2012 ANNUAL REPORT
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

INTRODUCTION

In 2012, the National Agency for Medicines and Medical Devices (NAMMD) carried out the same concentrated work to reach the goals imposed by the Agency's foremost mission, namely assessment of the authorisation dossier for marketing of quality, safe and effective medicinal products and surveillance of the safety of medicinal products for human use in the therapeutic circuit, via inspection and pharmacovigilance activities.

As customary in recent years, the NAMMD's accomplishments in the medicinal product field for human use have been based upon the efforts undertaken by Agency experts in its scientific departments (The National Procedure Department - NPD, the European Procedures Department - EPD, the Pharmaceutical Inspection Department - PID, the Medicinal Products Quality Control Department - MPQCD, the Biological Products Evaluation and Control Department - BPECD, the Policies and Strategies Department - PSD), continuously supported by support departments (The Information Logistics and Electronic Management of Data Department – ILEMDD), the Human Resources and Payroll Department - HRPD, the Economic Department - ED, the General Administration Department - GAD). By means of an adequate communication strategy, the NAMMD has permanently aimed at strengthening its credibility to its partners as an authentic guardian and initiator of public health in Romania.

In the same way as for all competent authorities in the field of medicinal products for human use throughout the entire European Union, for the NAMMD too one of the main targets is to create an efficient liaison with all stakeholders e.g. healthcare, research and industry professionals, patients, the public and the media. All NAMMD specialists, pharmacists, physicians, biologists, involved in either assessment for authorisation, or control, inspection and/or pharmacovigilance, implicitly also contribute to implementation of the NAMMD communication strategy by actual involvement in the set-up of responses to media and/or any stakeholder queries, in identification of new requirements of the Agency's partners, in organising and participating to meetings. Increased openness towards streamlining of the communication with all partners in the field has resulted in to meetings with Marketing Authorisation Holders, associations of international and Romanian medicinal product manufacturers, patients, associations of companies coordinating conduct of clinical trials, associations of medicinal product suppliers etc.

Assessment of the 2012 outcomes proves full accomplishment by the NAMMD of tasks and duties as a national competent authority in the medicinal product field for human use; efforts undertaken by Agency employees have been more intense, in direct proportion with this year's severe deficit of specialised staff. In spite of such adverse circumstances, the has Agency managed to reach its targets and has continued, in the sixth year of Romania's membership to the European Union (EU), to perform key activities in addition to its current activity of marketing authorisation, inspection, quality control and pharmacovigilance, among which:

- **Active participations in bimonthly/monthly/quarterly meetings of scientific committees and coordinating European working groups in the field of the medicinal product for human use (European Medicines Agency-EMA, Heads of Medicines Agencies-HMA, European Directorate for the Quality of Medicines-EDQM, European Commission).**

All NAMMD scientific departments have ensured the participation, via assigned representatives, to meetings of scientific committees and European working groups, related to

various issues such as regulation and European procedures on medicinal products, particularly an active participation in:

- EMA's CHMP (The Committee for Medicinal Products for Human Use), as corapporteurs in re-examination procedures;
- EMA's PDCO (Paediatric Committee) - PIP (Paediatric Investigation Plan) assessment, participation in set-up of the 2012 Romanian Annual Paediatric Report forwarded to the EMA/PDCO for the European Commission and participation to teleconferences and monthly/bimonthly meetings of working subgroups (Extrapolation of safety and efficacy in the context of the development of paediatric medicinal product and Pharmaceutical Formulation– active participation and set up of assessment reports);
- the Committee for coordination of MRP and DCP-CMDh procedures and meetings of Working Groups on variations and active substance master file. Currently, Romania acts as Reference Member State in 16 decentralised procedures;
- the Committee on Herbal Medicinal Products, with RO as rapporteur/assessor of certain community monographs;
- the Pharmacovigilance Working Group and, as of July 2012, the newly set-up Pharmacovigilance Risk-Assessment Committee (PRAC);
- the EU Council Working Group for Medicines and Medical Devices, including participation to debates for set-up and harmonisation, in all Member States, of clinical trial legislation. A new regulatory proposal for introduction of the Regulation on clinical trials was made in July 2012, aiming to repeal Directive 2001/20/EC on regulation of clinical trials; the NAMMD has been assigned by the Ministry of Health for participation in debates over the new Regulation on clinical trials. Thus, the NAMMD has successfully proved its status as active participant to debates, by expressing opinions about:
  - NAMMD agreement with the need for support to the European Commission proposal concerning amendment of the previous clinical trial regulatory framework;
  - NAMMD disagreement concerning:
    - Election of the Rapporteur Member State by the sponsor, on account of the fact that the decision must lie with participating member states, which must consider the number of applications for authorisation of clinical trials;
    - Tacit authorisation of clinical trials, considering the obligation of the competent authority to protect the subjects enrolled in trials, which can only be accomplished by thorough assessment of documentation by the respective member state.
  - NAMMD comments concerning:
    - approach of ethical issues, requiring explicit specification of preservation/setup of an Ethics Committee (EC) as a body involved in assessment, as well provision for EC favourable opinion as a condition for start of the trial onset (i.e., compliance with the Declaration of Helsinki is required);
    - deadlines proposed for assessment of documentation, considered too short considering the need for expert opinion (e.g. in case of clinical trials on advanced therapy medicinal products) as well as the risk of insufficient time for the Reference Member State to manage Interested Member States' comments/requests for clarification or supplementation.
  - the need to also provide for the option for withdrawal ("opt-out"), on scientific grounds, considering that the sole purpose of clinical trials is assessment of efficacy and safety of the investigational medicinal products, not comparative assessment of clinical practices in various Member States;
  - ensurance of operation of the EU platform, as mandatory condition for conduct of the procedure for clinical trial authorisation.

- **Transposition into national legislation of provisions of Directive 2010/84/EU on the new manner of approach of pharmacovigilance and of Directive 2011/62/EU as regards the prevention of the entry into the legal supply chain of falsified medicinal products**

The steadfast efforts of two working groups assigned by the NAMMD President for transposition into national legislation of provisions of Directive 2010/84/EU and Directive 2011/62/EU, have resulted in draft and issuance of two Emergency Ordinances of the Romanian Government (Emergency Government Ordinance 35/July 2012 amending certain healthcare regulations and Emergency Government Ordinance 91/December 2012, amending Law 95/2006 on healthcare reform, as amended, as regards pharmacovigilance and the prevention of the entry into the legal supply chain of falsified medicinal products).

- **Regulatory work and technical support to the Ministry of Health, upon request.**

In July 2012, the NAMMD Scientific Council agreed on Scientific Council Decision (SCD) on approval of mandatory monthly reporting of placement on the market in Romania, respectively of sales of medicinal products for human use by authorised wholesale distributors/importers/manufacturers. Approval of this regulatory Scientific Council Decision through Order of the Minister of Health is pending.

The NAMMD provides technical support to the Ministry of Health in:

- set up of the lists for national tenders for supply of medicinal products in hospital sections and national programs (draft of the Annexes to Order of the Minister of Health on medicinal products included in national health programs);
- ensuring technical support for quarterly appearance of the CANAMED (the national price catalogue), based on update of the Index of medicinal products.

- **Participation in reunions/workshops/informal meetings with stakeholders concerning legislation and procedure issues.**

- active participation in the "Pharmacovigilance Workshop" organised by the Romanian College of Pharmacists, in collaboration with ARPIM and APMGR, Bucharest, 31 August 2012.
- participation in informal reunions with the Romanian Association of International Medicines Manufacturers (ARPIM), the Generic Drug Manufacturers Association in Romania (APMGR) and independent Marketing Authorisation Holders (MAHs) in view of debating over legal issues such as:
  - implementation of new pharmacovigilance legislation,
  - the list of medicinal products exempt from safety elements imprinted on the packaging,
  - other regulations in the field of the medicinal product (approval of variations to MAs, approval of clinical trials etc.).
- meetings with the management of the Cantacuzino Institute to find solutions for the current situation.

- **Audit by representatives of the World Health Organisation (WHO)**

During 9-12 October 2012, the NAMMD hosted the WHO audit "Strengthening of the National Competent Authority", for assessment of the status of the national regulatory system (NRS) in the field of vaccines, in 6 areas:

- marketing authorisation,
- pharmacovigilance,
- official batch release,
- laboratory access,
- pharmaceutical inspection,
- clinical trials.

Implementation in the various audited areas was rated between 94% - 100%.

The audit team's report highlighted the following strengths:

- thoroughly documented and established system of legal provisions,
- batch release granted for locally manufactured vaccines (document testing and analysis) and imported vaccines (Mutual Recognition Procedure),
- thoroughly established quality management system, providing effective document control,
- involvement of the same staff in assessment, control and inspection activities, thus allowing for comprehensive outlook upon vaccine quality.

The following strengths have been listed as regards control laboratories:

- Staff aware of its responsibilities;
- High level of technical expertise;
- Thoroughly established quality management system;

The following strengths have been highlighted in marketing authorisation work:

- Legal provisions in place;
- Implementation of a European legislation;
- Similarity with competent regulatory bodies (EMA/European national competent authorities);
- Existence of a large scale of experience levels;
- Detailed requirements and directions, made public on the NAMMD website, available to all applicants.

- **Participation with specialised papers in various scientific events:**

- Farmacist.ro Forum, Bucharest, April 2012

- Forum of the pharmaceutical industry, Bucharest, June 2012

- Romania and Bulgaria HealthCare&Medical Investments Conference, Bucharest, July 2012

- National Conference of Pharmacy, Bucharest, November 2012

In the frame of NAMMD current activities, a few figures may be of significance for the scope of assessment and authorisation. In 2012, the three commissions for marketing authorisation/marketing authorisation renewal (the Marketing Authorisation Commission for National Procedure, the Marketing Authorisation Commission for European Procedures, the Marketing Authorisation Commission for Marketing Authorisation Renewal) reunited in 24 individual working meetings for discussion of assessment reports for decision on marketing authorisation of various medicinal products for which applications had been submitted. The Commissions have decided upon grant of 1125 Marketing Authorisations (MAs), of which 914 through European procedures (decentralised, mutual recognition, mutual recognition-repeat-use) and 211 through national procedure.

The database provided by the Index of medicinal products for human use has been supplemented with MA-related information: trade name, Marketing Authorisation Holder (MAH), batch release responsible person, packaging, Summary of Product Characteristics, leaflet.

Information regarding medicinal products included in the Index on the NAMMD website has been updated for availability to external users.

Among other activities, the Pharmaceutical Inspection Department (PID) conducted 24 inspections for assessment of compliance with Good Manufacturing Practice (GMP) rules in manufacturing/import/GMP certification authorisation, 6 inspections on Good Laboratory Practice (GLP) in laboratories performing bioequivalence studies, 4 inspections on Good Analytical Laboratory Practice (GALP) for authorisation of independent sites for control of medicinal product quality, 3 inspections for authorisation at the sites of medicinal product importers, 6 inspections for assessment of compliance with Good Clinical Practice (GCP), 2 pharmacovigilance inspections at the sites of Romanian MAHs and MAH representatives in Romania, 110 inspections for authorisation. In other respects, 3 follow-up inspections have been carried out for assessment of the manufacturing process and implementation of corrective measures proposed as included in measure plans submitted to the NAMMD for authorisation; 13 follow-up inspections have been carried out for assessment of the distribution process and implementation of corrective measures proposed as included in measure plans submitted to the NAMMD for authorisation; export declarations have been approved for 1855 medicinal products manufactured/marketed in Romania.

As of April 2012, the PID has undertaken assessment of documentation submitted for approval of medicinal product donations, in accordance with legislation in force; 81 approvals for donations were released by the end of 2012.

As regards "parallel import" activities, 52 parallel import authorisations (PIAs) have been released for the Romanian pharmaceutical market.

"Parallel export" consisted in 560 responses to requests for information from 19 EU competent authorities (in addition to about 120 responses for clarification and supplementation of initially provided information), for grant of parallel import authorisation for the respective member states. Therefore, there is an obvious disparity between "parallel import" and „parallel export", as shown by large number of requests from the 19 fellow EU competent agencies regarding provision of information about MAs issued in Romania, required for grant of parallel import authorisation by a national agency in the respective country. „Parallel export" is known to actually represent intracommunity trade performed within the EU. In its respect, although national competent authorities have little room for intervention, they should nevertheless be aware of the true scope of the phenomenon. This underlies adoption by the NAMMD Scientific Council of Decision (SCD) no. 9/10 July 2012 on Approval of mandatory monthly reporting of placement on the Romanian market and of sales of medicinal products for human use by authorised wholesale distributors/importers/manufacturers; the decision has been submitted for approval through Order of the Minister of Health. The decision comes in response to findings by NAMMD inspectors of non-compliances in wholesale distribution, i.e. failure of all parties concerned to meet their obligation regarding compulsory monthly reporting of placement on the Romanian market and sales of medicinal products for human use, in accordance with SCD no. 5/2011 and SCD no. 17/2011 on extension of term provided in Article 4 of NAMMD Scientific Council Decision No.5/22.02.2011, set for 01.11.2011.

Clinical trials, performed in accordance with European regulations in force, attest the clinical efficacy and safety of medicinal products proposed for authorisation. Authorisation of medicinal products requires conduct of many clinical trials, their number varying depending on the individual product and its stage of development. As a rule, all four clinical trial stages should be accomplished in relation to one medicinal product. In 2012, the number of applications for authorisation for conduct of clinical trials is practically constant in comparison to 2011, showing a slight decrease from previous years, as results from comparison between the yearly numbers of applications (248 in 2012, 246 in 2011, as opposed to 266 in 2010, 253 in 2009 or 275 in 2008).

This year as well, therapeutic areas for which authorisation of clinical trials has been required have been as follows: psychiatry, neurology, oncology, diabetology, rheumatology, gastroenterology, pneumology, infectious diseases, hematology, cardiology, endocrinology.

Throughout 2012, the NAMMD granted 221 authorisations for conduct of clinical trials, mostly for Phase III (146) and Phase II (60) clinical trials.

Moreover, following assessment in the National Procedure Assessment Service of protocols of bioequivalence clinical trials, 73 authorisations were granted in this respect.

It is worth mentioning that year 2012 involved participation of the NAMMD through its representatives to meetings of working groups of European bodies in the medicinal product field, for debate on proposed amendment of EU legislation for clinical trials.

As regards pharmacovigilance, the scope of work carried out in the Pharmacovigilance and Risk Management Service as part of the European Procedures Department, year 2012 proved increased responsibility of Romanian physicians in what concerns adverse reaction (AR) reporting. If, for instance, in 2008, there were 280 spontaneous reports submitted, their number increased to 525 in 2009 and 939 (serious and non-serious) in 2010. In 2011, the NAMMD received 1011 adverse reactions reports (448 non-serious and 563 serious), directly by physicians (105 non-serious and 83 serious) and by MAHs, from physicians in respective areas (343 non-serious and 480 serious). Apart from submission of serious adverse reactions to the Agency, MAHs also have to submit them directly into the European database for adverse reactions to medicinal products (EudraVigilance). In 2012, 1272 ARs were reported to the NAMMD (719 serious and 553 non-serious adverse reactions).

The increasing numbers of reports speak for the growing importance physicians assign to their patients' safety; however, intensified involvement on behalf of healthcare professionals is expected in this respect.

The new European legislation (transposed into Romanian legislation through Emergency Government Ordinance 35/2012 amending certain healthcare regulations), has meant amendment, under the chapter *Pharmacovigilance* of Law 95/2006 on healthcare reform, as amended, also empowering other professional categories, apart from physicians, and even patients, to report adverse reactions to medicinal products to the competent authority/MAH. Each AR occurrence submitted to the European database (EudraVigilance) or the database of the World Health Organisation (WHO) means a step forward as regards better knowledge of medicinal products.

Even the possibility of AR reporting by a category called "*consumer*/consummator" has even been introduced through law (including, apart from patients, jurists, patient's next of kin, neighbours). In accordance with the recommendations of the European Good Pharmacovigilance Practice Guideline, for confirmation of adverse events/reactions reported by persons included in this category, the NAMMD Pharmacovigilance Service intends to require reporter consent to contact the prescribing physician.

More accurate determination of the safety profile of the medicinal product is thus expected through joint physician-pharmacist-assistant-consumer effort.

It is thus worth mentioning that the first steps for implementation of the new pharmacovigilance approach have already been taken in 2012. Of the 1272 ARs reported, 1003 were submitted by physicians, 12 by pharmacists, 60 by assistants and 32 by consumers.

In the context of completion of transposition into national legislation of Directive 2011/62/EU as regards the prevention of the entry into the legal supply chain of falsified medicinal products and setup of the new frame for implementation of the new provisions, the establishment of a general framework for bilateral cooperation and exchange of information in the field of medicinal products counterfeiting has been one of the main objectives, in cooperation with the General Inspectorate of Romanian Police.

The main lines for NAMMD - General Inspectorate of Romanian Police collaboration have been:

- Compliance with the legislation for medicinal products for human use;
- Exchange of information to meet legal assignments of both institutions;
- Supervision of operation of markets for identification of cases of non-compliance with national and/or community legislation in terms of falsification of medicinal products and legal provisions on medicinal products for human use, enabling the two authorities to take the required measures, in accordance with the abilities of each of them and their correlation;
- Media coverage and notification of the general public and businesses in medicinal products for human use, concerning measures taken in cases of violation of national and/or community legislation on medicinal product counterfeiting;
- Mutual support to ensure effective operation and security of the medicinal product for human use, also as regards regulatory amendments required.

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

In 2012, a control activity has been carried out. It consisted of periodic check-up of medical devices and concerned all medical devices assembled and commissioned, with a high risk degree, at the sites of all users of medical devices, in both public and private sector, and consists of assessment of performances and safety of medical devices in use; the bulletin for periodic check-up is one of the documents required in view of signing the medical service contract between health insurance houses and cabinets/hospitals/medical centres.

In March 2012, RENAR conducted the surveillance of laboratories for testing and assay of medical devices within the Laboratories Technical Department (LTD) and the Nuclear Unit (NU), which analysed the manner of performance of field testing. Results have been found appropriate.

In 2012, due to tremendous efforts, the List of medical devices undergoing control through periodic check-up was reviewed, so as to contain only medical devices with the highest risk for patients and users. Thus, the replacement of Order of the Minister of Health no.1662/2007 on periodic check-up control of medical devices is envisaged, as amended.

Having few employees, the Technical-Medical Units Assessment Department must ensure activity of approval of medical technique units (medical optics, medical devices and auditive/orthopaedic/other types of prosthesis) throughout the country, by performing the initial evaluation of organisations in view of granting an operation approval, surveillance evaluations every two years, as well as observation and sanctioning of contraventions in accordance with Law 176/2000 on medical devices, as amended.

NAMMD ACTIVITIES IN 2012

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

In 2012, the Scientific Council adopted 9 Scientific Council Decisions; out of these, 4 regulatory decisions are pending approval through Order of the Minister of Health (OMH) and are to be published in the Official Gazette of Romania, Part I; the remainder of 5 SCDs are posted on the NAMMD website and published in the bilingual NAMMD Newsletter of 2012.

For implementation of provisions of Title XVII - The medicinal product of Law 95/2006 on healthcare reform, published in the Official Gazette of Romania, Part I, no. 372/28.04.2006, and in accordance with provisions of Government Decision 734/2010 on organisation and operation of the NAMMD, the Agency establishes rules, directions and other mandatory

regulations, concerning its specific activity in the field of the medicinal product for human use, submitted for approval to the Ministry of Health as regulatory SCDs. Approval is expressed through Order of the Minister of Health, subsequently published in the Official Gazette of Romania, Part I.

As regards regulatory SCDs (as shown in the details provided under section 3 of this Report. "Regulatory activity", it should be noted that regulatory provisions of SCD no. 9/10 July 2012, setting up mandatory monthly reporting of marketing in Romania, namely of sales of medicinal products for human use by authorised wholesale distributors/importers/ manufacturers aim at provision of traceability of medicinal products throughout the entire chain, from manufacturing and/or distribution to community pharmacy, hospital pharmacy, drugstore.

Non-regulatory SCDs referred to:

- approval of the Guideline on NAMMD use of the EU Administration Procedure on official release of biological product batches;
- approval of the Regulations on the manner of handling of proposals for "umbrella" trade names and other trade names for medicinal products for human use in relation to food supplements, cosmetics and medical devices;
- approval of the Guideline on Good Manufacturing Practice for medicinal products for human use;
- approval of amendment of the Annex to SCD no. 29/16.12.2010 on approval of Regulations on authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania.

2. Activity of the NAMMD Administration Council (AC)

In 2012, the Administrative Council (AC) adopted 5 Administration Council Decisions (ACDs).

Thematically speaking, ACDs have covered various aspects of current activities, such as amendment of the Regulation on the organisation and operation of the AC, draft of amendment of Order of the Minister of Health no. 1369/2009 on approval of fees required by the (former) Technical Office for Medical Devices, as amended, approval of investments and others.

3. Regulatory activity

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

- Emergency Ordinance on amendment and supplementation of Law 95/2006 on healthcare reform concerning transposition of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, published in the Official Journal of the European Union no. L384/74 of 31 December 2010;
- Emergency Ordinance on amendment and supplementation of Law no. 95/2006 on healthcare reform for transposition of Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, published in the Official Journal of the European Union no. L174/86 of 01.07.2011;

- Order of the Minister of Health for amendment of Order of the Minister of Health no.716/2009 on approval of tariffs and marketing authorisation maintenance fee required by the National Medicines Agency;

- Order of the Minister of Health for amendment of Order of the Minister of Health no. 1369/2009 on approval of fees required by the Technical Office for Medical Devices for activities performed, published in the Official Gazette of Romania, Part I, no. 752/04.11.2009.

Given growth in complexity of NAMMD activity as a national authority within the network of EU competent authorities in the medicinal product field for human use, work of the NAMMD Scientific Council for approval of certain regulatory SCDs was continued in 2012 as well.

Of the 9 Scientific Council Decisions approved, 4 have been submitted for Ministry of Health approval through Order of the Minister of Health. These SCDs refer to:

- approval of NAMMD procedure for cancellation of applications for marketing autorisation/ marketing autorisation renewal for medicinal products for human use;

- approval of the procedure and rules for accreditation by the NAMMD of national Good Clinical Practice training providers;

- amendment of SCD no. 19/07.11.2008 on approval of Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and grant of the Good Manufacturing Practice certificate to manufacturers of medicinal products for human use and/or active substances;

- Approval of the mandatory monthly reporting of placement on the Romanian market and of sales of medicinal products for human use by authorised wholesale distributors/importers/manufacturers.

Compliance with the mandatory monthly reporting of inputs/outputs by all manufacturers/importers/wholesale distributors means provision of traceability of medicinal products throughout the entire chain, from manufacturing and/or distribution to the level of community pharmacy, hospital pharmacy, drugstore, enabling the NAMMD to:

- assess the justness of release of medicinal products with or without medical prescription,

- track falsified medicinal products and

- prevent their entry into the authorised distribution network,

- fight the existence of illegal parallel circuits for medicinal product sales, namely

- grant fast recall of non-compliant medicinal product batches or in case of health emergencies.

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions (CAPP)

As in previous years, in 2012, as a consequence of the setup of 3 commissions for marketing authorisation/marketing authorisation renewal approved through NAMMD Administration Council Decision (CAPP-National Procedure, CAPP-European Procedures, CAPP-Renewals), whose structure has been established through Decision of the NAMMD President), assessment reports have been discussed, in order to provide an opinion concerning marketing authorisation of various medicinal products for human use for which an application has been submitted in this respect, as well as other aspects related to the marketing authorisation of medicinal products for human use.

In 2012, 24 working sessions took place with the participation of various commissions.

The Commissions approved the issuance of 1125 marketing authorisations, of which 914 through European procedures (decentralised, mutual recognition, mutual recognition-repeat-use) and 211 through national procedure.

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

In accordance with its own regulation for organisation and operation, approved through a NAMMD Administration Council Decision and in a structure approved through President Decision, the Commission continued its activity in 2012 as well. The Commission reviews inspection reports issued by Agency inspectors, concerning the manner of compliance by inspected units with Good Manufacturing Practice, Good Distribution Practice, Good Laboratory Practice, Good Analytical Laboratory Practice, Good Clinical Practice rules and/or with other issues concerning work of the Pharmaceutical Inspection Department.

The Commission acts as mediator in cases of inspection decisions disputed by the inspected site.

In 2012, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 181 inspection reports, of which:

- 34 inspection reports on compliance with Good Manufacturing Practice rules;
- 123 inspection reports on compliance with Good Distribution Practice rules;
- 6 unexpected inspection reports on compliance with Good Distribution Practice rules;
- 4 inspection reports on compliance with Good Analytical Laboratory Practice rules;
- 2 pharmacovigilance inspection reports.

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

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

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

In 2012, there were no requests for summons of the Commission.

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

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

In 2012, there were no requests for summons of the Commission.

5. Marketing authorisation and related activities

In direct relation to the increasingly stricter regulation of activities specific to a competent authority in the EU medicinal product field, year 2012 was as complex as the previous year with regard to assessment of documentation submitted to the NAMMD for marketing authorisation (MA), renewal of marketing authorisation and post-authorisation surveillance of medicinal products.

Performed in accordance with specific provisions related to national and European procedures (mutual recognition, decentralised, repeated mutual recognition procedures), in 2012, marketing authorisation and related activities were conducted in line with the organisational structure of 2011, established in 2010 and approved through Order of the Minister of Health on the organisation and setup of the National Procedure Department and the European Procedures Department.

5.1. Marketing authorisation through national and European procedures

In 2012, a number of 1400 applications for marketing authorisation/marketing authorisation renewal were received, 402 through national procedure and 998 through European procedures (Decentralised Procedure-DCP, Mutual Recognition Procedure-MRP and "*repeat use*" procedure).

Assessment work performed within the European Procedures Department resulted in grant of 914 marketing authorisations and Annexes 1-5, which represents an increase compared to last year (883).

As regards assessment through national procedure, this resulted in grant of 211 marketing authorisations, confirming the decreasing tendency for the number of applications for marketing authorisations granted through national procedure, in favour of authorisations granted through European Procedures (EPs).

Overall, it is evident that, in the context of the past few years, the number of MAs granted by the Agency in 2012 was larger, namely: MAs through NP and EPs: 2009=927, 2010=813, 2011 = 1030 and 2012 = 1125.

A comparative perspective shows an almost unchanged number of decisions for discontinuation of authorisation/renewal procedure, on MAH request for trade reasons, in 2009 and 2011, namely: number of MA applications discontinued: 2009=134 and 2011=131, compared to 2010=202 and 2012=247.

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

In 2012, a number of 6429 applications for variation to MA terms were submitted concerning medicinal products authorised through national and European procedures, of which 3102 applications for type IA, IB and II variations to MA terms, MA notifications for nationally authorised products and 3327 for type IA, IB and II variations to MA terms, MA notifications through European procedures.

The above numbers do not include either applications for discontinuation of applications for variation (for medicinal products whose marketing authorisation has expired and in relation to which no application has been submitted for renewal as well as medicinal products for which decisions were issued for discontinuation of marketing authorisation or variation procedures on company request), or applications for variation in accordance with SCD 30/2010 on approval of the manner of handling of Type IA and IB variations not amending marketing authorisation terms for nationally authorised medicinal products.

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

- 3151 applications for type I variations;
- 596 applications for type II variations;
- 87 applications for MA transfer;
- 226 changes of packaging design and printing;
- 969 safety and efficacy variations.

5.2.2. In 2012, as regards **post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures**, for medicinal products for human use authorised through decentralised/mutual recognition/repeated mutual recognition procedure, the Agency approved:

- 1994 applications for type IA variations with Romania as a concerned member state; 7 applications for type IA variations for Romania as a reference member state;
- 2116 applications for type IB variations with Romania as a concerned member state; 19 applications for type IB variations with Romania as a reference member state;
- 535 applications for type II variations with Romania as a concerned member state;
- 80 applications for MA transfer with Romania as a reference member state;
- 42 notifications in accordance with Article 61 (3) of Directive 2001/83/EC;
- 5 safety and efficacy variations.

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

In 2012, the number of applications for authorisation of clinical trials has remained constant and following slight decrease in 2011, as evident from comparing the yearly number of applications submitted (248 in 2012 vs. 246 in 2011, 266 in 2010, 253 in 2009 or 275 in 2008).

Most of these are Phase III clinical trial applications (158 applications in 2012), 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 (75 applications in 2012); these are exploratory studies concerning the most effective dose for medicinal products whose safety and tolerability have been proven.

In Romania, there are few applications for performance of Phase I clinical trials (4 applications in 2012), which requires special conditions.

Therapeutic areas for which clinical trial authorisation was required in 2012 have been the following: psychiatry, neurology, oncology, diabetology, rheumatology, gastroenterology, pneumology, infectious diseases, haematology, cardiology, endocrinology.

In 2012, the NAMMD granted 221 authorisations for performance of clinical trials, mostly for Phase III (146) and II (60) clinical trials.

Moreover, 50 applications for observational clinical trials were received; acknowledgement letters have been issued on 25 observational studies.

In 2012, the Clinical Trial Service of the National Procedure Department approved 615 substantial amendments and 222 amendments for new investigational sites; moreover, 73 authorisations for conduct of bioequivalence clinical trials were granted after assessment by the National Procedure Assessment Service of the protocol of bioequivalence clinical trials.

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

In 2012, the National Medicines Agency and Medical Devices assessed for approval 495 advertising materials to the general public concerning OTC medicinal products; 465 advertising materials for OTCs have also been assessed for re-approval.

Of these, 16 applications for advertising material were not approved and respective applicants have received notifications of rejection of advertising.

As regards advertising materials to be used in educational programmes, 139 educational items were assessed and approved.

In the same way as during the previous two years, in 2012 as well the same special emphasis was placed upon surveillance and control of advertising of medicinal products for

human use. Thus, under the special heading on the Agency's website, "Advertising", various notifications to healthcare professionals have been posted, dealing with certain medicinal products for which withdrawal from the press has been required, following non-compliance with advertising regulations provided for in the Guideline on evaluation of advertising in medicinal products for human use, approved through SCD no. 21/2011.

5.5. Pharmacovigilance

Issues related to safety of medicinal products currently authorised in Romania are managed through the NAMMD's Pharmacovigilance and risk management service, part of the Agency's European Procedures Department, whose activity is entirely compliant with Law no. 95/2006 and specific European Guidelines.

As confirmed by recent increasingly manifest concern with regulation, pharmacovigilance represents an extremely dynamic and interactive field of activity, developed in time as a requisite for patient safety. According to public documents of the European Commission, pharmacovigilance is "the science relating to the detection, assessment and prevention of adverse effects and all related activities".

As key part of authorisation of medicinal products for human use, pharmacovigilance work already has considerable history in Romania, as detailed in the NAMMD Activity report, 2011 .

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

Pharmacovigilance also involves approval of direct healthcare professional communications concerning special warnings on medicinal product safety, as well as translation of EMA press releases and Q&A documents, actually notifications from the monthly CHMP meetings, for posting on the NAMMD website. An additional NAMMD pharmacovigilance task is response to requests for non-urgent information from the European and international rapid alert system.

For protection of public health, in line with European regulations in force, all types of information available related to medicinal product safety are currently posted on the NAMMD website.

To increase their awareness concerning the importance of spontaneous suspected adverse reactions reporting, an appeal to reporting is addressed to physicians both directly, during scientific symposia, national conferences and congresses as well as through direct healthcare professional communications.

In this context, the incentive designed by the Agency for AR reporting, in cooperation with the Romanian College of Physicians, after entry into force of Emergency Government Ordinance no. 35/July 2012, consists of granting Continuing Medical Education (CME) and Continuing Pharmaceutical Education (CPE) Credits to reporters (physicians and pharmacists), in accordance with the procedure agreed by the two institutions.

Romanian physicians have proven increased interest in AR reporting for patient safety throughout the past years.

Therefore, for instance, 280 spontaneous reports were submitted in 2004, 525 were reported in 2009, 938 in 2010 and 1011 (serious and non-serious adverse reactions) in 2011.

In 2012, pharmacovigilance activities mainly materialised in the following:

a) management of safety data issued from spontaneous reporting:

- validations/confirmations of adverse reaction (AR) reporting to the European database for adverse reactions, EudraVigilance (ICSR and SUSAR) - 1750
- spontaneous adverse reactions
  - non-serious: 554 (of which 95 to physicians)
  - serious: 978 forwarde3d to the EudraVigilance (of which 109 to physicians)
  - 345 follow-up reports.
- 323 electronic transmissions of adverse reactions to the WHO database (the Uppsala Monitoring Centre) via the VigiFlow electronic channel;
- 198 confirmations of submission of spontaneous reporting of adverse reactions from physicians in the network;
- 388 information points for physicians on grant of Continuing Medical Education (CME) credits for adverse reaction reporting;
- 252 responses to MAH requests concerning adverse reactions reported to the NAMMD involving medicinal products authorised in Romania;
- 158 response letters on MAH requests concerning pharmacovigilance-related aspects.

b) Collection, validation and archiving of 2218 Periodic Safety Update Reports (PSURs) for medicinal products authorised through national or European procedures (decentralised, mutual recognition, mutual recognition – repeat use procedures).

- 1 PSUR assessment report was issued for medicinal products undergoing MA renewal through national procedure.

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

- Handling of EMA press releases and "Questions and Answers" documents – documents for request of information, handling and proofreading of translations, sent for publication on the NAMMD website: 74;

- "Lines to take" documents approved by the EMA;

- management of documents (record, archiving, notification of the press officer), notification of the Pharmacovigilance and Risk Management Service on provision of responses to potential requests of information: 52;

- approval and management of 50 Direct Healthcare Professional Communications (DHPCs) related to safety concerns raised in relation with medicinal products;

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

- activities concerning MAH notification for SmPC and leaflet harmonisation following referral procedure, upon request of the PhWWP/CHMP/CMDh for individual medicinal products or groups of medicinal products: 13;

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

- replies (INU) upon request for information by certain EU national authorities concerning information about individual medicinal products or medicinal products categories, other information concerning measures for enforcement of pharmacovigilance legislation: 23

e) assessment of MA applicant compliance with requirements for detailed description of the pharmacovigilance system:

- assessment reports of the summary of the MA applicant's pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) for authorisation through decentralised/mutual recognition/mutual recognition – repeat use procedure:
    - Romania as a concerned member state: 1612 reports
    - Romania as a reference member state: 5 reports
- assessment reports of the MA applicant's pharmacovigilance system concerning requirements for Detailed Description of the Pharmacovigilance System (DDPS) for authorisation through national procedure: for 174 medicinal products from 65 MAHs/applicants.
- assessment reports of applications for variation to MA applicant's summary of the pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) for authorisation:
    - ✓ Applications for national procedure approved:30
    - ✓ Applications for national procedure assessed:63
    - ✓ Applications assessed for DCP/MRP/MRP-RU procedures:73
    - ✓ Applications for parallel import procedure: 80

f) assessment and approval of educational materials included in the Risk Management Plan (RMP) for centrally authorised medicinal products based on European Commission Decision in accordance with Article 127a of Directive (EC) 2001/83

- 51 completed dossiers containing 92 educational materials;
- 14 dossiers in progress (17 educational materials).

5.6. Other activities

- Management of the database for the Index of medicinal products for human use consisted of introduction of new medicinal products authorised through national, European and centralised procedures, implementation of MA changes for already authorised medicinal products, introduction of approved variations to approved MA terms, keeping track of medicinal products undergoing MA renewal and of MA withdrawal/discontinuation decisions. Thus, the National Procedure Department (with support from IT experts in the Information Logistics and Electronic Management of Data Department) managed to ensure:

a) Maintenance of the database of authorised medicinal products:

- Addition of 945 medicinal products (authorised through national/European/ centralised procedure) – introduction of information concerning MA granted: trade name, MAH, batch release responsible person, packagings and set-up of *links* for SmPC, packagings, leaflets and MAs;
- Addition of 4950 variations to MAs granted through national/European/centralised procedure (introduction of information concerning amendments to MA terms): Trade name, MAH, batch release responsible person, packagings etc.);
- Set-up of links for SmPCs, packagings, leaflets and labelling – containing updated information, enabling easy access of external users to Annexes 1, 2, 3 of the Index of Medicinal Products posted on the NAMMD website;
- Issuance of 247 decisions for MA withdrawal/discontinuation (withdrawal of national MA when the same product is granted marketing authorisation through European procedure; discontinuation of a valid MA on request by the company);
- Management of data concerning MA maintenance fee: 4230 medicinal products;

- Assessment of the National Brochure of the prices of medicinal products 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 for reception of SIIS (single integrated information system) data (quarterly and whenever required by the NHIH);
- 24425 PDF files, as current versions of Annexes I, II and III, have been published on the NAMMD website, via the Index of medicinal products in web format, for the aforementioned products.

b) Various responses to requests of the Ministry of Health, NHIH, other institutions, legal and natural entities): 97.

As regards ”parallel import” activities, 52 parallel import authorisations (PIAs) have been granted.

In this respect, 74 requests for information (plus 30 requests for disambiguation and completion of information received) delivered to 9 EU competent authorities required for PIA release and amendment of PIAs granted (13 variations to PIAs were sent);

”Parallel export” activities consisted of:

- issuance of 560 responses to requests for information received from 19 EU competent authorities (plus another about 120 responses for disambiguation and completion of initially forwarded information), for grant of a parallel import authorisation for the respective member states;

The following activities have also been continued:

- management of responses received under application of provisions of Article 729 and 730 of Law no. 95/2006, i.e. notification of temporary or permanent discontinuation of manufacturing and notification of actual medicinal product marketing (“*sunset clause*“);

As regards *“sunset clause”* implementation, assessment of the database set up according to documents submitted by the MAH is worth mentioning. About **115** reports have been submitted from companies/representations (dossiers and electronic formats), on behalf of 194 MAHs**.** Work related with application of the clause is expected to be completed by the first quarter of 2013.

- Management of the database related to EMA authorised medicinal products based on provisions of Article 127a of Directive 2001/83/EC and monitoring of implementation of conditions and restrictions placed on the MAH by the European Commission;

- Management of European Commission (EC) decisions related to referrals, draft of the letters to MAHs involved for request of submission of variation applications for implementation of the EC Decision.

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

In the course of 2012, the Pharmaceutical Inspection Department (PID) continued to perform activities mentioned in specific legislation (Law no. 95/2006, Title XVII – The medicinal product and secondary legislation thereof), in accordance with the department’s *Standard Operating Procedures (SOPs)*, endeavouring to effectively accomplish its tasks by the deadlines stipulated by law.

The following have been prepared and issued in the PID Processes Administration Service:

- 30 Good Manufacturing Practice (GMP) certificates (for Romanian and foreign manufacturers);

- 54 manufacturing authorisations, annexes included;
- 49 import authorisations, annexes included;
- 7 Good Laboratory Practice (GLP) certificates;
- 18 certificates for Qualified Persons;
- 1 authorisation for independent control units;
- 150 dossiers for the inspected units, and for units requesting update of annexes to manufacturing/import authorisations have been issued and handled;
- 147 applications for waiver from legal provisions concerning medicinal product packaging/labelling have been solved;
- management of databases of inspection encoding, the list of authorised/certified manufacturing units, authorised importers, medicinal products for which the export declaration has been approved, and Qualified Persons.

Inspection work in the fields of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Analytical Laboratory Practice (GALP), Good Clinical Practice (GCP), and Good Pharmacovigilance in 2012 consisted of:

- 24 GMP inspections in Romania, for manufacturing authorisation;
- 3 follow-up inspections, for assessment of manufacturing work and the manner of implementation of corrective measures proposed in measure plans forwarded to the NAMMD in view of authorisation;
- 3 inspections to medicinal prodcut importers, for authorisation purposes;
- 1 certification inspection for GMP compliance of pharmaceutical companies from third countries;
- 6 GLP inspections in laboratories performing bioequivalence studies;
- 4 GALP inspections in independent sites for medicinal product quality control;
- 6 inspection assessing compliance with GCP rules;
- 2 pharmacovigilance inspections at Romanian MAH sites, and Romanian MAH representatives sites, according to the yearly inspection plan of the Pharmaceutical Inspection Department.

In February and March 2012, a NAMMD-PID inspector, an inspector from the Agence Française de Sécurité Sanitaire des Produits de Santé and other inspectors from the Czech State Institute for Drug Control participated in two inspections requested by the European Medicines Agency (EMA), enforcing the reconfirmation of GMP compliance by two US manufacturers for centrally authorised medicinal products.

In June 2012, a NAMMD PID inspector acted as lead in the inspection at the site of a manufacturer in Romania, organised in the context of the PIC/S programme (Pharmaceutical Inspection Co-operation Scheme) for joint visit; 2 GMP inspectors (France and Poland) also took part in this inspection.

As regards inspection of Good Distribution Practice (GDP), inspections conducted in 2012 were as follows:

- 110 inspections for authorisation;
- grant of 243 wholesale distribution authorisations and their annexes;
- 13 follow-up inspections to assess distribution and the manner of corrective actions implementation as submitted to the NAMMD for authorisation purposes;
- together with representatives of the Ministry of Health (the Supervisory Body of the Ministry of Health), the Fraud Squad and local police inspectorates, 6 unexpected inspections were conducted at several sites of a wholesale distribution unit authorised by the NAMMD; no critical deficiencies concerning the performed activity have been found.
- 4 inspections for supervision of the quality of distributed medicinal products, consisting of check of traceability of medicinal products purchased/traded by wholesale

distributors. This resulted in enforcement of penalties and suspension of the wholesale distribution authorisation for 3 inspected units;

- 149 dossiers for the inspected sites, namely applicants for update of Annexes to wholesale distribution authorisations, were set up and handled;

- the dossier for 372 applications for approval of export declaration was approved, leading to approval of export declarations for 1855 medicinal products manufactured/sold in Romania.

As regards certification of Qualified Persons, the dossier for grant of the Certificate attesting the Qualified Person status was checked and assessed; 18 such certificates were granted.

As of April 2012, the PID has undertaken assessment of documentation submitted for approval of donations of medicinal products, in accordance with legislation in force; 81 approvals for donation and the associated annexes were released before the end of 2012.

In 2012 as well, the PID collaborated with the department responsible for approval of advertising material on medicinal products for human use (The Information Logistics and Electronic Management of Data Department), assessing issues related with MAH non-compliance with legislation concerning advertising of medicinal products for human use.

This year, in accordance with provisions of SCD no. 4/22.02.2011 on approval of basic criteria for NAMMD inspectors' acceptance of free sample provision and approval of the Annex to Scientific Council Decision No. 3/23.03.2010 on approval of Implementation rules on provision of free samples of medicinal products for human use, 75 applications for provision of samples were received and assessed for 80 authorised products; the PID has authorised provision of samples for 64 medicinal products; moreover, reports on the situation of samples offered to healthcare professionals have been received and assessed, of which 19, submitted by 16 MAHs or their representatives, have been accepted. A database has been set up on MAH management of medical samples provision.

Surveillance of medicinal product quality and management of rapid alerts consisted of:

a) Execution of the sampling scheme for medicinal product quality monitoring:

- Of the 32 products proposed, 27 were sampled and 5 were not found in the distribution network;

- 26 samples have been declared compliant, following laboratory testing; 1 has been declared non-compliant (the product has been recalled and destroyed).

In addition to the sampling plan, the following have been sampled in 2012:

- 3 medicinal products sampled on request of the Quality Control Department, for participation in market surveillance studies proposed by the OMCL network (Official Medicines Control Laboratories); all samples of medicinal products have been declared appropriate;

- 12 medicinal products sampled for resolution of medicinal product quality complaints; all medicinal products sampled have been found compliant;

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

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

- 330 thematic inspections in 2025 wholesale and retail distribution units.

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

- 200 were carried out in hospitals across the country to stop use of unauthorised oxygen (liquid oxygen is provided by GMP certified producers, whereas compressed oxygen for 13

hospitals (6.5 %), less than the previous year, is still provided by unauthorised manufacturers). The Ministry of Health has been informed on the situation.

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

- 8 joint actions with specialised local bodies, carried out by field inspectors (1 Cluj, 2 Târgu Mureş, 3 Galaţi, 2 Bacău).

e) Resolution of 28 complaints relating to possible quality noncompliances of medicinal products for human use:

- all complaints received have been resolved as follows: 20 have been filed without additional measures, 6 have been found justified, resulting in recall of the respective medicinal products from the market (4), request for submission of application for variation (1) or imposition of penalty on wholesaler (1). Two complaints have been redirected as outside the NAMMD scope. Most complaints were submitted (20) by NAMMD field inspectors and referred to inappropriate imprinting of primary/secondary packaging or set up of Leaflets of certain medicinal products. Remaining complaints have been filed by patients or healthcare professionals.

f) Recall from the market of quality noncompliant medicinal products: in 2012, the NAMMD requested recall of 60 medicinal products (more than during the previous year), of which:

- 34 medicinal products were identified with intrinsic quality nonconformities and have therefore been proposed for destruction (4 following complaints, 23 due to rapid alert/nonconformities with GMP rules), 7 voluntary recalls performed by manufacturers);

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

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

- 4 medicinal products recalled following withdrawal of marketing authorisations.

g) Rapid alert system:

- in 2012, 112 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Of these, 8 have envisaged products authorised and imported/distributed in Romania; in 2012, the NAMMD issued no Rapid Alert.

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

- measures decided in accordance with joint authorities' decisions related to 14 cases reported of non-compliance with GMP rules by active substances or medicinal products manufacturers from third countries;

- steps taken to change active substance suppliers related suspension/withdrawal by the EDQM of 12 certificates of conformity with the European Pharmacopoeia.

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

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

In October 2012, the PID was audited by representatives of the World Health Organisation, as part of the audit mission to Romania for assessment of NAMMD regulatory activities concerning vaccines for human use. The audit ended with favourable conclusions regarding PID activity and recommendation for improvement.

In December 2012, a NAMMD-PID inspector took part as facilitator, in conjunction with PIC/S inspectors from Belgium and Singapore, in the workshop organised by the World Health Organisation for training of GMP inspectors, conducted in China.

In 2012, PID activity related to harmonisation with EU legislation of inspection legislation consisted of participation to transposition of Directive 2011/62, amending Directive 2001/83. The new regulations have been approved through Emergency Government Ordinance no. 91/2012.

7. Quality control of medicinal products for human use

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

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

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

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

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

The main activities performed in 2012 envisaged:

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

In 2012, 58 medicinal products were submitted for MPQCD testing (27 – as part of the Annual Plan for Sampling and Testing, 15 – products subject of complaints, 16 – international collaborations), of which 47 have been concluded and 10 are currently undergoing various stages of testing. For medicinal products still under testing, microbiological and pharmacotoxicological tests have been performed. These have not been concluded in 2012, because of objective grounds (supplementation of the analytical documentation concerning the product's purity has not yet been submitted by the manufacturer, deadline: April 2013, in accordance with the deadline required through MRP etc.)

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

For the 47 medicinal products tested within the MPQCD in 2012, 410 individual parameters were analysed, according to the techniques described in the European Pharmacopoeia or the manufacturer's pharmaceutical files.

Among frequent and complex analytical techniques used in 2012, in the context of medicinal product quality control, the following are worth mentioning: HPLC, pH-metry, Karl Ficher, spectrophotometry (IR, UV-Vis), pharmacotechnical testing (dissolution, mechanical resistance), volumetric dosing, determination of substance melting points, determination of liquid densities, determination of refractive indices, antibiotic microbiological dosage, sterilities (parenterals) and microbiological contaminations (ophthalmic solutions, syrups and paediatric solutions, certain film-coated tablets and capsules), endotoxin determinations (LAL test).

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

Laboratory investigations of medicinal products included in this category have not revealed quality deficiencies, except for one product, for which a non-compliant certificate of analysis has been issued and has subsequently been recalled from the market.

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

As regards medicinal products subject to complaints from patients or healthcare units, the PID has required laboratory testing (physico-chemical, pharmacological or microbiological, as required), for 15 medicinal products received/sampled locally, suspected of quality deficiencies. Among these, only one complaint was just, the other 14 being compliant with approved quality provisions.

In 2012 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).

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

- PTS (Proficiency Testing Scheme) studies – Inter-laboratory studies for measurement of professional performance, based on analytical protocols forwarded by the EDQM.

In 2012, 3 inter-laboratory studies have been conducted within the MPQCD.

The evaluation of performances and testing capability in resolution of difficult issues related to medicinal product control relies on interpretation of outcomes obtained by each laboratory, depending on several statistical operators (average of determinations, standard deviation, relative standard deviation).

An integrated value, "the Z-score", is obtained by processing the above operators, expressing professional capacity and ability for each laboratory and considered a performance indicator when ≤ 2.

As shown by data from the 3 studies as communicated by the EDQM, as far as the 6 samples analysed by the MPQCD are concerned, values obtained comply with the specified performance criterion, since „the Z-score" scored lower than 2.

- CRS studies - Chemical reference substances - 1 sample, tested for assessment of the laboratory technique, described in the PhEur monograph, concerning assay of antifungal activity by microbiological dosage in the tested substance. The outcomes, found compliant by the EDQM, are to be used in the next review of the monograph of the respective substance.
    - MRP studies for surveillance of the quality of medicinal products authorised through European procedures - 1 sample.

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

Laboratory testing performed within the MPQCD for the respective sample, has ascertained reproducibility of the control methodology underlying the approved documentation, whereas the medicinal product was found appropriate in terms of quality. According to procedure, results obtained have been forwarded to the EDQM and entered into the EDQM-MRP electronic database.

- Inter-laboratory studies initiated by the International Pharmaceutical Federation (IPF);

Inter-laboratory PTS studies were performed (a HPLC dosage, pH determination through potentiometry, of two unknown samples, assessment of purity through determination of the melting point for a sample).

All such tests have been compliant with the analytical requirements of IPF laboratories, according to evaluation documents forwarded.

b) Assessment of chemo-pharmaceutical documentation (DSSA, finished products, clinical trials);

The MPQCD has conducted work in that respect since 2005, interconnected with control activities.

In 2012, the following were performed within the MPQCD:

- Assessment of Active Substance Master Files (DSSAs) through European procedures;
- Assessment of quality – through European procedures;
- Assessment of ASMFs through national procedure;
- Assessment of quality – through national procedure;
- Assessment of clinical trial documentation.

In 2012, of 711 assessments for medicinal products undergoing authorisation procedure, 642 ASMFs were assessed (90.3%).

As regards assessment of clinical trial documentation, 26 complete quality studies were assessed (active substances, Investigational Medicinal Products - IMPs), all for the Voluntary Harmonisation Procedure (VHP) (voluntary harmonisation procedure for assessment of multinational clinical trials in the EU), as well as 8 amendments to IMP documentation.

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

a) Current laboratory control activity of quality parameters of national and imported biological products for human use.

In 2012, no applications for testing of biological product batches have been submitted, mainly in result of suspension of the manufacturing activity of the internal manufacturer, INCDMI "Cantacuzino" (whose products undergo "batch to batch testing" for batch release procedure within the BPECD).

In accordance with quality assurance requirements and recommendations of external audits, for maintenance of operators' skills under circumstances of no requests for testing, specific exercises have been planned and performed.

Thus, conduct of a skill practice exercise by staff of the Laboratory for Determination through Serology Tests (LDST) was deemed necessary, as regards vaccine control (and particularly influenza vaccine control). Skill practice exercises have been performed for **2** testing methods (double diffusion, single radial immunodiffusion) according to SOPs of the LDST.

Results obtained have been analysed and compared with previous ones.

The Laboratory for Physical-Chemical Determinations and Immunochemistry (LPCDI) has performed the following activities:

- method validation: *pH potentiometric determination;* preparation of validation report;
- performance of calibrations and determinations for assessment of correct operation of the newly acquired Karl-Fischer volumetric titrator;
- performance of determinations for maintenance of testing skills and assessment of understanding of working methods.

b) Laboratory control of quality parameters for biological products for human use for grant of marketing authorisation/marketing authorisation renewal.

Applications lacking in 2012, no testing was conducted on biological product samples submitted within the marketing authorisation/marketing authorisation renewal procedure.

c) Postmarketing surveillance via registration of all imported biological products;

In the context of the postmarketing surveillance, MAHs submitted data relative to 185 biological product batches, which have been assessed by the specialist assigned and stored in electronic format.

d) Assessment of dossiers submitted for grant of MA/MA renewal of national/imported products or for approval of Type I/II variations or approval of applications for MA transfer/changes of design or approval of applications for performance of clinical trials, activities followed by issuance of reports for assessment of biological product quality, reports for support of variations or other amendments.

Starting with January 2012, the BPECD has also performed validation of applications for variations to MAs (type IB and II) for biological products (responsible person: biol. Adina Chende-Roman).

During 2012, this activity consisted of:

- 138 validations of applications for Type IB and II variations
- 6 invalidations of applications for Type IB and II variations.

In 2012, the BPECD assessed 2 products submitted for authorisation through national procedure for which 1 report requiring supplementation has been issued and 62 products submitted for MA renewal through national procedure (58 foreign and 4 national), for which 86 reports have been issued:

- 46 reports with request for supplementation, 33 with proposal for MA approval; 7 assessment reports of postauthorisation supplementations.

The BPECD has also assessed dossiers for variations / changes of design / MA transfer, submitted through national procedure, for which 486 reports have been issued, as follows:

- 122 applications for type IA variations;
- 99 applications for type IB variations;
- 236 applications for type II variations;
- 24 applications for modification of design;
- 5 applications for MA transfer.

In 2012 as well, quality documentation has been assessed as related to products submitted through the mutual recognition and decentralised procedures, concluding in submission of assessment reports according to deadline, as follows:

Mutual recognition procedure

33 reports have been issued for 23 products:

- 4 reports with proposal for authorisation;
- 8 reports – conditions for authorisation;
- 6 reports proposing MA renewal;
- 15 reports containing MA conditions for renewal.

The BPECD also assessed support dossiers for variations submitted through Mutual Recognition Procedure, for which 95 reports have been issued, of which: 29 assessment reports for Type IB variations and 66 assessment reports for Type II variations).

Decentralised procedure

12 reports have been issued for 9 products pending authorisation:

- 1 final report;
- 4 assessment reports for authorisation, with request for supplementation;
- 7 reports containing the conditions for authorisation.

In 2012, the BPECD also assessed quality documentation submitted for approval of applications for performance of clinical trials for 19 biological products; 25 assessment reports have been issued, of which:

- 17 reports containing requests for supplementation of quality documentation;
- 8 final (positive) reports for assessment of quality documentation

As regards amendment of marketing authorisation terms for biological medicinal products for human use, following approval of Type I or II variations or following proofreading, the BPECD has performed 47 changes to MAs in 2012.

8. Ensuring communication and transparency

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

8.1. External communication

In 2012, in line with *its communication strategy for 2011-2015,* the Agency ensured:

- internal and external communications, opinions, communication with the written press and the media (by telephone, e-mail, TV interviews), relationship with other Romanian and foreign specialised institutions in this field;
- free access to public information in accordance with provisions of Law 544/2001, readily or upon request, for media representatives and any stakeholder, providing information about NAMMD work or the safety of medicinal products for human use;
- Cooperation of all departments for transparency purposes in Agency work, to ensure public accessibility/availability and passive transparency by providing for reactive information following application;
- The pooling of data from scientific departments and structuring of information requested for preparation of responses required by stakeholders;
- notification of the mass-media and/or other applicants within deadlines stipulated by regulations in force, on publication of information as stipulated under Article 5 of Law 544/2001, also specifying site of publication;
- notification of the applicant, within deadlines stipulated by regulations in force, on waivers from free access of the requested information;
- distribution to the media of NAMMD official releases and opinions.

The Agency provides correct information to its partners concerning work performed in all fields within its scope.

On its website, the NAMMD publishes quarterly bilingual Newsletters, reflecting its regulatory work in the area of medicinal products in line with European legislation and other Agency priority activities. The content of the NAMMD Newsletter includes:

- Laws, ordinances, Government decisions on medicinal products for human use or other areas of NAMMD interest;
- Orders of the Minister of Health for approval of NAMMD Scientific Council decisions and Orders of the Minister of Health in other areas of NAMMD interest;
- Decisions of the NAMMD Scientific Council;
- Decisions of the NAMMD Administration Council;
- Quarterly list of applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD;

- Quarterly List of EMA newly centrally authorised medicinal products, for which the European Commission has issued the decision on translation into Romanian of medicinal product information;

- Quarterly list of medicinal products authorised for marketing by the NAMMD;

- A quarterly list of medicinal product batches recalled by the NAMMD for quality defects.

The NAMMD develops the Index of medicinal products for human use, including all medicines authorised for circulation on the pharmaceutical market in Romania, with data on trade name, International Non-proprietary Name (INN), marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, manner of release etc. and posts it on its website. In 2012, implementation was continued, for each medicine, of electronic versions of the Summary of Product Characteristics (SmPC), leaflet and information on labelling and inscription.

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

- Press releases relating to safety of medicinal products;

- Direct healthcare professional communications;

- Notifications to Marketing Authorisation Holders (MAH) or other interested parties on issues of interest;

- Information related to medicinal products authorised through centralised procedure

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

- SmPCs for medicinal products authorised in Romania through national procedure;

- List of NAMMD employees assigned as full members/alternates in the Management Board, scientific committees and working groups of the European Medicines Agency (EMA);

- List of EMA experts appointed by the NAMMD.

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

- List of Romanian manufacturers of medicinal products and active pharmaceutical substances;

- List of third country manufacturers, certified by the NAMMD;

- List of Romanian importers of medicinal products;

- List of Romanian distributors of medicinal products;

- List of laboratories of control of medicinal products;

- List of recalled batches;

- List of Qualified Persons approved by the NAMMD,

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

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

- <CP> (centralised procedure)

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

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

a) Medicinal product legislation, structured according to type:

- Laws, Ordinances, Government Decisions;

- Orders of the Minister of Health;

- NAMMD Scientific Council Decisions;
- NAMMD Administration Council Decisions.

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

c) Important notifications and EMA and NAMMD Press releases.

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

Moreover, in 2012, the NAMMD continued to inform stakeholders about its activity, otherwise than by means of NAMMD Newsletters. Thus, several articles have been published in Romanian professional magazines ("Farmacist.ro", "Medical Business", "Medica Academia, "Pharma Business") referring to various issues related to Agency work.

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

8.2. Internal communication

In 2012, the Agency continued supplementation and update of information (available to NAMMD staff on the Intranet), for optimal and efficient professional/organisational information.

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

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

9. Quality management activity

Activities performed by the QAB aim to establish, document, implement, maintain and permanently improve the efficacy of NAMMD Quality Management System (QMS).

Considering the Policy on quality and quality objectives, established by the top management, as well as processes identified and implemented, the size and structure of the NAMMD and *SR EN ISO 9001* and *9004* principles in force, in 2012, the QAB, together with the other organisational structures, has participated to implementation, development and improvement of the NAMMD Quality Management System.

Activities have been performed as follows:

- The internal quality audit process was carried out in accordance with the Internal Quality Audit Program in 2012, approved by the President of the organisation.

Findings and conclusions of internal quality audits, whose objectives consisted of ensuring compliance with *Standard Operating Procedures (SOPs)* applying to audited processes, are established in accordance with SOP ANMDMAC/G/00 in force.

Other processes performed by the Quality Assurance Bureau:

- Counselling in quality management system (QMS) issues provided to various NAMMD organisational structures, for set up of objective proof, related to the External audit conducted by the WHO team, October 2012.

Note: the following copies have been requested by the WHO audit team: *NAMMD Quality Manual (MC-ANMDM), SOPs*, codes: ANMDMAC/G/ 003 and 005, in force, as well as tables of contents of the other *general PSOs* (001…015), applicable at organisational level (NAMMD).

External auditors of the WHO team have not found/communicated any non-compliances in that respect.

- Set-up of the documents requested by the Ministry of Health, related to the stage of implementation of internal/management control system on: 25.01, 23.07.2012 [in collaboration with the Internal (public) Audit Bureau].
- New update of declarations of interests/confidentiality undertakings/individual and non-individual job descriptions.
- Set-up/update of QAB databases (in electronic format).
- Monitoring/Improvement of staff health.

QAB schedule for 2012 as approved by the President of the institution, has been observed.

The NAMMD has a robust Quality Management System (QMS), based on *international standards 9001, 9004, 17025, 19011* etc. in force.

PSO status at organisational/departmental level is as follows:

General PSOs: 15
Specific PSOs: 290
Interdepartmental PSOs: 16
All PSOs/NAMMD departments: 321

NAMMD top management is involved in QMS-related activities, showing its preoccupation with implementation of a process-based approach.

10. Medical devices

10.1 Control activity through regular check of medical devices

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

In 2012, control activities consisting of regular check-up of medical devices were carried out for all higher risk medical devices installed and operating at the sites of all medical device users, both private and public. Checks have consisted of assessment of performance and safety of medical devices in use, regular check-up bulletins being documents required for set up of medical care agreements between health insurance houses and medical practices/hospitals/medical centres.

In 2012, work of the Laboratories Technical Departments and the Nuclear Unit was as follows:

- Total number of applications registered: 1037
- Total number of periodic check-up bulletins issued: 1938
- Total number of approvals for use issued: 231
- Total number of medical devices assessed: 6430
- Total number of trial reports issued: 6079
- Total number of negative trials (rejected medical devices): 92

In March 2012, the RENAR conducted an activity for surveillance and monitoring of laboratories for testing and assay of medical devices within the Technical Department - Laboratories (TD-L) and the Nuclear Unit (NU), examining the manner of field testing performance. Results have been found appropriate.

In 2012, intense efforts have been made to ensure review of the List of medical devices submitted for control through regular check-ups, so as to ensure inclusion into the List of medical devices only of highest risk to patients and users, required for future replacement of Order of the Minister of Health no. 1662/2007 on control through regular check-up of medical devices, as amended.

In spite of several barriers encountered (insufficient staff, financial difficulties), the TD-L and the Nuclear Unit have made special efforts to ensure steadfast activity in the context of mandatory preservation of acceptable safety and performance level of medical devices in use.

10.2 Inspection and assessment of technical-medical units

The Technical-Medical Units Assessment Service works under Law No. 176/2000 on medical devices, as amended, and Order No. 1636/2004 on approval of Methodological rules for implementation of Law No. 176/2000, as amended, on licensing of medical technical units, involving assessment of organisations' ability to perform services requiring Ministry of Health approval.

In spite of its small number of employees, the department is assigned for work over the entire country, performing not only initial unit assessment for approval and surveillance as well as biennial assessments, but also detection and application of penalties for breach of legal provisions as per Law No. 176/2000, as amended.

Staff in this Department has accomplished the following results:

- Number of registered applications for assessment: 156;
- Number of assessment performed and reports issued: 79;
- Number of ongoing works: 30;
- Number of activities cancelled (for reason of unsubmitted assessment dossier): 16;
- number of ongoing assessment activities:12
- number of assessment-surveillance activities: 376
- number of assessment-surveillance activities, completed, with finalised reports: 183
- number of assessment-surveillance activities, undergoing assessment: 92
- number of assessment-surveillance activities, in process of completion: 55
- number of assessment-surveillance activities, for confirmation of termination or approval for performance: 46
- missions for assessment and surveillance activities: 83

Six control activities were performed, resulting in application of 3 penalties for breach of legal provisions.

11. International relations

In 2012, NAMMD specialists continued to take part in activities of various collaborator European institutions and organisations:

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

Since 2003, at the initiative of the European Medicines Agency, NAMMD representatives have actively participated as active observers to EMA working groups,

scientific committees and groups for implementation of medicinal product related information technology.

This involvement has always been the optimal means of keeping the Agency connected to European activities related to medicinal products for human use.

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

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

11.2. Participation in activities of the “Heads of Medicines Agencies” body

NAMMD representatives are actively involved in meetings of the “Heads of Medicines Agencies” (HMA) European body as well as meetings of its working group, namely:

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

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

In 2012, NAMMD experts participated in meetings of the Council of the European Union and of the European Commission (EC), i.e. the Working group on medicinal products and medical devices of the EU Council, preparing proposals for amendment of Directive 84/2010/EU and proposals for a new Regulation on clinical trials for repeal of Directive 20/2001/EC on clinical trials in the EU, the Standing Committee, the Pharmaceutical Committee, Notice to Applicants, the United Nations Interregional Crime and Justice Research Institute for the „SAVEmed Microstructure secured and self-verifying medicines" project.

11.4. Participation in World Health Organisation (WHO) activities

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

In 2012, the Agency released the Certificate of the product in WHO format for 529 medicinal products of Romanian manufacturers seeking authorisation for these products in other states.

11.5. Participation in European Council activities

In 2012, NAMMD representatives participated in the two meetings of the **Working Group** on the classification for release of medicinal products for human use.

11.6. Participation in European Pharmacopoeia Commission activities

As member of the European Pharmacopoeia Commission, the NAMMD representative has been actively involved in specific working sessions in 2012, as well as in the yearly meeting of the secretaries of national Pharmacopoeias in Convention on the Elaboration of a European Pharmacopoeia member countries.

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

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

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

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

For description of these activities, please see points 7.1 c) and 7.2 d).

12. Information, Logistics and Electronic Management of Data

In 2012 as well, the Logistics and Information Service managed preservation of optimum parameters of communication channels with the EMA and provision of real-time information exchange between the Agency and external collaborators (MAHs, distributors, healthcare professionals, patients, organisations and associations).

In 2012, maintenance, amendment and update was continued of the Product Index of medicinal products for human use database. Moreover, statistical data reports were extracted periodically on request by the Minister of Health, the National Health Insurance House, the NAMMD President and various Agency departments.

As regards cooperation with other institutions, upon EMA request, responses to various forms on information technology were prepared; the database concerning NAMMD experts was administered and related information was updated via the application made available by the EMA, necessary steps have been taken to ensure access to the "External experts" database under EMA administration, participation in EudraPharm, EudraNet and EUTCT working groups has been ensured in accordance with nominations made in 2012 (participation in 8 events).

Throughout the year, maintenance of connections to the European EudraNet network (EudraCT, EudraLink, EudraMail, EudraPharm, EudraVigilance, PIM, CTS, EPITT) was monitored in the context of the activity of administration, configuration and repair of local equipment.

Maintenance of the NAMMD website (*www.anm.ro*) and other software applications has been ensured throughout the year (search engines – Index, search after key words, management of recalled medicinal products, management of GMP units - all pending); a new section, "Suggestions", and a new website, "Counterfeiting" (ongoing project – *www.crimemedicine.ro)*; at the same time, many activities concerning updating of the website various sections (Newsletters, Orders of the Minister of Health, press releases, Q&A documents, Important notifications, Direct Healthcare Professional Communications etc.) have been ensured; the Agency's intranet website has been maintained, amended and updated.

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

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

Also, maintenance and troubleshooting of software and hardware of existing computers was performed and installation and configuration of new computers were ensured. Maintenance and troubleshooting of the NOD32 antivirus programme and other safety programmes on NAMMD servers have also been provided.

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

A number of 1125 marketing authorisations and their annexes have been issued in 2012, namely 914 through European procedures and 211 through national procedure.

Also, typing/drafting has been insured for:

- 529 product certificates in WHO format for Romanian medicinal products;
- 182 letters for 666 medicinal products, confirming status of the medicinal product undergoing renewal of marketing authorisation, bearing the "suitable for marketing" specification";
- 596 notification letters sent to manufacturers on MA release in accordance with President directions and maintenance of a copy in the product dossier.

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

- 420 applications for marketing authorisation/marketing authorisation renewal through national procedure;
- 998 applications for marketing authorisation/marketing authorisation renewal through DCP/MRP;
- 3102 applications for Type IA, IB, II variations, MA notifications through national procedure;
- 3327 applications for Type IA, IB, II variations, MA notifications through decentralised/mutual recognition procedure;
- 7718 drafts and payment forms for issue of invoice for marketing authorisation/marketing authorisation renewal and variations through decentralised/mutual recognition procedure;
- 27473 documents (responses to NAMMD requests for MA authorisation/renewal documentation, variations, clinical trials, advertising, adverse reaction reporting etc.).

24 meetings of the Marketing Authorisation Commission(s) have been organised and 1003 product dossiers have been assessed.

The NAMMD server has been updated with its 1125 marketing authorisations issued in 2012 and the 5 corresponding Annexes, concerning the leaflet, Summary of Product Characteristics, packaging, data on the qualitative and quantitative composition of the medicinal product, data on the product manufacturing.

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

In 2012, in collaboration with other departments, the Policies and Strategies Department (PSD) contributed to fulfilment of the NAMMD mission, by setting up the 2011-2015 NAMMD organisational strategy, namely by:

- strengthening NAMMD status as expert and reliable source of accurate medicinal product related information, provided to stakeholders in due time;
- active and priority participation to implementation of the Agency's *Communication Strategy* 2011-2015, internally and externally, permanently aiming at identification of areas and manners of improvement, as well as adaptation to new requirements and the dynamics of legal and socio-economic amendments.
- - *The organisational strategy,* establishing strategic objectives and Guidelines of the Agency's activity, in accordance with the legal framework in force, and the relationship between the NAMMD and the Ministry of Health and between the NAMMD and stakeholders;
- - *The communication strategy,* establishing objectives of internal and external Agency communication activity and strengthening its status as expert and reliable source of accurate information in the medicinal product field, provided in due time to stakeholders: healthcare, research and industry professionals, patients, general public and the media.

In 2012, constant efforts have been made towards transposition into Romanian legislation of two new European Directives concerning a new pharmacovigilance approach (Directive 2010/84/EU) as well as prevention of entry of falsified medicinal products into the legal supply chain (Directive 2011/62/EU), which have both amended Directive 2001/83/EC on the Community code relating to medicinal products for human use.

The transposition, examination of transpositions and preparation of emergency ordinance drafts have been performed within two working groups, assigned through Decisions of the NAMMD President, as well as through collaboration with the Ministry of Health and the Ministry of Justice.

In spite of its main involvement in transposition of the directive on pharmacovigilance (Directive 2010/84/EU), the PSD however took part in two working groups, as well as in talks with the Ministry of Health and the Ministry of Justice for completion of transposition legislation.

These activities resulted in draft of 2 emergency ordinances (Emergency Ordinance no. 35 of July 2012 Emergency Ordinance no. 91 of December 2012), amending Law 95/2006 on healthcare reform, as regards pharmacovigilance and prevention of the entry of falsified medicinal products into the legal supply chain.

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

- Management and monitoring of participation of NAMMD staff assigned as full members or alternates to scientific committees and working groups of the EMA, HMA, EDQM, European Council, EU Council, European Commission, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);
- Periodic update of the List of NAMMD employees assigned as full members or alternates to scientific committees and working groups, in accordance with President decisions and their posting on the NAMMD website;
- Insuring communication with the EMA for assignment of NAMMD experts as full members/alternates;
- Check-up/Summarization of the forms prepared by NAMMD experts;
- Communication with the secretariats of working groups/scientific committees of the cited bodies for transmission of forms;
- electronic evidence of documents received on paper from the WHO, EDQM, OMCL etc. and their distribution for information or grant of opinion; the Policy and Strategy Department has prepared the NAMMD Annual Activity Report for 2011 by corroboration of data from NAMMD departments activity reports.

Similarly to 2012, the Policies and Strategies Department managed to provide secretarial and organisation work for the NAMMD Scientific Council (SC) (in accordance with the *interdepartmental SOP*) through:

- handling and centralisation of 9 Scientific Council Decisions (SCDs), 4 of which regulatory, from draft to publication, in accordance with the *interdepartmental SOP*;
- set-up of the SC meeting agenda, submission of documents to Scientific Council members review, on paper/in electronic format;
- ensurance of scientific secretarial work for 1 Scientific Council meeting in 2012 and for approval of 2 SCD drafts through written procedure;
- set-up of the documentation of drafts of Minister of Health Orders on approval of regulatory SCDs;
- Drafting of the minutes of SC meetings;
- Handling of the electronic versions of SCDs from draft to publication (both in the Official Gazette of Romania, Part I, for SCDs approved through Order of the Minister Health, as well as on the NAMMD website, under the headings “Legislation” and “Newsletters”) in the directories for Scientific Council meetings;
- updating the record of contact coordinates of SC members;
- set-up of the integrated evidence of Decisions approved by the SC in 2012, while mentioning, as required, the stage of approval of the Order of the Minister of Health/ Order of the Minister of Health on approval of a SCD, date of publication in the Official Gazette of Romania, Part I and the publishing Newsletter.

Set-up of NAMMD Newsletters has been continued, which have been posted on the NAMMD website, namely:

- 4 newsletters in Romanian (no. 4/2011; no. 1/2012; no. 2/2012; no. 3/2012)
- 7 newsletters in English (no. 4/2010; no. 1/2011; no. 2/2011; no. 3/2011; no. 4/2011; no. 1/2012; no. 2/2012).

The PSD participated as interface between the NAMMD and stakeholders for update and improvement of information available on the NAMMD website, in collaboration with the other departments, by posting:

- 65 regulatory documents, in Romanian and English version;
- 24 supplementations, amendments, recalls, proofreading;
- NAMMD Newsletters into Romanian and English;
- updated information about SC members' declarations of interest;
- Updated list of NAMMD employees assigned as full members or alternates to scientific committees and working groups of the European Medicines Agency (EMA) and updated List of EMA experts appointed by the NAMMD.

The PSH has also ensured:

- translation into English of **7** quarterly Informative Bulletins of 2010 and 2011 (no. 4/2010; no. 1/2011; no. 2/2011; no. 3/2011; no. 4/2011; no. 1/2012; no. 2/2012);
- Checking translation of 159 EMA press releases, EMA Q & A documents, Direct Communications to Healthcare Professionals, action lines proposed by the EMA ("Lines to take"), educational materials etc.;
- Follow-up of various sites in view of ensuring compliance of the terminology with European terminology (particularly EMA and EUDRA);
- accessing other sites for documentation in view of identifying information for various presentations;
- translation/ensurance of consultancy for translation of 11 SCDs;
- Provision of advice for check of translation of 13 SmPCs and leaflets, message exchanges and communication in English with European bodies;
- Checking translation of **4** assessment reports and documents in English, in the context of the Mutual Recognition Procedure;
- Ensurance of linguistic consultation for issuance of about **514** articles for correspondence and communication with various international bodies and representatives of companies or the pharmaceutical industry, on behalf of the Economic Department and of the Information Logistics and Electronic Management of Data Department;
- update of the English version of the NAMMD website via translation of legislation, notifications and press releases:
- translation and/or provision of consultation for translation of **2** papers in English, presented abroad by NAMMD specialists;
- translation of 25 documents and presentation materials for the WHO audit of December 2012 and of all materials connected to this visit;
- translation of the quality manuals of the NAMMD, BPECD and the Pharmacovigilance Service;
- translation of 7 CVs requested by NAMMD representatives to EMA working groups;
- translation, upon request of various departments, of 95 addresses and specific communications.

In line with the *2011-2015 NAMMD Communication Strategy*, in 2012, the PSD ensured:

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

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

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

- pooling from scientific departments and adjustment of required information in view of set-up and issuance of the reply required by stakeholders;

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

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

- Set-up/Verification and distribution of official communications and NAMMD position to the media;

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

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

Communication with Romania's permanent representation at EU/Brussels was performed through:

- More than 500 e-mails received from the permanent representative of Romania to the EU and / or the Ministry of Health were monitored / entered into electronic records, regarding participation of NAMMD experts assigned to working groups of the European Council, to the Pharmaceutical Committee and the Standing Committee of the European Commission and redirecting them to NAMMD appointed experts.

- coordination and monitoring of participation of NAMMD experts appointed to meetings of previously mentioned working groups/committees and provision of mail with the Representation on this issue, as required;

- coordination and participation to the monitoring/handling in electronic databases of 49 European Commission Decisions referring to: conditionally authorised medicinal products (based on Article 127a of Directive 2001/83/EC), MA suspension/withdrawal/amendment (based on Article 107, 29, 31 of Directive 2001/83/EC) and forwarding these documents to NAMMD specialists appointed for implementation.

The PSD has also ensured conduct of Pharmacopoeia related activities by coordination of technical-scientific work resulted after Romania's accession to the "Convention on the Elaboration of the European Pharmacopoeia" within the European Council, namely by:

- participation, by an assigned representative, to the yearly sessions of the European Pharmacopoeia Commission, as its member;

- centralisation and analysis of the dossier forwarded in electronic version by the European Pharmacopoeia Commission/EDQM.

14. NAMMD legal work

Professional activities of the Legal Department (LD) have mainly envisaged accomplishment of tasks specified in the NAMMD Regulation on the Organisation and Operation (ROO), approved through Order of the Minister of Health no. 1031/2011, as well as other activities.

For accurate description of activities performed in 2012 from a statistical viewpoint, the following activities were performed:

- grant of approval on legality of measures to be taken and of any other documents which could determine the institution's patrimonial liability;

- grant of approval concerning the correct interpretation of legislation related to NAMMD's field of activity;

- Preparation of minutes and Decisions of the NAMMD Administration Council;

- Participation via representatives assigned by NAMMD management to meetings of the scientific councils and EMA working groups, to other working groups of competent authorities in the field of the medicinal product, e.g. the participation of 2 experts of the Legal Department to the Legislation working group (EMACOLEX - European Medicines Agencies Cooperation on Legal and Legislative Issues) reunited in Copenhagen, Denmark, March 2012;

- Management of activities related to exchanges for petition resolution in accordance with Ordinance no. 27/30.01.2002 regulating the resolution of petitions.

- draft and approval of 196 Decisions of the NAMMD President.

- other activities:

  - management of the NAMMD security structure activities;
  - participation, as members, to work of commissions for assessment of procedures for purchase of equipment and services;
  - participation to work of commissions for yearly inventory of assets;
  - participation to counselling upon request by departments;
  - provision of visa for preventive financial control of the institution's financial-accounting documents;
  - preparation of documents required for external travels of NAMMD staff to meetings of scientific councils working groups of the EMA or other European or international medicinal product related bodies.

Moreover, in collaboration with other departments, the Legal Department contributed to control of falsified medicinal products, which determined continuation in 2012 as well of the existing cooperation with the General Inspectorate of the Romanian Police, based on the cooperation protocol signed in March 2010, aiming at establishing a framework for bilateral cooperation and exchange of information on falsification of medicinal products for human use, in accordance with specific attributions and competences stipulated by the legislation in force.

A noteworthy initiative in 2012 has been start of the "SAVEmed Microstructure secured and self-verifying medicines" project for action against counterfeiting of medicinal products, initiated by the United Nations Interregional Crime and Justice Research Institute (UNICRI). In that respect, the NAMMD Legal Department representative took part in two of the meetings occasioned by the respective project (March and November 2012). As regards Romania, the project in question envisages achievement of two targets:

● implementation of a single point of control (SPOC) in Romania, with the Romanian General Prosecutor's Office as a national contact point;

● preparation,, in cooperation with 15 participant countries, of a good practice guideline on communication between the public and private sector for facilitating exchange of information on prevention of entry of falsified medicinal products into the legal supply chain.

It should be noted that the duty concerning implementation of a SPOC system is expressly provided for by Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, transposed into national legislation through Government Emergency Ordinance no. 91/2012.

Following assessment of the Romanian regulatory field, it has been concluded that a system is applicable in Romania, as in other EU member states, implying:

● as primary stage – signing of collaboration protocols/memoranda between national institutions involved, namely: the General Prosecutor's Office, the General Inspectorate of Police, the Border Police, the Customs 'Authority, the Ministry of Health, the National Agency for Medicines and Medical Devices;

● second stage – set up of a data system with single point of contact with Romania's General Prosecutor's Office.

Such approaches are instrumental for set up the framework for implementation of provisions of Directive 2011/62/EU, transposed into national legislation through Government Emergency Ordinance no.91/December 2012.

15. Management of human resources

15.1. Human resources policy

Obviously, similar to previous years, objectives of the Human Resources and Payroll Department have been preserved, as follows:

- Provision of human resources for NAMMD structures, especially in sectors where department and top management reviews highlighted lack of qualified university graduates (particularly medico-pharmaceutical) among staff, for proper covering of jobs in specialised departments, whose work practically ensures accomplishment of the Agency's scope.

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

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

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

- Training, improvement and evaluation of NAMMD staff; it is worth mentioning that such training is carried out according to yearly plans at department level, according to each employee's specific activity and training. Training has been delivered on both hiring and afterwards, organised regularly as ongoing training provided both internally and, depending on the Agency's financing possibilities, externally, provided by institutions specialised in various areas such as quality assurance management (ISO 9001 and 9004), training specific to pharmaceutical inspection, pharmacovigilance, assessment and authorisation of clinical trials, financial-accounting legislation etc.

Moreover, the following have to be noted:

- active participation with presentations at various congresses in the medicinal product field, as well as constant and remarkable participation of NAMMD experts in working groups of European and international bodies in the medicinal product field;

- Identification of means for staff motivation given the lack of any possibilities in 2012 for wage-related compensations (bonuses, pay rises etc.) for special professional merits. Potential solutions:

- assignment to management positions of staff selected for abilities demonstrated in accomplishment of tasks and responsibilities pertaining to the respective position;

- strengthening of an adequate system for assessment of performance.

15.2. Ensuring human resources within NAMMD structures

In 2012, personnel-related activities were performed within the Human Resources and Payroll Department (HRPD). As regards accomplishment of the main departmental goal, namely provision of qualified personnel, this has been gravely impeded by the applicable legal framework set up through Government Emergency Ordinance No. 34/2009 on budget rectification for 2009 and regulation of certain financial-fiscal measures ("Measures on public expenditure" providing for "freeze of examination/contest based hiring proceedings in relation to vacancies in public institutions").

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

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

Continual Agency involvement in the decision making process at European level by active participation in European scientific committees and working groups, with proposals for viable solutions able to contribute to amendment of current legislation in the area of medicinal products for human use, requires high level of competence among NAMMD specialists. This target can only be reached by means of a programme for ongoing training, specific to professional development, on Agency site, and by participation to training organised nationally and internationally by various authorities and bodies in the field.

According to possibilities of funding by European bodies and the Agency's limited available budget, part of NAMMD specialists were able to benefit from training. In 2012, significant participation can be noted, occasionally with presentation of specialist papers, to the following professional training sessions provided in Romania:

- "The Pharmacovigilance Workshop" - Management and reporting of adverse reactions to medicinal products – Handling and reporting of adverse reactions to medicinal products", organised by the Romanian College of Pharmacists, Bucharest, 31 August 2012;
- Informal meetings with the ARPIM, APMGR and independent MAHs dealing with legal issues related to implementation of new pharmacovigilance legislation;
- The "Mass spectrometry and Atomic emission spectometry" seminar, organised by Viola – Shimadzu Romania, 27 March 2012, Bucharest;
- The national seminar on "Ionic chromatography", organised by Metrohm, Romania, 29 March 2012, Bucharest;
- The seminar "Bucharest User Forum - United States Pharmacopeia", organised by Chromaktiv SRL, 19 April 2012, Bucharest;
- The symposium "Fascinating by Analytics - reliable and reproducible HPLC analysis with Merck-Millipore", organised by Merck-Millipore, 26 April 2012, Bucharest;
- The conference of nuclear medicine "Actualities and perspectives in nuclear medicine" organised in the context of Expomedica 2012, 8 June 2012, The Parliament House - Bucharest;
- The course "Sartorius Single Use Systems School", organised by the Sartorius Company, 5 September 2012, Bucharest;
- The seminar "Steritest School", organised by Merk Millipore Romania, 24 October 2012, Bucharest;
- "PHARMA – Standards, reference materials and impurities", seminar organised by LGC Standards, 22 November 2012, Bucharest;
- The course "Estimate of measurement uncertainty and validation of testing methods in accordance with SR ISO 15189:2007", organised by the Association for Quality in Laboratories (CALILAB) at the Faculty of Biology, 19-20 October 2012, Bucharest;

- The 8th National Conference of the Order of Biologists, Biochemists and Chemists in the Health System in Romania (OBBCSSR), the Faculty of Biology, 21 October 2012, Bucharest;

- The National Conference of Pharmacy, interdisciplinary pharmacist-physician conference organised by the Romanian College of Pharmacists, 15-17 November 2012;

- The ”Public relations and communications assistant“ course, provided by SC Tak Education Group SRL, 11-13 May 2012, Sinaia.

The following training sessions have been provided abroad:

- the course addressing clinical assessors on efficacy of orphan medicinal products, „Workshop on significant benefit of orphan drugs”, organised by the European Medicines Agency (EMA), London, 12.01.2012;

- Course for clinical assessors on assessment of paediatric data, EMA headquarters, London, 22-23 October 2012;

- Training course ”HMPC Assessors Training on non-European Traditional Medicines”, London, 25 September 2012;

- Course for clinical assessors on the quality of the opinion of Scientific Committees, organised by the EMA through Adobe Connect Teleconference;

- Conference: ”Formulation strategies for pharmaceutical products”, Berlin, 21-22 March 2012;

- EudraVigilance Data Analysis System (EVDAS) Training for National Competent Autorities – training course, London, 13 April 2012;

- Yearly meeting related to centrally authorised medicinal products and mutual/decentralised procedure, organised and sponsored by the EDQM, 15-16 November 2012, Sofia;

- The ”Quality control of the influenza vaccine” (“Control of bacterial endotoxins” test - LAL), organised by the World Health Organisation and the NIBSC, 14-18 May 2012, South Mimms, Hertfordshire;

- The training symposium “Batch release for medicinal products derived from human blood and plasma: principles, procedures and tools”, organised by the EDQM, Strasbourg, 10-11 May 2012;

- “The 5th meeting of international partners on the possible transfer of flu vaccine technology to vaccine manufacturers in developing countries” - 27-29 March 2012, Belgrade,

- Annual meeting of the Official Medicines Control Laboratories (OMCL), organised by the EDQM, Copenhagen, Denmark, 11-15 June 2012;

- successful examination for the degree of Microbiology specialist – May 2012 – by Daniela Motounu, Biologist;

- European Pharmacopoeia related course, organised by the EDQM in the context of the meeting of the EMA Biological Working Group, 12 September 2012, London;

- Course on assessment of similar biological medicinal products containing monoclonal antibodies, organised by the EMA, 23 October 2012, London.

16. Economic activity

In 2012, the Economic Department developed and managed a balanced budget of revenues and expenses from the state budget, amounting to 17,736,000 lei; expenses amounted to 17,205,505 lei.

These expenses consisted of: staff expenses (12,731,418 lei), expenses on goods and services (3,389,004 lei) and capital expenses (1,085,083 lei).

All expenses did not exceed the approved 2012 budget in accordance with legal provisions on economic and financial discipline.

All financial activities were performed by the Economic Department (ED).

It should be emphasised that the Budget approved and allocated in 2012 has been lower than required by the NAMMD, thus leading to insufficient means as compared to real Agency needs.

17. General administration activity

In the same way as during previous years, the General Administration Department (GAD) has been able to fulfil its objectives as well as provide prompt and efficient response to requests from other NAMMD structures.

Thus, the GAD most substantial achievements consisted in conduct and completion of activities related to equipment and refurbishment of NAMMD buildings *(NAMMD main headquarters located on 58 Titulescu Av. and the headquarters located on 20 Demostene Str.),* aiming to reduce the costs of utilities and furnishing of an optimal and operational area of work to improve the work setting.

Moreover, the Public Purchases Service organised and accomplished the entire purchase process needed for proper NAMMD operation, consistent with its objective needs and the approved budget, thus preparing documentation needed for 420 applications (purchase requisitions).

18. Internal audit

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

In 2012, the activity of the Internal Audit Bureau consisted of 4 audit missions:

- Assessment of activities of the Human Resources Department;
- Assessment of activities of the Policies and Strategies Department;
- Assessment of activities of the National Procedure Department;
- Assessment of activities of the Technical-Laboratory Department, the Technical-Medical Units Assessment Department and the Nuclear unit.

The objectives established in the context of missions performed at the sites of audited structures have been as follows:

- Organisation and operation of activities performed by audited structures;
- Manner of performance of activities undertaken by audited structures;
- Compliance with Revenues and Expenses Budget established values and terms; Working programs at the level of audited structures.

Risks potentially affecting NAMMD activity during the period assessed are of organisational, operational, legislative and financial nature.

The main recommendations provided consist of continued compliance with legislation in force and with NAMMD Regulation for Organisation and Operation.

As regards monitoring of implementation of recommendations, it should be noted that all recommendations of the Internal Audit Bureau to audited structures are provided in line with notifications made on preparation of the public internal audit report.

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

19. Difficulties encountered

In performance of its activities, the NAMMD has encountered several difficulties, the primary of which has been recruitment and maintenance of specialised staff, coping with the lack of financial means to ensure continual training of staff and access to the latest scientific progress in general and particularly in their own professional field, limited character of data bases.

20. Priorities for 2013

As in past years, at the end of 2012, the NAMMD outlined its priorities for 2013 as follows:

- Strengthening of Agency scientific staff following cessation of hiring freeze in the healthcare field;
- Strengthening of Agency's role in terms of medicinal product policy – amendment of legislation for establishment of the manufacturer and supplier public responsibility and the Agency's capacity for application of penalties, in case of non-compliance;
- Implementation of legislation on traceability and Agency control of medicinal products throughout the entire chain, for actual avoidance of the entry of falsified medicinal products into the authorised supply chain;
- Preparation and submission to the Ministry of Health of proposals for amendment of clinical trial legislation, for clarification of the definition of *Contract Research Organisations (CRO)* as well as of rules to be followed by clinical monitors, investigators and structures performing clinical trials, namely their responsibilities towards the hospital, investigators etc.,
- Agency increasing involvement in decisions made at European level, by active participation in European working groups, proposal of workable solutions amending current legislation in the medicinal product field, by increasing NAMMD degree of integration into the issue of medicinal products at European level by means of rapporteurship, pharmacovigilance assessment, assessment of authorisation dossier at high level of scientific competence as Reference Member State in the context of the decentralised procedure for marketing authorisation.
- Agency involvement in completion of the "SAVEmed Microstructure secured and self-verifying medicines" project (initiated by the UNICRI - United Nations Interregional) by accomplishment of the two targets established for Romania:
  - implementation of a single point of control (SPOC) in Romania, with the Romanian General Prosecutor's Office as a national contact point;
  - preparation,, in cooperation with 15 participant countries, of a good practice guideline on communication between the public and private sector for facilitating exchange of information on prevention of entry of falsified medicinal products into the legal supply chain.
- continued participation of certain representatives of NAMMD management to working meetings with representatives of all stakeholders and parties involved in the pharmaceutical market (manufacturers, suppliers) for regulatory endeavour to implement a medicinal product traceability system in Romania and identify all issues possibly instrumental as starting points for viable solutions in this respect;
- participation to meetings of various patient associations with speeches on various issues of interest e.g. generic vs. innovative medicinal product, clarification of the term "falsified medicinal product", the meaning of clinical trials and their significance to patients enrolled as clinical trial subjects, use of *off-label* medicinal products according to NAMMD perspective, importance of suspected adverse reaction reporting by both healthcare professionals and patients, in the light of the new community approach of pharmacovigilance transposed into national legislation in July 2012 and others.

- Revision of Order of the Minister of Health no. 1369/2009 on approval of tariffs imposed by the (former) Technical Office for Medical Devices, as amended, for clarification of certain issues related to travelling expenses and undertaking of measures enabling main credit officer understanding of the need for hiring, thus leading to better control at national level of application of Law 176/2000 on medical devices, as amended.

CONCLUSIONS

Throughout its self-assessment process, the NAMMD has been fully aware of the importance of establishing its targets and as well as of an adequate number of options appropriately prepared; the NAMMD equally acknowledges the importance of monitoring and assessment of its policy for protection and promotion of public health.

To ensure adequate compliance with stakeholders‘ needs (healthcare professionals, pharmaceutical industry, patients, the general public, the media), as well as its capacity for performance of effective regulatory policy, meant to help it reach its main target, namely to safeguard public health, the NAMMD is constantly involved in self-assessment.

From NAMMD perspective, year 2012 has involved:

- Active participation in debates, bimonthly/monthly/biannual meetings of scientific committees and working groups of coordinating European bodies in the field of medicinal products for human use (the European Medicines Agency - EMA, ‘the Heads of Medicines Agencies - HMA, the European Directorate for the Quality of Medicines and Healthcare - EDQM, the European Commission);
- Transposition into national legislation of provisions of Directive EU 2010/84 on new pharmacovigilance approach and Directive EU 2011/62 as regards prevention of the entry into the legal EU supply chain of falsified medicinal products;
- Regulatory work resulting in adoption of NAMMD Scientific Council Decisions and grant of technical support on request by the Ministry of Health;
- Continued implementation of NAMMD strategies: organisational and communication strategies (2011-2015);
- Continued participation to reunions/workshops/conferences/informal meetings with stakeholders, debates on various issues arising in the area of medicinal products for human use;
- Conduct of NAMMD audit by the WHO team on “Strengthening of the national competent authority”, for assessment of the status of the national regulatory system (NRS) in the vaccine field;
- Participation of NAMMD representatives, with specialist papers, to various scientific events, displaying openness towards communication and transparency in the respective area of activity.

The NAMMD has a thoroughly established Quality Management System based on international *standards 9001, 9004, 17025, 19011* etc. in force.

NAMMD top management is involved into Quality Management System activities, at the same time being concerned with implementation of a process-based approach.

The following difficulties have been encountered in conduct of the Agency’s activity: under-financing, insufficient human resources, insufficient staff training, communication barriers, low motivation of staff.

To ensure QMS improvement, in October 2012, the WHO external audit team recommended appropriate financing to provide for human resources required for conduct of specific processes, dedicated and specialised human resources, which can only be ensured by means of ongoing training and motivation.

Projects:

- Strengthening of Agency role as regards medicinal product policy – amendment of legislation for establishment of manufacturer and supplier public responsibility and ensurance of Agency capability to enforce penalties in case of non-compliance;
- Ensuring a better understanding of the clinical trial issue;
- Continued participation of NAMMD management representatives to working meetings with representatives of all stakeholders involved in the pharmaceutical market (manufacturers, suppliers, patients);
- Review of Order of the Minister of Health no. 1369/2009 on approval of fees required by the Technical Office for Medical Devices, as amended, for clarification of issues related to travelling expenses;
- Taking the necessary steps to ensure main credit officer understanding of the need for hiring for better control of implementation, at national level, of Law 176/2000 on medical devices, as amended.
- Increased Agency involvement in decision making at European level, by active participation in European working groups, proposal of workable solutions for amendment of current legislation in the medicinal product area, by increased NAMMD integration in medicinal product related issues at European level, rapporteurship, pharmacovigilance assessment, assessment of authorisation documentation at high level of scientific competence as Reference Member State in the context of the decentralised procedure for marketing authorisation.
- Agency involvement in completion of the ”SAVEmed Microstructure secured and self-verifying medicines” project, initiated in 2012 by the United Nations Interregional Crime and Justice Research Institute (UNICJRI), through contribution for accomplishment of the two main objectives for our country:
  - Implementation of a SPOC (single point of control) system in Romania, with the General Prosecutor’s Office as a national contact point;
  - Preparation, in cooperation with 15 participant countries, of a good practice guideline on communication between the public and private sector for facilitating exchange of information on prevention of entry of falsified medicinal products into the legal supply chain.

The above represent projects requiring more staff specialised in medicinal products for human use and medical devices, as well as more flexibility in the hiring process and last but not least (perhaps by return to self-financing status), a budget allowing direct competition with the other EU competent authorities in medicinal products for human use.