Report of the National Agency for Medicines and Medical Devices 2013

Introduction

The National Agency for Medicines and Medical Devices (NAMMD) is the national competent authority in the field of the medicinal products for human use, fully aware of the importance of monitoring and evaluation of its policy for protection and promotion of public health, by guaranteeing both compliance with European standards related to medicinal products authorised for marketing - in terms of their quality, efficacy and safety, and maintenance of a high level of performance and safety of medical devices in use in healthcare networks from around the country.

The NAMMD is continually preoccupied with the requirements and expectations of stakeholders (healthcare professionals, the pharmaceutical industry, patients, public, the mass-media) and makes the effort to ensure adequate and responsible regulatory policy in its field of work.

The NAMMD's customary activity in 2013 consisted of grant and issue of 773 marketing authorisations (MAs) (195 through NP - national procedure for marketing authorisation and 578 MAs through EP (European procedures) for marketing authorisation.

New authorisations were granted in the following therapeutic areas:

A – Digestive tract and metabolism – 82 MAs
B – Blood and blood-forming organs – 47
C – Cardiovascular system – 40
D – Dermatologicals – 9
G – Genitourinary and sex hormones – 42
H – Systemic hormonal preparations (sex hormones exclusively) and insulin – 5
J – Anti-infectives for systemic use – 56
L – Antineoplastic and immunomodulating agents – 117
M – Musculo-skeletal system – 29
N – Nervous system – 167
P – Antiparasitic products, insecticides and repellents – 5
R – Respiratory system – 51
S – Sensory organs – ophthalmologicals, otologicals, ophthalmological and otological preparations – 8
V – Various (therapeutic radiopharmaceuticals, contrast media etc.) – 5.

As regards MA discontinuation, 320 discontinuations were performed in 2013, in the following therapeutic areas:

A – Alimentary tract and metabolism – 33 decisions for MA discontinuation
B – Blood and blood forming organs –16
C – Cardiovascular system – 62
D – Dermatologicals – 6
G – Genito-urinary system and sex hormones – 17
J – Antiinfectives for systemic use – 20
L – Antineoplastic and immunomodulating agents – 31
M – Musculo-skeletal system –16
N – Nervous system – 84
P – Antiparasitic products, insecticides and repellents – 1
R – Respiratory system – 24
S – Sensory organs – 7
V – Various (radiopharmaceuticals, contrast substances etc.) – 3.

At the top of marketing authorisations in 2011 and 2012, generics have preserved their status in 2013 as well.

Of the 8582 medicinal products entered into the Index of medicinal products for human use in 2013, 33% are original products, authorised through centralised procedure by the European Medicines Agency (European Medicines Agency-EMA), placed on the Romanian market upon MAH request.

Regarding the status of pending dossiers at the end of December 2013 , existent in various stages of assessment in the marketing authorisation procedure (through the national and European procedures), the following data should be outlined, noting that several MAs may be issued for the same active substance(s), depending on strength(s) and / or approved pharmaceutical forms and that assessment work as such is carried out for each strength and / or pharmaceutical form submitted for authorisation. Therefore:

- Total number of dossiers in progress in the European procedures: 741 (DCP-decentralised procedure, mutual recognition procedure - MRP, MA renewal procedure). Out of 741 cases, Romania was appointed the Reference Member State – RMS in 7 instances, therefore assigned with mandatory coordination and development of the assessment report on documentation for authorisation; for the other 734 cases, Romania was appointed Concerned Member State - CMS, therefore allowed, when deemed appropriate by NAMMD assessors, to make notes, comments on RMS assessment report);

- total number of dossiers in progress for assessment through national procedure: 364 dossiers for new MAs and 380 dossiers for MA renewal.

Pharmacovigilance work performed throughout the past years by the Pharmacovigilance and Risk Management Service gradually grows in complexity. The number of reported adverse reactions (ARs) is growing, which shows the increasing importance assigned to patient’s safety by physicians and the medical staff; however, more resolute involvement is required from healthcare professionals in this respect, as well as from patients, empowered by

the European legislation (transposed into Romanian legislation through Emergency Government Ordinance 35/2012 amending certain healthcare regulations). Each instance of adverse reaction occurrence entered into the European database (EudraVigilance) or the World Health Organisation database is a step forward to more in-depth knowledge of medicinal products. It is the duty of any medicinal product competent authority to appeal for adverse reaction reporting, highlighting the importance of physician-pharmacist-assistant-consumer partnership for best possible knowledge of the safety profile of medicinal products by means of such reporting as well. This is the only manner allowing proper review of the risk-benefit balance for certain medicinal products or groups of medicinal products.

Thus, it is worth mentioning that, in 2012, the first steps in implementation of the new pharmacovigilance approach had already been taken. Out of 1272 ARs, 1003 were reported by physicians, 12 by pharmacists, 60 by healthcare assistants and 32 by users.

Year 2013 meant the reporting of 1847 ARs (935 – serious ARs and 912 - non-serious ARs). Of these, 295 ARs were notified by physicians directly to the NAMMD and 1552 by MAHs (100 submitted by users, 34 by pharmacists, 59 by medical assistants, and the rest mostly by physicians, articles from specialised literature included).

Work of the Pharmaceutical Inspection Department (PID) consisted of 28 inspections for assessment of compliance with Good Manufacturing Practice (GMP) rules for authorisation for marketing/import/GMP certificate, 1 inspection on Good Laboratory Practice (GLP) in laboratories performing bioequivalence studies, 3 inspections on Good Analytical Laboratory Practice (GALP) for authorisation of independent sites for control of medicinal product quality, 22 inspections for authorisation at the sites of medicinal product importers, 7 inspections for assessment of compliance with Good Clinical Practice (GCP), 1 pharmacovigilance inspection at the site of a MAH representative in Romania, 118 inspections for authorisation of wholesale distributors of medicinal products. Two follow-up inspections were carried out for assessment of the manufacturing process and implementation of corrective measures proposed as included in plans submitted to the NAMMD for authorisation purposes; export declarations were approved for 3731 medicinal products, upon request by 40 medicinal product manufacturers/distributors. As opposed to 2012, when export declarations were approved for 1855 medicinal products manufactured/marketed in Romania, there is an obvious increase in export to third countries. when export declarations have.

In 2013, certain falsified medicinal products entered into the legal supply chain, as never before July 2013 in Romania. The case of falsified products entering the legal supply network, i.e. Sutent and Pegasys, resulted in emergency measures for notification of patients on the issue impacting public health (including description of differing features between the original and the

falsified product) and recall from the market of the two medicinal products batches, whose identification numbers were found imprinted on boxes established as falsified.

Medicinal products were in both cases a matter of life or death. Pegasys treatment (peginterferon alfa-2a) is costly and granted free of cost to patients, according to waiting lists. At that specific time, press articles highlighted the viewpoint of specialists, stating that the treatment with Pegasys was "difficult to tolerate because of its adverse reactions. Nevertheless, patients are willing to take the risk and they continue their treatment, because they understand this is their opportunity to heal". In this case, administration of a falsified medicinal product instead of the original one practically means discontinuation of the treatment, which, in the context of potential benefits for chronic hepatitis patients, means murder. On the other hand, data provided by specialised literature on Sutent (sunitib), a comparatively new treatment on the Romanian market, indicate its remarkable effects according to studies, namely doubling of the life expectation for patients suffering from certain types of cancer, as opposed to patients who have received classical treatment.

In both cases, a detailed enquiry was conducted by competent police authorities with support from the NAMMD and the holder of the marketing authorisation for the original product.

A further landmark for year 2013 as regards NAMMD work was failure of market launch of the flu vaccine manufactured by the Cantacuzino Institute (CI) for the 2013-2014 season, following noncompliant results for f *Bacterial endotoxins* content. The NAMMD performs official batch release for immunological medicinal products and medicinal products derived from human blood/plasma manufactured in Romania, third countries or EU member states for which official batch release has not been performed by a control authority and which can only be marketed in Romania, in accordance with Law 95/2006 on healthcare reform, Title XVII - The medicinal product (Article 826), transposing Directive 2001/83/EC of the European Parliament and of the Council on a community code relating to medicinal products for human use, as amended.

Samples of all the 8 batches of flu vaccine manufactured by the Cantacuzino Institute were tested in NAMMD laboratories in accordance with the monograph of the European Pharmacopoeia, the edition in force. Following laboratory analysis of the samples, out-of-specification results were found for one of the tested parameters, namely *Bacterial endotoxins*, for all tested samples. It is worth remembering reminding that, for all other tested parameters, results were within the limits. As a result of noncompliance identified for all new batches of vaccine manufactured by the CI, samples were retested within the NAMMD, followed by retesting in the manufacturer's presence.

Results after retesting performed at both the NAMMD and at the manufacturer's sites, have confirmed the non-compliance of exceeding limits allowed for Bacterial endotoxins content (maximum 100 IU / vaccine dose).

On 23.12.2013, the NAMMD submitted a notification to the Ministry of Health on the noncompliance found, resulting in failure of official batch release for the vaccine manufactured by the Cantacuzino Institute, results obtained requiring issue of non-compliance bulletins.

The activity of the Technical-Medical Units Assessment Department consists of evaluation of the various organisations' ability to perform services for which they apply for Ministry of Health approval. Services assessed include medical optics, medical devices and prosthetics (hearing, orthopaedic, other).

With a minimum number of employees, this service must ensure national coverage of work in this area and perform both initial assessment of organisations for approval for operation, surveillance evaluations every two years, as well as finding of contraventions and implementation of civil fines, in accordance with Law no.176 / 2000 on medical devices, as amended.

Works performed:

- Applications for assessment: 170
- Completed assessments, with issue of reports: 88
- Works undergoing assessment:17
- Cancelled assessments (no dossier submitted for assessment): 21
- Nearly completed assessments: 23
- Notifications issued for completion of the assessment dossier:122
- Fees issued for assessment:128
- Number of assessment-surveillance works: 371
- Finished assessment-surveillance works, with issued reports: 160

As regards Human Resources, year 2013 brought many changes. After 5 years' suspension of hiring contests/exams for positions included in the job title list, in accordance with provisions of Article 22 of Emergency Government Ordinance 34/2009, according to which "hiring for public institution positions by contest/exam is suspended", the aim to provide the NAMMD with qualified staff could be partially implemented in 2013 only, following entry into force of Emergency Government Ordinance 77/2013 for measures to be taken in order to ensure the operation of local public administration, the number of jobs and a cut in expenses in public institutions and authorities subordinated to, under the authority of or in coordination with the Government or ministries. Emergency Government Ordinance no. 77/2013 lifting the ban on employment by competitive examinations to cover vacancies, provided that they are occupied according to the "one-to-one" principle, namely one hiring for one vacant position". Considering restrictions imposed by compliance with the "one-to-one" principle, the institution had to decide on pension off of a number of

employees who were paid both pension and wage; consequently, in November 2013, the required steps were taken to make available 27 positions for higher education healthcare professionals.

As regards NAMMD administrative work, the institution also took advantage of the opportunity of hiring by contest/exam, by employing 21 new employees in November and December 2013, of which 18 university graduates in administration and 3 with secondary education in administration. An additional negative impact of Emergency Government Ordinance 77/2013 on our institution was decrease of management positions so as to represent 12% of all approved jobs, which has meant reduction by half of the number of management positions with implications for respective employee motivation.

Other aspects related to the NAMMD activity:

- Active participation in debates, at bimonthly/monthly/quarterly meetings of scientific committees and coordinating working groups of European bodies in the field of the medicinal products for human use (the European Medicines Agency - EMA, the Heads of Medicines Agencies - HMA, the European Directorate for the Quality of Medicines - EDQM, the European Commission)

As every year starting with 2007, in 2013 as well the NAMMD was represented by participation, via nominated representatives, in meetings of scientific committees and working groups of European bodies, concerning various regulatory issues and issues related to European procedures in the medicinal product field, such as:

- EMA's CHMP (Committee for Medicinal Products for Human Use), being assigned as co-rapporteur in re-examination procedures;
- EMA's PDCO (Paediatric Committee) - PIP (Paediatric Investigation Plan) assessment, participation at the preparation of the 2012 Yearly Paediatric Report for Romania for submission to the European Commission via the EMA/PDCO and participation in teleconferences and monthly/bi-monthly meetings of working subgroups (on extrapolation of safety and efficacy in paediatric medicinal product development and Pharmaceutical formulation – active participation and preparation of assessment reports);
- The Coordination Group for Mutual Recognition and Decentralised Procedures – Human - CMDh;

Romania is Reference Member State in several decentralised procedures.

- The Committee on Herbal Medicinal Products, Romania as rapporteur/assessor for certain community monographs;
- Meetings of EMA's Pharmacovigilance Risk Assessment Committee (PRAC);

- The Working Group for medicinal products and medical devices of the EU Council, where NAMMD representatives join debates for draft and harmonisation of clinical trial- related legislation in all Member States.

The Minister of Health assigned the NAMMD to participate at debates on the new clinical trial Regulation, the proposal for repeal of Directive 2001/20/EC being launched in July 2012. In 2013 as well, the NAMMD has continued in its position, through assigned specialists, as active participant in debates, supporting and contributing to amendment of the previous clinical trial legislative framework.

- meetings of the European Pharmacopoeia Commission.

- Transposition into national law of provisions of Directive 26/2012/EU on new amendments to pharmacovigilance activity

Intense NAMMD legislative transposition in 2012, consisting of issue of two Emergency Government Ordinances (Emergency Government Ordinance 35/July 2012 and Emergency Government Ordinance 91/December 2012, amending Law 95/2006 on healthcare reform, as regards prevention of the entry into the legal supply chain of falsified medicinal products), was also continued in 2013 related to the new Directive 26/2012/EU, once again amending, with regard to pharmacovigilance, Directive 2001/83/EC on the community code relating to medicinal products for human use.

In 2013, upon request of the Ministry of Health, the NAMMD contributed to set-up of the regulatory draft for amendment and supplementation of Law 95/2006 on healthcare reform, including changes brought about by transposition of Directive 26/2012/EU, amendments of Emergency Government Ordinance 35/2012 and Emergency Government Ordinance 91/2012, supplementations concerning the "public service" concept, new sanctions for non-compliance with legal provisions in the field of the medicinal product.

- Regulation and provision of technical support upon request of the Ministry of Health

- In 2012, the Scientific Council (SC) of the NAMMD approved a Scientific Council Decision (SCD) on approval of mandatory monthly reporting of placement on the market in Romania, respectively of sales of medicinal products for human use by authorised wholesale distributors/importers/ manufacturers. This regulatory SCD was approved through Order of the Minister of Health no. 502/April 2013 on approval of mandatory monthly reporting of placement on the market in Romania and of sales of medicinal products for human use, respectively, by authorised wholesale distributors/ importers/manufacturers.
- In 2013, the NAMMD Scientific Council approved a revised version of the

Guideline on assessment of advertising for medicinal products for human use; the NAMMD succeeded to approach this type of assessment with the same accuracy and rigour as for assessment of documentation on medicinal product quality, efficacy and safety.

- It is worth mentioning that two Scientific Council Decisions were adopted in October 2013, referring to a new NAMMD activity, namely issue of scientific approval on quality and safety of the active substance ancillary to a medical device, in which it is incorporated as an integral part. These Decisions established:

  - NAMMD manner of handling requests from a notified body on issue of the aforementioned scientific approval

  - implementation rules related to the procedure for NAMMD consultation by a notified body, concerning issue of the respective scientific approval.

- as defined through Order of the Minister of Health no. 85/07.02.2013 on approval of Implementation rules related to provisions of Article 699 (1) and (2) of Law No. 95/2006 on healthcare reform concerning medicinal products for special needs, a new duty has been assigned to the NAMMD: grant of authorisation for provision of medicinal products for special needs, in accordance with conditions specified in the Order.

- The NAMMD has provided technical support to the Ministry of Health for issue of Order of the Minister of Health no. 456/02.04.2013 on approval of the List of International Non-proprietary Names of medicinal products at high unavailability risk, as provided to insurants in the health insurance system and agreement on a measure to secure their market availability in Romania.

  The Order of the Minister of Health refers to temporary suspension, according to Law 95/2006, of distribution outside Romania of medicinal products specified in the List attached to the Order of the Minister of Health.

- The NAMMD responds to Ministry of Health requests concerning:

  a) ensurance of technical support for set-up of Lists for national actions taken to provide the needed amounts of medicinal products:

  - in hospital sections

  - for national programmes (compliance with Annexes to Order of the Minister of Health on medicinal products involved in national health programmes)

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

Projects: the NAMMD seeks further development of such issues as:

- Clinical trials, by definition of public information on clinical trials,
- Rules for NAMMD accreditation of providers of Good Clinical Practice

(GCP) rules courses.

- The Organisational strategy and the Communication strategy of the National Agency for Medicines and Medical Devices (2013 – 2015), approved through NAMMD Scientific Council Decisions.

The organisational strategy defines the NAMMD mission, vision and strategic objectives for 2013-2015 and establishes its update whenever the legislative and pharmaceutical framework require.

The Communication Strategy states that safeguard of public health is the most important of NAMMD strategic goals. This is the result of fulfilment of the Agency's primary role, i.e. to guarantee compliance with standards set for human medicinal products authorised for marketing, ensuring their effectiveness and acceptable safety level. To successfully meet this strategic objective, the NAMMD seeks to continuously strengthen the status of expert and trusted source of accurate information in the field of medicinal products for human use, of information provided in a timely manner to the most important stakeholders, who are expected to become real and active partners in dialogue and action.

- Attendance at meetings/workshops/conferences/informal meetings with stakeholders on issues related to legislation and procedures during 2013

Among other developments, the year 2013 was also marked by:

- Participation in meetings of various patient associations (the Federation of Cancer Patients Associations, Association of Patients with Liver Disease) with presentations on generic and innovative medicinal products, on falsified medicinal products, the importance and meaning of clinical trials, off-label use, the importance of reporting suspected adverse reactions to medicinal products (August and October 2013);
- Participation in organisation of the NAMMD-ARPIM-APMGR Workshop (June 2013) on quality of medicinal products for human use. NAMMD specialists presented papers on topics of interest to representatives of Marketing Authorisation Holders (MAHs) relating to approval of variations to MAs for paediatric products, pharmacovigilance activity, the frequent deficiencies encountered in assessment of biological medicinal products, medicinal product quality control;
- participation in debates of the International Health Forum (September 2013) organised by the APMGR on the issue of generic medicinal products on the Romanian market.

The NAMMD and the ARPIM have proposed conducting joint campaigns to inform the public on:

- the generic medicinal product versus the generic medicinal product;
- the danger of buying counterfeit medicinal products online.

By means of its Communication Strategy 2013-2015 (approved by decision of the Scientific Council in April 2013), the NAMMD has proposed organisation in the first quarter of 2014 of a campaign to inform the public and

patients about the meaning of the black top down triangle and additional monitoring of drugs.

Participation with expert papers in various scientific events

The NAMMD has shown openness to communication and transparency in its activity and participation with important scientific papers in:

- Bucharest Forum HealthCare, organised by the Aspen Institute of Romania, Adevarul Group, with support from the National Bank of Romania, Bucharest, February 2013.
- The National Paediatric Conference, Bucharest, April 2013
- Farmacist.ro – Bucharest, June 2013
- The Summer school for journalists, Sighisoara, July 2013
- The National Conference of Family Medicine - Bucharest, October 2013
- The National Conference of Pharmacy, Bucharest, November 2013

Specialist papers presented by NAMMD representatives:

- Ensuring the quality, safety and efficacy of medicinal products for human use, the priority mission of the NAMMD.
- General considerations in light of the revised version of the Guidelines on advertising of medicinal products for human use.
- Off-label use of drugs in NAMMD vision (work awarded - Third Prize at The National Paediatric Conference, April 2013)
- Paediatric Regulation Impact - more medicinal products for EU children.
- Pharmaceutical and regulatory issues specific to development and formulation of medicinal products for paediatric use.
- Medication errors in terms of pharmacovigilance activities.

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

NAMMD ACTIVITIES IN 2013

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

In 2013, the Scientific Council adopted 27 Scientific Council Decisions; out of these, 6 regulatory decisions are pending approval through Order of the Minister of Health (OMH); the remainder of 21 non-regulatory SCDs are posted on the NAMMD website under the heading “Legislation/Scientific Council Decisions” and also published in the bilingual NAMMD Newsletter of 2013.

Non-regulatory SCDs concern:

- Approval of the Organisational strategy of the National Agency for

Medicines and Medical Devices (2013 – 2015);
- Approval of the Communication strategy of the National Agency for Medicines and Medical Devices (2013-2015);
- Approval of priority evaluation of applications for marketing authorisation by national procedure for the International Non-proprietary Names (INNs) identified as deficient on the pharmaceutical market
- Procedure on resolution of cases of serious non-compliance with Good Manufacturing Practices (GMP) or of cancellation / suspension of Ph.Eur. compliance certificates requiring coordinated administrative action
- A procedure on resolution of serious non-compliance with Good Manufacturing Practices (GMP) announced by authorities in third countries or international organisations
- Adoption of the Guideline on training and qualification of inspectors conducting inspections at wholesalers' sites
- Approval of formats for declarations of serious non-compliance with wholesale distribution practice and with Good Distribution Practice for pharmaceutical active substances
- Approval of the Good Pharmacovigilance Practice - Annex I - Definitions
- Approval of the Good Pharmacovigilance Practice - Module I - Pharmacovigilance systems and their quality systems
- Approval of new Romanian Standard Terms for certain pharmaceutical forms, primary packaging, closure and delivery devices, routes and manners of administration, consistent with those approved by the European Pharmacopoeia Commission
- Approval of the revised version of the Guideline on the assessment of advertising of medicinal products for human use,
- Approval of the Guideline on the details of the various types of variations to the terms of marketing authorisations and their handling by the National Agency for Medicines and Medical Devices in the context of the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended by Regulation (EU) no. 712/2012
- Approval of abbreviated Romanian Standard Terms, used for labelling of parenteral, ophthalmic, ear and nasal preparations, in accordance with those approved by the European Pharmacopoeia Commission
- Approval of the Guideline on Good Pharmacovigilance Practices, Module IV – Pharmacovigilance Audits.

It is worth mentioning that 2 SCDs were adopted during the meeting of the Scientific Council of October 2013 referring to a new NAMMD activity, namely:

- NAMMD's manner to handle requests of an informed body concerning issue of a scientific approval on the quality and safety of the ancillary active substance incorporated, as an integral part, into a medical device

- Approval of the norms for implementation of the procedure for consultation of the NAMMD by a notified body concerning issue of a scientific approval on the quality and safety of an ancillary medicinal substance incorporated as an integral part into a medical device.

2. Activity of the NAMMD Administration Council (AC)

In 2013, the Administrative Council (AC) adopted 4 Administration Council Decisions (ACDs). As concerns topics involved, ACDs have covered various aspects of current activities, such as approval of the NAMMD annual report, approval of the collective labour contract for 2013-2015, approval of proposals of fees for NAMMD activities, disoperation of fixed assets, decommission of materials such as inventory objects and retirement of stocks of materials.

3. Regulatory activity

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

- The Emergency Ordinance on amendment and supplementation of Law 95/2006 on healthcare reform transposing Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, published in the Official Journal of the European Union (the OJ) no. 299 of 27 October 2012;
- The Order of the Minister of Health on amendment of Order of the Minister of Health no.716/2009 on approval of tariffs and amount of marketing authorisation maintenance fee required by the National Medicines Agency;
- Order of the Minister of Health on repeal of Order of the Minister of Health no.1369/2009 on approval of fees required by the Technical Office for Medical Devices for activities performed, published in the Official Gazette of Romania, part I, no. 752/04.11.2009.

In view of implementing provisions of Title XVII – The medicinal product of Law 95/2006 on healthcare reform, as amended, and in accordance with provisions of Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, the Agency sets up norms, instructions and other mandatory regulations, concerning its activity in the field of the medicinal product for human use which, as regulatory SCDs, are submitted for approval to the Ministry of Health through Minister of Health Order and subsequently published in the Official Gazette of Romania, Part I.

Given growth in complexity of NAMMD activity as a national authority within the network of EU competent authorities in the field of the medicinal product for human use, work of the NAMMD Scientific Council for approval of certain regulatory SCDs was continued in 2013 as well.

3 regulatory Scientific Commission Decisions have been submitted for Ministry of Health approval through Order of the Minister of Health. These SCDs refer to:

- The Guidelines on consultations with target patient groups for the package leaflet and criteria for certification/recertification by the National Agency for Medicines and Medical Devices of operators performing consultations with target patient groups
- Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and grant of the Good Manufacturing Practice certificate
- The procedure on registration of manufacturers, importers or distributors of active substances used as starting materials for medicinal products for human use.

Moreover, three other regulatory SCDs were subject to repeal of Minister of Health Orders:

- repeal of Orders of the Minister of Health no. 1450/2010 and no. 399/2006 on approval of European models of package leaflet, summary of product characteristics and label information for medicinal products authorised for marketing in Romania (national procedure)
- repeal of Order of the Minister of Health no. 279/2005 on approval of implementation of changes to marketing authorisations approved by the National Medicines Agency
- repeal of Order of the Minister of Health no. 1483/2010 on approval of the norms on the administrative procedure of the National Agency for Medicines and Medical Devices for handling of variations.

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions (CAPP)

In 2013, as well, as a consequence of the setup of 2 commissions for marketing authorisation/marketing authorisation renewal approved through NAMMD Administration Council Decision (CAPP-National Procedure, CAPP-European Procedures, CAPP-Renewals), whose structure has been established through Decision of the NAMMD President), assessment reports have been discussed, in order to provide an opinion concerning marketing authorisation of various medicinal products for human use for which an application has been submitted in this respect, as well as other aspects related to the marketing authorisation of medicinal products for human use.

In 2013, 25 working sessions took place with the participation of various commissions (12 for CAPP-National Procedure and 13 for CAPP-European Procedures).

The Commissions approved the issue of 1124 marketing authorisations, of which 727 through European procedures (decentralised, mutual recognition, mutual recognition-repeated) and 397 through national procedure.

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

In accordance with its own regulation for organisation and operation, approved through a NAMMD Administration Council Decision and in a structure approved through President Decision, the Commission continued its activity in 2013 as well. The Commission reviews inspection reports issued by Agency inspectors, concerning the manner of compliance by inspected units with Good Manufacturing Practice, Good Distribution Practice, Good Laboratory Practice, Good Analytical Laboratory Practice, Good Clinical Practice rules and/or with other issues concerning work of the Pharmaceutical Inspection Department.

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

In 2013, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 185 inspection reports, of which:

- 60 inspection reports on compliance with Good Manufacturing Practice rules;
- 117 inspection reports on compliance with Good Distribution Practice rules;
- 5 inspection reports on compliance with Good Clinical Practice rules;
- 1 inspection report on compliance with Good Laboratory Practice rules;
- 1 pharmacovigilance inspection report.

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 2013, 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 2013, there were no requests for summons of the Commission.

5. Marketing authorisation and related activities

In 2013, the Agency's main activities with regard to assessment of documentation submitted to the NAMMD for marketing authorisation (MA), renewal of marketing authorisation and post-authorisation surveillance of medicinal products, have been conducted in accordance with the increasingly stricter regulation of activities specific to a competent authority in the EU medicinal product field. These are activities specific to competent authorities in the field of the medicinal product and are carried out in accordance with specific provisions related to national and European procedures (mutual recognition, decentralised, repeated mutual recognition procedures). Marketing authorisation and related activities were conducted in line with the organisational structure established in 2010 and approved through Order of the Minister of Health on the organisation and setup of the National Procedure Department and the European Procedures Department.

5.1. Marketing authorisation through national and European procedures

In 2013, the NAMMD granted 773 marketing authorisations (MAs), of which 578 through European procedures (PE) (75 %). Of 578 MAs through EPs, 364 MAs (63%) were granted through DCP, 15 (2.6%) through MRP, 38 (6.66%) through MRP-RU ("*repeat use*" procedure) and 161 (27.85%) through renewal procedure. The percentage of authorisations renewed through European Procedures was two times larger than in 2012.

As regards assessment through national procedure, this resulted in grant of 195 marketing authorisations.

The decreasing tendency for the number of applications for marketing

authorisations granted through national procedure, in favour of authorisations granted through European Procedures (EPs) is worth mentioning.

A comparative perspective shows an almost unchanged number of decisions for discontinuation of authorisation/renewal procedure, on MAH request for trade reasons, in 2009 and 2011, namely: number of MA applications discontinued: 2009=134 and 2011=131, compared to 2010=202 and 2012=247. In 2013, the number of MA applications discontinued has raised to 320, which obviously represents a substantial increase as opposed to previous years.

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

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

- 2965 applications for type I variations;
- 290 applications for type II variations;
- 65 applications for MA transfer;
- 365 changes of packaging design and printing;
- 784 safety and efficacy variations.

5.2.2. In 2013, as regards **post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures**, for medicinal products for human use authorised through decentralised/mutual recognition/repeated mutual recognition procedure, the Agency approved:

- 1702 applications for type IA variations with Romania as a concerned member state; 2 applications for type IA variations for Romania as a reference member state;
- 1600 applications for type IB variations with Romania as a concerned member state; 20 applications for type IB variations with Romania as a reference member state;
- 422 applications for type II variations with Romania as a concerned member state;
- 102 applications for MA transfer with Romania as a reference member state;
- 31 notifications in accordance with Article 61 (3) of Directive 2001/83/EC.

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

In 2013, the number of applications for authorisation of clinical trials has recorded a slight decrease as opposed through previous years, as evident from comparing the yearly number of applications submitted (246 in 2011 vs. 266 in 2010, 266 in 2010, 253 in 2009 or 275 in 2008).

Most of these are Phase III clinical trial applications (146 applications in 2013), meaning that the respective medicinal products undergo advanced research and are therefore nearing authorisation. Phase II clinical trials are the second most frequent type of clinical trial applications (49 applications in 2013); these are exploratory studies concerning the most effective dose for medicinal products whose safety and tolerability have been proven.

In Romania, there are few applications for performance of Phase I clinical trials (12 applications in 2013, more than 4, in 2012), which require special conditions.

In 2013, the NAMMD granted 199 authorisations for performance of clinical trials, mostly for Phase III (134) and II (46) clinical trials; 7 Phase I and 12 Phase IV clinical trials were approved.

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

In 2013, the Clinical Trial Service of the National Procedure Department approved 538 substantial amendments and 213 amendments for new investigational sites. Moreover, 68 authorisations for conduct of bioequivalence clinical trials were granted after assessment of the protocol of bioequivalence clinical trials for medicinal products undergoing national procedure in view of authorisation/renewal of authorisation.

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

In 2013, **507** advertising materials to the general public concerning OTC medicinal products have been assessed for approval.

609 advertising materials to the general public concerning OTC medicinal products have also been assessed for re-approval.

As regards advertising materials to be used in educational programmes, **184** educational items were assessed and approved.

12 addresses for rejection of the advertising approval have been issued.

In the same way as during the previous two years, in 2013 as well the same special emphasis was placed upon surveillance and control of advertising of medicinal products for human use. Thus, under the special heading on the

Agency's website, "Advertising", various notifications have been posted, dealing with non-compliance with advertising regulations in force.

Year 2013 has also meant approval through Scientific Council Decision, in august, of the revised version of the Guideline on evaluation of advertising in medicinal products for human use and, in October, approval through SCD of certain amendments and supplementations brought to the revised version of the Guideline. Revision of the Guideline on Advertising is in line with the principles issued in it, according to which:

"Article 2. – (1) For all activities related to advertising of medicinal products, standards and rules to order and regulate the respective activities should be established and observed.

(2) All activities of advertising and promotion of medicinal products must be made responsibly, ethically and to the highest standard to ensure safe use of medicinal products, irrespective of their manner of release (with or without prescription).

Article 3. – (1) Advertising of medicinal products is accepted provided it is compliant with the legislation in force."

5.5. Pharmacovigilance

The NAMMD's Pharmacovigilance and risk management service, part of the Agency's European Procedures Department and whose activity is entirely compliant with Law 95/2006 and specific European Guidelines, ensures safety of medicinal products authorised in Romania.

In Romania, pharmacovigilance is conducted based on European legislation, transposed into national law. In addition to other pursuits, pharmacovigilance includes assessment and submission of adverse reactions through the EudraVigilance system (the European network for pharmacovigilance data-processing and management), assessment of Periodic Safety Update Reports (PSURs) as forwarded by pharmacovigilance systems of authorisation holding companies, assessment of Risk Management Plans. Pharmacovigilance also involves approval of direct healthcare professional communications concerning special warnings on medicinal product safety, as well as translation of EMA press releases and Q&A documents, actually notifications from the monthly CHMP and PRAC meetings, for posting on the NAMMD website. An additional NAMMD pharmacovigilance task is response to requests for non-urgent information from the European and international rapid alert system.

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

Via direct communications to healthcare professionals, by means of

national medicine and pharmacy symposia, conferences and congresses, as well as NAMMD representatives' participation in meetings of various patient organisations, an appeal for suspected spontaneous adverse reaction reporting is sent to physicians, pharmacists, medical and pharmacy assistants, but also to patients, as of July 2012. The NAMMD message remains the same: reporting adverse reactions is vital; only thus can complex information be obtained about medicinal products, following their marketing authorisation, upon impact with the public.

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

During the previous years, each Agency report analyses the progress recorded in AR reporting through presentation of the numbers. In 2004, 280 spontaneous reports were recorded, as opposed to 525 in 2009, 938 in 2010, 1011 (serious and non-serious) in 2011. It is worth mentioning that, in 2012, the Agency started the implementation of the new manner of pharmacovigilance approach. Of 1272 ARs, 1003 were signalled by physicians, 12 by pharmacists, 60 by assistants and 32 by consumers.

In 2013, 1847 ARs were signalled (935 – serious and 912 non-serious). Of these, physicians have reported 295 ARs directly to the NAMMD, and the MAHs 1552 ARs (100 of these coming from consumers, 34 from pharmacists, 59 from medical assistants, and the rest, the majority, from physicians, also from special articles).

In 2013, pharmacovigilance activities performed by the Pharmacovigilance and Risk Management Service mainly materialised in the following:

a) management of safety data issued from spontaneous reporting:

- validations/confirmations of adverse reaction (AR) reporting to the European database for adverse reactions, EudraVigilance (ICSR and SUSAR) – 2529
- retransmission of cases received by the NAMMD in the EV inbox sent to EVHUMAN in electronic format: 1196 serious adverse reactions
- transmission of serious and non-serious adverse reaction reports straight to the NAMMD on paper, by fax, post, email: 267 (SARs: 190, NSARs: 77);
- local handling and archiving of spontaneous adverse reaction reports

received from all sources: 1847

- non-serious: 912 (of which 105 from physicians)
- serious: 935 forwarded to the EudraVigilance (of which 89 from physicians)
- 345 follow-up reports

- Electronic retransmissions of adverse reactions in VigiFlow, the World Health Organisation database (Uppsala Monitoring Centre) - 685
- Quarterly notification of the College of Pharmacists for transmission of spontaneously reported adverse reactions in Romania, validated by the NAMMD – The National Pharmacovigilance Centre: 4
- Quarterly notifications of the College of Pharmacists for transmission of spontaneously reported adverse reactions in Romania, validated by the NAMMD - The National Pharmacovigilance Centre: 3
- letters of confirmation of receipt of AR reporting forms from physicians from the network: 173
- 18 confirmations of submission of spontaneous reporting of adverse reactions from pharmacists in the network;
- 905 information letters for physicians on grant of Continuing Medical Education (CME);
- 18 information letters to pharmacists on grant of Continuing Medical Education (CME) credits for spontaneous adverse reaction reporting in Romania, validated by NAMMD's National Pharmacovigilance Center;
- 185 responses to MAH requests concerning adverse reactions reported to the NAMMD involving medicinal products authorised in Romania;
- 335 response letters on MAH requests concerning pharmacovigilance-related aspects.

b) Gathering, validation, archiving of Periodic Safety Update Reports (PSURs):

- PSURs for medicinal products authorised through national or European procedures DCP/MRP/MRP-RU: 900
- PSUR assessment reports for medicinal products undergoing MA renewal: 1

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

- EMA press releases (55) and Questions and Answers documents (9) – documents for notification, handling and verification of translation, forwarded for posting on the NAMMD website: 64

- "Lines to take" documents approved by the EMA - management of

documents (record, archiving, notification of the press officer), notification of the Pharmacovigilance and Risk Management Service on provision of responses to potential requests of information: 37;

- approval and management of 68 Direct Healthcare Professional Communications (DHPCs) related to safety concerns raised in relation with medicinal products;

- transmission of 43 medicinal product safety information letters to the Ministry of Health, the National Health Insurance House (NHIH), the College of Physicians, the College of Pharmacists;

- activities concerning MAH notification for SmPC and leaflet harmonisation following referral procedure, upon request of the PhWWP/CHMP/CMDh for individual medicinal products or groups of medicinal products: 3;

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

- replies (INU) upon request for information by certain EU national authorities concerning information about individual medicinal products or medicinal products categories, other information concerning measures for enforcement of pharmacovigilance legislation: 28

e) Assessment for requirements for description of the pharmacovigilance system

- assessment reports of the pharmacovigilance system of the MA applicant, concerning requirements of the detailed description of the Detailed Description of the Pharmacovigilance System (DDPS) for authorisation through decentralised/mutual recognition/repeated mutual recognition procedure:

- Romania as a concerned member state: 1589 reports
- Romania as a reference member state: 3 reports (2 DCP + 1 R)
- Assessment reports of the summary of the MA applicant's pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) for authorisation through national procedure: 184

- Assessment reports of applications concerning description of the pharmacovigilance system for grant of a Parallel Import Authorisation (PIA)

- Applications for parallel import procedure: 148

- assessment reports of applications for variation to MA applicant's summary of the pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) for authorisation:

- Applications for national procedure approved:14

- Applications for national procedure assessed:221
- Applications assessed for DCP/MRP/MRP-RU procedures:95

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

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

5.6.Other activities

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

a) Maintenance of the database of authorised medicinal products:

- Addition of 799 products (authorised through national/European/ Centralised procedures); introduction of information concerning MA granted: trade name, MAH, batch release responsible person, packagings and set-up of *links* for SmPC, packagings, leaflets and MAs;

–Addition of 7255 variations to MAs granted through national/European/centralised procedure (introduction of information concerning amendments to MA terms: trade name, MAH, batch release responsible person, packagings etc.);

- Set-up of links for SmPCs, packagings, leaflets and labelling – containing updated information, enabling easy access of external users to Annexes 1, 2, 3 of the Index of Medicinal Products posted on the NAMMD website;
- Issue of 292 decisions for MA withdrawal/discontinuation (withdrawal of national MA when the same product is granted marketing authorisation through European procedure; discontinuation of a valid MA on request by the company);
- Management of data concerning MA maintenance fee: 7469 medicinal products;

- Transmission of the Index of Medicinal Products to the NHIH in the format agreed for reception of SIIS (single integrated information system) data (quarterly and whenever required by the NHIH);
- **9816** PDF files, as current versions of Annexes I, II and III, have been published on the NAMMD website, via the Index of medicinal products in web format, for the aforementioned products.

b) Various responses to requests of the Ministry of Health, NHIH, MAHs, other institutions, legal entities): 876.

As regards" parallel *import"* activities, 117 parallel import authorisations (PIAs) have been granted (assessment of documentation submitted, of additions forwarded by applicants and set-up of PIAs and their Annexes).

In this respect, 138 requests for information were delivered to 11 EU competent authorities required for PIA release and amendment of PIAs granted (36 variations to PIAs were sent);

"Parallel export" activities consisted of:

- issue of 386 responses to requests for information received from 18 EU competent authorities (plus another about 180 responses for disambiguation and completion of initially forwarded information), for grant of a parallel import authorisation for the respective member states. The correspondence for clarification and supplementation of initially forwarded data contains individualised information referring to: MA number of the medicinal product in Romania; MAH; manufacturers involved in the entire manufacturing process; details on the qualitative and quantitative composition of the medicinal product; ATC code, manner of presentation; storage conditions.
- permanent update of the internal database concerning "*parallel export".*

The following activities have also been continued:

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

As regards *"sunset clause"* implementation, assessment of the database set up according to documents submitted by the MAH is worth mentioning. About **76** reports have been submitted from companies/representations (dossiers and electronic formats)**.** 14 decisions for MA discontinuation were issued in accordance with provisions of Article 729 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product. Work related with application of the clause is expected to be completed by the first quarter of 2014.

- Management of the database related to EMA authorised medicinal products based on provisions of Article 127a of Directive 2001/83/EC and

monitoring of implementation of conditions and restrictions placed on the MAH by the European Commission;

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

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

In the course of 2013, the Pharmaceutical Inspection Department (PID) continued to perform activities mentioned in specific legislation (Law no. 95/2006, Title XVII – The medicinal product, as amended, and secondary legislation thereof), in accordance with the department's *Standard Operating Procedures (SOPs)*, endeavouring to effectively accomplish its tasks by the deadlines stipulated by law. The following inspections have been performed:

- 28 GMP inspections for release of the manufacturing authorisation
- 3 follow-up inspections, for assessment of the manufacturing activity and of the manner of implementation of corrective measures into the measure plans forwarded to the NAMMD for authorisation
- 1 inspections for assessment of the activity of the importer's qualified person
- 22 inspections for authorisation at the sites of importers

Each authorisation/certification process meant setup of lists with deficiencies, and setup of an inspection report after transmission of the corrective measure plan and its evaluation. Manufacturing/import authorisations, as well as GMP compliance certificates, have been issued for units in which the authorisation/certification process has ended favourably.

As regards importers of medicinal products, it was found that, in most cases, the qualified person had released the manufacturing batch correctly; there are documents showing this fact, which has allowed issue of import authorisations.

In 2013, 11 inspections were conducted, related to assessment of compliance with the GMP Guideline upon request of pharmaceutical companies in third countries (India, Moldova, Ukraine, China) leading to issue of 42 GMP compliance certificates for both medicinal products for human use and active pharmaceutical substances. The certification process is during execution for the 11th company inspected.

A NAMMD-PID inspector has participated, together with EDQM inspectors, in 4 inspections required by the EDQM for starting materials for pharmaceutical use at sites in China and South Korea (the respective inspector

was the leader of the team in 2 inspections). Inspections led to issue of the GMP compliance certificate for 1 company in China and of GMP non-compliance declarations for 3 companies in China and Korea.

In 2013, 2 NAMMD-PID inspectors have participated, together with inspectors of the British authority in the field of the medicinal product (MHRA), and with inspectors of the Italian authority in the field of the medicinal product (AIFA), in 2 inspections requested by the European Medicines Agency (EMA), concerning reconfirmation of GMP compliance by a USA manufacturer and by an Indian manufacturer, for centrally authorised medicinal products.

1 GLP follow-up inspection at a bioequivalence centre (clinical unit and bioanalytical laboratory) conducting bioequivalence studies.

As regards inspections for authorisation of independent units controlling medicinal product quality - GALP, 3 inspections at the sites of independent control units have been requested in 2013 for physico-chemical and/or microbiological laboratories, leading to issue of 4 authorisations and Annexes.

7 GCP inspections scheduled for verifying compliance with good clinical practice were performed in 2013.

Moreover, the evaluation of documentation submitted in support of the application for approval of donations of medicinal products for human use has been assessed; 141 approvals have been issued, with annexes.

According to the yearly inspection plan of the PID, 1 pharmacovigilance inspection was performed at the site of the MAH representative in Romania.

The activity of consultancy was continued in 2013 as well, performed by the inspectors of territorial units in clinics, hospitals, family doctors' offices, to boost its reporting of spontaneous adverse reactions on the territory. 1158 reports resulting from pharmacovigilance consultancy visits on the territory have been issued. As a consequence, an increasing number of adverse reaction reports submitted to the NAMMD by MAHs/healthcare professionals.

In 2013, GDP inspections led to:

- wholesale distribution authorisation of distribution units in Romania in accordance with the legislation in force and set-up of the national database containing information related to issued wholesale distribution authorisations;
- handling of the database of wholesale distributors and medicinal products in accordance with periodic reports received from distributors;
- coordination of territorial inspectors concerning performance on the territory of inspections for authorisation of wholesale distributors;
- assessment through follow-up inspections of the wholesale distribution activity in authorised units.

In 2013, 118 inspections for authorisations have been performed, leading to issue of 112 wholesale distribution authorisations with Annexes; 34 units undergo various stages of the authorisation process. 3 units have not been

granted a wholesale distribution authorisation, since major findings have been discovered.

For all units for which wholesale distribution authorisations have been issued in 2013 the conduct of follow-up inspections concerning the manner of performance of the distribution activity has been established, every 1 to 3 years, according to the risk assessment.

2 follow-up inspections were conducted in 2013, for assessment of the distribution activity and of the manner of implementation of corrective measures proposed in measure plans forwarded to the NAMMD for authorisation. The two inspections have been unexpected, one leading to withdrawal of the wholesale distribution authorisation and enforcement of a fine.

In view of assessing the product's traceability, 2013 also meant input of medicinal products distributed by wholesale distributors into the NAMMD-PID database, according to the reports received after April, in accordance with Order of the Minister of Health no. 502/2013.

Both the inspectors from the central site and those from the12 territorial inspection units have been involved in surveillance of the quality of medicinal products authorised for marketing in Romania. In 2013, this activity consisted of:

a) Achievement of the sampling plan for supervision of medicinal product quality (sampling, analyses, results)

In line with the selection criteria underlying the yearly sampling plan, 32 medicinal products were proposed for sampling in view of checking their quality. Of these 32, 23 were sampled, since the other 9 could not be found in the distribution network.

Results obtained from laboratory analyses performed have been the following:

- 12 samples have been declared compliant and the others are undergoing analysis.

In addition to the sampling plan, the following samples have been taken:

- 1 biological product (8 batches) sampled for official batch release;
- Two medicinal products have been sampled to resolve complaints regarding medicinal product quality; both were declared fit in terms of quality;
- 2 medicinal products sampled from distribution units within the programme coordinated by the EMA/EDQM for surveillance of centrally authorised products; testing has been performed by laboratories of other EU competent authorities, results being compliant.

b) Follow-up inspections of the quality of medicinal products from the distribution network (storehouses, pharmacies) performed by TIU inspectors: storage conditions, documents on quality, medicinal product advertising, compliance with the MA of the primary and secondary packaging and of the leaflet, assessment of manner of withdrawal of medicinal products with quality

issues. In this respect, 231 thematic inspections have been conducted (1894 checked units) in wholesale and retail distribution units;

c) Inspections for assessment of the quality of the oxygen used in hospital units

Given the risks involved by use of medical gases in hospitals and emergency services, the action of checking their source was continued in 2013 to stop the use of unauthorised oxygen. This action taken in the second and third quarters covered 219 hospitals across the country; the compressed and the liquid oxygen have been found to come only from certified manufacturers authorised for Good Manufacturing Practice.

d) Collaboration with other bodies to address problems related to medicinal product legislation and / or quality of products marketed in Romania

Provision of specialised assistance at the request of various bodies and institutions (such as: Customs, Police Inspectorates, Offices for Consumer Protection, Public Health Inspectorates, the College of Pharmacists), during 2013, resulted in four joint actions with the local special bodies performed by territorial inspectors (4 - Galati).

e) Resolution of complaints regarding potential quality noncompliances of medicinal products for human use.

16 complaints were received in 2013, of which 15 were solved (one is pending). Of the 15 complaints, 12 were solved without trace, 2 were found to be substantiated and resulted in withdrawal from the territory of the concerned medicinal products or in endorsement of a retail distribution unit (pharmacy).

To resolve complaints, NAMMD inspectors conducted 26 inspections at distribution units and have performed 2 samples of products for laboratory testing within NAMMD - MPQCD.

It is noteworthy that the majority of complaints received (12) were from NAMMD territory inspectors and were related to improper imprinting of the primary/secondary packaging or to the drafting of the leaflet of certain medicinal products. The rest of the complaints received were from patients or healthcare professionals.

f) Withdrawal from the market of medicinal products with quality non-compliances

In 2013, the NAMMD imposed the withdrawal or voluntary withdrawals were decided for 61 medicinal products (similar to the previous year), of which:
- 18 medicinal products identified with quality issues have been proposed for destruction (of which 9 as a result of rapid alerts);
- 37 medicinal products withdrawn in accordance with Order of the Minister of Health no. 279/2005 or following the expiry of the MA.
- 6 medicinal products withdrawn following decisions of the European Commission

g) Rapid Alert System

157 rapid alerts were received in 2013 (6 awaiting) issued within the

EMA and PIC/S Rapid Alert System. Of these:

- 98 for products unauthorised for marketing in Romania;
- 17 for products authorised for marketing in Romania but unimported/undistributed;
- 11 for products authorised and imported/distributed in Romania.

In 2013, the NAMMD has issued a rapid alert and a follow-up alert.

h) Collaboration with European bodies (EMA, EDQM), European competent authorities concerning surveillance of quality of starting materials/finished products manufactured in third countries

There were 32 reported cases in 2013 (3 reported by Romania) of non-compliance with Good Manufacturing Rules by active substance manufacturers (including suspension/withdrawal of the certificate of compliance with the European Pharmacopoeia) or medicinal products from third countries, for which endeavours have been made in accordance with joint decisions taken by authorities;

i)Coordination of the activity of Territorial Inspection Units (TIUs) concerning medicinal product quality surveillance.

7. Quality control of medicinal products for human use

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

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

The activities of both control departments are performed by process-based approach, in accordance with the requirements of standards *SR EN ISO 9001/2008* and *SR EN ISO 17025/2005*.

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

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

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

The main activities performed in 2013 envisaged:

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

In 2013, 59 medicinal products were submitted for MPQCD testing (28 – as part of the Annual Plan for Sampling and Testing, 6 – products subject of quality complaints, 12 – international collaborations – EDQM/FIP, 3 sampled products – assessed through mutual recognition procedure, 10 – biological products assessed through official batch release procedure).

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

273 analyses were thus performed:

- 216 pharmacochemical/instrumental analyses;
- 11 pharmacotoxicological analyses;
- 46 microbiological analyses.

For the 59 medicinal products tested for analysis, 273 individual parameters were analysed, according to the techniques described in the European Pharmacopoeia or the manufacturer's pharmaceutical files. Practically, these parameters reflect in an objective manner the laboratory activities performed within the MPQCD. Moreover, there were all operations and activities (over 1000) preceding or accompanying every analysis: equipment checks and calibration (IR; HPLC; UV, analytical balances); assessment of volume measurement systems (droppers, biurets, measuring bottles, graded cylinders); titre tests - volumetric solutions; preparation and solutions and growth media; preparation of chemical, pharmacological, biological reactives; preparation of pH buffer solutions; scale weighing; monitoring of environment conditions in each laboratory; cleaning and decontamination of tools, equipment, glass, work surfaces, premises etc. All these tasks are performed according to procedures and in accordance with approved work instructions and are included, following performance, in work sheets (equipment cards, environment surveillance cards, temperatures etc.)).

Among frequent and complex analytical techniques used in 2013, in the context of medicinal product quality control, the following are worth mentioning: HPLC, pH-metry, Karl Ficher, spectrophotometry (IR, UV-Vis), pharmacotechnical testing (dissolution, mechanical resistance), volumetric dosing, determination of substance melting points, determination of liquid densities, determination of refractive indices, antibiotic microbiological dosage, sterilities (parenterals) and microbiological contaminations (ophthalmic solutions, syrups and paediatric solutions, certain film-coated tablets and capsules), endotoxin determinations (LAL test).

The 28 products sampled by the Pharmaceutical Inspection Department (PID) as included in the Sampling and Testing Plan have been assessed on a

case-by-case basis, from a physico-chemical, pharmacological, microbiological or radiopharmaceutical viewpoint.

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

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

As regards medicinal products subject to complaints, the PID has required laboratory testing (physico-chemical, pharmacological or microbiological, as required), for 6 medicinal products received/sampled locally, suspected of quality deficiencies. Among these, no complaint was just, all products were found compliant with quality provisions approved.

In 2013 as well, the MPQCD has continued its collaboration with European institutions on medicinal product quality control, by participation to studies initiated by the EDQM and the International Pharmaceutical Federation (IPF).

- Studies initiated and coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM):
- PTS (Proficiency Testing Scheme) studies – Inter-laboratory studies for measurement of professional performance, based on analytical protocols forwarded by the EDQM.

In 2012, 4 inter-laboratory studies have been conducted within the MPQCD.

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

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

As shown by data from the 4 studies as communicated by the EDQM, as far as the 7 samples analysed by the MPQCD are concerned, values obtained comply with the specified performance criterion, since the “Z-score” registered lower than 2.

- CRS (chemical reference substance) studies: - 1 study performed (Assessment of the microbiological dosage method for zinc bacitracin)

for revision of the PhEur monograph, in accordance with the protocol forwarded by the EDQM

- MRP (mutual recognition procedure) studies for surveillance of the quality of medicinal products authorise through European procedures - 3 probe

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

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

- Inter-laboratory studies initiated by the International Pharmaceutical Federation (IPF) (4 studies);

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

- Biological products analysed in the context of the official batch release procedure

As regards this activity, it is worth mentioning that 8 batches of purified inactivated trivalent flu vaccine, suspension for injection, manufactured by the Cantacuzino institute in 2013 have been found noncompliant under parameter „ Bacterial endotoxins contents".

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

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

In 2013, the following were performed within the MPQCD:

- Assessment of Active Substance Master Files (DSSAs) through European procedures;

- Assessment of quality – through European procedures;

- Assessment of ASMFs through national procedure;

- Assessment of quality – through national procedure;

- Assessment of clinical trial documentation.

In 2012, of 618 assessments for medicinal products undergoing authorisation procedure, assessed ASMFs represent a 90% percentage.

As regards assessment of clinical trial documentation, 1 complete quality study was assessed (active substances, Investigational Medicinal Products - IMPs), as well as 1 amendment to IMP documentation.

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

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

In 2013, 8 batches of inactivated flu vaccine (INCDMI "Cantacuzino", Romania) have been rejected following registration of non-compliant results for testing the Bacterial endotoxins level, test performed within the MPQCD. Non-compliance bulletins have been issued and released for all 8 batches.

In accordance with quality assurance requirements and recommendations of external audits, for maintenance of operators' skills under circumstances of no requests for testing, specific exercises have been planned and performed. Thus, conduct of a skill practice exercise by staff of the Laboratory for Determination through Serology Tests (LDST) was deemed necessary, as regards vaccine control (and particularly influenza vaccine control). Skill practice exercises have been performed for **2** testing methods (double diffusion, single radial immunodiffusion) according to SOPs of the LDST.

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

- method validation: *pH potentiometric determination;* preparation and draft of validation report;

- performance of calibrations and determinations for assessment of correct operation of the Karl-Fischer volumetric titrator;

- performance of determinations for maintenance of testing skills and assessment of understanding of working methods.

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

No requests for testing samples of biological products submitted within the marketing authorisation/marketing authorisation renewal procedure have been sent in 2013.

In 2013, the BPECD, via the LPCDI, has participated to a PTS (**P**roficiency **T**esting **S**cheme) study, performed at the initiative and under the coordination of the EDQM (PTS139: *Potentiometric determination of pH*), ranked *Satisfactory*. 97 laboratories have participated in the PTS study, of which 94 were ranked "*Satisfactory*", the BPECD being one of them.

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

In the context of the postmarketing surveillance, MAHs submitted data relative to 240 biological product batches, which have been assessed by the specialist assigned and stored in electronic format.

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

Starting with 2012, the BPECD has also performed validation of applications for variations to MAs (type IB and II) for biological products.

During 2013, this activity consisted of:

- 179 validations of applications for Type IB and II variations
- 14 invalidations of applications for Type IB and II variations.

In 2013, the BPECD assessed 4 products submitted for authorisation through national procedure for which 4 reports requiring supplementation of the chemical-pharmaceutical documentation have been issued and 48 products submitted for MA renewal through national procedure (47 foreign and 1 national), for which 55 reports have been issued:

- 31 reports with request for supplementation, 19 with proposal for MA approval; 2 assessment reports of postauthorisation supplementations and 3 reports of conditions for renewal of updated MAs.

Support documentation for variations/changes of design/MA transfer, submitted through national procedure, have also been analysed within the BPECD.

250 assessment reports have been issued for type II variations and for grouped type II variations, as follows:

- 85 assessment reports with requests and 123 assessment reports with proposal for approval for type II variations
- 11 assessment reports with requests and 16 approved/finished approval reports for grouped type II variations
- 11 post-approval assessment reports for type II variations
- 8 assessment reports with proposal for withdrawal of type II variations

Following assessment of the documentation of 333 addresses (sent to the proponent) have been issued for Type IA and IB variations/ design changes/ MA transfer/ Braille imprinting.

In 2013 as well, assessment of quality documentation was continued for products submitted for authorisation through the mutual recognition and decentralised procedures, leading to submission of assessment reports according to deadlines, as follows:

Mutual recognition procedure

19 reports have been issued for 12 products:

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

The BPECD also assessed support dossiers for variations submitted through Mutual Recognition Procedure, for which 24 Annexes to MAs for type IB variations and 57 assessment reports and Annexes for type II variations have been issued.

Decentralised procedure

1 report has been issued for 1 product pending authorisation:

- 1 assessment report with request for supplementation;

In 2013, the BPECD also assessed quality documentation submitted for approval of applications for performance of clinical trials for 32 biological products; 53 assessment reports have been issued, of which:

- 31 reports containing requests for supplementation of quality documentation;
- 22 final (positive) reports for assessment of quality documentation

As regards amendment of marketing authorisation terms for biological medicinal products for human use, following approval of Type I or II variations or following proofreading, the BPECD has performed 56 changes to MAs in 2013.

8. Ensuring communication and transparency

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

8.1. External communication

In 2013, in line with *its communication strategy for 2013-2015,* the Agency ensured:

- internal and external communications, opinions, communication with the written press and the media (by telephone, e-mail, TV interviews), relationship with other Romanian and foreign specialised institutions in this field;
- free access to public information in accordance with provisions of Law 544/2001, readily or upon request, for media representatives and any stakeholder, providing information about NAMMD work or the safety of medicinal products for human use;
- cooperation of all departments for proactive and reactive communication, following request, namely for insurance of transparency in the Agency's activity, of public accessibility/availability of information in the field of the medicinal products

for human use.

The Policies and Strategies Department (PSD) has ensured:

- The pooling of data from scientific departments and structuring of information requested for preparation of responses required by stakeholders;

- notification of the mass-media and/or other applicants within deadlines stipulated by regulations in force, on publication of information as stipulated under Article 5 of Law 544/2001, also specifying site of publication;
- notification of the applicant, within deadlines stipulated by regulations in force, if the requested information is identified as exempt from free access;

- distribution to the media of NAMMD official releases and opinions.

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

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

- Laws, Ordinances, Government decisions on medicinal products for human use or other areas of NAMMD interest;
- Orders of the Minister of Health for approval of NAMMD Scientific Council decisions and Orders of the Minister of Health in other areas of NAMMD interest;
- Decisions of the NAMMD Scientific Council;
- Decisions of the NAMMD Administration Council;
- Quarterly list of applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD;
- Quarterly List of EMA newly centrally authorised medicinal products, for which a marketing price has been established in Romania;
- Quarterly list of medicinal products authorised for marketing by the NAMMD;
- A quarterly list of medicinal product batches recalled by the NAMMD for quality defects.

The NAMMD develops the Index of medicinal products for human use, including all medicines authorised for circulation on the pharmaceutical market in Romania, with data on trade name, International Non-proprietary Name (INN), marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, manner of release etc. and posts it on its website. In 2013, implementation was continued, for each medicine, of electronic versions of the Summary of Product Characteristics (SmPC), leaflet and information on labelling and inscription.

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

- EMA and NAMMD press releases relating to safety of medicinal products;

- Direct healthcare professional communications;

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

- Information related to medicinal products authorised through centralised procedure

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

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

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

- List of EMA experts appointed by the NAMMD.

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

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

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

-List of Romanian importers of medicinal products;

- List of Romanian distributors of medicinal products;

- List of laboratories of control of medicinal products;

- List of recalled batches;

- List of Qualified Persons approved by the NAMMD

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

The NAMMD always tries to help the NAMMD website external users to benefit from updates of sections related to medicinal product legislation, structured depending on the type of regulatory document:

- Laws, Ordinances, Government Decisions;

- Orders of the Minister of Health;

- NAMMD Scientific Council Decisions;

- NAMMD Administration Council Decisions.

In 2013, the NAMMD continued to inform stakeholders about its activity, otherwise than by means of NAMMD Newsletters. Thus, several articles have been published in Romanian professional magazines by NAMMD specialists ("Farmacist.ro", "Medical Business", "Medica Academia, "Pharma Business").

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

8.2. Internal communication

In 2013, the Agency continued supplementation and update of information (available to NAMMD staff on the Intranet), for optimal and efficient professional/organisational information.

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

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

9. Quality management

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

Considering the Policy on quality and quality objectives, established by the top management, as well as processes identified and implemented, the size and structure of the NAMMD and *SR EN ISO 9001* and *9004* principles in force, in 2013, the QAB, together with the other organisational structures, has participated to

implementation, development and improvement of the NAMMD Quality Management System.

The internal quality audit process was carried out in accordance with the Internal Quality Audit Program in 2013, as approved by the President of the organisation.

Considering the necessary elaboration of the report on pharmacovigilance audits, in order to be sent to the European Commission and to the EMA and reporting to the EMA Administration Council and, in accordance with Article101(2) of Directive 2001/83/EC, as amended, stipulating the fact that Member States are required to audit the pharmacovigilance system and to inform the Commission about the results, before September 2013 and biannually afterwards, in line with Article 28f of Regulation (EU) no. 726/2004, establishing the fact that EMA should perform independent periodic audits of pharmacovigilance-related tasks and to biannually report the results to the EMA Administration Council, the *2013 quality internal audit programme* has been supplemented, as approved by the NAMMD President, with a pharmacovigilance audit, during: 16 - 31.07.2013.

The Pharmacovigilance audit report conducted on behalf of the National Agency for Medicines and Medical Devices of Romania has been set up in August and forwarded to the European Commission on 06.09.2013.

Other processes performed by the Quality Assurance Bureau:

- Grant of counselling in quality management system (QMS) issues provided to various NAMMD organisational structures, for set up of the *Risk Registry* by the Internal Audit Bureau.
- Set-up of the *documents* requested by the Internal Audit Bureau (IAB), related to the stage of implementation of internal/management control system.
- Set-up/update of QAB databases (in electronic format) *(key performance indicators - KPI of the NAMMD, SOP registers – NAMMD / Quality ensurance glossary, Situation of NAMMD SOPs, Situation of the NAMMD Quality Manual etc.)*).
- The NAMMD top management is involved in activities related to QMS (quality management system), and preoccupied by implementation of a process-based approach.

10. Medical devices

10.1 Control activity through regular check of medical devices

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

The Nuclear Unit (UN) carries out the same type of activities as the Technical

Department-Laboratory (TECHNICAL LABORATORY DEPARTMENT), on medical devices with ionizing radiation. For this reason, work is reported in a joint report and necessary specifications are made. As previous years, 2013 was busy for the Technical Department - Laboratories and Nuclear Unit; the largest share in their work was periodic control of medical devices. This activity is performed for all medical devices in use, of significant risk to all users in both the public and the private sectors. This consists of assessing the performance and safety of medical devices in use, the periodic check bulletin being one of the necessary documents for medical service contracts between the health insurance funds and individual practices/hospitals/medical centres. A test report is prepared for each medical device checked, which is kept in the respective file and only provided to the customer on request, for a fee, together with the periodic verification report.

Given the fact that the number of medical devices on an order varies from one to a dozen hospitals, while the number of specialists and appropriate measuring instruments is limited, it is obvious that the activity has been conducted by appointment.

A large number of requests was registered from the public hospitals, which are exempt from tariffs. These requests have also been made for most devices.

Therefore, the situation of works completed in 2013 is as follows: Total applications registered: 985 (of which 597 in the private sector).

Total number of issued periodic check bulletins: 349

Total number of approvals for use: 149

Total number of medical devices checked: 5697

Total number of test reports issued: 1595

Total number of negative test reports (medical devices rejected): 77

In October 2013, surveillance of the medical devices checks and assays laboratory within the Technical Laboratory Department and the Nuclear Unit has been performed by RENAR and it kept trace of the manner of implementation of SR EN 17025 standard for accredited assays. Results have been adequate.

In 2013, intense efforts have been made to ensure review of tariffs practiced by the NAMMD for medical device related activities. Thus, Order of the Minister of Health no. 1369/2009 was replaced by Order of the Minister of Health no.1356/13.11.2013 which, among others, provides specifications meant to enlighten beneficiaries on the manner of invoicing of travel expenses and ensures conformity between required tariffs and the Order of the Minister of Health on periodic check-ups, considering that the list of medical devices submitted for control through regular check-ups has diminished.

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

The priority for 2014 is resolution of qualified staff issues (staff qualified for performance of medical devices issues) and update of the endowment of assay

laboratories in order to be able to keep up with the continually modernising and developing medical-hospital technique.

10.2 Inspection and assessment of technical-medical units

The Technical-Medical Sites Assessment Department works under Law No. 176/2000 on medical devices, as amended, and Order No. 1636/2004 on approval of Methodological rules for implementation of Law No. 176/2000, as amended, on licensing of medical technical units, as amended.

Respective work consisted of assessment of units' capability to provide services requesting Ministry of Health approval. Activities assessed are related to services for optical devices, services related to medical devices, prosthetic devices (hearing, orthopaedic, other).

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

Staff in this Department has accomplished the following results:

- Number of registered applications for assessment: 170
- number of finished assessment works and reports issued: 88
- number of ongoing works:17
- number of cancelled assessment works (no dossier submitted for assessment): 21
- number of cancelled assessment works (the organisation only performs marketing activities): 21
- number of assessment works undergoing finalisation:23
- notifications issued for completion of the assessment dossier:122
- fees issued for assessment:128

- number of assessment-surveillance activities: 371
- number of assessment-surveillance activities, completed, with finalised reports: 160
- number of assessment-surveillance activities, undergoing assessment: 83
- number of assessment-surveillance activities, in process of completion: 93
- number of assessment-surveillance activities, for confirmation of termination or approval for performance: 35
- missions for assessment and surveillance activities: 82

8 control activities were performed, resulting in application of 1 penalty for breach of legal provisions.

11. International relations

In 2013, NAMMD specialists continued to take part in activities of various collaborator European institutions and organisations:

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

Since 2003, at the initiative of the European Medicines Agency, NAMMD representatives have actively participated as active observers to working groups, scientific committees and groups for implementation of medicinal product related information technology.

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

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

- The Committee for Medicinal Products for Human Use - CHMP;
- The **Committee for Orphan Medicinal Products - COMP;**
- The **Committee for Herbal Medicinal Products - HMPC;**
- The **Paediatric Committee - PDCO;**
- The **Committee for Advanced Therapies - CAT;**
- *The CHMP Safety Working Party*;
- The Pharmacovigilance Risk Assessment Committee - PRAC;
- *The CHMP Blood Products Working Party*;
- *The CHMP Biologics Working Party*;
- *The CHMP Vaccines Working Party*;
- *The CHMP/CVMP Quality Working Party*;
- *The GMP/GDP Inspectors Working Group;*
- *The EudraGMP database sub-working group;*
- *The GCP Inspectors Working Group;*
- *The GLP Inspectors Working Group;*
- *The Pharmacovigilance Inspectors Working Group;*
- The Working Group on the database of medicinal products authorised in the EU (EudraPharm TIG);
- The Working Group on the database of adverse reactions (EudraVigilance TIG);
- The Working Group on the European database for clinical trials (EudraCT Clinical trials TIG);
- *The Working Group on the European network (EudraNet TIG);*
- The Working Group on the electronic transmission of data (e - Submission);
- The Working Group on European Union Telematics Controlled Terms (EUTCT);
- The Working Group on Product Information Management (PIM);

- The Working Group of the Quality Review of Documents;
- *The Invented Name Review Group.*

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

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

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

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

In 2013, NAMMD experts participated in meetings of the Council of the European Union and of the European Commission (EC), i.e. the Working group on medicinal products and medical devices of the EU Council, preparing proposals for amendment of Directive 20/2001/EC on clinical trials in the EU, the Standing Committee, the Pharmaceutical Committee, Notice to Applicants, the United Nations Interregional Crime and Justice Research Institute for the „SAVEmed Microstructure secured and self-verifying medicines" project.

11.4. Participation in World Health Organisation (WHO) activities

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

In 2013, the Agency released the Certificate of the product in WHO format for 591 medicinal products of Romanian manufacturers seeking authorisation for these products in other states.

11.5. Participation in European Council activities

In 2013, the NAMMD representative participated in the meeting of the Working Group on the classification for release of medicinal products for human use (CD-P-PH/PHO).

Moreover, NAMMD representatives assigned for participation in the works 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 (CoE), meeting organised by the European Directorate for the Quality of Medicines (EDQM).

11.6. Participation in European Pharmacopoeia Commission activities

As member of the European Pharmacopoeia Commission, the NAMMD representative has been actively involved in specific working sessions in 2013, as well as in the yearly meeting of the secretaries of national Pharmacopoeias in Convention on the Elaboration of a European Pharmacopoeia member countries.

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

11.8. Participation in activities of the Official Medicines Control Laboratories

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

12. Information, Logistics and Electronic Management of Data

In 2013 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 2013, maintenance, amendment and update was continued of the Product Index of medicinal products for human use database. Moreover, statistical data reports were extracted periodically on request by the Minister of Health, the National Health Insurance House, the NAMMD President and various Agency departments.

Maintenance of the NAMMD website (*www.anm.ro*) and other software applications has been ensured throughout the year (maintenance, amendment and update on the website of search engines – Index, search after key words, management of recalled medicinal products, management of GMP units, of the "Counterfeiting" section (ongoing project – *www.crimemedicine.ro*, involving: setup of the website, participation in special courses investigations on the internet, setup of investigation dossiers); at the same time, many activities concerning updating of the website various sections (Newsletters, Forms, NAMMD Scientific Council Decisions, Laws and ordinances, Orders of the Minister of Health, Press releases, Q&A documents, Important notifications, Direct Healthcare Professional Communications etc.); the Agency's intranet website has been maintained, amended and updated.

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

Moreover, an EMAIL server has been set up and configured on the Linux platform for the new domain, anmdm.ro, containing future users' accounts. During April-May, a series of tests have been performed in collaboration with the person responsible with the EudraMail service of the EMA, which have led to successful server configuration.

Work stations have been configured in order to be used in webinars via the Adobe Connect service – 20.

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

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

A number of 773 marketing authorisations and their annexes have been issued in 2013, namely 578 through European procedures and 195 through national procedure.

- Also, typing/drafting has been insured for:
- 591 product certificates in WHO format for Romanian medicinal products;
- 211 letters for 1226 medicinal products, confirming status of the medicinal product undergoing renewal of marketing authorisation, bearing the "suitable for marketing" specification";
- 418 notification letters sent to manufacturers on MA release in accordance with President directions and maintenance of a copy in the product dossier.

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

- 246 applications for marketing authorisation/marketing authorisation renewal through national procedure;
- 840 applications for marketing authorisation/marketing authorisation renewal through DCP/MRP;
- 2725 applications for Type IA, IB, II variations, MA notifications through national procedure;
- 3350 applications for Type IA, IB, II variations, MA notifications through decentralised/mutual recognition procedure;
- 8209 drafts and payment forms for issue of invoice for marketing authorisation/marketing authorisation renewal and variations through

decentralised/mutual recognition procedure, national procedure and clinical trials;

- 25256 documents (responses to NAMMD requests for MA authorisation/renewal documentation, variations, clinical trials, advertising, adverse reaction reporting etc.).

25 meetings of the Marketing Authorisation Commissions have been organised and 1134 product dossiers have been assessed.

The NAMMD server has been updated with its 773 marketing authorisations issued in 2013 and the 5 corresponding Annexes, concerning the leaflet, Summary of Product Characteristics, packaging, data on the qualitative and quantitative composition of the medicinal product, data on the product manufacturing.

13. Ensurance of implementation of NAMMD policies and strategies

In 2013, the Policies and Strategies Department (PSD):

Has elaborated and collaborated, together with the other departments, at setup of the NAMMD *Organisational Strategy* for 2013-2015, following, in its primary field of activity, communication, reinforcement of the Agency's status as expert source of profile information, forwarded in due time to healthcare professionals in the pharmaceutical industry, patients, the public, to the media;

- active and priority participation to implementation of the Agency's *Communication Strategy* 2013-2015**,** as well as adaptation to new requirements and the dynamics of legal and socio-economic amendments.

Initiator of the NAMMD *Communication strategy (2013-2015)*, in 2013, the Policies and Strategies Department has ensured:

- drafting and sending responses to the media and decision making by the NAMMD management through:
- TV interviews, including live broadcasts;
    - written replies for the media and the written press;
    - telephone interviews for the written press, TV and radio;
    - *press releases* and *important notifications* posted on the NAMMD website;
    - participation at scientific events, with papers exposing NAMMD's viewpoint in various issues related to the medicinal product for human use;
    - communication with other specialised institutions in the field in Romania and abroad.
- free access to public information in accordance with Law 544/2001, by default and / or upon request for both media representatives and for any interested person, providing information on the NAMMD activity or information concerning the safety of medicinal products for human use;
- Informing the media representatives and / or other applicants within the time limits on norms in force, if the requested information is already communicated by default in one of the specified forms mentioned in Article 5 of Law no. 544/2001,

indicating the location where the requested information can be found;

- To inform the applicant within the time limits established by the norms in force, if the requested information is identified as exempt from free access;
- To collaborate with all NAMMD departments to collect and systematize the information requested by the media for issue and drafting of the requested response.

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

- Handling and monitoring of participation of the Agency's employees assigned as full or alternate members in scientific committees and working groups of the EMA, HMA, EDQM, the Council of Europe, the EU Council and of the European Commission;
- Management and monitoring of participation of NAMMD staff assigned as full members or alternates to scientific committees and working groups of the EMA, HMA, EDQM, European Council, EU Council, European Commission;
- Periodic update of the List of NAMMD employees assigned as full members or alternates to scientific committees and working groups, in accordance with President decisions and their posting on the NAMMD website;
- Insuring communication with the EMA for assignment of NAMMD experts as full members/alternates;
- Check-up/Summarisation of the forms prepared by NAMMD experts;
- Communication with the secretariats of working groups/scientific committees of the cited bodies for transmission of forms;
- electronic evidence of documents received on paper from the WHO, EDQM, OMCL etc. and their distribution for information or grant of opinion;

The Policy and Strategy Department has prepared the NAMMD Annual Activity Report for 2012 by corroboration of data from NAMMD departments activity reports.

PSD also ensured:

- handling and centralisation of 27 Scientific Council Decisions (SCDs), from draft to publication (under "Legislation" and "Newsletters", in accordance with the *interdepartmental SOP*;
- set-up of the SC meeting agenda, submission of documents to Scientific Council members review, on paper/in electronic format;
- ensurance of scientific secretarial work for the Scientific Council meeting and set-up of the minute;

Setup of NAMMD Newsletters, posted on the NAMMD website, was continued, namely:

- 4 newsletters in Romanian (4/2012; 1/2013; 2/2013; 3/2013) and
- 4 newsletters in English (3/2012, 4/2012, 1/2013, 2/2013).

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

- Regulatory documents, notifications in Romanian and English;
- NAMMD Newsletters into Romanian and English;
- Updated list of NAMMD employees assigned as full members or alternates to scientific committees and working groups of the European Medicines Agency (EMA), the Heads of Medicines Agencies (HMA), the European Directorate for the Quality of Medicines and HealthCare (EDQM), the European Council, the EU Council, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the European Commission.

The PSD has also ensured:

- Translation into English of NAMMD quarterly Informative Bulletins;
- Checking translation of EMA press releases, EMA Q & A documents, Direct Communications to Healthcare Professionals, action lines proposed by the EMA ("Lines to take"), educational materials etc.;
- Follow-up of various sites in view of ensuring compliance of the terminology with European terminology (particularly EMA and EUDRA);
- Provision of advice for check of translation of SmPCs and leaflets, message exchanges and communication in English with European bodies;
- Checking translation of assessment reports and documents in English, in the context of the Mutual Recognition Procedure;
- Ensurance, upon request of various NAMMD structures, of counselling/translation of the correspondence and communication with various international bodies and/or representatives of pharmaceutical companies;
- Update of the English version of the NAMMD website via translation of legislation, notifications and press releases.

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

- More than 500 e-mails received from the permanent representative of Romania to the EU and / or the Ministry of Health were monitored / entered into electronic records, regarding participation of NAMMD experts assigned as full or alternate members to working groups of the EMA, HMA, EDQM, European Council, to the Pharmaceutical Committee and the Standing Committee of the European Commission and redirecting them to NAMMD appointed experts.
- coordination and monitoring of participation of NAMMD experts appointed to meetings of previously mentioned working groups/committees and provision of mail with the Representation on this issue, as required;
- monitoring/handling in electronic databases of 41 European Commission (EC) received from the EU/RP external registry of Romania, referring to: conditionally authorised medicinal products, MA suspension/withdrawal/

amendment (following the ending of referral procedures on quality, safety, efficacy issues) and forwarding these documents to NAMMD specialists appointed for implementation of these in Romania.

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

- participation, by an assigned representative, to the yearly sessions of the European Pharmacopoeia Commission, as its member, and to the yearly meeting of the secretariats of Pharmacopoeias of national competent authorities;
- centralisation and analysis of the dossier forwarded in electronic version by the European Pharmacopoeia Commission/EDQM.

- Maintenance and update of the "INFO-Pharmacopoeia Service" database, from the NAMMD intranet network, containing the electronic versions of evidence of provided documentation, of Romanian standard terms and other useful information;
- Evidence in dossiers/directories of national and international pharmacopoeias, and other documents from the European Pharmacopoeia Commission, the United States Pharmacopeia (USP), magazines (Pharmeuropa, Pharmeuropa-Bio, Pharmeuropa Scientific Notes) etc.

14. NAMMD legal work

One of the main tasks of the Legal Department is representation of the institution within courts of justice, done in 2013, through 32 litigations related to insolvency procedure, work litigations, violation complaints, summons for payment, appeals, tort liabilities, litigations concerning public acquisitions, communication of information of public interest.

As regards the areas addressed, they have focused on activities and actions related to most branches of law (labour law, civil law, civil procedure, administrative law, contentious administrative matters etc.).

In pursuit of the second object of its activity, the Legal Department and professional departments within the NAMMD have set up the documentation (draft legislation, substantiation notes, approval papers) to promote more regulatory acts through the chief credit officer (the Ministry of Health), as listed in section 3 "Regulatory activity".

The professional activities of the Legal Department have mainly aimed at ensuring that the duties specified in Chapter IV, Section 13 of the Regulation on the Organisation and Functioning (ROF) al ANMDM, as well as other activities, are met, as approved through Order of the Minister of Health no.1031/2011.

For accurate description of activities performed in 2013 from a statistical viewpoint, the following activities were performed:

- grant of approval on legality of measures to be taken and of any other documents which could determine the institution's patrimonial liability;
- grant of approval concerning the correct interpretation of legislation related to NAMMD's field of activity;
- draft and approval of 151 Decisions of the NAMMD President.

Moreover, in collaboration with other departments, the Legal Department contributed to control of falsified medicinal products, which determined continuation in 2013 as well of the existing cooperation with the General Inspectorate of the Romanian Police, based on the cooperation protocol signed in March 2010, aiming at establishing a framework for bilateral cooperation and exchange of information on falsification of medicinal products for human use, in accordance with specific attributions and competences stipulated by the legislation in force.

The main directions of NAMMD collaboration with the General Inspectorate of the Romanian Police:

- compliance with the legislation in the field of the medicinal product for human use;
- exchange of information in order to fulfil their legal obligations;
- performance of market studies and analyses, in view of acquiring the most precise knowledge on the Romanian market of medicinal products for human use, particularly at manufacturing, import and distribution level;
- supervision of market functioning in order to identify cases of violation of national and / or Community legislation on counterfeit and of legal provisions in the field of medicinal products for human use, for taking the necessary steps by the two authorities, according to their skills and correlation;
- publicity and information of population and economic agents operating on medicinal product markets on the measures taken in cases of breach of national and / or Community legislation concerning counterfeiting;
- mutual support to ensure efficient functioning and safety of the medicinal products for human use sector, including the necessary legislative amendments.

Moreover, the **"SAVEmed Microstructure secured and self-verifying medicines"** project was continued in 2013 as well**,** initiated by the **UNICRI (United Nations Interregional Crime and Justice Research Institute);** the NAMMD president, vice-president and the head of the Legal Department have taken part in this project.

Such approaches are instrumental for set up of the framework for implementation of provisions of Directive **2011/62/EU of the European Parliament and of the Council of 8 June 2011** on the Community code relating to

medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products**, transposed into national legislation through Government Emergency Ordinance no. 91/2012.**

15. Management of human resources

15.1. Human resources policy

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

- Provision of human resources for NAMMD structures lacking qualified personnel, particularly medico-pharmaceutical, whose work practically ensures accomplishment of the Agency's scope.
- Improvement of human resources through employee training and continued professional improvement by:
- Training and professional improvement of existing specialised personnel, for training of highly qualified specialists, able to deal with the entire range of issues involved in the NAMMD object of activity;

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

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

15.2. Ensuring human resources within NAMMD structures

In 2013, personnel-related activities were performed within the Human Resources and Payroll Department (HRPD). As regards accomplishment of the main subject of this Department's activities, namely provision of qualified personnel, it should be mentioned that the first part of 2013 was characterised by maintenance of the legal framework set up through Emergency Government Ordinance 34/2009 on budget rectification for 2009 and regulation of certain financial-fiscal measures ("Measures on public expenditure" providing for "freeze of examination/contest based hiring proceedings in relation to vacancies in public institutions"). To

conclude, the deficit of staff that has been recorded starting with 2009 remained the same throughout most of the year. The goal of providing the NAMMD with qualified staff has been partially attainable, no sooner than the last quarter of 2013, as a consequence of entry into force of Emergency Government Ordinance 77/256.06.2013 for establishment of measures on ensurance of the functional character of public local administration, number of jobs and diminution of expenditures in public institutions and authorities or coordinated by the Government or Ministries. Emergency Government Ordinance 77/2013 has lifted the ban on employment by competitive examinations to cover vacancies, provided that they are occupied according to the "one to one" principle, namely one occupied job for one vacant job". Considering the restriction imposed by compliance with the "one to one" principle, a number of employees who added the pension to the wage, were retired and, as a consequence, in November 2013, measures have been taken for making available by contest 27 vacant jobs for medical-sanitary higher education. Moreover, the NAMMD has offered vacant jobs related to administrative activities, which means that, in November and December 2013, 21 new employees were hired, of which 18 with higher education in the administrative field, and 3 with administrative high school education. For the NAMMD, Emergency Government Ordinance 77/2013 has meant a partial resolution of stringent issues related to special and support staff encountered by the Agency throughout the past years, but also had a negative impact upon our institution, since the number of leading jobs had to be reduced so as to represent 12% of all approved jobs. At Agency level, this legal provision lead to reduction by half of the number of management jobs, having implications upon the motivation of employees dismissed from their previous jobs, acquired for the ability proven when performing tasks and responsibilities related to such jobs.

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

Involvement in the decision-making process at European level, active involvement in groups of European bodies in the field of the medicinal product for human use require a high level of competence among NAMMD specialists. This is, of course, a main objective of the Agency, which can only be reached by means of an ongoing training programme, specific to professional development in this field, at the site of the Agency, yet particularly without involving participation to training organised nationally and internationally by various authorities and bodies in the field.

According to possibilities of funding by European bodies and the Agency's limited available budget, part of NAMMD specialists were able to benefit from training. Following training activities, activities related to administrative validation of applications and authorisation dossier, related to handling of medicinal product information, scientific assessment dossier, have been improved. Initiation and

appropriate performance of this activity were possible, at a level similar to that of European competent authorities, ranked as having a high level of competence and exigency, in the context of European procedures for authorisation (mutual recognition procedure, "repeat use" mutual recognition procedure and decentralised procedure).

In 2013, significant participation can be noted, with presentation of specialist papers, to the following professional training sessions provided:

- **in Romania**:
- The NAMMD-ARPIM-APMGR workshop on "Quality of the medicinal product", Bucharest, 14 June 2013
- Informal meetings with the ARPIM, APMGR and independent MAHs dealing with legal issues related to implementation of new pharmacovigilance legislation;
- the „Sterilizing Filter and Single Use System Validation" training course, organised by *Pall Austria Filter GmbH and Life Science* at the NAMMD site, Bucharest
- The seminar "Sterilizing Filter and Single Use System Validation", organised by Merk Millipore Romania, 24 October 2012, Bucharest;
- The National Conference of Pharmacy, interdisciplinary pharmacist-physician conference organised by the Romanian College of Pharmacists, 14-16 November 2013;
- The 2nd National Conference, with international participation, of the Romanian Hypertension Society, Bucharest 19-21September 2013.
- The National Conference on Clinical Homeopathy: Contribution of the homeopathic medicinal product to paediatric practice" - Buzias, Romania
- Training "Sterilizing Filter and Single Use System Validation", held by Pall Life Sciences, Bucharest, 10 April 2013
- The "TEKNOLEB" symposium on „Laboratory apparatus and gear", Bucharest, 16 October 2013;
- The training course on „Total contamination control for pharmaceutical production. Sterilising filtration" organised by Pall Austria Filter GmbH at the NAMMD site in April 2013;
- The conference on „The Directive on counterfeit medicinal products", organised by Mach FTD, Bucharest, November 2013
- the "*Life Science Research with Merck Millipore*" seminary, organised by Merck Romania SRL, 25 September 2013, Bucharest (Senior Biologist Cătălin Puiu, Senior Biologist Madalina Doru, Senior Biochemist Cristina Popa, Special Biochemist Adina Chende Roman, Special Biochemist Daniela Motounu)
- scientific manifestation referring to the "Update in Immunogenetics & Histocompatibility", organised by the "Carol Bucharest and by the Centre for Immunogenetics and Virology of the Fundeni Clinical Institute and the European Federation For Immunogenetics, 25-27 June 2013, Bucharest – Senior Biologist Madalina Doru, Special Biochemist Adina Chende Roman

- the “Phytotherapy” course, organised by OAMGMAMR (The Order of Medical Assistants in Bucharest) during 17.06.2013- 18.06.2013, Bucharest (with participation certificate) (special senior referent Dobriţa Trâpcea).
- the “Basic first aid notions”, organised by OAMGMAMR during 19.06.2013 – 20.06.2013, Bucharest (with participation certificate) (special senior referent Dobriţa Trâpcea).
- the course “The impact of parasitic diseases upon public health”, organised by OAMGMAMR during 21.06.2013 – 22.06.2013, Bucharest (with participation certificate) (special senior referent Dobriţa Trâpcea).
- Supporting and promotion of the exam for senior degree – Clinical immunology – May 2013 – by a biologist from the BPECD
- Supporting and promotion of the exam for specialist degree – Clinical immunology – May 2013 – by a biologist from the BPECD
- Training related to „Joint measures in control and prevention of the commerce with counterfeit products” – Bucharest, September 2013
- National Congress for Clinical Homeopathy – October 2013, Bucharest
- course – The new civil procedure code, 2013, Major changes in Civil procedure - Bucharest, 7-10 March 2013.

- **abroad:**

– The course for clinical efficacy assessors referring to the Guideline on investigation of interaction between medicinal products, organised by The European Medicines Agency (EMA) in London, 13-14 February 2013
– The 9th yearly conference on Bioavailability/Bioequivalence, Dissolution and Biowaivers, organised by the EMA, Budapest, Hungary, 15-16 May 2013
- Yearly meeting of the Official Medicines Control Laboratories (OMCL), meeting organised by the European Directorate for the Quality of Medicines (EDQM) in Helsinki, Finland, 11-14 June 2013
- Yearly meeting of secretariats of National Competent Authorities pharmacopoeias, Oslo, Norway, June 2013;
- Workshop for experts in validation of the manufacturing process of biological medicinal products, organised by EMA, 9 April 2013, London.
- Participation to the yearly training course for GCP inspectors organised by EMA, London, Great Britain;
- The Conference on the traffic of counterfeit medicinal products, organised by the UNODC,
  Vienna, February 2013

Participation to online training:

– the course organised by the EMA – „EU Regulatory Workshop on Medication Errors”, 28.02.2013 – 01.03.2013;

– the course “Webinar training on referral procedure”, 5 June 2013;
– the training course "Major changes to European Variations Regulations" – 27 June 2013;
– two courses for clinical assessors concerning quality of opinion of Scientific Committees organised by The European Medicines Agency (EMA) through Adobe Connect Teleconference
– three courses for clinical assessors concerning contents and manners of presentation of data included in the Summary of Product Characteristics organised by The European Medicines Agency (EMA) through Adobe Connect Teleconference
– two courses for clinical assessors concerning biostatistical analysis of clinical trial outcomes organised by The European Medicines Agency (EMA) through Adobe Connect Teleconference
- the course “Webinar VigiLyze” organised by UMC – Uppsala, 2013.
- the course “Awareness session on a new version of EVDAS”, held on 21.08.2013.
- the webinar “*Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples*”, organised by EMA via Adobe Connect, between 28-19 November 2013

In 2013 as well, **internal training** was added to the training activity:

- trainings based on materials and papers issued by senior members within the BPECD, in accordance with the training plan;
- work-related training for staff with secondary education – handling of the specific SOP;
- the training for safety and health at work, for both staff with higher education, staff with secondary education and ancillary staff;
- training in the field of emergency situations, for both staff with higher education, staff with secondary education and ancillary staff;
- Continual training, at the NAMMD site, related to personal development, has been performed while taking into account specialists’ (inspectors, assessors) training requirements.
- Also, the entire NAMMD staff has benefited, in accordance with the yearly program, from the training in the field of Health norms, labour safety and emergency situation safety.
- In 2013, NAMMD employees participated at various training programs related to classified information.

16. Economic activity

In 2013, the Economic Department developed and managed a balanced budget of revenues and expenses from the state budget, amounting to 17,897,000 lei; expenses amounted to 17,614,366 lei. These expenses consisted of: staff expenses (14,020,436 lei), expenses on goods and services (3,262,040 lei) and capital expenses (331,890 lei).

All expenses did not exceed the approved 2013 budget in accordance with legal provisions on economic and financial discipline.

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

17. General administration activity

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

The Public Purchases Service organised and accomplished the entire purchase process needed for proper NAMMD operation, consistent with its objective needs and the approved budget, thus preparing documentation needed for 448 applications (purchase requisitions).

Handling of goods was represented by evidence and handling of fixed assets, inventory objects and setup of corresponding documents.

The activity of the administration, maintenance, repair, safety and PSI was mainly represented, in 2013, by:

- Organisation and ensurance of support services (**secretariat, transportation of goods and persons, delivery, telephone communication, cleaning, guard, prevention of emergency situations**) required for a good performance of the activity within the organisation;
- Maintenance of the NAMMD infrastructure (maintenance of buildings, equipment and tools, except for complex laboratory gear);
- Permanent ensurance of cleaning in the NAMMD.

The metrology compartment – ISCIR within the GAD has been directly involved in:

- mandatory metrological checks for gear in the MPQCD, BPECD and the Storehouse;
- surveillance and monitoring of internally checked means of measurement as well as ;
- ISCIR fixing and authorisation of:

-elevator for persons and elevator for goods (renewal of authorisation);

-heating system ANMDM (capital reparation);
-NAMMD water supply plants (capital reparation and reauthorisation);
-the steam apparatus of the Microbiology Laboratory (renewal of authorisation).

18. Internal audit

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

In 2013, the activity of the Internal Audit Bureau consisted of 4 internal audit missions:

- Assessment of activities of the Medicinal Products Quality Control Department;
- Assessment of activities of the Biological Products Evaluation and Control Department;
- Assessment of activities of the European Procedures Department;
- Assessment of activities of the Economic Department.

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

- Manner of organisation and operation of activities performed by audited structures.
- Compliance with tasks, duties and specific legislation within audited structures.
- Evidence keeping and reporting of activities within the audited structures.
- Document archiving.

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

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

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

19. Difficulties encountered

As of 2009, the NAMMD has encountered several difficulties in performance of its activities, the primary of which has been recruitment and maintenance of specialised staff, coping with the lack of financial means to ensure continual training of staff and access to the latest scientific progress in general and particularly in their own professional field, limited character of data bases.

20. Priorities/projects for 2014

At the end of 2013, the NAMMD outlined its priorities and projects for 2014. These would require:

- Several highly qualified specialists in the field of the medicinal products for human use and of medical devices, in order to ensure that all Agency duties are met according to the established deadlines, and that reclaiming of delays determined by severe lack of staff happening ever since 2009.
- More hiring flexibility.
- A budget allowing direct competition with the other competent authorities in the field of the medicinal products for human use from the European Union through:

- ensurance of an adequate number of specialists in all NAMMD departments, particularly for assessment of the authorisation dossier, for appropriate management of the national procedure and DCP/MRP European procedures, but for the centralised procedure as well; ensurance of an appropriate expertise of NAMMD specialists could allow Romania to actively participate in the activities of EMA structures (The Committee for Medicinal Products for Human Use - CHMP, The Paediatric Committee - PDCO, The Committee on Herbal Medicinal Products-HMPC, the Pharmacovigilance Risk Assessment Committee - PRAC etc.)) considering the fact that the authorisation through centralised procedure is done with the existing expertise at national level in EU member states;

- The Agency's increasing involvement in decision-making at European level, by active participation in European working groups, proposal of workable solutions amending current legislation in the field of the medicinal product for human use, by increasing NAMMD's degree of integration into the medicinal product issue at European level by the activity of rapporteurs, pharmacovigilance assessment, assessment of authorisation dossier at high level of scientific competence, as Reference Member State in the context of the decentralised procedure for marketing authorisation.

- Training of physicians from the Pharmacovigilance Service in electronic transmission of adverse reactions to EudraVigilance – courses which take place at the sites of EMA and the World Health Organisation – Uppsala Monitoring Centre and which are mandatory for members of competent authorities, yet require coverage of transportation and lodging expenses;

- Elimination of difficulties occurred during this activity, through facilitation of implementation of technical validation and of assessment of *Electronic Common Technical Document*s (eCTD) and use of the Extedo EURS is Yours programme, feasible by endowment of assessors with new computers, 2-monitor computers, performant and reliable, so that each assessor can properly assess and setup assessment reports, ensurance of visualisation of the information available on the server, the possibility of rapid actions in the Intranet or in databases,

as required, and ensurance of backup for the databases;

- set-up of an integrated informational program, which is versatile, multi-tasking, for medicinal product related information throughout their entire life cycle and in order to ensure strong NAMMD databases which are useful to the activities conducted by the NAMMD, also ensuring technical support for the Ministry of Health, the National Health Insurance House etc.) ;
- increased staff participation at national and international symposia and congresses, for training and update of information in their field of activity.

Other priorities/recommendations/projects for 2014:

- strengthening NAMMD's role in the setting up a medicinal product policy
- amendment of national legislation by establishing public responsibility of the manufacturer and distributor towards the citizen and the Agency's role concerning sanctioning, if this responsibility is not observed;
- participation at working meetings, more frequent than during previous years, of NAMMD management representatives with representatives of various stakeholders (manufacturers, distributors, professionals in the medical and pharmaceutical field, patients);
- continuation of Agency's involvement in closure of project "SAVEmed Microstructure secured and self-verifying medicines", initiated in 2012 by UNICRI (United Nations Interregional Crime and Justice Research Institute), by its contribution to reaching Romania's two main objectives:
  - implementation of a SPOC (single point of control) in Romania, with its national contact point at the General Inspectorate of the Romanian police;
  - development, in collaboration with 15 participating countries, of a Guideline on good communication practices between the public and private sectors to facilitate the exchange of information on prevention of entry of falsified medicines.
- thoroughness and resolution of clinical trial issues:
  - a document containing the fields which require clinical trial regulation has been forwarded to the Ministry of Health for assessment and decision making. Regulation of the following fields has been proposed: CRO (for which regulation through Order of the Minister of Health is proposed), situation of monitors, for which introduction of a mandatory minimum qualification in the field is proposed.
  - Particular importance is placed upon the need for regulation of certain aspects related to performance of clinical trials in public institutions (compensation of costs of the institution and of the investigator's activity); a clarification on the type of institution which can get involved in performance of clinical trials and the manner of compensating associated costs is required.
  - the issue of the need of keeping an evidence of investigators is also mentioned in the same document, highlighting the importance of

existence of a database containing the clinical investigation centres and investigators.

- o the opportunity of authorisation by the Ministry of Health of institutions solely meant for performance of clinical trials is also suggested.
- o The NAMMD Scientific Council shall also aim to establish the types of information included in clinical trials which could be made public, in view of establishing a final strategy of increasing the degree of transparency in this field, by posting this information on the NAMMD website.

- Ensuring complete and efficient coordination of the pharmaceutical market by control of the entire supply chain (manufacturer, distributor, storehouse, pharmacy) by the same person.
- By complying with the mandatory reporting of inputs/outputs of all manufacturers/importers/distributors in order to ensure traceability of medicinal products throughout the entire chain, from manufacturing and/or distribution to community pharmacy, hospital pharmacy, drugstore, the NAMMD will be able to:
  - detect falsified medicinal products and
  - prevent their entry into the authorised distribution network,
  - To combat the existence of illegal parallel circuits for medicinal product sale, respectively
  - To ensure the rapid withdrawal of noncompliant product batches or in case of health emergency.

The following measures are proposed in order to strengthen and improve the internal audit activity:

- organisation of training courses of public internal audit by the Ministry of Health – in in the field related to accessing European funds by the NAMMD.
- set-up and publication of Procedural guidelines by Ministry of Health specialists – concerning public internal audit of activities in the health sector.

CONCLUSIONS

The National Agency for Medicines and Medical Devices (NAMMD) is the competent authority in the field of the medicinal product for human use, whose entire activity is performed by grant of compliance of medicinal products authorised for marketing with European standards – as regards their quality, efficacy and safety, as well as by maintenance of a high level of performances and safety of medical devices in use within all health networks throughout the country.

The NAMMD always tries to ensure proper partnership, in the interest of Romanian patients, with healthcare professionals, pharmaceutical industry, the media – as opinion makers, by performing sustained efforts to promote an effective regulatory and control policy, in line with its main role, namely to safeguard public health.

Current activity of the NAMMD in 2013 meant grant of 773 marketing authorisations (MAs) (195 through NP - national procedure for marketing authorisation and 578 MAs through EPs (European procedures) for marketing authorisation.

If in 2011 and 2012, generics were in the top of entries on the market, they also maintain this status in 2013.

Of 8582 medicinal products registered in the Index of medicinal products for human use in 2013, 33% are original products, centrally authorised by the European Medicines Agency (EMA), introduced on the Romanian market upon request of the MAH.

The pharmacovigilance activity performed during the past 2 years by the Pharmacovigilance and Risk Management Service becomes more and more complex. The number of reported spontaneous adverse reactions continues to grow, showing the increased importance given to patient safety by physicians and the medical staff, although increased involvement is expected from healthcare professionals in this respect. The best knowledge of the medicinal product safety profile is expected by implementation of the new pharmacovigilance legislation, by joint effort of physician-pharmacist-assistant-consumer. While the first steps have been taken for implementation of the new pharmacovigilance approach in 2012, year 2013 brought the reporting of 1847 ARs (935 serious and 912 non-serious ARs). Of these, physicians reported straight to the NAMMD 295 ARs, MAHs have forwarded 1552 ARs (of which 100 from consumers, 34 from pharmacists, 59 from medical assistants, while most of the others adverse reactions have been reported by physicians, also via specialised literature).

In 2013, the NAMMD has also aimed to ensure surveillance of safety of products within the therapeutic circuit, both via pharmacovigilance and pharmaceutical activities.

Year 2013 was characterised by entry of falsified products into the authorised distribution chain of medicinal products, fact unseen in Romania before July 2013. The case of falsified products which have entered the legal supply chain of medicinal products, as Sutent and Pegasys, has determined emergency safety measures for

notification of patients about this fact impacting public health (description of Summary of Product Characteristics making the difference between the original and the falsified product) and withdrawal from the market of the two product batches, whose identification numbers have been found imprinted on boxes identified as being falsified.

In 2013, the Cantacuzino Institute could not launch on the market the manufactured flu vaccine for 2013-2014, following noncompliance of the content of *Bacterial endotoxins.*

As regards human resources, 2013 was marked by changes. 5 years after opening for recruitment of vacant jobs in the job title list, due to enforcement of provisions of Article 22 of Emergency Government Ordinance 34/2009, provision of the NAMMD with qualified staff has been only partially feasible no sooner than 2013, following entry into force of Emergency Government Ordinance 77/2013 for measures to be taken in order to ensure the functionality of local public administration, the number of jobs and a reduction in expenses in the public institutions and authorities subordinated to, under the authority of or in coordination with Government or ministries

From NAMMD perspective, year 2013 has involved:

- Active participation in debates, bimonthly/monthly/biannual meetings of scientific committees and working groups of coordinating European bodies in the field of medicinal products for human use (the European Medicines Agency - EMA, 'the Heads of Medicines Agencies - HMA, the European Directorate for the Quality of Medicines and Healthcare - EDQM, the European Commission);
- Transposition into national legislation of provisions of Directive 26/2012/EU of the European parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance - contribution, upon request of the Ministry of Health, to elaboration of drafting of a regulatory document for amendment and supplementation of Law 95/2006 on healthcare reform, project which includes amendments brought by transposition of Directive 26/2012/EU, amendments of Emergency Government Ordinance 35/2012 and Emergency Government Ordinance 91/2012, supplementations referring to the notion of "public service", to new sanctions for noncompliance with legal provisions in the field of the medicinal product.
- Support of the regulatory activity by adoption of new Scientific Council Decisions and grant of technical support upon request of the Ministry of Health;
- Implementation of NAMMD strategies: organisational and communication strategies (2013-2015);
- Continued participation to reunions/workshops/conferences/informal meetings with various stakeholders (representatives of the pharma industry, patient associations, mass-media representatives, organisations of healthcare professionals), debates on various issues arising in the area of medicinal products for human use;

- Participation of NAMMD representatives, with specialist papers, to various scientific events, displaying openness towards communication and transparency in the respective area of activity.

In 2013 as well, the NAMMD top management and all structures of the Agency have aimed at the implementation, development and improvement of the NAMMD QMS, according to the *SR EN ISO 9001* and *9004* principles in force.

The same difficulties regarding NAMMD activity have been identified in 2013, perpetuated since previous years, caused by underfunding, insufficient human resources (witnessing slight improvement at the end of the year, in line with Emergency Government Ordinance no. 77/2013 lifting occupation by contest/exam of vacant jobs, according to the "one to one" principle, namely one occupied job instead of a vacant job"), insufficient staff training, communication blockages, failure to motivate the staff.

For the Agency, an appropriate funding would mean the possibility to ensure necessary highly specialised human resources for performance of organisation-specific processes, which could only be obtained by ensurance of ongoing professional training.

Projects:

Future projects of the Agency also include resolution of the lack of staff highly trained in the field of the medicinal product for human use and of medicinal products, as well as ensurance of a budget allowing direct competition with other national competent authorities in this field, in EU.

The following projects are worth mentioning:

- Strengthening of Agency role as regards medicinal product policy – amendment of national legislation for establishment of manufacturer and supplier public responsibility and ensurance of Agency capability to enforce penalties in case of non-compliance;
- A more increased participation, as opposed to previous years, of NAMMD management representatives to working meetings with representatives of all stakeholders (manufacturers, suppliers, medical-pharmaceutical staff, patients);
- Continuation of Agency involvement in completion of the "SAVEmed Microstructure secured and self-verifying medicines" project, initiated in 2012 by the United Nations Interregional Crime and Justice Research Institute (UNICJRI);
- NAMMD involvement in:
  - prevention of entry of falsified medicinal products into the legal supply chain.
  - fight the existence of illegal parallel circuits for medicinal product sales
  - grant fast recall of non-compliant medicinal product batches or in case of health emergencies, by observance of reporting inputs/outputs by manufacturers/ importers/suppliers ensuring medicinal product traceability throughout the entire supply chain, from manufacturing and/or distribution to community pharmacy, hospital pharmacy, drugstore.

- Thoroughness and resolution of clinical trial issues;
- Ensurance of complete and efficient coordination of the pharmaceutical market through control of the entire distribution chain (manufacturer, distributor, storehouse, pharmacy) by the same entity.
- Consolidation of the dialogue and partnership with all stakeholders in order to facilitate public health promotion and safeguard activities, primary mission of the NAMMD.