REPORT

of the activities performed by the National Agency for Medicines and Medical Devices in 2010,

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INTRODUCTORY WORD

In 2010, as a national competent authority in the field of medicinal products for human use, the National Agency for Medicines and Medical Devices fulfilled its attributions and duties, even in the context of the international financial crisis. The efforts made by the Agency's employees were deemed even more substantial since during the previous two years, the institution has undergone ongoing major transformations. Ever since 2009, several changes in the inner structure of the Agency have been performed, in view of improving its activity, starting with the manner of structuring and operation of the European Medicines Agency (EMA). If by the end of 2009, the National Medicines Agency (NMA) has been reorganised as a public institution entirely financed from the state budget, in accordance with Law No. 329/2009 related to the restructuring of some public authorities and institutions, in 2010, the National Agency for Medicines and Medical Devices (NAMMD) has been founded in accordance with Government Emergency Ordinance No. 72 of June 2010, after the NMA and the Technical Office for Medical Devices merged. The organisation and operation of the NAMMD have been subsequently established through Government Decision No. 734 of July 2010.

As shown in the contents of Government Emergency Ordinance No. 72/30 June 2010 on reorganisation of healthcare facilities, the streamlining of the activity of healthcare institutions, in accordance with the priorities of the Public Administration Reform Government, to establish economic and financial measures at the level of institutions financed by the state budget subordinated to the Ministry of Health, following the severe economic crisis represented the reason for founding the NAMMD. The consequence was a supplementation of the Agency's mission with other tasks related to the medical device field, such as:

- maintaining an elevated level of performance and security of medical devices in use throughout Romanian healthcare networks, regardless of their type of ownership;

- optimal assessment of technical-medical units, service providers in the medical device field, so that any type of prosthetic services and other services

related to the fixing and maintenance of medical devices are carried out at optimal quality and competence level;

- drawing up specific technical procedures in the field of medical devices.

Moreover, the permanent contribution to adapting the secondary legislation in the field of medical devices was another objective that has been added to the strategic objectives of a European authority in the medicinal product field.

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

The Agency displayed an enhanced interest in the improvement of the communication with all partners in this field of activity; meetings with Marketing Authorisation Holders (MAHs), Romanian and international associations of medicinal product manufacturers, patients, associations of clinical trial coordinating companies, associations of medicinal product distributors etc. have been organised in this respect. This is the considerable proof for the partnership established between the Agency and other stakeholders, who should practically ensure a balanced pharmaceutical market, accessible to the general public. This is a proof for transparency of the activity conducted by the Agency, based on the cooperation with all its partners, in the context of the decision-making process.

The Agency had to carry on with its activity, to fulfil its mission under the circumstances of reorganisation imposed by the severe financial recession. Through consistent effort of the specialists and of the auxiliary personnel, the NAMMD continued to represent a European regulatory authority in the field of medicinal products for human use, perfectly in line with community requirements.

Apart from the current, priority activity of the NMA/NAMMD, which represents the Agency's mission, a certain activity started in 2009 was carried on, namely the Agency's preparatory activity for the *"peer-review"* type of the quality management system audit within the self-assessment exercise, namely the "*Benchmarking European Medicines Agencies (BEMA)*", initiated by the Heads of European Medicines Agencies; the audit shall be held in May 2011.

This is an ongoing, correct and realistic self-assessment process of the Agency's performance, depending on pre-established performance indicators and on the use of assessment results in view of constantly meeting the proposed strategic goals. BEMA's ultimate target is to improve the European regulatory system in the pharmaceutical field, based on a medicines agencies network that operates at full capacity, as well as to contribute to the development of the international regulatory system in the pharmaceutical field.

In 2010, the NMA/NAMMD was faced with a significant shortage of specialised staff. Despite this fact, the Agency managed to fulfil its target objectives and continued its active involvement in activities of European bodies in the medicinal product field, during its 4th year of EU accession. The activity of NAMMD departments in 2010 has been particularly complex; its main purpose has been to fulfil the main mission of the Agency, namely the assessment at the highest scientific level of the authorisation dossier, in view of ensuring marketing quality, safe and efficient medicinal products for human use and the supervision of the safety of human medicinal products within therapeutic circuit by means of inspection and pharmacovigilance activities.

Moreover, in 2010, the structure of the Authorisation Department (AD) and the Post-Authorisation Department (PAD) has been changed, once again; these have been reorganised in two new departments:

- The National Procedures Department (NPD) – which assesses the documents in view of marketing authorisation / marketing authorisation renewal of medicinal products for which the authorisation through national procedure has been required;

- The European Procedures Department (EPD) – which assesses the documents in view of marketing authorisation / marketing authorisation renewal of medicinal products for which the authorisation through European procedure has been required.

While the number of Marketing Authorisations (MAs) through European Procedure (EP) [(decentralised procedure (DCP), Mutual Recognition Procedure (MRP) and Repeat-use mutual recognition procedure] has increased, namely:

MAs through European procedure: 2010 - 623 compared to 2009 - 568,

The number of Marketing Authorisations through National Procedure (NP) has decreased in 2010, compared to 2009, as follows:

MAs through national procedure: 2010 - 190 compared to 2009 – 359.

This is, however, natural, considering the fact that we are an EU member state with a pharmaceutical market undergoing the harmonisation process with European requirements.

However, the overall number of MAs granted by the Agency in 2010 has been smaller than in 2009. Thus:

MAs through national and European procedure: 2010 - 813 compared to 2009 - 927.

The low numbers were due to the Agency's recent lack of staff, not to a smaller number of applications!

The number of decisions related to the discontinuation of MAs, at the request of the Marketing Authorisation Holders (MAHs), due to commercial reasons, has increased in 2010, compared to 2009, namely**:**

Discontinued MAHs: 2010 - 202 compared to 2009 - 134.

Moreover, in 2010, 3 years after Romania's EU accession, the "*sunset clause"* has been enforced for 177 MAs for products which had not actually been marketed between 2007 - 2010.

At the end of 2010, the Index of medicinal Products included 8168 trade names corresponding to 1252 International Non-proprietary Names (INNs).

The activity of the National Pharmacovigilance Centre operating within the NMA was particularly complex in 2010, ensuring handling of safety data issued from spontaneous reporting and periodic safety update reports concerning medicinal products, as well as a wide range of pharmacovigilance activities within the system of EU national authorities, coordinated by the EMA and within the rapid alert/non-urgent information, plus the assessment of requirements concerning the pharmacovigilance system of the Marketing Authorisation applicant through national and European procedures.

During 28–29 September 2010, NAMMD's European Procedures Department – The Pharmacovigilance and risk management service was visited by a commission from the Centre for Adverse Drug Reaction Reporting of the World Health Organisation - Uppsala Monitoring Centre - UMC. The discussions focused on the theoretical and practical aspects concerning the spontaneous reports of the Agency's pharmacovigilance activity in line with the European legislation, on the cooperation with the UMC in view of reporting to the „*VIGIMED"* through „*Vigiflow"* and on the possibility to detect the signal by using „*VIGISEARCH".*

The NMA/NAMMD similarly performed an intense activity in the pharmaceutical inspection field. Intense NMA pharmaceutical inspection activity represented a consequence of amendments to Law No. 95/2006 on healthcare reform, regarding supplementation of NMA assignments with authorisation for functioning and inspection of medicinal product wholesale distribution units.

Having commenced in 2009, through amendment of Law No. 95/2006 on healthcare reform, as amended, Title XVII – The medicinal product, the activities related to Good Distribution Practice inspection (GDP) performed in 2010 were the following:

- 112 inspections in view of authorisation;
- 70 wholesale distribution authorisations have been released.

7 units were not granted wholesale distribution authorisations, in result of finding critical deficiencies during authorisation inspections;

In 2010, following 40 unexpected inspections at the sites of wholesale distribution units, 17 authorisations were suspended and 3 withdrawn. This activity was carried on in 2010; apart from GDP inspections, other types of inspections were carried out, e.g. inspections to assess compliance with Good Manufacturing Practice (GMP) rules, Good Laboratory Practice (GLP) rules and Good Analytical Laboratory Practice (GALP) rules, Good Clinical Practice (GCP) rules, pharmacovigilance rules.

As regards the supervisory activity of the quality of medicinal products authorised for marketing in Romania, both the inspectors from the central headquarters and the inspectors from the 12 territorial inspection units (TIUs) have been involved. This is a complex activity, yearly aiming to:

- comply with the sampling plan concerning the supervision of the quality of medicinal products (sampling, analysis, results);
- supervise the quality of medicinal products included in the distribution chain (warehouses, pharmacies), inspections conducted by TIU inspectors;
- assess the quality of the oxygen used in hospital units;
- cooperate with other bodies, in view of solving certain issues related to the legislation in the field of the medicinal product for human use and/or the quality of certain medicinal products marketed in Romania;
- solve the notifications concerning potential quality non-compliances of medicinal products for human use;
- withdraw non-compliant products from the market;
- handle the rapid alerts issued in the context of the EMA, PIC/S rapid alert system;
- handle rapid alerts for counterfeit medicinal products received from the Working Group of Enforcement Officers (WGEO) of the Heads of Medicines Agencies (HMA);
- cooperate with European bodies: the European Medicines Agency (EMA), the European Directorate for the Quality of Medicines and Healthcare (EDQM), European competent authorities in view of supervising the quality of starting material/finished product manufacturing in third countries;
- introduce into the EudraGMP database information related to the manufacturing/import authorisation activity and to the GMP certification activity of the NAMMD.

Activities regarding quality control of medicinal products were aligned to the Agency's general policy and have been carried out within the following two departments: the Department for medicinal product quality control (DMQC) and the Department for biological products control (BPCD).

As in previous years, the NAMMD continued as well its cooperation with renowned European institutions in the quality control field, by taking part in studies initiated and coordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM) in 2010, namely:

- Proficiency Testing Scheme (PTS), performed yearly, whose purpose is to test each laboratory included in the Official Medicines control laboratories (OMCL) network in view of assessing the ability to deal with difficult issues related to the control of the medicinal product's quality;

- Surveillance studies on the quality of medicinal products authorised through European procedures;

- Market Surveillance Studies (MSSs) for the surveillance of the European market. In 2010, the professional activity of the BPCD distinguished itself through involvement in a Proficiency Testing Scheme (PTS) study, conducted at the initiative and under the coordination of the EDQM for which the laboratory received the "Satisfactory" marks. Once again, the result confirmed the competition level for performance of laboratory testing within BPCD.

NAMMD's regulatory activity continued in an alert rhythm in 2010, considering the fact that the legislation in the medicinal product field undergoes an ongoing development/updating/amendment, in accordance with the technical and scientific progress reached in the research/development of medicinal products fields, both in the EU and worldwide.

As always, the NMA/NAMMD Scientific Council supported the Agency in this regulatory mission in the field of the medicinal product for human use; by assessing and adopting/updating norms, scientific guidelines and procedures**,** it contributed to the harmonious performance of the activity of the Agency and of external partners.

As a competent authority in the field of the medicinal product for human use, the NAMMD has fully undertaken its important role by fighting against the counterfeiting of medicinal products and against illegal marketing with medicinal products; it continued to inform and warn the general public, as well as to develop cooperation relationships with other institutions and bodies involved in this activity. In this respect, the NAMMD continued to cooperate with national institutions involved in the fight against counterfeit medicinal products sold online, as well as with similar institutions from EU member states and from other countries outside the EU, in view of restricting such unlawful phenomena, which can sometimes have serious consequences on public health.

The necessary measures in view of preparing the enforcement framework for the provisions of the upcoming European directive on the prevention, within the legal distribution chain, for the entry of falsified medicinal products (as regards their identity, history or source) on the market, in the project stage, debated over by the European parliament and the EU Council (debates also assisted by the assigned representative of the NAMMD, who explains and supports Romania's viewpoint on this matter).

In view of continually informing the public in this respect, the updating of the „Counterfeiting" heading on the Agency's website, where information related to counterfeiting has been forwarded through the rapid alert system, was continued in 2010.

Year 2010 also meant active participation to scientific committees and working groups of EMA, The Heads of Medicines Agencies (HMA), the European Union Council, the European Commission, the European Council, The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-

operation Scheme (PIC/S), the European Pharmacopoeia Commission, the Official Medicines Control Laboratories (OMCL).

NAMMD specialists assigned to participate in the meetings of the Working Group for medicinal products and medical devices of the EU Council have displayed and supported Romania's viewpoints concerning directive draft projects on amendment of Directive 2001/83/EC, as regards both the avoidance of the entering of counterfeit medicinal products on the authorised distribution chain, and pharmacovigilance. The draft directive referring to pharmacovigilance has been approved in its finished form, on 15 December 2010, as Directive 2010/84/EU of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the community code relating to medicinal products for human use.

Just like the previous year, the participation to the monthly meetings of the Paediatric Committee (PDCO) was thoroughly carried on through:

- the assessment of 20 Paediatric Investigation Plans (PIPs) and of the applications for their amendment as Rapporteur/CoRapporteur,
- the participation to teleconferences for applicant counseling,
- the set up of reports and stage presentations of procedures during Committee meetings.

The involvement of the NAMMD in the activities of the EU competent authorities network was similarly manifested through the participation to Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) inspections of EMA centrally authorised medicinal products.

Moreover, there were numerous thesis submitted for scientific events such as congresses, conferences and seminars held in Romania and abroad.

As during the previous year, the NMA/NAMMD carried out various activities not only for development of relationships with European partners, but with international partners as well, such as China and India, countries which undergo rapid development in the fields of research and manufacture. In view of promoting an efficient safeguard of public health, the NAMMD continued to develop cooperation relationships with those countries which are potential major suppliers of medicinal products for the Romanian pharmaceutical market.

Particular attention was given to ensure communication with stakeholders and transparency of the activity.

This year as well, the Agency manifested openness towards communication with partners in this field; several meetings were organised with Marketing Authorisation Holders, with the associations of medicinal product manufacturers (foreign and Romanian), patient associations, associations of clinical trial coordinating companies, associations of medicinal product suppliers etc. The goal was to ensure transparency in the Agency's activity. During these meetings, the main cooperation fields between the parts involved in the pharmaceutical market, as well as the means to improve communication in these fields of activity have been discussed.

Moreover, the communication with the media was enhanced; issues of general interest have been approached, such as the safe use of medicinal products.

A large amount of useful data has been published on the NMA/NAMMD website, meant for both healthcare professionals in the medical and pharmaceutical field and the general public.

The Agency carried on with the enforcement of the provisions of Law No. 95/2006, Title XVII – The medicinal product on the transparency in the activity of the competent authorities in the field of the medicinal product in the EU, by periodic update of the Regulations on the organisation and cooperation of the Agency's professional commissions (the Marketing Authorisation Commission, the Commission for GMP, GDP, GLP, GALP, GCP and pharmacovigilance inspections) and their publication on the website after approval by the Agency's Administration Council, by the set up, by request, of the versions available to the public of the agendas and press releases of the Marketing Authorisation Commission and of the Commission for GMP, GDP, GLP, GALP, GCP and pharmacovigilance inspections, and of the versions of the Assessment Reports of the products' authorisation dossiers available to the public.

In 2010, the institution's top management has paid proper attention to the Quality Management System (QMS), being interested in enforcing a process-based approach.

The NMA owns a well established Quality Management System, in accordance with the international standards in force.

In view of fulfilling its objectives, the NMA/NAMMD was supported in 2010 by the Administrative Council (AC), in 6 ordinary meeting (4 of the NMA and 2 of the NAMMD); 42 Administrative Council Decisions (ACDs) have been approved, of which 27 as NMA ACDs and 15 as NAMMD ACDs. 3 of these have been approved through Order of the Minister of Health. Although 2 regulatory decisions have been initiated (the approval of tariffs for new activities, identified after the set up of the Order of the minister of Health No. 716/2009), they could not be finished.

Thematically speaking, ACDs have covered various issues of the current activity, their average being given, as a consequence to actual circumstances, by regulatory documents whose regulatory goal consists of organisational issues – consecutive structure-related amendments within the institution i.e. of the collective labour contract at unit level, approval of the job list and of the organisational structure, and other issues related to the current activity.

As regards the fulfilment of the objective of the Human Resources Department (reorganised in 2010 as the Human Resources and Payroll Department), concerning the insurance of qualified staff, it is deemed worthy of mention that, starting from April 2009 and throughout 2010, it was obviously rendered difficult by the legal framework enforced by Emergency Government Ordinance No. 34/2009. Moreover, the negative impact upon human resource management has been increased by the unfavourable economic conjuncture

created in the law field by Law No. 118/2010 regarding some measures needed to restore budget balance. Due to the enforcement of those economic and legislative measures, a significant number of employees trained by the NMA quit their jobs. As a consequence, following the legal provisions enforced in 2010, the human resources deficit encountered since 2009 increased by cessation of a large number of individual work contracts.

In 2010, the relocation of the Biological Product Evaluation and Control Department, located in Demostene street, to the NMA headquarters was completed; this move result in creating an optimal environment in laboratory work, and solving the problem of biological samples transportation from the former to NMA headquarters.

Just like during previous years, in 2010, the General Administration Department (namely GAD, set up through reorganisation throughout the year of the former Department of General Administration and Heritage - DGAH) managed to fulfil its objectives and to answer promptly and efficiently to the requests of other NMA/NAMMD structures. Therefore, the most substantial achievements of the GAD consisted of the performance and ending of various acquisitions in view of endowment and renovation of the NAMMD building. Several important acquisitions have been made:

- the access control system in the building of NAMMD headquarters;
- video surveillance systems (in the headquarters and on 20 Demostene Street), acquisition whose purpose has been to establish safe and effective measures to protect the cameras, by eliminating the odd of unauthorised persons entering the areas containing secret or confidential documents.

The NAMMD carried on with activities such as the maximisation of headquarter areas, the performance of sanitation activities, the division of certain areas so as to transform these into offices and a plethora of activities in view of fitting up the workplaces.

Moreover, the Agency carried on with its policy for automation and extension of the internal computer network.

The fulfilment of the objectives established for 2010 could only be performed through an adequate financial policy, based on a strict financial discipline, through compliance with legal provisions on budget execution for judicious spending of allocated resources in accordance with the approved income and expenses budget.

In 2010, the institution's Economic Department set up and handled a balanced budget of revenues and expenditures from state budget. In spite of all issues encountered, the new NAMMD department – The Technical Laboratory Department managed to perform an activity in line with Law No. 176/2000 concerning medical devices, as amended, and to maintain an acceptable level of performance and safety for the medical devices.

In 2010, within the „CERF" project on the enhancement of expertise in the field of pharmaceutical regulations, the NMA/NAMMD and the "Carol Davila"

University of Medicine and Pharmacy have initiated and held several classes and workshops:

1. The „Advertising of medicinal products" workshop – 17 May 2010;
2. „New regulations on the set up of the Summary of Product Characteristics of medicinal products for human use" – 25 May 2010;
3. „Manners of consultation with target patient groups in view of issuing the leaflet" – 7 June 2010;
4. „Regulations concerning the pharmacovigilance activity in accordance with the legislation in force" – 24 June 2010;
5. "Basic criteria and requirements on the documentation of the active substance dossier" – 16 September 2010;
6. "Module 3 – Quality for the product's authorisation dossier" – 17 September 2010;
7. "Incursion into the field of assessment of the quality of biological medicinal products for human use" – 18 September 2010;
8. "Regulations concerning the performance of clinical trials in Romania in accordance with the legislation in force" – 24 September 2010;
9. "Performance of clinical trials at the investigator's site in accordance with Good Clinical Practice rules" – 13 October 2010;
10. The "Advertising of medicinal products" workshop – 2 November 2010;
11. "Performance of clinical trials at the investigator's site in accordance with Good Clinical Practice rules" – 9 November 2010;
12. "Norms on the administration procedure of the National Agency for Medicines and Medical Devices on the handling of variations" – 18 November 2010;
13. Bioequivalence course – 10 December 2010;
14. Pharmacovigilance course – 17 December 2010.

In 2010, the NMA/NAMMD and the Competition Council carried on with their cooperation on the basis of the cooperation protocol ended during the last quarter of 2009, in view of ensuring and promoting competition in the field of the medicinal products for human use, in accordance with the provisions of Competition Law No. 21/1996, which forbids the withdrawal, hindrance or distortion of competition on the Romanian market. Extrapolating to the Romanian pharmaceutical market, the management of the two institutions found convenient the coordination of their activities in view of a homogenous enforcement of general legislation and specific legislation (to ensure proper functioning of this market sector of the human medicinal product) in the field of competition. The purpose of the document has been to establish manners to create and maintain a balanced pharmaceutical market, without being detrimental to any of the participants, be they manufacturers of innovative medicines or importers/distributors.

In December 2010 has taken place the first meeting of NAMMD management with the stakeholders involved in the set up of a Romanian regulatory framework concerning medicinal product traceability; the purpose of this meeting consisted of the detection of all the elements which can be starting points in finding feasible solutions for the set up of this framework.

As a decision factor in the field of the medicinal product for human use, the Agency should and intends to get involved in everything that's "regulatory" in view of attaining a balance on the medicinal product market, in line with the recommendations of the European Commission, for the good of the final consumer: the patient.

NMA/NAMMD ACTIVITIES IN 2010

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

During the first half of 2010, the NMA Scientific Council activities developed in line with the provisions of Section 3 "Scientific Council organisation and operation" of Government Ordinance no. 125/1998 on the set up, organisation and operation of the National Medicines Agency, approved by Law no. 594/2002, as amended.

After the issuance of Emergency Government Ordinance No. 72 of June 2010, which led to the foundation of the National Agency for Medicines and Medical Devices (NAMMD), the organisation and operation of the NAMMD and its Scientific Council have been regulated through Government Decision No. 734 of 21 July 2010.

It should be considered that, from an institutional viewpoint, as opposed to the administrative procedures set up by Government Ordinance No. 125/1998, the Scientific Council decisions no longer require approval of the Minister of Health within 15 days from adoption; the competent minister is strictly informed about this matter. As far as regulatory Scientific Council Decisions are concerned, they are compliant with the enforcement of general jurisdiction – approval through Order of the Minister of Health and publication in the Official Gazette of Romania, Part I.

The new NAMMD Scientific Council has been set up based on the Order of the Minister of Health No. 1123/18.08.2010; its activity is performed in line with the provisions of Art. 12 of Government Ordinance No. 734/21.07.2010 related to the set up, organisation and operation of the National Agency for Medicines and Medical Devices and with the NAMMD Organisation and Operation Rules, approved in the meeting of 03.09.2010 through SCD No. 18, subsequently repealed by SCD No. 33/13.12.2010.

The Scientific Council establishes NAMMD's scientific policy, in accordance with the Agency's tasks.

The regulations concerning NAMMD's professional activity are discussed and approved as Scientific Council Decisions (SCDs) during Scientific Council meetings.

Regulatory decisions of the Scientific Council are sent for approval to the Minister of Health and are published as Minister Orders in the Official Gazette of Romania, Part I; the other decisions shall be first forwarded to the Ministry of Health, then posted on the NAMDM website and published in the Informative Bulletin of the NAMMD.

In 2010, the Scientific Council was summoned in 5 working sessions; 33 SCDs have been adopted.

Out of the 33 decisions, 3 have been approved through Order of the Minister of Health and published in the Official Gazette of Romania, Part I; 2 are undergoing approval through Order of the Minister of Health, of which 31 shall be posted on the NAMMD website and published in the bilingual Informative Bulletin of the NAMMD.

As in previous years, the activity of the Scientific Council mainly consisted of adopting regulations, guidelines and procedures ensuring quality performance of the NAMMD and of its partners directly interested in the medicinal product for human use. The Scientific Council's regulatory activity is hereby described in detail, under section 3.

It is worth mentioning that the 2010 – 2014 organisational strategy (SCD No. 1/23.03.2010) and communication strategy (SCD No. 9/07.06.2010) of the Agency have been approved during Scientific Council meetings. These strategies, of maximum importance in view of reaching NAMMD's goals, shall be updated yearly.

Moreover, in line with the new legislative framework of Government Decision No. 734/2010, the following actions were deemed mandatory:

- the election of a Scientific Council President of the NAMMD (SCD No. 17/03.09.2010);
- the adoption of a new regulation on the organisation and operation of the Scientific Council of the NAMMD (initially through SCD No. 18/03.09.2010, then repealed through SCD No. 33/13.12.2010);
- the approval according to which all NMA SCDs issued prior to Government Decision No. 734/2010, remain in force until new regulations are issued (SCD No. 19/03.09.2010).

2. **Activity of the Administrative Council (AC) of the NMA/NAMMD**

During the first 6 months of 2010, the activity of the NMA Administrative Council was performed in line with the provisions shown under section 2 "The Organisation and operation of the Administrative Council" of Government Ordinance No. 125/1998 on the set up, organisation and functioning of the

National Medicines Agency, approved as amended through Law No. 594/2002, as amended.

After the issuance of Emergency Government Ordinance No. 72 of June 2010, which led to the set up of the National Agency for Medicines and Medical Devices (NAMMD), the organisation and operation of the unit, as well as the organisation and operation of the Administrative Council, have been regulated through Government Decision No. 734 of 21 July 2010.

The new Administration Council of the NAMMD has been set up based on Order of the Minister of Health No. 1275/2010; it activates in line with the provisions of Art. 10 and 11 of Government Decision No. 734/21.07.2010 on the organisation and operation of the National Agency for Medicines and Medical Devices and with the Agency's Regulation on the Organisation and operation, adopted during the first meeting of the Administrative Council of 31 August 2010.

From the institutional viewpoint, it should be noted that compared to the administrative procedures enforced by Government Ordinance No. 125/1998, the Administrative Council Decisions do no longer require approval of the Minister of Health 15 years after being adopted; the Minister is only informed about such Decisions; as regards the regulatory documents, they are compliant with the enforcement of general jurisdiction – approval of the Minister of Health and publication in the Official Gazette of Romania, Part I.

In 2010, the Administrative Council carried out 6 ordinary meetings (4 of the NMA, 2 of the NAMMD), adopting 42 Administrative Council Decisions (ACDs), 27 of which belong to the NMA and 15 to the NAMMD, 3 of which have been approved through Orders of the Minister of Health. Although 2 regulatory decisions have been initiated (approval of tariffs for new activities, detected after the Order of the Minister of Health No. 716/2009), they could not be finished.

Thematically speaking, ACDs have covered various issues of the current activity, their average being given, as a consequence to actual circumstances, by regulatory documents whose regulatory goal consists of organisational issues – consecutive structure-related amendments within the institution i.e. of the collective labour contract at unit level, approval of the job list and of the organisational structure, and other issues related to the current activity.

We hereby mention a couple of important issues of the current activity:

- approval of the 2009 Activity Report of the NAMMD;
- approval for granting of additional remuneration for particular working conditions;
- update of the Regulations on the organisation and operation of NMA Commissions;
- approval for the invalidation of certain permanent goods such as inventory objects, as well as the depreciation and invalidation of certain material goods.

3. **Regulatory activity**

The activity of the NAMMD in the field of legislative regulation continued at a fast pace in 2010, taking into consideration that the legislation in the field of the medicinal product undergoes a continual process of development/update/change, keeping up with the technical and scientific progress recorded throughout the activity of research/development of medicinal products.

Some regulatory Decisions, approved by the Scientific Council in 2010, have been/are to be approved through Order of the Minister of Health; These SCDs refer to:

- Approval of the Norms on the NMA administrative procedure for the management of variations (SCD No. 4/23.03.2010 approved through Order of the Minister of Health No. 1483/9.12.2010);

- Approval of the amendment of SCD No. 10/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, as regards advanced therapy medicinal products (SCD No. 8/26.04.2010, approved through Order of the Minister of Health No. 615/2010);

- Approval of the Norms on the classification for supply of medicinal products for human use (SCD No. 12/07.06.2010 approved through Order of the Minister of Health No. 1602/2010);

- Completion of the Guideline on Good Wholesale Distribution Practice approved through Order of the Minister of Health No. 1963/2008 (SCD No. 2/23.03.2010, SCD No. 34/13.12.2010, undergoing approval through Order of the Minister of Health).

Other SCDs of 2010 refer to the approval/completion/amendment of certain guidelines, namely:

- Approval of the Guideline on consultations with target patient groups for the package leaflet (SCD No. 6/23.03.2010). The Guideline provides data on consultations with target patient groups by listing and stating the chapters which should be included in the study report.

The purpose of these consultations with target patient groups is to ensure and assess the legibility, accuracy and simple use of the leaflet;

- Amendment of the deadline for enforcement/supplementation of the Guideline on consultations with target patient groups for the package leaflet approved through SCD No. 6/23.03.2010 (SCD No. 16/07.06.2010 and SCD No. 35/13.12.2010). Considering the numerous applications in view of marketing authorisation/renewal applications, as well as MA variations, Art. 4 of this Guideline, approved through SCD No. 6/23.03.2010, was amended through the supplementation with several provisions related to the enforcement term. The dossier concerning NAMMD'S accreditation and inspection criteria for the performers of consultations with target patient groups in view of issuing the package leaflet has been approved through SCD No. 35/13.12. 2010;

- Approval of the Guideline on the expression of strength in the name of centrally authorised medicinal products for human use (SCD No. 11/07.06.2010).

This Guideline is a translation into Romanian and a transposition of the „Recommendations on the expression of strength in the name of centrally authorised medicinal products for human use", issued by the Working Group on Quality Review of Documents (QRD) of the European Medicines Agency (EMA). The Guideline provides recommendation on the accurate expression of strength in the marketing authorisation, under section „Authorisation name", as well as in its Annexes;

- Approval of the Guideline on Romanian specific „Blue box" on the secondary packaging of medicinal products for human use authorised through centralised procedure (SCD No. 13/07.06.2010). The Guideline adapts the basic principles included in the „Guideline on the packaging information of centrally authorised medicinal products for human use" published in the Notice to Applicants (NtA) in February 2008, which describes the manner of enforcement of the updated provisions of Directive 2001/83/EC;

- Approval of the Guideline on the investigation of bioequivalence (SCD No. 15/07.06.2010). The Guideline provides the requirements concerning the projection, performance and assessment of the results of bioequivalence studies for immediate-release pharmaceutical forms with systemic action.

- Approval of the Guideline on evaluation on advertising in medicinal products for human use (SCD No. 20/03.09.2010). This Guideline aims to facilitate the enforcement of the legal norms in force through a detailed explanation of certain issues. Thus, the advertisement of any medicinal product, regardless of its manner of presentation and regardless of the target persons to whom it is addressed (general public/healthcare professionals), may be assessed by NAMMD specialists and promoted by Romanian MAHs by compliance with the legal norms in the field;

- Approval of the Norms on the enforcement of the rules on supply of free medicine samples for human use authorised for marketing in Romania, approved through SCD No 17/27.11.2009 (SCD No. 3/23.03.2010). This SCD provides valuable explanations concerning the regulation of one of the human medicinal product advertising issues;

- Approval of Regulations for advertising of medicinal products of human use (SCD No. 31/01.11.2010). The SCD of November 2010 approved new regulations in the field, which supplement this Guideline. Thus, through the Pharmaceutical Inspection Department, the NAMMD shall be able to take all measures in view of complying with the legal framework in which this advertising activity should be performed;

- Approval of the Guideline on the writing of the marketing authorisation and annexes to marketing authorisation (SCD No. 21/03.09.2010). The Guideline provides recommendation on the writing of the marketing authorisation and annexes to marketing authorisation for medicinal products authorised by the NAMMD through national/decentralised/mutual recognition procedure, replacing former Norms;

- Approval/amendment of the detailed Guideline on the request for authorisation of a clinical trial on a medicinal product for human use, notification of substantial amendments and declaration of the end of the clinical trial (SCD No. 22/03.09.2010 and SCD No. 32/18.11.2010). This Guideline is a translation into Romanian and an adaptation of the European Commission (EC) Communication (2010/C 82/01) on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1).

Through SCD No. 32 of November 2010, two administrative amendments have been approved, related to the notion of „day zero" as being the „day of receipt of the application" and to the „confirmation of payment in accordance with the tariff for assessment of the documentation in view of authorising the performance of clinical trials with medicinal products for human use, in accordance with the provisions of the Order of the minister of Public Health No. 716/11.06.2009 and of the payment Order";

- Approval of the Guideline on the Good Manufacturing Practice for medicinal products for human use (SCD No. 23/3.09.2010). While Order of the Minister of Health No. 905/2006 approves the Principles and guidelines for Good Manufacturing Practice (GMP) in respect of medicinal products for human use and investigational medicinal products for human use, transposing EC Directive 2003/94/EC into Romanian legislation, this Guideline details and explains these GMP principles and Guidelines. The Guideline has two parts: one containing the main requiremenst for medicinal product manufacturing and another containing the main requirements for the active substances used as starting materials;

- Approval of the Guideline on the elaboration of the assessment report on nonclinical documentation (SCD No. 27/01.11.2010). The Guideline is a translation into Romanian and a transposition of the *CHMP Day 80 Critical Assessment Report Non - clinical* EMA Guideline. The Guideline may be used in the assessment of the documentation shown in CTD (Common Technical Document) and eCTD formats and contains recommendations concerning the set up of the assessment report of nonclinical documentation.

Moreover, SCDs related to the regulations/norms for enforcement of certain rules set up for various activities of the NAMMD have been approved, such as:

- The approval of the regulations concerning the authorisation by the NAMMD of clinical trials/notification to the NAMMD of non-interventional studies on medicinal products for human use in Romania (SCD No. 29/13.12.2010).

- The approval of the manner of resolution of applications for marketing authorisation/marketing authorisation renewal for medicinal products for human use submitted to the NMA prior to 2007 (SCD No. 24/03.09.2010).

4. **Activity of the NMA/NAMMD commissions**

4.1. **Marketing authorisation commissions**

Between 01.01.2010 and 23.02.2010, a Single Marketing Authorisation Commission (SMAC) functioned within the NMA; it carried out its activity in accordance with the Decision of the NMA President No. 654/2009 and with its own regulation on organisation and operation, approved through NMA Administrative Council Decision. The set up of 3 commissions for marketing authorisation/marketing authorisation renewal was approved through ACD No. 2/23.02.2010, namely: CAPP – National Procedure, CAPP – European Procedures, CAPP - Renewal, whose structure has been established through NMA President Decision No. 165/25.03.2010.

Assessment reports are discussed by the Commission, in order to issue an opinion concerning the marketing authorisation, as well as other aspects related to the marketing authorisation of medicinal products for human use.

In 2010, the Marketing Authorisation Commission conducted 47 working sessions to discuss 1172 evaluation reports for medicinal products for human use and to formulate an opinion regarding their marketing authorisations.

Therefore, out of the 1172 medicinal products which have been reviewed by the commission:

- 1118 medicinal products have been accepted for grant of marketing authorisation, and
- the decision for 54 has been postponed.

On seeing the necessity to ensure the ongoing character of the Agency's specific professional activity, after the issuance of Emergency Government Ordinance No. 72/2010 and Government Decision No. 734/2010 on the organisation and operation of the NAMMD through Decision of the NAMMD Interim President No. 33/03.08.2010, it has been convened that the Marketing Authorisation/Marketing Authorisation Renewal Commissions set up through ACD No. 2/2010 should carry on with its activity, maintaining the same structure and operating procedures.

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**

After the set up of the NAMMD, through Interim President Decision No. 33/03.08.2010, the commission was allowed to carry on with its activity in the structure previously updated through Decision No. 652/2009 of the NMA President and in accordance with NMA's Regulation on the organisation and operation approved through NMA's Administrative Council Decision. The Commission receives inspection reports issued by the Agency's inspectors, concerning the manner in which the inspected units comply with Good

Manufacturing Practice, Good Distribution Practice, Good Laboratory Practice, Good Analytical Laboratory Practice, Good Clinical Practice rules and/or with other issues concerning the activity of the Pharmaceutical Inspection Department.

The Commission mediates in case an inspector's decision is disputed by the inspected unit, the decision belonging to the majority.

In 2010, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 14 working sessions for examination of 306 inspection reports (285 compliant and 21 non-compliant), of which:

- 70 inspection reports on compliance with Good Manufacturing Practice rules, of which 6 have observed the non-compliance with GMP rules;
- 207 inspection reports on compliance with Good Distribution Practice rules, of which 15 have observed the non-compliance with GDP rules;
- 18 inspection reports on compliance with Good Clinical Practice rules;
- 2 inspection reports on compliance with Good Laboratory Practice rules;
- 2 inspection reports on compliance with Good Analytical Laboratory Practice rules;
- 7 pharmacovigilance inspection reports.

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

The commission functions based on Decision No. 651/2009 of the NMA President and according to its own organisational and operation regulation, as approved by Administration Council decision.

The goal of the Commission is to check compliance with the Ethic and deontology code by NMA staff with inspection tasks, as approved through Order of the Minister of Health No. 160/2004.

In 2010, no violations of the Ethic and deontology code by NMA/NAMMD staff with inspection tasks were notified.

4.4 **Commission for management of crisis situations caused by problems in medicinal product quality, safety and/or efficacy**

The Commission for management of crisis situations functions based on the NAMMD President Decision and on its own regulations for organisation and function, as approved through decision of the NAMMD Administration Council.

In 2010, the membership of the commission has been updated through NAMMD President Decision No. 55/2010.

In 2010, the Commission convened in 9 working sessions to discuss issues related to:

- the assessment of the development stage of the clinical trial performed in view of administering the Cantgrip pandemic vaccine to children;
- the assessment of the state created by numerous critical and major findings

signalled by the inspections carried out by the NMA at the Cantacuzino Institute in view of granting a manufacturing authorisation for Cantgrip and BCG vaccines;

- the assessment of the Corrective Measures Plan proposed by the Cantacuzino Institute according to the NMA inspection report on 08.02.2010 in view of proposing rapid solutions to restart the manufacturing of the Cantgrip vaccine, according to conditions approved by the NMA;

- the assessment of the manner of enforcing corrective measures for critical findings detected by NMA inspection in the BCG vaccine manufacturing flow in view of issuing a new manufacturing authorisation, following the expiry of the manufacturing authorisation.

Set up and operation of this commission proved their efficiency in rapid, consistent and unified resolution of crisis situations through involvement of NMA specialised structures, having immediate and positive effect for the safety of medicinal products in therapeutic circulation in Romania.

5. **Marketing authorisation and related activities**

In 2010, activities related to the documentation submitted to the NAMMD in view of evaluation, marketing authorisation, renewal of marketing authorisation, post marketing authorisation surveillance were particularly complex and were conducted in line with National and European procedures (mutual recognition/decentralised/repeat-use mutual recognition procedure).

Throughout 2010, the National Procedure and European Procedures Departments were set up after the reorganisation of two departments, namely the Authorisation and Post-authorisation Departments; this reorganisation has been approved through Order of the Minister of Health No. 1275/30.09.2010.

The organisational structure of the National Procedure Department is as follows:

- The National procedure administration service
    - The administrative verification and product index bureau
    - The parallel import bureau
- The national procedure variation service
- The national procedure evaluation service
    - The medicinal products and active substances quality bureau
    - The efficacy bureau
    - The non-clinical safety bureau
    - The medicinal product information bureau
- The clinical studies service.

The organisational structure of the European Procedures Department is as follows:

- The European procedure administration service
- The validation bureau

- The centralised procedure administration bureau
- The European procedure evaluation service
- The medicinal products and active substances quality bureau
- The non-clinical safety bureau
- The efficacy bureau
- The medicinal product information bureau
- The European procedure variations service
- The pharmacovigilance and risk management service.

5.1. **Marketing authorisation through national and European procedures**

If the number of MAs granted through European Procedures (EPs) [(decentralised procedure (DCP)], mutual recognition procedure (MRP) and repeat use procedure] increased:

MAs through EPs: 2009 - 568 compared to 2010 - 623,

the number of MAs through national procedure (NP) was smaller in 2010 compared to 2009, namely:

MAs through NP: 2009 - 359 compared to 2010 - 190

is perfectly normal, given the fact that Romania is a EU Member State with a pharmaceutical market undergoing harmonisation with European requirements.

However, as a whole, the number of MAs granted by the Agency in 2010 was smaller than in 2009. Thus: MAs through NP and EP: 2009 - 927 compared to 2010 – 813.

The reason for this is not related to a smaller number of requests, but to the Agency's recent lack of staff.

The number of Decisions for MA discontinuation, at request of MAHs, due to commercial reasons, has increased in 2010, namely:

Discontinued MAs: 2009 - 134 compared to 2010 – 202.

Moreover, in 2010, 3 years after Romania's EU accession, the "*sunset clause"* was enforced for 177 MAs for medicinal products effectively marketed during 2007 - 2010.

5.2. Variation assessment activity of the terms of the Marketing Authorisation (MA)

5.2.1. In 2010, a number of 5211 applications for variation of MA terms were submitted for medicinal products authorised through national procedure or undergoing MA renewal procedure, of which 3296 applications for type I variations, 638 applications for type II variations, 151 applications for MA transfer, 261 applications for modification of design and package labelling and 865 applications for clinical variations.

The NMA assessed and approved 2922 applications for variations for medicinal products (received in 2007, 2008, 2009 and 2010) authorised through national procedure or undergoing MA renewal procedures, of which:

- 1666 type I variations;
- 357 type II variations;
- 94 applications for MA transfer;
- 116 applications for modification of the design and package labelling;
- 689 clinical variations.

5.2.2. As far as the post-authorisation assessment activity for variations to the terms of marketing authorisation (MA) through European procedures (except for clinical variations) is concerned, the NMA received the following in 2010:

- 1743 applications for type IA variations and 1936 applications for type IB variations;
- 575 applications for type II variations;
- 142 applications for MA transfer;
- 39 notifications in accordance with Art. 61 (3) of Directive 2001/83/EC.

In 2010, 2258 variations for medicinal products authorised through decentralised/mutual recognition/repeat-use mutual recognition procedure have been approved, namely:

- 965 type IA variations and 890 type IB variations;
- 403 type II variations;
- 102 applications for MA transfer;
- 9 notifications in accordance with Art. 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 2010, the NMA/NAMMD received 266 applications for clinical trial approval, as follows:

- 10 applications for phase I clinical trial approval;
- 61 applications for phase II clinical trial approval;
- 173 applications for phase III clinical trial approval;
- 22 applications for phase IV clinical trial approval;
- 44 applications for observational clinical trials;
- 61 applications for bioequivalence studies.

Until the end of 2010, 215 clinical studies were assessed and 201 authorisations were issued for:

- 7 phase I clinical trials;
- 60 phase II clinical trials;
- 118 phase III clinical trials;
- 16 phase IV clinical trials.

The following have been assessed and approved:

- 44 observational clinical trials.

The following have been approved:

- 1267 amendments to submitted studies, of which
    - 158 amendments for new clinical investigation sites.

The following have been assessed:

- 61 bioequivalence studies, of which 43 were authorised and 2 discontinued; protocol amendments were sent for 16 such studies.

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

In 2010, the National Medicines Agency assessed for approval **474** advertising materials for OTC medicinal products, addressing the general public.

7 notifications on denial of advertising approval were issued.

48 advertising materials to be used in educational programmes were assessed and approved.

The content of **207** advertising materials addressing persons qualified for prescription or supply of medicinal products was assessed and approved.

Monitoring and control of advertising for medicinal products for human use found further concrete form in:

- **37** responses to advertising related complaints.

In 2010, special emphasis has been placed upon the regulatory, surveillance and control activities in view of advertising of medicinal products for human use. Thus, a special heading has been created on the agency's website, namely „Advertising", which contains important announcements for stakeholders, related to this topic, as well as penalties addressing the MAH for non-compliance with advertising regulations (e.g. broadcasting unapproved advertising materials, using unapproved advertising channels, broadcasting advertising materials which are different from the material approved by the Agency etc).

5.5. **Pharmacovigilance**

The NAMMD manages the safety of medicinal products currently authorised in Romania via the Pharmacovigilance and risk management service, which is part of the Agency's European Procedures Department, whose activity is entirely compliant with Law No. 95/2006 and with specific European Guidelines. Pharmacovigilance represents an extremely dynamic and interactive field of activity, which was developed throughout the years as a must for patient safety. Perhaps the most complex definition of pharmacovigilance is as seen in a Q&A public document of the European Commission (December 2010), stating that pharmacovigilance is the science which detects, assesses and prevents the occurrence of adverse reactions in medicinal products and all related activities.

The pharmacovigilance activity already has a substantial history in Romania.

In 1973, the National Pharmacovigilance Network was founded in Romania. This network consists of Reference Centres organised at the level of University hospitals and of Pharmacovigilance centres organised at other Romanian hospitals. The coordination of the National Pharmacovigilance Network was attributed to the Institute for the State Control of Medicinal Products and Pharmaceutical Research (ICSMCF), subsequently transformed into the National Medicines Agency (NMA).

In 1976, Romania became a member of the WHO (World Health Organisation) Medicinal Product Monitoring Centre in Genoa, transformed in 1978 into the WHO Collaborative Centre for International Drug Monitoring in Uppsala, Sweden. The National Pharmacovigilance Centre was set up within the ICSMCF; its duty was to ensure a permanent relationship between Romania and the WHO centre for the Adverse Drug Reaction Monitoring Centre in Uppsala in view of validating the spontaneous reports of adverse reactions collected through the Pharmacovigilance Centre and preliminarily assessed by Reference Centres in university hospitals. In the 70s, the National Pharmacovigilance Centre published the "Pharmacovigilance" review, which provided details related to various issues of the pharmacovigilance activity and was distributed free of charge to healthcare professionals, physicians and pharmacists. Unfortunately, after 1990, the Romanian pharmacovigilance activity started to decline, thus leading to the discontinuation of the activity of the National Pharmacovigilance Network, discontinuation of publishing of the „Farmacovigilenţa" magazine and the drastic diminution of the number of spontaneous reports registered at the National Pharmacovigilance Centre.

After 1999, following the transformation of the ICSMCF into the NMA, the pharmacovigilance activity was seriously reconsidered according to the principles applied throughout the European Union. The starting signal consisted of the participation of NMA representatives in various forms of convenient training, as well as of the transposition of certain European regulations and Guidelines on pharmacovigilance into NMA Scientific Council Decisions (SCDs).

After Romania's EU accession on 1 January 2007, Romania's pharmacovigilance activity was firmly relaunched, according to European laws, which have been transposed and enforced as NMA Scientific Council Decision. The pharmacovigilance activity has been considerably enhanced, from the assessment and transmission of adverse reactions through the EudraVigilance system (the European network for pharmacovigilance data-processing and management), to the assessment of Periodic Safety Update Reports (PSURs), from the Pharmacovigilance systems of Holding companies, to the assessment of Risk Management Plans, to the harmonisation of the Summary of Product Characteristics (SmPCs) by enforcement of the Decisions of the Committee for

Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in the sections referring to product safety. Moreover, the pharmacovigilance activity ensured (and still does) direct healthcare professional communications referring to special warnings for product safety, as well as the translation and posting of press releases and Q&A documents (which actually represent notifications from the monthly meetings of the CHMP) on the NAMMD website. The Romanian pharmacovigilance field also answers to non-urgent information and to information from the European and International rapid alert system.

In view of encouraging adverse reaction reporting, all types of available data related to medicinal product safety have been posted on the NMA/NAMMD website (from posting the regulations on the pharmacovigilance activity and the reporting records, to other types of important information for stakeholders).

By means of symposia, national conferences and congresses, physicians receive a call for reporting the spontaneous adverse reactions (ARs) suspected.

A useful incentive enforced by the Agency for AR reporting, in cooperation with the Romanian College of Physicians was and still is the granting of Continuing Medical Education (CME) Credits to rapporteurs (10 CME credits for each adverse reaction reported). Every adverse reaction validated by the NAMMD is confirmed through a thank-you note addressed to the rapporteur and is accompanied by an Adverse Reaction Reporting Form; the Romanian College of Physicians is informed on a quarterly basis about the number of adverse reactions reported by territory physicians, so as to release the CME credits.

These incentives led to an increase in the number of reports performed during the previous years in Romania. If, for example, 280 spontaneous reports were recorded in 2004, 525 were reported in 2009 and 938 (serious and non-serious adverse reactions) in 2010. The numbers are optimistic, since they reveal the increasing importance of the safety in the administration of medicinal products manifested by healthcare professionals.

In 2010, pharmacovigilance activities materialised in the following:

a) Management of safety data from spontaneous reporting;

- 938 adverse reactions (AR) reporting sheets from Romania;
- 1071 validations/confirmations of adverse reaction reports imposed by the monitoring of the single European electronic database of adverse reactions, EUDRAVIGILANCE, for medicinal products used in Romania and 805 transmissions/retransmissions of adverse reactions;
- 63 electronic transmissions of adverse reactions to the WHO database (the Uppsala Monitoring Centre) via the VigiFlow electronic channel;
- 4 notifications of the College of Physicians concerning spontaneous adverse reactions reported in Romania and validated by the NAMMD – the National Pharmacovigilance Centre.
- 333 confirmation points of receipt of Spontaneous reporting records of adverse reactions from network physicians;

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

- 266 answers to MAH applications concerning adverse reactions transmitted to the NAMMD related to medicinal products authorised in Romania; 138 adverse reaction reports were handled;

- 141 response points on MAH requests concerning pharmacovigilance-related aspects.

b) Collection, validation and archiving of 2201 Periodic Safety Updated Reports (PSUR) related to safety of medicinal products;

- 1419 Periodic Safety Updated Reports (PSUR) related to the safety of imported medicinal products;

- 782 Periodic Safety Updated Reports (PSUR) related to the safety of Romanian medicinal products.

78 PSUR assessment reports have been issued for medicinal products undergoing a MA renewal process through national procedure.

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

- handling of 42 EMA press releases of 16 EMA questions and answers documents, 24 Lines to take proposed by the EMA for request of information, 35 Direct Healthcare Professional Communications related to safety concerns raised by medicinal products, handling of 70 information points from the MAHs on safety issues of medicinal products, 24 translations for SmPC harmonisation to be posted on the NAMMD website.

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

- 9 NUI replies to applications by certain EU authorities;

- 2 actions in collaboration with the Pharmaceutical Inspection Department with regards to rapid alerts;

- 1 reply to complaints from patients concerning safety issues of medicinal products.

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

- 815 assessment reports of the summary of the pharmacovigilance system of the marketing authorisation applicant through decentralised/mutual recognition/repeat-use mutual recognition procedure (Romania as Concerned Member State);

- 211 assessment reports of the summary of the pharmacovigilance system of the marketing authorisation applicant through national procedure.

The new procedure, namely 2010/84/EU of the European Parliament and of the Council of 15 December 2010 on the amendment, as far as pharmacovigilance is concerned, of Directive 2001/83/EC on the community code relating to medicinal products for human use (which shall be transposed into the Romanian legislation, amending the Pharmacovigilance chapter of Law No.

95/2006) shall also make the patients accountable about the reporting of adverse reactions to medicinal products. Thus, by physician-patient effort, it is expected to detect as many adverse reactions as possible in view of enriching product-related information. Certainly, the final outcome shall be the attainment of the highest possible level of safety in the product's administration within the EU.

5.6. **Other activities**

- The database represented by the index of medicinal products for human use was handled by introducing new medicinal products authorised through national/European/centralised procedure, enforcement of MA changes for medicinal products which are already authorised, introduction of the approved variations to issued MAs, to keep track of medicinal products undergoing MA renewal and of the MA withdrawal/discontinuation decisions.

At Ministry of Health request, the statutes of innovative, original, generic, biosimilar and homeopathic were established for the medicinal products included in the successive versions of Canamed in 2010. At the end of the year, there were 8168 trade names corresponding to 1252 International Non-proprietary Names (INNs) in the NMA product index.

- Activities related to „parallel import"
  - the release of parallel import authorisations (PIAs) (24 PIAs)
  - request of information from other authorities in EU Member States, in view of PIS release (55)
  - variations to PIAs (17)
- Activities related to „parallel export"
  - reply to the request of information submitted by other competent authorities in view of releasing PIAs for the concerned Member States (298).

The activities derived from NMA status as a competent authority in an EU Member State continued, namely:

- Management of responses received in application of Art. 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");

- Verification of the **8168 medicinal products** included in the product index at the end of 2010, of which **2100** authorised through centralised procedure, their handling concerning enforcement of the "*sunset clause*" being the responsibility of the European Medicines Agency (EMA); in 2010, 3 years following the EU accession, the "*sunset clause"* has been enforced for 177 MAs for medicinal products which have not been actually placed on the market between 2007 and 2010.

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

- Management of the European Commission (EC) decisions related to referrals, issuing of the points to the involved MAHs, in view of requiring the transmission of variation applications for the enforcement 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 2010, the Pharmaceutical Inspection Department (PID) continued to perform the activities mentioned in specific legislation (Law No. 95/2006, Title XVII – The medicinal product and the secondary legislation pertaining to it), in accordance with the department's *Standard Operating Procedures (SOPs)*, endeavouring to solve the tasks within the deadline stipulated by law.

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

- 62 Good Manufacturing Practice (GMP) certificates (for Romanian and foreign manufacturers);
- 54 manufacturing authorisations, annexes included;
- 65 import authorisations, annexes included;
- 7 Good Laboratory Practice **(**GLP) certificates;
- 29 qualified person certificates;
- 2 authorisations for independent control units;
- 163 dossiers for the inspected units, and for the units which have requested updates of the annexes to manufacturing/import authorisations have been issued and handled;
- 134 applications for waiver from legal provisions concerning the packaging/labelling of medicinal products have been solved;
- The databases referring to inspection encoding, the list of the authorised/certified manufacturing units, authorised importers, medicinal products for which the export declaration has been approved, and qualified persons have been administered.

Inspection activities in the fields of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Analytical Laboratory Practice (GALP), Good Clinical Practice (GCP), and Good Pharmacovigilance in 2010 consisted of:

- 33 GMP inspections in Romania, in view of manufacturing authorisation;
- 25 inspections in view of authorisation at the sites of medicinal product importers;

- 21 certification inspections of GMP conformity of pharmaceutical companies from third countries;

- 2 unexpected inspections at the sites of Romanian manufacturers of medicinal products in view of attesting GMP compliance;

- 5 GLP inspections to laboratories performing bioequivalence studies;

- 4 GALP inspection at independent quality control units;

- 31 inspections in view of assessing compliance with GCP rules;

- 15 pharmacovigilance inspections at the MAH, of which 9 inspections of Romanian MAHs and of Romanian representatives of the MAHs, according to the yearly inspection plan of the Pharmaceutical Inspection Department and 6 unexpected inspections at the MAH.

In September 2010, a team of GCP inspectors has been assigned to participate in the GCP inspection through centralised procedure of two centres, one of whom was the head of the GCP inspection team, responsible with issuing the inspection reports, the inspection plans, the correspondence in view of inspection (correspondence with EMA, with the inspectors from Member States who participate in the inspection).

In the context of Good Distribution Practice (GDP) inspections conducted in 2010:

- 112 inspections in view of authorisation have been conducted;

- 70 wholesale distribution authorisations have been released;

- 40 unexpected inspections following which:

- 17 authorisations have been suspended;

- 3 authorisations issued by the Ministry of Health have been withdrawn, in accordance with previous legal regulations, following the discovery of critical findings during the inspections in view of authorisation;

- the dossier for 362 applications for approval of export declarations was checked, leading to the approval of export declarations for 1129 medicinal products manufactured in Romania.

As far as the certification of qualified persons, the dossier containing 45 applications for issuance of the Certificate attesting the Qualified Person status was checked and assessed; 29 such certificates were released.

The surveillance activity of medicinal product quality and handling of rapid alerts consisted of:

a) Carrying out the recall scheme on monitoring the quality of medicinal products:

- From the **29** products proposed, **23** were sampled, and 6 were not found in the distribution network;

The results issued from laboratory analysis have been the following:

- 22 samples have been declared compliant;

- 1 product is undergoing analysis.

In addition to the recall scheme, the following samples were provided in 2010:

- 6 medicinal products sampled on request of the Quality Control Department, in view of participating in market surveillance studies proposed by the OMCL network (Official Medicines Control Laboratories); all samples of medicinal products are currently being tested;

- 10 medicinal products have been sampled in view of solving a finding concerning the medicinal product quality, of which **5** have been declared noncompliant with quality standards and have been withdrawn from the territory;

- 4 medicinal products sampled from distribution units within the programme coordinated by EMA/EDQM in view of surveilling centrally authorised medicinal products; the testing of these products has been performed by laboratories belonging to other EU competent authorities, and the results were found compliant.

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

- 373 thematic inspections were carried out in retail and wholesale distribution units.

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

- 234 inspections were carried out in hospitals across the country, in view of abolishing the use of unauthorised oxygen (liquid oxygen is provided by GMP certified producers, while the compressed oxygen for 17 hospitals (8%) still comes from unauthorised manufacturers. This stuation has been communicated to the Ministry of Heath).

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

- 14 common actions with specialised local bodies, carried out by territorial inspectors (9 Cluj, 3 Târgu Mureş, 2 Deva).

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

- from 34 resolved complaints, 18 have resulted in classification and have resulted in withdrawal from the territory of the respective medicinal products.

f) Withdrawal from the market of medicinal products showing quality noncompliances: in 2010, the NMA/NAMMD requested the withdrawal of **54** medicinal products, of which:

- 12 medicinal products were identified to have intrinsic quality nonconformities, thus have been proposed for destruction (3 following complaints, 5 due to rapid alert, 4 voluntary withdrawals performed by the manufacturers);

- 34 medicinal products had nonconformities with the inscriptions on the packaging/leaflet which has been proposed for remedy of the respective nonconformity/destruction;

- 8 medicinal products withdrawn following EMA recommendation due to the recall of MAs for centrally authorised products.

g) Rapid alert system:

- in 2010, 79 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

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

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

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

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

j) Coordination of the activities of the Regional Inspection Units (RIU) related to the surveillance of the quality of medicinal products.

7. **Quality control of medicinal products for human use**

Quality control of medicinal products for human use is part of the NMA general policy and aims at objectifying its mission of ensuring medicinal product quality, safety and efficacy.

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

Both departments' activities, the main and the support activities, are accomplished by a process-based approach, in conformity with the requirements of standards SR EN ISO 9001/2001 and SR EN ISO 17025/2005.

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

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

Core activities in 2010 dealt with:

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

In 2010, 308 medicinal products were analysed, of which:

- 54 obtained through chemical synthesis; 205 laboratory analyses have been conducted to investigate their quality: cromatographic (HPLC - High Performance Liquid Chromatography and TLC – Thin Layer Cromatography), spectrophotometric (UV, IR) and potentiometric analyses, physico-chemical identifications, dissolution testing and others;

- 258 biological medicinal products (vaccines, sera), the majority of which (254) manufactured by the "Cantacuzino" Institute; 4 imported vaccines.

The analysis of the 258 medicines required 625 physico-chemical, pharmacological, immunological and microbiological determinations. To this, 900 internal analyses of environmental checks, calibration of equipment, testing of the suitability of the systems and equipment used were added.

Out of the full number of medicinal products analysed, 7 were non-compliant from the quality viewpoint; several non-compliances have been reported, e.g. unpleasant, persistent odour, batch and manufacturing date counterfeiting, counterfeit product devoid of active substance.

a) Evaluation of chemical documentation (DSSA, clinical studies, finished products).

In 2010, the DCCM was assessed for 921 medicinal products in course of authorisation.

As regards the assessment of the clinical trial dossier, 16 phase III clinical trial dossiers have been assessed, 1 study undergoing VHP procedure.

a) External cooperations concerning medicinal product quality.

As in previous years, the DCCM continued in 2010 to collaborate with European institutions dedicated to medicines quality control, by taking part in studies initiated and coordinated by The European Directorate for the Quality of Medicines and HealthCare (EDQM):

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

** 1 study on the quality of medicinal products authorised through Mutual Recognition Procedure (MRP).

*** 1 MSS (Market Surveillance Study) for the surveillance of the European market, organised by the EDQM. Since 2010, the MSS consisted of the classification of the dissolution profile, batching, assessment of the profile of chemically-related substances (impurities) for two Romanian products, study conducted as a comparison with a similar medicinal product on the European market.

7.2. The activity of the Biological Product Control Department (BPCD) in 2010 was marked and influenced by the involvement in a PTS (Proficiency

Testing Scheme) study conducted at the request and under the coordination of EDQM for which the laboratory received the mark "satisfactory". The result has once again confirmed the competitive level of laboratory testing within the BPCD.

The activity of the BPCD in 2010 was influenced by the department's relocation in the NAMMD headquarters; the department was relocated on the 5th floor during May-June 2010. The relocation involved complex activities for the transportation of documents and specialised transport of the laboratory and furniture equipment, as well as the reworking of the equipment required in view of restarting laboratory activity.

Activity of the department covers the following aspects:

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

a) Laboratory control:

- 196 sets of product samples have been analysed corresponding to a number of 750 laboratory tests;
- 202 test reports have been issued, including:
- 199 bulletins for finished products;
- 3 bulletins for intermediate and bulk products.

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

For the purposes of official batch release procedure, product sampling is necessary to carry out product testing in the laboratory.

Finished, intermediate and bulk products were sampled during 10 sampling sessions.

For the biological products tested, 326 batch release certificates were issued and no bulletin of non-compliance.

139 commercial intentions were recorded related to products for which the official batch release was performed in the EU.

c) Control of biological products for human use contested or included in the recall scheme, coming from the PID.

As regards complaint solving, a vaccine sample which has received a complaint related to the physical aspect has been tested, at the request of the PID. Following the check-up, it was concluded that the sample has been compliant with the specifications.

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

Throughout 2010, via the Cell culture laboratory - measurements and specific microbiology, the BPCD participated in one Proficiency Testing Scheme (PTS) study, performed at the initiative and coordinated by EDQM (PTS098: *MEASLES VACCINE POTENCY ASSAY*); the laboratory was awarded the „*Satisfactory"* status. 16 European laboratories which have obtained a similar

outcome au have been involved in the study, while two laboratories were awarded „*Unsatisfactory*”.

B. As regards the documentation submitted through national, mutual recognition and decentralised procedures, in view of marketing authorisation/marketing authorisation renewal and variation approval:

- 33 products have been assessed through national procedure and 59 reports have been issued;
- 233 MA variations have been assessed through national procedure;
- 28 products have been assessed through mutual recognition procedure; 36 reports have been issued;
- 60 variations have been assessed through the mutual recognition/decentralised procedure; 68 reports have been issued.

Moreover, in 2010, the procedure has been initiated and the required steps have been taken for participation, as a reporting state, in the assessment of a biological product for the enforcement of provisions of Article 46 of Paediatric Regulation No. 1901/2006 (a *worksharing* procedure).

C. Amendment of the terms of the MAs for biological products for human use, following the approval or Type I/II variations or due to editorial revisions:

- 26 marketing authorisations have been amended, starting with September 2010.

D. Assessment of the documentation submitted in view of approval of the application for clinical trial performance (assessment of the non-clinical and quality documentation):

- The quality and pre-clinical documentation submitted for approval of the application for performance of clinical trials for biological products for human use has been assessed: 3 reports (2 assessment reports of the quality documentation and one assessment report for pre-clinical safety).

E. Post-authorisation surveillance of biological products for human use:

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

8. **Ensuring communication and transparency**

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

8.1. **External communication**

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

On its website, the NAMMD publishes bilingual Informative Bulletins (IBs), which are a reflection of intense regulatory activity in the area of medicines in line with European legislation and other priority activities of the Agency. The content of the NMA/NAMMD Informative Bulletin includes:

- Laws, ordinances, Government decisions in the field of medicinal products for human use or other areas of NMA/NAMMD interest;
- Orders of the Minister of Health for approval of NMA/NAMMD Scientific Council decisions and Orders of the Minister of Health in other areas of NMA/NAMMD interest;
- Decisions of the NMA/NAMMD Scientific Council;
- Decisions of the NMA/NAMMD Administrative Council;
- Quarterly list of marketing authorisation/marketing authorisation renewal applications submitted to the NMA;
- Quarterly List of EMA newly centrally authorised medicinal products, for which the European Commission issued the decision on translation into Romanian of medicinal product information;
- Quarterly list of medicinal products authorised for marketing by the NMA/NAMMD;
- A quarterly list of medicinal product batches recalled by the NMA/NAMMD for quality defects.

The NAMMD develops the product index of medicinal products for human use, including all medicines authorised for circulation in the pharmaceutical market in Romania, with data on trade name, International Non-proprietary Name, active substance, marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, manner of release etc. and publishes it on its website. In 2010, implementation began, for each medicine, of electronic versions of the Summary of Product Characteristics (SmPC), leaflet and information on labelling and inscription.

The NAMMD develops and keeps updated information which can be found on the Agency's bilingual website. Hence, the NMA website has published and continually updated the following information and documents:

- Press releases relating to safety of medicinal products;
- Information points for physicians/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 medicinal products authorised for circulation within Romania, released on medical prescription;

- List of over-the-counter (OTC) products authorised for circulation in Romania;

- List of valid orphan medicinal products;

- List of NMA/NAMMD employees assigned as full members/replacing members in the Administrative Council, scientific committees and working groups of the European Medicines Agency (EMA);

- List of EMA experts appointed by the NMA/NAMMD.

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

- <CP> (centralised procedure)

- <MRP and DCP> (mutual recognition procedure and decentralised procedure) which contain the contact persons and several useful information for the authorisation of these procedures, namely: regulatory documents, required forms, bank accounts, announcements and warnings addressed by the NMA/NAMMD to the MAHs involved in European Procedures.

This information has been improved and updated, in both Romanian and English, with updated information classified by themes.

A new section related to the national procedure has been added to the new NAMMD website, which has been under construction in 2010; just like the other two sections for the centralised/mutual recognition/decentralised procedure, it provides information about contact persons, special warnings, SmPC, leaflets and labelling. Moreover, section „National Procedure" of the new NAMMD website provides the „List of parallel import authorisations" issued by the NMA/NAMMD since 2009.

The external users of the NMA/NAMMD found the following headings particularly interesting:

- medicinal product legislation;

- useful information on European procedures;

- Product index of medicinal products for human use authorised for marketing in Romania;

- forms and useful information.

The enhanced interest of stakeholders in the information published on the NMA/NAMMD website is reflected in the large number of website visitors, which keeps on growing, namely 271491 visitors in 2010 (an average of 22625 visitors per month).

The Agency continued to ensure the transparency of the activity performed in accordance with the provisions of Law No. 95/2006, Title XVII – The medicinal product, Art. 845 (2) and Art. 726 (4) on transparency in the activity of competent authorities in the EU medicinal product field, by:

- periodically updating the regulations on the organisation and operation of NAMMD commissions, approving them in the Administrative Council and posting them on the website;

- setting up, upon request, the versions available to the public of the agendas and press releases of NAMMD Commissions;

- setting up, upon request, the versions of assessment reports of the authorisation dossier available to the public in view of marketing human medicinal products through national procedure.

In 2010, the NMA/NAMMD continued to inform stakeholders about its work through means other than its own Informative Bulletins. Thus, the 2009 NMA Activity report continued to be posted online as a bilingual brochure; it received the appreciation of NMA partners.

Moreover, in 2010, several articles have been published in Romanian professional magazines („Farmacist.ro", „Medical Business", „Viaţa Medicală, „Pharma Business") referring to various issues concerning the Agency's activity.

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

8.2. **Internal communication**

In 2010, the Agency continued to supplement and update the information (which can be found by NMA staff on the Intranet), aiming to receive the best and fastest information in the professional field and/or at organisation level.

NAMMD staff has access to the following information that can be found on the "Intranet":

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

9. **Quality management activity**

In 2010, taking into consideration the *quality and quality objectives policy*, established by the top management, as well as the identified and enforced processes, the size and structure of the NAMMD and *SR EN ISO 9001* and *9004* principles in force, the Quality Assurance Bureau, together with the other organisational structures, has taken part in the enforcement, development and improvement of the QMS in the context of the organisation (NAMMD).

Other activities have been performed, namely:

- The internal quality audit process was carried out in accordance with the *Internal Quality Audit* Program in 2010, approved by the President of the organisation.

The findings and conclusions of internal quality audits, whose objectives consisted of ensuring compliance with the *Standard Operating Procedures (PSOs) applying to the audited processes*, have been mentioned in *internal quality audit reports*, which have been submitted to the audited organisational structures and top management in view of improving the audited processes/products (services). *The internal quality audit reports* have been accompanied by *improvement action plans* issued by audited departments and by reports *on the level of enforcement of improvement actions* proposed due to previously conducted internal quality audits.

- The amendment (review) process of general *PSOs* (research, set up, drafting, approval, dissemination) was carried out through the amendment (review) of 14 *PSOs*, in accordance with the requirements of *international standards* in force and with the amended circumstances (*Government Ordinance No. 734/ 21.07.2010* and *Order of the Minister of Health No. 1275/ 30.09.2010).*
- The set up of the *"Statistical study on the release process for marketing authorisations (MAs) by the National Medicines Agency, January – February 2010"*
- The study has been issued in conjunction with the Information Logistics and Electronic Management of Data Department.
- The set up of the *documents* requested by the Ministry of Health – Secretary-general Cabinet.
- New update of the *declarations of interest, privacy commitments/ individual and general job description.*
- The set up and update of Quality Assurance Bureau *databases* (in electronic format).
- Counselling in the field of quality.

The Quality Assurance Bureau was compliant with the *2010 Activity Program*, approved by the organisation's President.

In accordance with *Order No. 43/16.04.2010*, issued by the head of the Control Department of the Prime Minister, in the context of the process for the assessment of legal provisions concerning the activity performed by the NAMMD, the activity of

the Quality Assurance Bureau (QAB) has also been assessed. *The control report* issued following this assessment has not detected any non-compliance of processes/activities belonging to the QAB.

- Participation of NAMMD experts in specialised quality management training.

In 2010, quality assurance staff from each department participated in the training course „Elements of strategic management" supported by the qualified institution QUASARO.

10. **Medical devices**

- **Control activity through periodic update of medical devices and attempts in view of certification**

In 2010, after merging with the Technical Office for Medical Devices, the NAMMD has become the single institution abilitated to assess the performances and safety of medical devices in use. The new control activity, namely the periodic check-up of medical devices, was, thus, carried out for all installed and commissioned medical devices, characterised by a high risk degree, at the sites of all medical device user, both in the private and public field.

The 2010 Technical Laboratory Department staff activity was the following:

Number of applications in view of registration: 1882 (1554 at the Technical Office for Medical Devices, 328 at NAMMD)
Number of issued periodic check-up bulletins: 3325
Number of issued notices for use: 36
Number of issued notifications following periodic check-up: 27
Number of assessed medical devices: 7741
Umber of assessed mobile intervention units: 1250
Number of issued reports on negative laboratory tests (repealed medical devices): 56 (of which 26 repealed by the nuclear unit).
In terms of laboratory tests:
Laboratory attempts in view of certification: 11 papers
Participation in technical expertise: 5 actions
Cooperation in police enquiries: 2 actions.

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

The Technical-Medical Units Assessment Service conducts its activity in accordance with Law No. 176/2000 regarding medical devices, as amended and with Order No. 1636/2004 on approval of the Methodological norms on enforcement of Law No. 176/2000, as amended, referring to the notification of medical technique units. This activity consists of assessing the ability of the organisations to perform services requiring a notification from the Ministry of

Health. The assessed activities deal with optics, reworking, fixing and maintenance of medical devices, prosthesis manufacture (auditory/orthopaedic/other types).

Despite the reduced number of employees, the service must cover this type of activity throughout the country, having to perform not only the initial assessment of the organisations in view of obtaining a notification and the surveillance assessments every two years to maintain the notification, but also to find and sanction the infringements on the enforcement of Law No. 176/2000.

The situation of the projects conducted in 2010 by the staff of this service is as follows:

- Number of registered assessment applications: 163
- Number of performed assessments and issued reports: 121
- Number of cancelled activities (the dossier for assessment has not been submitted): 21
- Number of cancelled activities (the organisation only performs marketing activities): 11
- Number of ongoing projects: 10
- Number of assessment-surveillance projects: 323
- Number of conducted assessment-surveillance projects, reported: 200
- Number of ongoing assessment-surveillance projects at the end of the year: 83
- Number of assessment-surveillance projects whose activity has been ceased or whose performance notice has been cancelled: 40

Several measures have been taken by the Ministry of Health in view of amending the Order of the Minister of Health No. 842/2009 establishing the pattern of the minute for finding and sanctioning the contravention of Law No. 176/2000, enabling the NAMMD to enforce this Order.

11. **International relations**

In 2010, NMA/NAMMD specialists continued to take part in the activities of various cooperating European institutions and organisations:

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

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

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

Full members since 2007, participating in EMA scientific committees and working parties, the NMA/NAMMD experts participated in over 100 meetings in 2010.

The Scientific Committees and Working Groups of the EMA are the following:

- The Committee for Medicinal Products for Human Use (CHMP)
- The Committee for Orphan Medicinal Products (COMP)
- The Committee on Herbal Medicinal Products (HMPC)
- The Committee for Paediatric Medicinal Products (CPMP)
- The Committee for Advanced Therapies
- CHMP Biotechnology Working Party
- CHMP Efficacy Working Party
- CHMP Safety Working Party
- CHMP Pharmacovigilance Working Party
- CHMP Blood Products Working Party
- The Vaccines Working Party
- The common CHMP/CVMP Quality Working Party
- The CHMP Patients' and Consumers' Working Party
- The GMP/GDP Inspectors Working Group
- The Subworking Group on the EudraGMP Database
- The GCP Inspectors Working Group
- The Pharmacovigilance Inspectors Working Group
- The GLP 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 EudraNet Working Group on the European Telecommunication Network
- 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 the activities of the "Heads of Medicines Agencies"**

NAMMD representatives are actively involved in the meetings of the European body called "Heads of Medicines Agencies" (HMA), as well as in the meetings of the Working Groups of this body, hereby mentioned:

- The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)
- EMACOLEX (Working group on legislation)
- The Working Group of Communications Professionals
- The Working Group on Transparency
- The Working Group on Counterfeit Medicines
- The Clinical Trials Facilitation Group
- The Homeopathic Medicinal Product Working Group
- The Working Group of Quality Managers.

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

NMA/NAMMD experts have participated to over 20 meetings of the Working Group for Medicinal Products and Medical Devices of the EU Council, where new draft directives concerning pharmacovigilance and counterfeiting have been discussed.

In the context of the meetings organised by the European Commission, NMA/NAMMD experts have participated in meetings of the Permanent Committee for Medicinal Products for Human Use and in the meetings of the Pharmaceutical Committee – Notice to Applicants, as well as in the meeting of the EC ad-hoc group on development of enforcement of the Guidelines on Directive 2001/20/EC concerning clinical trials.

11.4. **Participation in World Health Organisation (WHO) activities**

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

In 2010, the Agency has released the Certificate of the product in WHO format for 381 medicinal products of Romanian manufacturers who intended to gain authorisation from these prodcts in other states.

11.5. **Participation in European Council activities**

In 2010, the NMA/NAMMD representatives have participated to the meetings of the Working Group on the classification for release of medicinal products for human use and to the ad-hoc Committee for Counterfeit Prevention.

11.6. **Participation in European Pharmacopoeia Commission activities**

The representative assigned by the NMA/NAMMD, having the membership of the European Pharmacopoeia Commission, has actively participated to its working sessions in 2010, as well as to the yearly meeting of the secretaries of the national Pharmacopoeia coming from countries which belong to the Convention for Elaboration of a European Pharmacopoeia.

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

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

The activity of the NMA/NAMMD as a PIC/S member consisted of the participation in the Joint-visit PIC/S program at the joint inspection of 30.05. - 04.06.2010 organised by the French inspector from Group No. 99.

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

In 2010, in the context of the cooperation with European institutions in the field of medicinal product control, the NAMMD laboratory experts participated in 5 trials:

- 3 analytical Proficiency Testing Scheme (PTS) studies performed at the initiative and under the coordination of the EDQM;
- 1 study of surveillance of medicinal product quality authorised through mutual recognition procedure (MRP);
- 1 study of surveillance of medicinal product quality (MSS).

These activities are described under section 7.1 c).

12. The Information, Logistics and Electronic Management of Data

The Information, Logistics and Electronic Management of Data Department is structured as follows:

- The Information and Logistics Service
- The Data and Document Management Service
    - The Registry – Document Distribution and Release Service
    - The Inter/Intra-Departmental Communications Office.

In 2010 as well, the Logistics and Information Service managed to maintain the optimum parameters of communication channels with the EMA and to provide real-time information exchange between the agency and external collaborators

(MAHs, distributors, healthcare professionals, patients, organisations and associations).

In 2010, the database applications programming was continued, namely amendments to the structure of the Product Index of medicinal products for human use, designed to optimize the work in the field and meet the new requirements arising from its use; moreover, statistical data reports were extracted periodically at the request of the Minister of Health, the National Health Insurance, the NMA/NAMMD President and various departments of the Agency.

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

The maintenance of the NMA website (*www.anm.ro*) and other software applications have been ensured throughout the year (the new NAMMD website has been set up – ongoing project; the NEWCADREAC (*www.newcadreac.org*), the Agency's new intranet website has been maintained, modified and updated.

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

Also, maintenance and troubleshooting of the software and hardware of existing computers was performed, as well as the installation and configuration of new computers purchased in 2010.

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

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

The Documents release bureau provided the drafting of Marketing Authorisations (MA), of annex 4 "qualitative and quantitative data on the composition of the medicinal product" and annex 5 "drug manufacturing data" for the 813 drugs approved for authorisation.

Also, the typing of:

- 42 President Decisions on MA discontinuation for 177 medicinal products, following the enforcement of the „*sunset clause*".

- 84 Decisions on the withdrawal/discontinuation of MAs issued for 202 medicinal products (MA withdrawal for medicinal products authorised through national procedure, which have been replaced by MAs issued through European procedure; discontinuation of a valid MA at the request of the company).

381 product certificates in WHO format for Romanian medicinal products have been released upon request.

860 payment confirmations have been received for marketing authorisation/renewal applications.

47 meetings of the Marketing Authorisation Commission(s) have been organized and 1172 product dossiers have been assessed.

13. **Ensurance of set up and enforcement of NMA/NAMMD policies and strategies**

The Department for policies and strategies (DPS), resulting from reorganisation and renaming of the NMA structures, is composed of:

- The European Affairs Service
- The Communication, institutional relations and pharmacopoeia service.

In 2010, the Policies and Strategies Department contributed to the fulfilment of the NAMMD mission, among others, by setting up policies and strategies of the Agency in its fields of activity, namely:

- *The organisational strategy:*
- establishes the strategic objectives and Guidelines of the Agency's activity, in accordance with the legal framework in force;
- establishes the relationship between the NAMMD and the Ministry of Health, as well as the relationship between the NAMMD and the stakeholders;
- covers a 5-year period and is updated yearly.
- *The Communication strategy:*
- establishes the Agency's objectives of the internal and external communication activity for a 5-year period;
- is updated yearly.

Together with the other professional departments, the PSD participated in handling the proper functioning of the NAMMD within the European network of competent authorities in the field of the medicinal product, playing the role of ligand between the Agency and the European and international authorities in the field of activity through:

- handling and monitoring the participation of NAMMD staff assigned as full members or alternates to scientific committees and working groups of the EMA, HMA, EDQM, European Council, EU Council, European Commission, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);
- ensuring the communication with the EMA in view of assigning NAMMD experts as full members/alternates;
- communicating with the secretariats of working groups/scientific committees of the cited bodies in view of form transmission, as well as through:
- undertaking the role of ligand between various NAMMD departments, through monthly monitoring/centralisation of the attendance of assigned NAMMD experts at the meetings of working groups/committees to the attention of the Economic Department.

Just like during the previous year, the PSD managed to ensure the scientific secretariat activity of the NAMMD Scientific Council (SC) and to organize (in accordance with the interdepartmental SOP) the 5 SC meetings through:

- the centralisation and check-up of 33 SC draft decision projects, set up of the SC agenda, forwarding of documents to SC members in electronic format or on paper;
- handling the electronic versions of SCDs from project status to publication (both in the Official Gazette of Romania, Part I, for SCDs approved through Order of the Minister Health, as well as on the NAMMD website, under the headings „Legislation" and „Informative Bulletins") in the directories for Scientific Council meetings;
- sending the assessed documents in electronic format/on paper to SC members;
- updating the record of contact coordinates of SC members;
- elaborating the minutes of SC meetings;
- out of the 33 SCDs approved in 2010, 31 have been posted on the NAMMD website and published in the Agency's bilingual Informative Bulletins.

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

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

Development of the NMA Informative Bulletins (IB) was continued; these were posted on the NMA/NAMMD website, namely: 3 IBs in Romanian (No.: 4/2009, 1/2010, 2/2010).

Delays, for objective reasons, of IB translation into English were recovered and 7 IBs issues were completed (No.: 2/2008, 3/2008, 4/2008, 1/2009, 2/2009, 4/2009, 1/2010).

In collaboration with NMA departments, the PSD participated to update and improve the information contained on the Agency's website as well as the NAMMD intranet.

The Brochure containing the NMA Annual Report for 2009 was developed and presented bilingually and with enhanced graphic and illustrative material.

In 2010, the PSD helped to ensure the transparency of NAMMD activity in accordance with the provisions of Law No. 95/2006, Title XVII – The medicinal product, Art. 845 (2) and 726 (4) on transparency in the activity of EU competent authorities in the medicinal product field, through:

- The set up, upon request, of the version available for the public of one assessment report for a medicinal product authorised through national procedure and

- The verification of the translation into English of public versions of 31 European Public Assessment Reports (EPARs) through mutual recognition procedure and decentralised procedure, with Romania as interested member state.

The European Affairs Service ensured, via its trained staff:

- The translation of Directive 2009/102/EC on amendment of Directive 2001/83/EC of the European Parliament and of the Council on the community code relating to medicinal products for human use concerning advanced therapy products;

- The translation/verification of the translation of 6 European Guidelines;

- Checking the translation of 31 evaluation reports and documents in English, the mutual recognition procedures and decentralised procedures;

- Checking / translating 110 EMA press releases, questions and answers documents and DHPCs from the EMA as well as action lines proposed by the EMA ("Lines to take") etc.

- Providing advice to check the translation of SmPCs and leaflets, correspondence and communication in English with European bodies;

- Linguistic assessment of EMA's proposals of translation into Romanian of various specialized terms from the legislative field of the medicinal product and proposal of the terms agreed by the NAMMD.

In line with the NMA/NAMMD Communication Strategy, the following activities have been performed in 2010:

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

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

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

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

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

- Cooperation with all NAMMD departments in order to gather and organise the information required by the media and/or the stakeholders, in view of drawing up/drafting the required answer;

- The set up/verification and broadcast of official communications and standpoints of the NAMMD to the media;

- Participation to the drafting and submission of the correspondence with internal and external partners, related to issues specific to NAMMD activity;

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

The first steps have been taken in view of setting up a strategy to attract and involve the patients and the public in view of enhancing the activity of communication and information, by counselling and cooperation with these, namely:

- The organisation of a meeting of the Agency's management with the representatives of the Romanian Coalition of Patients with Chronic Diseases (COPAC), in view of identifying the needs and expectations of patients and the possibilities of cooperation in the context of the Agency's activities;

- Identification of the NMA need to provide general information on generic versus original/innovator medicinal product, as well as on counterfeiting-related issues, following the frequent confusions that patients make between generic and counterfeit medicinal products;

- Forwarding (in the context of the COPAC meeting in June 2010) the dossier related to the generic versus original medicinal product, as well as to counterfeiting-related issues, emphasizing the fact that generics are therapeutic equivalents of original medicinal products, having the advantage of being cheaper, thus representing a « crisis » solution for social health insurance systems.

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

The electronic database of the documents in debate, by theme, received from the Permanent Representation of Romania to the EU and/or from the Ministry of Health, set up in 2009, has been maintained in 2010.

E-mails received from the Representation referring to European Commission (EC) Decisions concerning medicinal products authorised conditionally (according to Art. 127a of Directive 2001/83/EC), the suspension/withdrawal/amendment of the MA (according to Art. 107 of Directive 2001/83/EC) and the decisions issued following the referrals (according to Art. 29, Art. 30, 31, 32, 33, 34 and 35 of Directive 2001/83/EC) have been monitored/handled into an electronic database and have been forwarded to NMA/NAMMD specialists assigned for their enforcement.

Electronic records have been set up for 25 European Commission Decisions, received on paper version from the Ministry of Foreign Affairs / Ministry of Health in 2010.

The activity of the commission secretariat was assured for handling crisis situations; 9 minutes of the commission meetings have been prepared.

The minutes of operating meetings of the Agency's management have been set up upon request.

14. **Judicial work of the NMA/NAMMD**

In 2010, from the organisational point of view, the Legal Department functioned during the first 4 months, in the following structure:

- The European Legislation Service;
- The National Legislation Service;
- The Administrative Legal Service.

Subsequently, following the reorganisation measures imposed by the main credit ordinator, namely the Ministry of Health, the three services have been merged in one; the structure has been maintained even after the institution's reorganisation by TOMD.

The legal department has covered a wide range of legal relationships, both in terms of legal relations within the institution and those of the NMA and other legal entities, public or private.

Regarding the areas addressed, they were aimed at activities and actions related to all branches of positive law - mainly labour law, civil law, civil procedure, administrative law, financial law, tax law, administrative etc.

Via the activities conducted in 2010, the Legal Department cooperated with all departments of the institution.

Thus, the following have been performed:

a) Various correspondence – 305 documents;
b) President Decisions – 324, 136 – NMA and 188 - NAMMD;
c) Solved administrative enquiries – 3;
d) Minutes of Administrative Council meetings – 6, of which 4 of the NMA Administrative Council and 2 of the NAMMD Administrative Council;
e) Administrative Council Decisions – 42, 27 of the NMA and 15 of the NAMMD.

Thematically speaking, AC Decisions managed to cover various issues of the current activities; due to the given circumstances, the balance was ensured by acts of disposal whose regulatory scope were organisational issues – gradual changes in the institution's structure, in the collective labour contract at unit level, approval of the job list and of the organisational structure, other aspects of the current activity.

In the context of the activity performed, the Legal Department set up the dossier representing the institution's legislative initiative, promoted by the main

credit ordinator, namely the Ministry of Health. Thus, the dossiers in view of advancing a regulatory addend of Law 95/2006 on healthcare reform, of a Government Decision (regulatory scope: the organisation and operation of the NAMMD – Romanian Government Decision No. 734/2010), and of 5 Orders of the Minister of Health have been set up.

Therewith, the dossier represents the addend to the collective labour contract at unit level, submitted to the Territorial Labour Inspectorate of Bucharest.

The institution was also represented within law courts; there have been 4 litigations in 2010, one of which is still under appeal. As in previous years, the institution has not been biased patrimonially or financially following the litigations solved in 2010.

Together with other departments, the Legal Department contributed to the prevention of medicinal product counterfeiting and of illegal marketing of counterfeit medicinal products; it informed and warned the public and also developed relationships of cooperation with other institutions and bodies involved in this activity.

In view of ensuring better information of the public this year, the NMA/NAMMD website's heading „Counterfeiting" contained notifications of counterfeiting reported via the rapid alert system.

The NAMMD has continued the cooperation, initiated through a protocol in 2009, with the Directorate for Investigation of Organised Crime and Terrorism (DIICOT) in view of combating counterfeit medicinal products and their illegal trade.

This step ensured the continuation of setting up the enforcement framework for the provisions of the future European Directive concerning the penetration in the legal supply chain of falsified medicinal products in terms of identity, history or source, now a draft under EU Council debate including the NMA/NAMMD appointed representative presenting and supporting the views of Romania.

15. **Management of human resources**

15.1. **Human resources policy**

The flow of the main activities included in the plan of substantial objectives of the Human Resources and Payroll Department, in 2010, managed to:

- ensure the human resources at the level of NAMMD structures, especially in those sectors where a lack of qualified staff with higher education (particularly medico-pharmaceutical) has been detected, in view of properly ensuring the scarce jobs from special departments, which practically ensure the accomplishment of the Agency's scope.

- Improve human resources through training and improving the employees by:

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

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

- Career administration, aiming to ensure long-term correspondence between the employees' career improvement needs and the available jobs in the Agency;

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

- Throughout 2010, staff motivation could not be performed by wage-related compensations (bonuses, pay rises, etc.) for special professional merits.

- A motivational endeavour consisted of stimulating the assigned persons to show their ability in performing tasks and responsibilities required by management jobs.

- Another motivational endeavour consisted of setting up an adequate system for assessment of performances;

- The organisational structure substantially amended in 2010 following Government Emergency Ordinance No. 72/2010 on the set up of the NAMMD by merging the National Medicines Agency with the Technical Office for Medical Devices; the new organisational structure has been approved through Order of the Minister of Health No. 1275/2010. The new structure aimed to:

- Ensure fluent communication between organisational structures, cooperation, task accomplishment, supply distribution and decision making in the most effective manner.

15.2. **Ensuring Human Resources within NMA/NAMMD structures**

As regards the accomplishment of the goal of the Human Resources Department, reorganised in 2010 into the Human Resources and Payroll Department**,** concerning the ensurance of qualified personnel, it is worth mentioning that, starting with April 2009 and throughout 2010, it was obviously loaded by the legal framework set up through Government Emergency Ordinance

No. 34/2009 on the rectification of the budget for 2009 and regulating certain financial-fiscal measures. This refers particularly to the provisions of Art. 22 of Chapter II „Measures on public expenditure" providing „suspension of employment proceedings by examination or contest for vacant positions in public institutions".

Moreover, the negative impact on the management of human resources was doubled by the unfavourable economic circumstance at legislative level by Law 118/2010 on certain measures necessary to reset the budgetary balance, stating that wages were diminished by 25%. The enforcement of the respective legislative-economic measures led to the departure of 38 employees from the NAMMD.

As a consequence, following the legal provisions entered into force in 2009 and 2010, the lack of staff recorded as of 2009 was enhanced by cessation of many individual labour contracts. However, it is worth mentioning that the only jobs which could temporarily be granted, by permission from the Ministry of Health, have been the jobs of the holders whose individual labour contracts have been suspended for strictly determined periods.

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

Apart from participation in the activities organised by various European institutions and bodies, the best manner to maintain the NMA/NAMMD connected to European activities in the medicinal product field was for the Agency's specialised personnel to yearly benefit from both a continual training program, specific to professional development, at the site of the Agency, and from training organised nationally and internationally by various authorities and bodies in the field:

- participating in a GMP course organised by the Centre for Professional Advancement in Bucharest, June 2010;
- participating in the course „Reference standards, impurities, pharmacopoeias and solvents" organised by the LGC Standards, Bucharest, November 2010;
- participating in the course „PK Assessors Training on a New Bioequivalence Guideline" organised by the EMA, June 2010;
- participating in the course addressing pharmacovigilance inspectors organised by the EMA, Belgium, November 2010;
- participating in the course addressing EMA GCP inspectors, London, November 2010;
- participating in the course concerning the 7th edition of the European Pharmacopoeia, - Istanbul, Turkey, December 2010.

16. **The economic activity**

In 2010, the Economic Department has developed and managed a balanced budget of revenues and expenses from the state budget, as follows:

- NMA 10,455,000 lei
- TOMD 1,560,000 lei
- NAMMD 9,676,000 lei

TOTAL 21,691,000 LEI

The expenditure amounted to the following sums:

- NMA 10,148,973 lei
- TOMD 1,559,658 lei
- NAMMD 8,847,084 lei

TOTAL 20,555,715 LEI

of which:

staff costs.

- NMA 8,741,858 lei
- TOMD 1,044,031 lei
- NAMMD 4,676,058 lei

TOTAL 14,461,947 LEI

to cover goods and services.

- NMA 1,407,115 lei
- TOMD 515,627 lei
- NAMMD 1,632,662 lei

TOTAL 3,555,404 LEI

capital expenditure.

- NAMMD 2,538,364 lei

TOTAL 2,538,364 LEI

All expenses were within the approved budget for 2010 in accordance with the legal provisions on economic and financial discipline.

The data reveals a balance between NMA/NAMMD revenue and expenditure, held in compliance with the budgetary principles and rules according to Law 500/2002 on public finance and in conjunction with specific legislation in force.

From an organisational perspective, in 2010, the Economic department has undergone several transformations and modifications in terms of management of the department and personnel, as well as in terms of the activities performed (NMA/TOMD closing balance, assuming balance accounts in accordance with the protocols and set up of NAMMD opening balance, merging of inventories in accordance with the protocols, establishment of the new NAMMD budget, closure of NMA accounts and opening of new accounts for the NAMMD).

All financial activities were conducted in the Economic Department, ensuring optimal and efficient performance of payments and receipts in the business.

In 2010, through its financial-accounting activities, the Economic Department provided proper performance of their objectives.

17. **General administration**

In 2010, the General Administration Department (GAD – set up throughout the year through the reorganisation of the former General Administration and Payroll Department - GAPD) managed to fulfil its objectives and to deal in a prompt and efficient manner with the requests coming from NMA/NAMMD structures. Thus, GAD's most substantial achievements consisted of the performance and finishing of activities related to the endowment and renovation of the NAMMD building. The most important acquisitions have been:

- The controlled access system in the building of NAMMD headquarters;
- Video surveillance systems (at the headquarters and on 20 Demostene Street), acquisition whose purpose was to establish safe and effective measures to protect the cameras, by eliminating the odd of unauthorised persons entering the areas containing secret or confidential documents.

Due to the department's structure, namely the various attributes of services/departments located in its structure, GAD employees have been directly involved in the reorganisation of the NMA/NAMMD:

- GAD took part in the placement of organisational structures at the NMA/NAMMD headquarters;
- In 2010, the DGAH initiated and completed the relocation of the Biological Product Evaluation and Control Department from its headquarters located in Demostene street to the NMA headquarters; this move shall result in creating an optimal environment in laboratory work, and shall solve the problem of biological samples transportation from the former to the NMA headquarters. The redundant space on Demostene street shall be used to expand the NMA/NAMMD archive.

The Public Acquisitions Service organised and tracked the planning, performance and acquisition of products, services and works needed for proper functioning of the NMA/NAMMD activity, consistent with its needs and objectives and with the approved budget, developing the documentation needed for all types of procurement.

133 public acquisition contracts and 165 additional documents have been signed throughout 2010; utility contracts, rental of areas, various services (for all NMA/NAMMD sites – 63 contracts) have been handled.

18. **Internal audit**

The internal audit structure set up at NAMMD level is subordinated to the NAMMD president, thus ensuring the freedom needed to perform internal audit

activities, in view of an objective assessment of deficiencies detected at the Agency's audited departments and the provision of adequate recommendations.

In 2010, 2 audit missions have been conducted in accordance with the yearly internal audit plan.

The risks of potential impact upon the activity performed by the NMA/NAMMD throughout the period under assessment were organisational, operational, juridical and financial.

As per legal requirements, a report on activities of the Internal Audit Office last year was submitted to the Ministry of Health.

19. **Difficulties encountered**

- Lack of higher education staff, employed full time, so much the more needed since more than doubling of the evaluation work due to Romania's accession to the European Union and initiation of authorisation of medicinal products through decentralised, mutual recognition and/or "repeat use" procedure with Romania as a Reference member state.
- Lack of specialised books needed in view of assessing clinical documentation and specialised training courses.
- Difficult archiving system and insufficient archiving space.

20. **Priorities for 2011**

Just like every year, the NAMMD formulated its priorities in the end of 2010 for the coming year, 2011:

- Ensuring proper performance of NAMMD objectives, as stipulated in the Regulation on the organisation and operation, supplemented with other tasks related to the field of medical devices, such as:
- Maintaining a high level of performance and security of medical devices when using healthcare networks throughout the country, regardless of the property right upon them;
- Exigent assessment of technical – medical units dealing with medical devices, so that any type of stenting or fixing and maintenance services for medical devices can be performed at optimal quality and competence level;
- The set up of specific technical procedures in the field of medical devices.
- Permanent contribution to the elaboration of secondary legislation in the field of medical devices.
- Strengthening the prestige acquired domestically and internationally through high quality performance with both internal and external partners;
- Meeting of all obligations in relation with internal and external partners, working closely with the direction of the Ministry of Health specialist, the National Authority for Health Insurance, competent authorities of the state, active

participation in actions and activities of the EMA, PIC/S and other specialised bodies to which the NAMMD is affiliated;

- Ensuring adequate human and financial resources to run a good business;
- Supplying NAMMD employees with efficient and reliable computers with intranet and internet connection;
- Producing complete integrated software that is versatile, multitasking, to manage medicinal product information throughout their lifecycle;
- Attracting young specialised personnel for training and specialisation;
- Continuation of personnel training at the workplace, in Romania and abroad, in view of professional improvement and thorough operation according to the European system;
- Strict adherence to the law in all fields of activity and enforcement of medicinal products legislation, in accordance with Law no. 95/2006 on healthcare reform, as amended;
- Continuous improvement of the quality management system;
- Ensuring proper communication with all partners in the pharmaceutical field (manufacturers of innovative and generic medicinal products, importers, distributors), with patient organisations, associations of companies which coordinate clinical trials etc., in view of ensuring transparency;
- Continuation of the institution's training for the audit of the quality management system of May 2011, performed by EMA experts - Benchmarking European Medicines Agencies (BEMA), complex activity which requires correct, realistic self-assessment.

Moreover, year 2011 will involve:

- The initiation of transposition into Romanian legislation of two new European directives, one referring to a new approach of pharmacovigilance and the other to the prevention of the entry of falsified medicinal products into the supply chain, both amending the community code of the medicinal product for human use (Directive 2001/83/EC).

The NAMMD shall also consider:

- The updating of its strategies (the organisational and communicational strategies);
- The set up of new Regulations on advertising of medicinal products for human use in line with the provisions of Directive 2001/83, with the Guideline on evaluation on advertising in medicinal products for human use (approved through NAMMD SCD) and, simultaneously, to settle all aspects of correct, non-misleading advertising, whether it addresses the general public or healthcare professionals.
- The organisation of meetings with the representatives of all stakeholders (manufacturers, distributors) in view of carrying out the regulatory measure for enforcement of a traceability system for a medicinal product, identification of all

elements which can represent a starting point in finding reliable solutions for this enforcement in Romania;

- The revision of the Medical Devices List for periodic control, so that this List contains solely the devices with maximum risk for patients and users.

- The revision of Order of the Minister of Health No. 1636/2004 on approval of the Methodological Norms for enforcement of Law No. 176/2000 concerning medical devices, as amended, referring to medical technique units, in order to explain certain issues which lead to various interpretations of this Order and the performance of steps, determining the main credit ordinator to understand the need to hire more staff so as to handle the enforcement of Law 176/2000 at national level more efficiently.

- The revision of Government Decision No. 734/2010 so as to exclude the Technical Office for Medical Devices (Certification of medical devices and management systems which no longer meet the accreditation requirements and cannot maintain its status of accredited body) from the NMA; the existence of a legally enforced entity, with a documented structure able to grant equity in fulfilling accreditation conditions is required.

CONCLUSIONS

In 2010, the NMA/NAMMD managed to dutifully fulfil its tasks and duties as a national competent authority in the medicinal product field, even in the context of the international financial crisis.

It is a well-known fact that the institution suffered major transformation throughout the last two years.

Several changes were made in 2009 in the internal structure of the Agency, starting from the manner of structuring and functioning of the European Medicines Agency (EMA), to optimise its activity.

If, by the end of 2009, the National Medicines Agency (NMA) has been reorganised as a public institution wholly financed from state budget, in accordance with Law 329/2009 on reorganisation of certain public authorities and institutions, in 2010, in line with Emergency Government Ordinance No. 72 of June 2010, the NAMMD was founded by merging the NMA with the Technical Office for Medical Devices. The organisation and functioning of the NAMMD have been subsequently established through Government Decision No. 734 of July 2010. As a consequence, the Agency managed to accomplish its mission, supplemented with other tasks related to the field of medical devices, even under the circumstances of the reorganisation imposed by the severe financial crisis.

In 2010, through management's permanent availability for cooperation and communication, in view of creating the conditions required for the manifestation of its human resources at full professional capacity, through the efforts undertaken by the Agency's staff (experts and auxiliary staff), the NMA/NAMMD managed to maintain its status of regulatory, competent European authority, entirely in line

with community requirements, active member in committees and working groups related to the medicinal product for human use.

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

In 2010, after merging with the Technical Office for Medical Devices, the NAMMD has become the single abilitated institution able to assess the performances and safety of medical devices in use. The new control activity, namely the periodic check-up of medical devices, was, thus, carried out for all installed and commissioned medical devices, characterised by a high risk degree, at the sites of all medical device users, both in the private and public field.

The organisations' ability to perform the services requiring the approval of the Ministry of Health has also been assessed; activities related to optics, operation, fixing, maintenance and stenting (auditory, orthopaedic, and other) of medical devices have been assessed.

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

In 2010, the NAMMD and the Competition Council continued their cooperation in accordance with the cooperation protocol signed in view of ensuring and promoting concurrence in the field of the medicinal product for human use, in accordance with the provisions of Competition Law No. 21/1996, forbidding competition restraint, prevention or adulteration on the Romanian pharmaceutical market. This document aimed to establish manners to enforce and maintain a balanced pharmaceutical market, without prejudice to any of the participants, be it manufacturer (of innovative/generic medicinal products), importer or supplier.

The Agency is one of the decision factors in the field of the medicinal product for human use and this status intends to promote the involvement in all "regulatory" issues in view of reaching a balance on the medicinal product market, in accordance with the advice of the European Commission, for the good of the final consumer: the patient.