communicating with Member States through strategies established within the COEN (Compliance and Enforcement Group) Working Group on preventing the placing on the market of non-compliant / counterfeit medical devices;
- Clarification of legislation on clinical investigation and examination of the opportunity of setting up a Clinical Investigation Bureau.

The above are the most important NAMMD projects for the next period, requiring, as a matter of priority, highly qualified specialists in its field of competence and appropriate budgeting.

**CONCLUSIONS**

The report highlights results obtained in 2016 of activities making up the mission of the National Agency for Medicines and Medical Devices (NAMMD). The NAMMD is the national competent authority in the field of medicinal products for human use, medical devices and medical technology assessment. In addition to assessment of authorisation documentation for the marketing of good quality, safe and effective human medicines, the Agency's current mission, also comprises assessment of documentation for authorisation of the clinical trials and of their sites in Romania, safety surveillance of human medicinal products in the therapeutic circuit through inspection and pharmacovigilance. Starting with 2014, the NAMMD has also become the national competent authority in the field of medical devices and medical technology assessment, based on scientific criteria adopted by national legislation in force, for inclusion in the national health insurance system. In other words, NAMMD work aims to protect and promote public health, both by guaranteeing marketing in Romania of medicines meeting European standards of quality, efficacy and safety, as well as by ensuring a high level of performance and security with regard to medical devices in use in healthcare systems across the country. It is a mission that requires constant self-evaluation, permanent adaptation of the proposed strategy to socio-economic

aspects, or to any other type of challenges potentially arising at a given moment, adjustment achieved through persistent efforts.

The NAMMD is constantly seeking to strengthen its partnership with healthcare professionals, the pharmaceutical industry, the media as an opinion maker and, last but not least, patients themselves, in order to promote appropriate authorisation, regulation and control policy in its areas of competence: medicines for human use, medical technology assessment and medical devices.

Communicating with all the actors involved in the pharmaceutical market has also been a major, constant concern this year, in the attempt, not always successful, to find viable solutions able to provide a legislative framework in support of the Ministry of Health (MS) policy to ensure patients' access to prescribed treatments, and in particular to new, modern therapies available in other European Union (EU) Member States in the health insurance system.

A landmark of 2016 has been the high-level visit of Prof. Guido Rasi, Executive Director of the European Medicines Agency (EMA). The purpose of the official visit of the EMA delegation to Romania was to develop cooperation between the coordinating agency of the European Network with the Ministry of Health (MS) and the NAMMD in the field of human medicines. Talks on this occasion have occasioned identification of several issues, of which the following needs should be listed as most important:

- development of multiannual plans in line with the EMA strategy;
- increase of the number of specialists involved in assessment;
- adoption of measures to ensure the motivation of staff to be assigned and involved in additional tasks at European level;
- adequate NAMMD funding for strengthening its equipment capacities for all work in support of scientific activities;
- appropriate training of existing and newly employed personnel;
- development of clinical trial inspection;
- patient involvement in NAMMD decision-making process pursuant to the model already implemented by the EMA;
- increased NAMMD involvement in achieving objectives of the European Union Medicines Agencies' Network Strategy by 2020, "Cooperation for Health Improvement".

In NAMMD view, the visit of the EMA highest level delegation has fully accomplished its envisaged goal to find issues requiring increased NAMMD and Ministry of Health focus required for initiation of measures able to facilitate the development of cooperation between the participating authorities: the EMA, Ministry of Health and the NAMMD.

One thing worth mentioning is that, in 2016, an actual increase has been noted in involvement of NAMMD specialists in work of scientific committees and working groups, especially those under the aegis of the European Medicines Agency - EMA and Heads of Medicines Agencies - HMA.

In the year 2016, the NAMMD granted 1100 marketing authorisations for medicinal products for human use, of which 718 (65.27%) were the result of assessment through the European procedures (343 by Decentralised Procedure (DCP), 5 by the Mutual Recognition Procedure (MRP), 49 by the Repeat-Use Mutual Recognition Procedure, 321 through MA renewal and 382 (34.7%) through the National Procedure (33 new MAs and 349 MA renewals).

In 2016 as well, generic drugs have been the top market entry. In the Nomenclature of Medicinal Products for Human Use in 2015, about one third are the original authorised drugs

through the centralised procedure, respectively by EMA, entering the Romanian market at the request of the APP holder, the remaining 2/3 being generic.

Further work in medical technology assessment in 2015 and 2016, actually implying Romanian patients' access to new, modern treatments, has resulted by the end of 2016 in 6 updates of Government Decision no. 720/2008 approving the List of compensated and free medicines. An ongoing process, medical technology assessment has allowed the listing of many medicines used in various and noteworthy in this respect is progress made related to the treatment of hepatitis C and rare diseases.

In recent years, the NAMMD has focused on implementation of a communication strategy for all stakeholders, among which patient organisations have held an important position. This has been proved by, on the one hand, the roundtables organised at the NAMMD headquarters addressing topics of interest to the patients, and on the other hand, by participation of NAMMD representatives in such meetings providing presentations and responses to participants' questions. In fact, policies for patient approach and involvement in Agency work aims at raising general public awareness of the significance of medicinal product benefit/risk ratio, of the importance of reporting adverse reactions, in the context of inherent adverse reactions to every medicine, a positive benefit/risk ratio being critical.

Pharmacovigilance activity conducted over the past years by the Pharmacovigilance and Risk Management Service is more complex every, in line with the regulatory dynamics and European guidelines in the field, respectively. The number of reported spontaneous adverse reactions (AR) is steadily increasing. Public awareness campaigns both at national and European level such as those run in the EU from 7 to 11 November on the importance of adverse reaction reporting are expected to deliver the targeted results. The actual aim it to bestow increased responsibility equally on professionals and patients with regard to contribution to understanding the safety profile of medicines. Following thorough assessment, adverse reactions reports can generate new medicinal product-related knowledge.

In 2016, the NAMMD has furthered post-marketing surveillance of human medicinal products not only through pharmacovigilance but also through pharmaceutical inspection, exacting penalties for non-compliance with regulations in force.

Together with all the Agency's structures, the NAMMD top management has also continued to pursue implementation, development and improvement in 2016 of the NAMMD Quality Management System, based on the principles of SR EN ISO 9001 and 9004 in force.

Since its creation in 2010 by merger of the former National Medicines Agency with the Medical Device Technical Office (OTDM), the NAMMD has been the only institution empowered and able to assess performance and safety of medical devices in use.

The Nuclear Unit (UN) carries out the same types of activities as the Technical Laboratory Department (DTL), applied to medical devices with ionizing radiation.

The Department for Evaluation of Technical and Medical Units (DEUTS) conducted its activity until September 2016, based on provisions of title XX of Law no.95/2006 republished as amended, and of Order of the Minister of Health no. 309 / 2015 approving the Methodological Rules for the application of Title XIX of Law no. 95/2006, as amended, regarding approval of the medical equipment units. In September 2016, Order of the Minister of Health no. 1008/2016 entered into force for the approval of the Methodological Norms for the application of Title XX of Law no. 95/2006 republished, as amended. Respective work consisted in assessment of organisations' capabilities to provide services related to medical devices (optics, prosthesis, repair, maintenance, installation/commissioning) requiring an operating notice and grant of

operating authorisations and their annexes, for both activities assessed and import and/or distribution of medical devices.

The Department for Regulatory, Authorisation, and Medical Device Market Surveillance (DRASP) carries out its work as:

- national market surveillance authority, through its Market Surveillance Service;
- competent authority in the field of medical devices, through its Regulatory and Authorisation Service.

Through market surveillance, the DRASP controls compliance of medical devices with requirements of applicable technical regulations as well as economic operators' work in accordance with their obligations, with an aim to bring non-compliant products in line with requirements of applicable technical regulations.

In 2016, the NAMMD specialised departments also received the constant support from all support departments (Legal Department, Economic Department, General Administration Department, Human Resources and Payroll Department, Department for Logistics IT and Electronic Data Management, the Quality Assurance Bureau, the Internal Audit Bureau, the Labour Safety and Health Prevention and Protection Service).

Together with scientific professional departments within the NAMMD, the Legal Department has prepared documents (draft regulatory acts, substantiation notes, approval papers) for promotion, through the chief credit officer, the Ministry of Health, of numerous draft regulatory provisions, primarily aiming to regulate areas within NAMMD competence.

NAMMD involvement in finding viable solutions for MAH, importer and wholesaler compliance with their public service obligation, involvement in the management of the dedicated email address, lipsamedicament@anm.ro, also serving, since September 2016, as support to the MS website http://medicamentelipsa.ms.ro/, have been an additional task undertaken since 2015, when the medicinal product shortage also became a reason for concern in Romania as well, for various reasons: manufacturing issues, lack of active substances, commercial reasons and others.

In 2016, the Agency faced the same difficulties perpetuated over all recent years, caused by under-funding, insufficient human resources, in spite of increased openness since 2013. The possibility arose for organising hiring competitions for the vacancies on condition of compliance with the approved income and expenditure budget for salaries. This restriction has resulted in partial achievement of the NAMMD objective of covering its qualified personnel shortage. Appropriate funding in a favourable regulatory environment would enable the Agency to both suitably motivate its highly specialised human resources, whose expertise has been acquired and maintained by means of ongoing professional training, and to provide laboratory and IT equipment compatible with the NAMMD status as national authority on its area of competence within the EU network.

The current report includes priorities / projects for 2017 for all NAMMD activities, designed to ensure accomplishment of the Agency's tasks the highest standards of competence. This concerns achieving NAMMD strategic objective, strengthening its status as EU authority with competitive performance at EU level, in its fields of expertise: human medicines, medical technology assessment and medical devices.