2011 ANNUAL REPORT
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

INTRODUCTION

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

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

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

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

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

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

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

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

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

Year 2011 witnessed the transposition into Romanian legislation of two new European directives, one related to a new pharmacovigilance approach and one to the prevention of entry of falsified medicinal products into the legal supply chain, both having amended Directive

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

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

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

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

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

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

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

Pharmaceutical inspection related work consisted of 47 inspections for assessment of compliance with God Manufacturing Practice (GMP) rules for authorisation of manufacturing/import/GMP certification, 3 Good Laboratory Practice (GLP) inspections, 6 Good Analytical Laboratory Practice (GALP) inspections for authorisations of independent control units assessing medicinal product quality, 2 inspections performed prior to grant of Marketing Authorisation at the sites of Romanian medicinal product manufacturers, 10 inspections for assessment of compliance with Good Clinical Practice (GCP) rules, 6 pharmacovigilance inspections, 101 authorisation inspections, resulting in grant of 50 wholesale distribution authorisations.

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

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

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

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

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

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

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

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

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

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

The new European legislation (which is to be transposed into the Romanian legislation by 21 July 2012, amending, under *Pharmacovigilance*, Law 95/2006) will also raise patient

awareness related to reporting adverse reactions to medicinal products. The Agency hopes for more effective determination of medicinal product safety profile, through joint physician-patient effort, by detection and reporting of all adverse reactions in due time, meant to enrich information available on medicinal products, aiming at accomplishment of the highest possible level of safety in medicinal product administration in the EU.

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

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

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

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

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

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

NAMMD ACTIVITIES PERFORMED IN 2011

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

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

Among the regulations, guidelines and procedures debated and adopted by the Scientific Council for improving and streamlining the Agency's activity given the increased level of complexity of its activity, as shown in the details provided under section 3, the NAMMD Scientific Council has updated and approved the NAMMD Organisational Strategy (SCD no. 14/12.05.2011) establishing the mission, vision and goals of the Agency as competent authority

in the Romanian field of the medicinal product for human use and covering the period 2011-2015.

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

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

2. Activity of the NAMMD Administration Council (AC)

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

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

3. Regulatory activity

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

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

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

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

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

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

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions (CAPP)

As a consequence of the setup of 3 commissions for marketing authorisation/marketing authorisation renewal approved through SCD no. 2/23.02.2010 (CAPP-National Procedure, CAPP-European Procedures, CAPP-Renewals, whose structure and manner of operation have

been established through Decision no. 165/25.03.2010 of the NAMMD President), assessment reports are discussed by the Commission, in order to provide an opinion concerning marketing authorisation of various medicinal products, as well as other aspects related to the marketing authorisation of medicinal products for human use.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Marketing authorisation and related activities

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

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

5.1. Marketing authorisation through national and European procedures

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

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

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

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

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

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

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

5.2.1. In 2011, a number of 12427 applications for variation to MA terms were submitted for medicinal products authorised through national and European procedures, of which 6067 applications for type IA, IB and II variations to MA terms, MA notifications for nationally authorised products and 6360 for type IA, IB and II variations to MA terms, MA notifications through European procedures.

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

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

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

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

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

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

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

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

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

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

Therapeutic areas for which clinical trial authorisation was required in 2011 have been the following, in descending order: psychiatry and neurology, oncology, diabetology,

rheumatology, gastroenterology, pneumology, infectious diseases, haematology, cardiology, endocrinology.

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

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

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

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

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

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

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

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

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

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

5.5. Pharmacovigilance

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

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

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

Pharmacovigilance activity is conducted in Romania according to European legal frame, transposed into national legislation; this includes, among other activities, assessment and submission of adverse reactions through the EudraVigilance system (the European network for pharmacovigilance data-processing and management), assessment of Periodic Safety Update Reports (PSURs) as forwarded by pharmacovigilance systems of holding companies, assessment of Risk Management Plans, harmonisation of Summaries of Product Characteristics

(SmPCs), by implementation of European Commission Decisions based on the recommendations of the Committee for Human Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA).

Moreover, pharmacovigilance activity has ensured (and will continue to ensure) direct healthcare professional communications referring to special warnings for product safety, as well as translation and posting on the NAMMD website of EMA press releases and Q&A documents, actually representing notifications from the monthly CHMP meetings. An additional pharmacovigilance task is NAMMD response to requests for non-urgent information from the European and international rapid alert system.

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

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

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

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

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

In 2011, pharmacovigilance activities materialised in the following:

a) handling safety data issued from spontaneous reporting:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- 27 NUI responses to requests by certain EU authorities;

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

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

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

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

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

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

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

5.6. Other activities

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

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

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

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

"Parallel export" related activities:

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

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

- Management of responses received in application of provisions of Article 729 and 730 of Law no. 95/2006, i.e. notification of temporary or permanent discontinuation of manufacturing and notification of actual medicinal product marketing ("sunset clause"); ca. 100 reports have been received on behalf of 166 MAHs, for implementation of the *"sunset clause"* involving medicinal products not actually placed on the market to 2011;

- Management of the database related to EMA authorised medicinal products based on provisions of Article 127a of Directive 2001/83/EC and monitoring of implementation of conditions and restrictions placed on the MAH by the European Commission;
- Management of European Commission (EC) decisions related to referrals, draft of the letters to MAHs involved for request of transmission of variation applications for the implementation of the EC Decision.

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

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

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

- 25 Good Manufacturing Practice (GMP) certificates (for Romanian and foreign manufacturers);
- 52 manufacturing authorisations, annexes included;
- 46 import authorisations, annexes included;
- 1 Good Laboratory Practice (GLP) certificate;
- 21 certificates for Qualified Persons;
- 7 authorisations for independent control units;

- 139 dossiers for the inspected units, and for units requesting update of annexes to manufacturing/import authorisations have been issued and handled;

- 123 applications for waiver from legal provisions concerning medicinal product packaging/labelling have been solved;

- management of databases of inspection encoding, the list of authorised/certified manufacturing units, authorised importers, medicinal products for which the export declaration has been approved, and Qualified Persons.

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

- 30 GMP inspections for manufacturing authorisation conducted in Romania;

- 17 inspections for authorisation conducted at the site of medicinal product importers;

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

- 2 unannounced inspections for certification of GMP compliance conducted at the sites of Romanian medicinal product manufacturers;

- 3 GLP inspections to laboratories performing bioequivalence studies;

- 6 GALP inspection at independent quality control units;

- 10 inspections for assessment of compliance with GCP rules;

- 6 pharmacovigilance inspections at Romanian MAH sites, and Romanian MAH representatives sites, according to the yearly inspection plan of the Pharmaceutical Inspection Department.

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

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

- 101 inspections for authorisation have been conducted;

- 50 wholesale distribution authorisations have been released;

- 88 follow-up inspections have been conducted to assess the distribution activity and the manner of enforcement of corrective actions proposed through measures submitted to the NAMMD for authorisation;

- 11 unannounced inspections at wholesale distribution units authorised by the NAMMD have been carried out, following which:

- 3 authorisations were suspended;

- 8 breach of law penalties were enforced;

- 24 authorisations were withdrawn following detection of major deficiencies during inspections for authorisation;

- 7 inspections for supervision of the quality of distributed medicinal products were performed, consisting of check of traceability of medicinal products purchased/traded by wholesale distributors. This led to application of a breach of law penalties and suspension of the wholesale distribution authorisation for 1 inspected unit;

- the dossier for 570 applications for approval of export declaration was approved, leading to approval of export declarations for 2043 medicinal products manufactured in Romania.

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

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

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

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

Laboratory testing results issued have been as follows:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

g) Rapid alert system:

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

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

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

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

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

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

7. Quality and control of medicinal products for human use

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

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

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

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

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

Core activities in 2011 dealt with:

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

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

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

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

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

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

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

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

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

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

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

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

c) European and international cooperation concerning medicinal product quality.

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

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

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

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

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

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

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

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

This important coordinate of BPECD laboratory activity involves:

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

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

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

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

No batches of biological products were rejected after laboratory testing.

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

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

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

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

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

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

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

d) External collaborations concerning biological product quality.

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

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

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

- 23 products have been assessed through national procedure and 46 reports have been issued;

- support documentation for 437 variations submitted through national procedure has been assessed;

- 20 products have been assessed through mutual recognition/decentralised procedure; 12 reports have been issued;

- 62 variations have been assessed through mutual recognition/decentralised procedure; 69 reports have been issued.

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

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

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

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

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

8. Ensuring communication and transparency

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

8.1. External communication

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

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

- Laws, ordinances, Government decisions in the field of medicinal products for human use or other areas of NAMMD interest;

- Orders of the Minister of Health for approval of NAMMD Scientific Council decisions and Orders of the Minister of Health in other areas of NAMMD interest;

- Decisions of the NAMMD Scientific Council;

- Decisions of the NAMMD Administrative Council;

- Quarterly list of applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD;

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

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

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

The NAMMD develops the Index of medicinal products for human use, including all medicines authorised for circulation in the pharmaceutical market in Romania, with data on

trade name, International Non-proprietary Name (INN), active substance, marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, manner of release etc. and posts it on its website. In 2011, implementation began, for each medicine, of electronic versions of the Summary of Product Characteristics (SmPC), leaflet and information on labelling and inscription.

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

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

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

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

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

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

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

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

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

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

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

c) Important notifications and EMA and NAMMD Press releases.

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

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

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

8.2. Internal communication

In 2011, the Agency continued supplementation and update of information (available to NAMMD staff on the Intranet), for best and least time-consuming professional/organisational information.

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

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

9. Quality management activity

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

Activities have been performed as follows:

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

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

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

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

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

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

- Quality-related counselling.

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

- Participation of NAMMD experts in specialised quality management training.

10. Medical devices

10.1 Control activity through periodic update of medical devices

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

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

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

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

- Laboratory testing for certification: 2 ample works, conducted in several stages;

- Participation in technical surveys: 1 action, conducted at the Emergency University Hospital Bucharest;

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

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

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

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

This activity consists of assessing the organisations' ability to perform services requiring notification from the Ministry of Health. Activities assessed deal with optics, medical device commissioning, repair and maintenance, prosthesis (auditory/orthopaedic/other types).

The service covers such work throughout the country, performing not only initial unit assessment for approval and surveillance assessments every two years for continued approval, but also detection and application of penalties for infringement of legal provisions as per Law No. 176/2000.

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

- Number of registered applications for assessment: 194;
- Number of assessment performed and reports issued: 117;
- Number of activities cancelled (for reason of unsubmitted assessment dossier): 22;
- Number of activities cancelled (for reason of purely trading character of the respective organisation): 11;
- Number of ongoing works: 44;
- Number of assessment-surveillance works: 325;
- Number of conducted assessment-surveillance works, reported: 116;
- Number of ongoing assessment-surveillance works at the end of the year: 110;
- Number of assessment-surveillance works resulting in acknowledgement of cessation of activity or approval of performance: 39.

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

11. International relations

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

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

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

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

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

- The Committee for Medicinal Products for Human Use (CHMP);
- The **Committee for Orphan Medicinal Products (COMP);**
- The **Committee for Herbal Medicinal Products (HMPC);**
- The **Paediatric Committee (PDCO);**
- The **Committee for Advanced Therapies (CAT);**
  The CHMP Safety Working Party);
- *The CHMP Pharmacovigilance Working Party – PhWP, whose activity will be discontinued on entry into force of Directive for amendment and supplementation, in the pharmacovigilance field, of Directive 2001/83/EC, by the beginning of July 2012, on replacement with the Pharmacovigilance Risk Assessment Committee - PRAC; CHMP Blood Products Working Party*;
- *CHMP Biologics Working Party*;
- *CHMP Vaccines Working Party*;

- *The CHMP/CVMP Quality Working Party*;
- *The GMP/GDP Inspectors Working Group;*
- The Subworking Group on the EudraGMP Database;
- *The GCP Inspectors Working Group;*
- *The GLP Inspectors Working Group;*
- *The Pharmacovigilance Inspectors Working Group;*
- The Working Group on the database of medicinal products authorised in the EU (EudraPharm TIG);
- The Working Group on the database of adverse reactions (EudraVigilance TIG);
- The Working Group on the European database for clinical trials (EudraCT Clinical trials TIG);
- *The Working Group on the European network (EudraNet TIG);*
- The Working Group on the electronic transmission of data (e - Submission);
- The Working Group on European Union Telematics Controlled Terms (EUTCT);
- The Working Group on Product Information Management (PIM);
- The Working Group of the Quality Review of Documents;
- *The Invented Name Review Group.*

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

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

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

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

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

11.4. Participation in World Health Organisation (WHO) activities

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

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

11.5. Participation in European Council activities

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

11.6. Participation in European Pharmacopoeia Commission activities

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

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

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

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

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

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

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

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

12. Information, Logistics and Electronic Management of Data

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

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

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

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

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

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

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

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

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

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

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

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

Also, typing/drafting has been insured for:

- 490 product certificates in WHO format for Romanian medicinal products;

- 185 letters for 761 medicinal products, confirming status of the medicinal product undergoing renewal of marketing authorisation, bearing the "suitable for marketing" specification";

- 516 notification letters sent to manufacturers on MA release in accordance with President directions and maintenance of a copy in the product dossier;

- 103 commitment notifications sent to manufacturers on MA release and their maintenance in the authorisation dossier.

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

- 1150 applications for marketing authorisation/marketing authorisation renewal through national procedure;

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

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

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

- *The organisational strategy*, establishing strategic objectives and Guidelines of the Agency's activity, in accordance with the legal framework in force, and the relationship between the NAMMD and the Ministry of Health and between the NAMMD and stakeholders;
- *The communication strategy*, establishing objectives of internal and external Agency communication activity and strengthening its status as expert and reliable source of accurate information in the medicinal product field, provided in due time to stakeholders: healthcare, research and industry professionals, patients, general public and the media.

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

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

- Handling and monitoring of participation of NAMMD staff assigned as full members or alternates to scientific committees and working groups of the EMA, HMA, EDQM, European Council, EU Council, European Commission, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);
- Insuring communication with the EMA for assignment of NAMMD experts as full members/alternates;
- Communication with the secretariats of working groups/scientific committees of the cited bodies in view of form transmission, as well as through:
- Intervention as interface between various NAMMD departments, through monthly monitoring/centralisation of attendance of NAMMD experts assigned in meetings of working groups/committees.

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

- Centralisation and check-up of 29 SC draft decision projects, set up of the SC agenda, forwarding of documents to SC members in electronic format or on paper;
- Handling of the electronic versions of SCDs from draft status to publication (both in the Official Gazette of Romania, Part I, for SCDs approved through Order of the Minister Health, as well as on the NAMMD website, under the headings "Legislation" and "Informative Bulletins") in the directories for Scientific Council meetings;
- Forwarding of documents assessed in electronic format/on paper to SC members; - updating the record of contact coordinates of SC members;
- Drafting of the minutes of SC meetings;
- Out of the 29 SCDs approved in 2011, 4 have been submitted for approval through Order of the Minister of Health and 25, non-regulatory, have been posted on the NAMMD website and published in the Agency's bilingual Informative Bulletins.

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

- 159 regulatory documents, in Romanian and English version;
- 57 amendments, supplementations, recalls of legislative documents published on the website;
- Outline and editorial style of applications and forms to be posted under the heading <Forms> on the website;
- NAMMD informative bulletins in English and Romanian;
- The bilingual brochure containing NAMMD's annual report.

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

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

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

The European Affairs Service ensured, via its trained staff:

- Translation of the NAMMD self-assessment questionnaire for the BEMA II audit in May 2011;
- Translation of the quality manuals of the NAMMD, BPECD and of the Pharmacovigilance and risk management service;
- Translations for elaboration of the consolidated glossary for harmonisation of terms used in medicinal product information in Romania;
- Translation/Review of 15 European guidelines;
- Translation of reports and updates related to the crisis situation determined by radioactive leaks in Japan;
- Checking the translation of 3 evaluation reports and documents in English, for mutual recognition procedures and decentralised procedures;
- Checking translation of /Translating 126 EMA press releases, questions and answers documents and DHPCs as well as action lines proposed by the EMA ("Lines to take") etc.;
- Provision of advice for check of translation of SmPCs and leaflets, message exchanges and communication in English with European bodies;
- Linguistic assessment of EMA's proposals for translation into Romanian of various specialised terms from the legislative field of the medicinal product and proposal of NAMMD agreed terms.

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

- The internal and external communication, namely formulation of views, communication with the written media and the television (by telephone, e-mail, broadcast interviews), relationships with other Romanian and foreign institutions specialised in this field;
- Free access was ensured to public information in accordance with Law 544/2001, *ex officio* and/or upon request, for both the media, and the general public, providing information on NAMMD activities or information on the safety of medicinal products for human use;
- Cooperation with all NAMMD departments for ensured transparency of the Agency's activity by ensuring public accessibility/availability, namely passive transparency by ensuring reactive information following request;
- Notification of media representatives and/or other applicants within deadlines imposed by rules in force, if the information required is already communicated *ex officio* by means of specified under Article 5 of Law No. 544/2001, also stating where the required information can be found;
- Notification of the applicant, according to deadlines imposed by rules in force, if the required information has been identified as waved from free access;
- Cooperation with all NAMMD departments for collection and organisation of information required by the media and/or stakeholders, for draft of the required answer;
- Set-up/Verification and broadcast of official communications and NAMMD standpoints to the media;
- Participation to draft and transmission of mail exchanges with internal and external partners, related to issues specific to NAMMD activity;
- Daily monitoring of the mass-media (TV press and written press) in the healthcare field.

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

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

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

- Conditionally authorised medicinal products (based on Article 127a of Directive 2001/83/EC);
- MA suspension/withdrawal/amendment (based on Article 107 of Directive 2001/83/EC);
- Decisions following referral procedures (based on Article 20 and Article 30 of Directive 2001/83/EC).

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

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

14. Legal work of the NAMMD

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

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

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

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

- Set-up by NAMMD management of regulations and instructions or of other regulatory documents;
- Grant of approval concerning the legal character of measures to be taken, and of any other documents possibly involving the institution's patrimonial liability;
- Grant of approval concerning the correct interpretation of regulatory documents applicable to the NAMMD sector of activity;
- NAMMD representation in law courts;
- Insurance of adequate performance of jurisdictional procedures within the institution;
- Set-up/Pooling of documents required for NAMMD employees travels abroad for participation in activities by external partners;
- Set-up of NAMMD Administration Council meetings;
- Set-up of regulations specific to the field of activity;
- Handling of activities ensuring message exchanges for petition resolution in accordance with Ordinance no. 27/30.01.2002 regulating the resolution of petitions.

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

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

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

15. Management of human resources

15.1. Human resources policy

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

- Ensure human resources at the level of NAMMD structures, especially in sectors where department and top management reviews evidenced lack of qualified higher education

(particularly medico-pharmaceutical) staff, for proper covering of jobs in specialised departments, whose work practically ensures accomplishment of the Agency's scope.

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

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

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

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

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

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

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

  - setting up an adequate system for assessment of performances.

15.2. Ensuring Human Resources within NAMMD structures

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

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

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

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

from training organised nationally and internationally by various authorities and bodies in the field, such as:

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

16. Economic activity

In 2011, the Economic Department developed and managed a balanced budget of revenues and expenses from the state budget, amounting to 17,354,000 lei; expenses reached 16,657,821 lei.

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

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

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

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

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

17. General administration

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

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

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

18. Internal audit

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

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

Audit missions conducted considered the following:

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

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

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

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

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

19. Difficulties encountered

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

20. Priorities for 2012

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

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

Romanian hospital, under the surveillance of a physician; this field involves the priority training of assessors and inspectors in the review of compliance with Good Clinical Practice and Good Manufacturing Practice rules.

In 2012, the NAMMD will envisage:

- Organisation of meetings with the representatives of all stakeholders (manufacturers, distributors) for implementation of regulatory measures for application of a medicinal product traceability system, identification of all elements, which can represent a starting point in finding reliable solutions for such implementation in Romania;

- Revision of the Medical Devices List for periodic control, for sole inclusion of devices of maximum risk to patients and users;

- Revision of Order of the Minister of Health No. 1636/2004 on approval of Methodological Rules for implementation of Law No. 176/2000 on medical devices, as amended, referring to medical technical units, for explanation of certain issues leading to various interpretations of this Order and performance of steps provided, and demonstration of the need to hire more staff for more efficient national implementation of Law 176/2000 provisions.

CONCLUSIONS

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

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

The activity of the Agency continued at the same pace required by the respective moment: the assessment and marketing authorisation of medicinal products, Good Manufacturing Practice (GMP) inspections, Good Distribution Practice (GDP) inspections, Good Clinical Practice (GCP) inspections, Good Laboratory Practice (GLP) inspections, pharmacovigilance, informing the stakeholders (healthcare professionals, media, patients and, last but not least, the general public) about the latest and most accurate information concerning medicinal products.

As the single abilitated institution able to assess the performances and safety of medical devices in use, the NAMMD carries out the periodic check-up of installed and commissioned medical devices characterised by a high risk degree, at the sites of all medical device users, both in the private and public field. Moreover, the NAMMD has undertaken the duty to authorise and reauthorise medical device control and testing laboratories.

The NAMMD has a solid Quality Management System (QMS), based on *international standards 9001, 9004, 17025* etc. in force. The Agency's top management showed particular interest and ongoing involvement in QMS-related activities, being preoccupied with the enforcement of the process-based approach.

In view of establishing the framework for bilateral cooperation and exchange of information in the field of the counterfeiting of medicinal products for human use, in accordance with the specific attributions and competences stipulated by the legislation in force, the agency has also collaborated with the General Inspectorate of the Romanian Police.

It is a well-known fact that the Agency is one of the decision factors in the field of the medicinal product for human use and, as such, it involves everything related to the set-up of a regulatory framework harmonised with the provisions of the European legislation, in accordance with the recommendations of the European Medicines Agency and with European Commission Decisions. Only in this manner can the NAMMD fulfil its primary mission to grant quality, efficacy and safety of medicinal products authorised for marketing in Romania.