2009 NATIONAL MEDICINES AGENCY ACTIVITY REPORT

INTRODUCTION

Introductory word by the NMA President

In 2009, the National Medicines Agency fulfilled its mission as a competent drug authority by persistently and determinedly carrying out its assignments and meeting its commitments and many additional tasks.

Within the same context of alignment to European standards, the NMA has adopted a complex institutional development programme, through internal reorganisation, in view of most efficient institutional compatibility with similar competent authorities.

Following assessment of the types of activities carried out by the NMA and in view of their optimisation, changes in the structure of NMA departments were established and enforced in 2009, also taking into account the manner of structure and function of the European Medicines Agency (EMA) and of other regulatory institutions in this field, on community level.

Thus, the Evaluation-Authorisation Department (EAD) has been split into two departments:

- The Authorisation Department (AD) – ensuring assessment of documents required for marketing authorisation of medicinal products (MA);
- The Post-Authorisation Department (PAD) – assessing post-authorisation documents, whereas certain structures previously belonging to the EAD (the Documentation and samples admission bureau, the MA release bureau and the Archives bureau) have been transferred to other departments.

In view of improved document flow within the NMA as well as better communication with marketing authorisation holders (MAHs) or third parties, the Department for Logistic, Information Technology and Electronic Data Management has been established.

The development of the legal framework regulating authorisation of medicinal products on both national and European level has imposed the set up of a juridical department.

In the context of NMA increasingly active involvement in activities of the European medicinal product field, placing special emphasis on communication with the media and stakeholders, the development of the Policy and Strategy Department has been necessary, so as to cover all NMA collaboration areas.

The Juridical Department and the Policy and Strategy Department are directly subordinated to the NMA President.

In 2009, action was taken well for renaming certain services and bureaus and set up of new services/bureaus, in line with current and future activities as issued from the various departments' assignments, in accordance with

requirements of current Romanian and European legislation in the medicinal product field in view of improved flow and increased efficiency of activities.

As of last year, the global economic crisis represents a major change in the NMA sphere of activities, with significant impact on both the trade and the public sectors.

At the end of 2009, the NMA was reorganised as a fully publicly funded institution, in accordance with Law No. 329/2009 on the reorganisation of public authorities and institutions, rationalisation of public expenditure, support of the business environment and compliance with the framework agreements with the European Commission and the International Monetary Fund.

In spite of the series of internal reorganisations carried out on NMA level in 2009 in view of improved activity, the institution was faced with a significant shortage of professional staff.

Despite this fact, the NMA has made tremendous efforts in order to meet its assignments and target objectives, while continuing its active involvement in activities of European institutions in the medicinal product field, as proof of its maturity as an institution fully capable of carrying out activities derived from its status of competent authority of an EU member state.

The activity of the NMA departments was particularly complex in 2009, meant to meet priority activities as mentioned in the Agency's mission, namely assessment at the highest level of scientific competence of authorisation dossiers, in view of marketing of safe, quality, effective medicinal products for human use and safety surveillance of medicinal products within the therapeutic circuit, by inspection and pharmacovigilance activities.

Thus, in 2009, in spite of all difficulties to be overcome, the NMA granted marketing authorisations (MAs) to a larger number of medicinal products as compared to the previous year, namely 942 medicinal products in 2009, versus 868 in 2008.

In 2009, the NMA issued:

- **359** MAs through national procedure
- **583** MAs through European procedures.

The number of applications for marketing authorisation through European procedures remained at a high level, namely **827** applications for marketing authorisation/ marketing authorisation renewal through European procedures with Romania as an interested Member State.

It should be emphasized that, in 2009, the first European decentralised authorisation procedure (DCP) was finalised with Romania as a Reference Member State.

The assessment performed by the NMA was accepted without objections by all 9 Concerned EU Member States.

The renown of the NMA with its beneficiaries and their trust in the institution is also proved by the large number of applications forwarded to the

NMA in view of authorisation through European procedures with Romania as a Reference Member State.

Therefore, **51** applications were made for marketing authorisation through European procedures with Romania as Reference Member State, of which **9** have been accepted in view of start-up in 2010.

At the end of 2009, the Index of medicinal Products included **7288** trade names corresponding to **1239** International Non-proprietary Names (INNs).

Taking into consideration that the "*sunset clause*" procedure is to be enforced as of 2010, in accordance with Art. 729 and Art. 730 of Law No. 95/2006, Title XVII – The medicinal product, the NMA has assessed **7288** medicinal products listed in the index by the end of 2009 (of which **2100** have been centrally authorised, whose management in view of "*sunset clause*" application lies with the European Medicines Agency - EMA)

The NMA has received reports concerning marketing authorisation for **5188** medicinal products, of which **400** identified as liable to *"sunset clause"* application, the final decision to be taken in 2010, after centralisation of updated information.

The activity of the National Pharmacovigilance Centre operating within the NMA was particularly complex in 2009, ensuring handling of safety data issued from spontaneous reporting and periodic safety updated reports concerning medicinal products, as well as a wide range of pharmacovigilance activities within the system of EU national authorities.

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.

As of March 2009, on approval of tariffs for activities performed by the Pharmaceutical inspection department in the NMA (PID), the respective department has applied legal provisions in the inspection field to wholesale distribution units.

In 2009, the following activities related to Good Distribution Practice inspection (GDP) were performed:

- **307** inspections in view of authorisation;
- **283** wholesale distribution authorisations have been released;
- **4** authorisations issued by the Ministry of Health have been recalled, according to previous regulations, in result of finding critical deficiencies during authorisation inspections;

In September 2009, the Pharmaceutical inspection department was audited by inspectors of EU competent authorities in France and Greece, who assessed compliance of GDP inspection legislation, GDP inspection techniques and the quality system implemented by the PID with European legislation and requirements in the field ("pre-MRA audit").

In its report, the audit team has estimated that the inspection system enforced by the PID is compliant with the same principles and regulations as the other EU Member States and that the Romanian inspectorate is ready for the inspection performed by the Canadian regulation authority in view of Romania's Mutual Recognition Agreement (MRA) with MRA member states.

Activities regarding quality control of medicinal products was aligned to the Agency's general policy and has been carried out within the two following departments: the Department for medicinal product quality control (DCCM) and the Department for biological products control (DCPB).

As in previous years, in 2009 as well the NMA continued its cooperation with renowned European institutions in the quality control field, by participating in PTS (Proficiency Testing Scheme) studies, studies for surveillance of quality of medicinal products authorised through European procedures, studies for verification of quality of medicinal products authorised by the EMA through centralised procedure.

In 2009, NMA activity was marked and influenced by the A/H1N1 flu pandemic, officially declared by the Order of the Minister of Health of 11 June 2009.

Taking into account the decision of the Ministry of Health and the "Cantacuzino" National Institute of Research and Development for Microbiology and Immunology (INCDMIC) regarding manufacture of a pandemic vaccine for the local market, the NMA was involved in intense activities starting with counselling for choice of the optimal solution to this purpose and then assessment and control of CANTGRIP (the monovalent pandemic vaccine).

In order to make the pandemic vaccine available on the market in due time, the NMA organised weekly meetings with the "Cantacuzino" Institute, analysing stages covered so far and those to be covered in this vaccine's authorisation process (the stage in the assessment process, provision of required documentation in due time, corroborated with findings by NMA inspectors during pre-marketing authorisation inspections of the vaccine, Good Clinical Practice and Good Laboratory Practice inspections as well as with respective corrective measure plans for correction of such findings etc.)

Following tremendous efforts, the NMA completed authorisation of the Cantgrip vaccine on 25.11.2009.

Depending on the stage, during both vaccine evaluation and on completion of authorisation, the NMA informed state institutions and bodies entitled to information on the progress of the authorisation procedure, problems encountered, conclusions of inspections performed at the Cantacuzino Institute, evaluation outcomes and the benefit/risk ratio.

NMA activity in the field of legislative regulation was intensely continued in 2009 with regard to set up of standards needed for full enforcement of provisions of Title XVII – The medicinal product of Law No. 95/2006.

To the same purpose of approximation of national legislation with European legislation, a number of European guidelines have been adopted (scientific/procedural guidelines). Moreover, a series of regulatory documents have been updated as a consequence of Romania's accession to the EU and of the NMA status as a European competent authority in the medicinal product field.

An important contribution to NMA support in its regulatory activity came from the NMA Scientific Council, which, by analysing and adopting standards, scientific guidelines and procedures**,** has contributed to sound progress of activities of both the Agency and its external partners.

Acknowledging the important role it owns in fighting medicinal product counterfeiting and the illegal trade of counterfeit medicinal products, the NMA has continued to improve its manner of public information and warning as well as development of collaborative relationships with other institutions and bodies involved in this activity.

In this respect, the NMA has enforced cooperations with national institutions involved in combating trade of counterfeit medicinal products over the Internet as well as with similar institutions in EU Member States or outside the European Community, in view of establishing new permanent contact points meant to limit such criminal phenomena.

The NMA initiated and signed a protocol for cooperation with the Directorate for Investigation of Organised Crime and Terrorism (DIICOT) in view of combating counterfeit medicinal products and their illegal trade.

Such proceedings set up the framework for application of provisions of the future Directive on prevention of introduction into the legal distribution network of medicinal products whose identity, history or source is counterfeited, whose draft is now under discussion in the EU Council, debates in which the appointed NMA representative will also participate to present and support Romania's viewpoints.

In view of better information of the public, a new section has been created on the NMA website, "Counterfeiting", which includes counterfeit alerts reported via the rapid alert system.

Year 2009 equally meant a very important active participation in works of EMA scientific committees and working groups, of the Heads of Agencies body, the Council of the European Union, the European Commission, the Council of Europe, the PIC/S Scheme, the Commission of the European Pharmacopoeia and of the European Network of Official Medicines Control Laboratories (OMCLs).

NMA representatives appointed to the Working Party on Pharmaceuticals and *Medical Devices* of the Council of the European Union have presented and supported Romania's viewpoints concerning drafts of Directives on counterfeiting and pharmacovigilance.

Moreover, NMA contribution is to be noted as made through its representative to activities of the EMA Committee for Medicinal Products for

Human Use (CHMP), involved in assessment of 24 Paediatric Investigation Plans (PIPs), both as a Rapporteur (14) and a Peer-reviewer (10).

NMA involvement in activities of the network of EU competent authorities has also materialised in participation in inspections for verification of compliance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) rules for medicinal products authorised through centralised procedure by the EMA. Within the same context, the NMA has also participated to sampling and testing of centrally authorised medicinal products.

Papers have also been elaborated for numerous scientific events such as congresses, conferences, seminars, held in Romania or abroad.

The NMA has launched action for development of international links going beyond Europe to such countries as India and China as well, where research and manufacture capacities undergo quick development.

Under circumstances anticipating continuation of the current trend as well as in view of effective public health safety, the NMA has to further develop its good working relations with countries it foresees as becoming major providers of medicinal products for the pharmaceutical market in Romania.

Special emphasis has been placed on ensuring good communication with stakeholders and transparency.

In view of developing and improving communication with stakeholders, top-level leadership has initiated a series of meetings with:

- The Romanian Association of Medicinal Product Manufacturers and Suppliers
- The Association of Clinical Study Coordinating Companies in Romania.

Throughout these meetings, the main cooperation fields between parties involved have been considered, as well as ways to improve communication in these fields.

Moreover, communication with the mass-media has intensified, important aspects have been approached such as safe use of medicinal products.

Much valuable information has been posted on the NMA website, for both healthcare professionals in the medical and pharmaceutical field, and/or the general public.

The NMA has initiated actions for increased media awareness of pharmacovigilance activities among healthcare professionals, part of which have already been undertaken. Thus, the NMA has contacted the College of Physicians, as well as a series of universities of medicine and pharmacy in order to propose a partnership in triggering pharmacovigilance educational action.

The NMA has taken part in 2 medical national events, where it presented the main elements required in reporting adverse reactions by healthcare professionals.

The NMA also started talks with the College of Pharmacists, in view of obtaining Ongoing Medical Education credits for pharmacists, envisaging their

increased awareness and motivation to report potential adverse reactions to medicinal products.

Enforcement of provisions of Law No. 95/2006 – Title XVII – The medicinal product concerning transparency in the activity of EU competent authorities in the medicinal product field has been continued, by issuing publicly available versions of the Agendas and Minutes of the Marketing Authorisation Commission and of the Commission for the Inspection of Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), Good Analytic Laboratory Practices (GALP), Good Clinical Practices (GCL) and Pharmacovigilance as well as publicly available versions of Medicinal product assessments reports.

In 2009, the institution's top management granted proper attention to the quality management system, placing great emphasis on the process-based approach. Update of quality dossiers has been monitored, in accordance with new regulatory provisions entered into force and applicable within the NMA, with amendments of the NMA organisational structure and compliance with Standard Operating Procedure (SOPs) in force, and involving new activities and processes, within the scope of new specific/interdepartmental SOPs.

In view of attaining its objectives, the NMA has been supported by the Administration Council, gathered in 11 working meetings in 2009 and adopting 52 decisions, 7 of which of regulatory character, approved by Order of the Minister of Health.

Mostly administrative and financial issues have been resolved relating to better NMA organisation and functioning: approval for change of the NMA organisational structure, approval of the NMA job title list, approval of the income and expense budget, approval of NMA tariffs, approval of the collective labour contract at unit level.

Mention should also be made of the drafted set up of a security structure, proposed and approved in the Administration Council, the respective structure now under organisation. This had been required by the complex character of information handled by the NMA and the need to secure its protection in accordance with Law No. 182/2002 on protection of classified information, as amended.

Having in view the considerable differences between salary scales for the NMA healthcare personnel and those for technical-administrative support staff, as proposed by the Human Resources Department, the Administration Council decided on a better balance of these two types of salary scales, depending on the level of education, qualifications, professional stages and degrees.

Following approval by the Administration Council, the proposed initiative was subsequently approved by the Ministry of Health as well, the new salary scales having been attached to the Collective Labour Contract in result.

Insurance of human resources policy has been strongly influenced by the negative impact on the Agency structure, personnel and activities of Emergency Government Ordinance 34/2009 concerning budget modifications in 2009, then

by enforcement of Law No. 329/2009 on the reorganisation of certain authorities and public institutions.

In spite of all hindrances occurred in 2009, the top-level management was permanently preoccupied with enforcement of the NMA human resource policy, emphasizing:

- insuring university trained, particularly medical – pharmaceutical staff for adequate coverage of deficient positions within specialised departments, ensuring accomplishment of the NMA object of activity
- 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 NMA objects of activity.

In spite of all efforts made in that respect, the records of staff dynamics in 2009 shows a negative balance: **21** new individual labour contracts, compared to **36** terminations of individual labour contracts.

A process concerning relocation of the Biological products control department was initiated in 2009, from their headquarters in Demostene Street to the central NMA headquarters, relocation to be finalised in 2010 and resulting in set up of an optimum setting for laboratory activities and finding solution for the issue of biological samples transportation from the former location to the central NMA headquarters.

Improvement of the central headquarters areas has been continued through cleaning works, division of rooms in view of their transformation into office rooms and a whole range of other works for set up of working posts.

At the same time, the NMA policy has been continued regarding information and extension of the internal NMA computer network.

Targets set up for 2009 could not have been put into practice with no adequate financial policy, based on strict financial discipline, compliance with legal provisions regarding budgetary execution and judicious expenditure of allocated resources, in line with the approved incomes and expenditures budget.

From this perspective, the annual NMA incomes and expenditures budget was a balanced construction aligning the level of expenditures with the level of incomes drawn through activities performed.

Moreover, tariffs for a range of activities performed by NMA departments have been approved, tariffs which have added to the system of money quantification of activities performed, ensuring full funding of all activities, in accordance with legal dispositions in force.

All progress made has been achieved due to NMA efforts towards adoption and enforcement of European rules in the field, to the higher interest of patients and society at large, according to its mission-oriented activity.

NMA ACTIVITIES IN 2009

1. Activity of the NMA Scientific Council (SC)

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

The Scientific Council establishes the scientific policy of the NMA, in line with its attributions.

In its meetings, the Scientific Council focuses on discussion and approval, as Scientific Council Decisions (SCD), of regulatory provisions concerning NMA professional activity.

Normative decisions of the Scientific Council are subject to approval by the Minister of Health and published as orders of the Minister of Health in the Official Gazette of Romania; other decisions are submitted to the Minister of Health for approval and enforced within 15 working days of submission, unless the Minister of Health expressly disagrees, following which they are uploaded into the NMA website and published in the NMA Informative Bulletin.

In 2009, the Scientific Council held 3 working meetings, in which they adopted 22 Council decisions, 6 of which are in the course of being approved through orders of the Minister of Health, while the other 16 have been posted on the NMA website and published in the NMA bilingual Informative Bulletins.

The Scientific Council activities consist mainly of adopting Regulations, Guidelines and procedures which contribute to improving the activity of the NMA and of its external partners.

The following have been discussed and approved: the regulations on the export of medicinal products for human use, the modifications on the regulations concerning marketing authorisations and surveillance of medicinal products for human use, the modification of regulations concerning the authorisations of clinical trials/notifications issued by the NMA of non-interventional studies carried out with medicinal products for human use in Romania, the repealment of Art. 20 and the completion of Art. 26 from the regulations concerning the manufacturing/import authorisation of manufacturers and importers dealing with medicinal products for human use, including investigational medicinal products and the granting of the Good Manufacturing Practice (GMP) certificate to manufacturers of medicinal products and/or active substances.

The following have been submitted for discussion and approval:

The Procedure for dealing with serious GMP non-compliance or voiding/suspension of CEPS which requires coordinated administrative action, modification of the procedure for issuing parallel import authorisations for medicinal products for human use, approval of the Community format of the Good Manufacturing Practice (GMP) inspection report, approval of the Regulations

concerning the supply of free medicine samples for human use authorised for marketing in Romania.

Eight scientific or procedural guidelines have been discussed and approved, issued by the translation and adaptation of the European Commission guidelines.

The approved guidelines refer to important aspects of NMA activities of which we hereby mention the following: Good Manufacturing Practice of medicinal products for human use, viral safety evaluation of investigational medicinal products for biotechnology, use in clinical trials of investigational medicinal products and other medicinal products, requirements concerning the clinical dossier for oral inhalation medicinal products, allergen products, change of classification for supply of medicinal products for human use, readability, clarity and ease in using information concerning the prospect and the labelling of medicinal products for human use etc.

Other Scientific Council Decisions aimed at the approval of the changes in the European models of the Patient's Leaflet, Summary of Product Characteristics (SmPC), information on the labelling of medicinal products authorised for marketing in Romania, approval of the modification of terms to be used when issuing the leaflet, SmPC and information on labelling, approval of new Romanian Standard Terms for pharmaceutical forms, label, closure systems, routes of administration, in accordance with those adopted by the Commission of the European Pharmacopoeia and approval of the consolidated version of the Romanian Standard Terms adopted throughout the years through Scientific Council Decisions.

In the course of the meetings of the Scientific Council, other important aspects in the medicinal product field were debated, as well as the evaluation of scientific arguments in view of modifying the status of certain medicinal products from the prescription viewpoint (on or without medical prescription), modifications proposed by Marketing Authorisation Holders (MAHs).

2. Activity of the NMA Administration Council (AC)

Activities of the Administrative Council develop according to provisions of Section 2, "Administrative Council organisation and functioning", of Government Ordinance no.125/1998 on the set up, organisation and functioning of the National Medicines Agency, approved by Law no. 594/2002, as amended.

From a procedural perspective, Administrative Council decisions of normative nature are approved through orders of the Minister of Health and published in the Official Gazette of Romania, Part I.

In 2009, the NMA Administrative Council (AC) carried out **11** working sessions, adopting **52** decisions, **7** of which are normative decisions, approved through orders of the Minister of Health.

The AC regulatory scope has covered the entire range of administrative activities under its competence, mainly ruling on administrative issues related to improving the organisation and functioning of the NMA: approval of changes in

the NMA organisational structure, approval of the NMA job list, of the NMA incomes and expenses budget, and approval of the collective labour contract at unit level.

An important goal of the Administrative Council was the approval of tariffs and maintenance fee value of the marketing authorisation carried out by the National Medicines Agency, a decision which was approved through an order of the Minister of Health.

The need for adopting new tariffs has been determined by the new administrative policy enforced by the Romanian Government concerning the reorganisation of the pricing system of the services performed by the public institutions for third parties (natural/legal persons). In this context, the number of NMA tariffs was diminished from 339 to 245, of which 229 maintained the same value from the latest regulation act, while 16 tariffs have been reconsidered by being merged.

As far as the theme is concerned, the Administrative Council decisions managed to cover the issues of the current activity:

- approval of the 2009 regulations regarding the organisation and functioning of the NMA;
- approval of the 2009 NMA Internal Regulation;
- update of the Regulations on the organisation and functioning of the NMA Commissions;
- approval of the 2008 NMA Activity Report.

Within the Administrative Council, the set up of an ongoing security structure has been proposed and approved. This has been imposed by the complex nature of the information handled by the NMA and by the need to ensure protection of the respective information in accordance with Law 182/2002 on the protection of classified information, as amended.

3. Regulatory Activity

The activity of the NMA in the field of legislative regulation continued at a fast pace in 2009, 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, including constant improvement of the regulation/authorisation activity, both at EU and international level.

The set up of standards required for the integral implementation of the provisions of Title XVII – The medicinal product of Law No. 95/2006 was continued.

Moreover, several regulatory documents have been updated as a consequence of Romania’s EU accession and of the NMA status as a European competent authority in the field of the medicinal product.

New rules and procedures have been issued:

- The Procedure for dealing with serious Good Manufacturing Practice (GMP) non-compliance or voiding/suspension of CEPS, which requires coordinated administrative action.

The purpose of this procedure is to ensure a coordinated approach of potential healthcare risks in all cases of serious non-compliance with GMP rules, observed in Manufacturing Authorisation Holders, in a manufacturer established in a third country or in an active substance manufacturer.

- Rules on providing free medicine samples authorised for marketing in Romania.

These rules have been issued through the additions brought to Art. 807 of Law No. 95/2006 on the granting of free medicine samples in order to have a clear situation and a perspective view on these.

A significant number of regulations and procedures issued and adopted in 2009 represent the updated versions of the previous ones, as amended:

- the modification of regulations on the marketing authorisation and surveillance of medicinal products for human use (approved through SCD No. 11/31.03.2006)
- the modification of the regulations on the authorisation by the NMA of clinical trials/notification to the NMA of non-interventional studies on medicinal products for human use in Romania (approved through SCD No. 52/2006)
- completion of Art. 26 and repealment of Art. 20 of regulations for manufacturing/import authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and granting of the Good Manufacturing Practice certificate to manufacturers of medicinal products for human use and/or active substances (approved through SCD No. 19/2008)
- the update of the regulations on the export of medicinal products for human use (approved through SCD No. 16/2006)
- modification of the issuing procedure of the parallel import authorisations for medicinal products for human use
- modification of the European patterns for the leaflet, Summary of Product Characteristics and information concerning the labelling of medicinal products authorised for marketing in Romania (approved through SCD No. 2/27.01.2006)
- modification of the terms which should be used when editing the leaflet, the summary of product characteristics and information on the labelling of medicinal products authorised for marketing in Romania (Approved through SCD No. 3/27.01.2006)

Similar to the harmonisation of the national legislation with the European legislation, 8 European guidelines have been adopted (scientific/procedural guidelines), issued by translation and adaptation of European Commission Guidelines:

- Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents
- Guideline on the use of Investigational Medicinal Products (IMPs) and of other medicinal products in Clinical Trials

This Guideline aims to clarify and provide additional recommendations concerning the definition of investigational medicinal products and specific recommendations on the use of non-investigational medicinal products, in accordance with the applicable EU legislation.

- Guideline on the viral safety evaluation of biotechnological investigational medicinal products

This Guideline enables a harmonised approach towards the European Union level for the sponsor and for the regulatory authorities, concerning the viral safety evaluation of biotechnological investigational medicinal products during clinical development.

- Guideline on allergenic products: manufacturing and quality aspects.

The new Guideline establishes recommendations concerning quality for biological products, including allergenic extracts derived from natural materials and allergens obtained through recombinant DNA, used in specific immunotherapy or for *in vivo* diagnosis of IgE-mediated allergic diseases.

- Guideline on Good Manufacturing Practice for medicinal products for human use

The previous GMP Guidelines have been updated, and 19 annexes were modified; in addition, a new annex was introduced, Annex 20, dealing with Quality Risk Management. The proposed modification is part of the measures taken by the European Community in view of implementing Guideline ICH Q9 on Quality Risk Management.

- Guidelines on change in classification for supply of certain medicinal products

The Guideline is intended for use by the marketing authorisation holders (MAHs), requiring the change of classification of a medicinal product, as well as by the competent authorities in order to facilitate harmonisation within the European Community (EC) of medicinal products released via medical prescription and medicinal products released without medical prescription.

- Guidelines on the readability, clarity and ease of use of information regarding the label, package and leaflet of medicinal products for human use

The purpose of this guideline is to provide guidance on how to set up projects related to labelling and leaflet, so that the patients are able to easily understand and use them.

- Guideline on the Summary of Product Characteristics (SPC).

The Guideline describes in detail how the information related to the medicinal product should be presented by the applicants under each section of the SPC.

Moreover, the following have been issued and approved:

- The community format of the Good manufacturing Practice (GMP) inspection report.
- New Romanian Standard Terms for certain pharmaceutical forms, label, closure and administration systems, in accordance with the Standard European Terms approved by the European Pharmacopoeia Commission.
- The consolidated version of the Romanian Standard Terms for pharmaceutical forms, primary packages, closure and administration systems.

4. Activity of the NMA Commission

4.1. Marketing Authorisation Commission

The marketing authorisation commission performs its activity in compliance with the Decision of the NMA President and with its own organisational and functioning regulation, approved by the Administration Council Decision.

The membership of the Marketing Authorisation Commission has been updated through NMA President Decision No. 654/2009 and consists of: the NMA President and Vice-president, the heads of the following departments: authorisation, post-authorisation, quality control, biological product control, pharmaceutical inspection, logistics-IT and electronic data handling, also of department and office heads within the authorisation and post-authorisation departments.

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 2009, the Marketing Authorisation Commission conducted **44** working sessions to discuss **975** evaluation reports for medicinal products for human use and to formulate an opinion regarding their marketing authorisations.

Therefore, out of the **975** medicinal products which have been reviewed by the commission:

- 942 medicinal products have been accepted for grant of marketing authorisation, and

- the decision for **33** has been postponed.

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

The commission functions based on the Decision of the NMA President and according to its own organisational and functioning regulations, as approved by the Administration Council decision.

The membership of the Commission has been updated through NMA President Decision No.652/2009 and is made up of the NMA President and Vice-president, the heads of the departments for pharmaceutical inspection, authorisation, post-authorisation, raw materials and finished products control, biological products evaluation and control and GMP, GLP, GALP, GCP and pharmacovigilance inspectors within the pharmaceutical inspection department.

The Commission examines inspection reports drafted by NMA inspectors, reports relating to compliance of inspected sites with GMP, GLP, GPAL, GCP rules and/or other problems regarding 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 2009, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted **11** working sessions for examination of **161** inspection reports, of which:

- 29 inspection reports on compliance with Good manufacturing Practice rules
- 116 inspection reports on compliance with Good Distribution Practice rules
- 9 inspection reports on compliance with Good Clinical Practice rules
- 2 inspection reports on compliance with Good Laboratory Practice rules
- 5 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 the Decision of the NMA President and according to its own organisational and functioning regulation, as approved by the Administration Council decision.

The membership of the Commission has been approved through NMA President Decision no. 651/2009 and is made up of the NMA President and Vice-president, the head of the Pharmaceutical Inspection Department and the head of the Juridical and Legislation Department.

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 2009, no violations of the Ethic and deontology code by NMA 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 caused by problems in medicinal product quality, safety and/or efficacy functions based on its own regulations for organisation and function, as approved through decision of the NMA Administration Council.

The membership of the commission has been updated through NMA President Decision No. 653/2009 consisting of the NMA President and Vice-president, heads of the following departments: authorisation, post-authorisation, quality control, biological product control, pharmaceutical inspection, logistics-IT and electronic data handling, juridical, policies and strategies, and the head of the pharmacovigilance department and of risk management.

In 2009, the Commission convened in 9 working sessions to discuss issues related to medicinal products safety, notified through the rapid alert system, EMA press releases or other information on certain quality non-compliances as transmitted by competent authorities in EU Member States or the European Economic Area, the PIC/S (Pharmaceutical Inspection Cooperation Scheme),

EDQM (European Directorate for the Quality of Medicines & HealthCare) or marketing authorisation holders.

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

5. Evaluation, post-authorisation and related activities

In view of optimizing the authorisation, post-authorisation and related activities and in view of the harmonisation of the structure/functioning of departments/services with the manner of structuring/functioning of the European Medicines Agency (EMA) and of other regulation authorities in the field, the Assessment-Authorisation Department (AAD) has been divided into 2 departments, the **Authorisation Department** (AD) – which ensures the assessment of documents related to the marketing authorisation of medicinal products and the **Post-Authorisation Department** (PAD) – assessing the documents related to the activities undertaken during the post-authorisation period.

Some structures which previously belonged to the AAD [Offices for receiving documentation and samples, issuing of marketing authorisations, and the archives] have been transferred to the logistics and IT department, and electronic data handling (newly established in order to optimize the documentation flux within the NMA and in view of a better communication with the MAHs or third parties) and in the general administration and heritage department.

Moreover, in 2009, certain services and offices have been renamed, while new services/offices have been set up, in accordance with current and prospective activities arising from the attributions of departments in accordance with the pharmaceutical and European legislation in force, aiming for flux fluidisation and improvement of the activity.

Therefore, at the end of 2009, the Authorisation Department had the following organisational structure:

- National Procedure Administration Service
- European Procedure Administration Service
- Centralised Procedure Administration Service
- European Procedure Evaluation Service
- National Procedure Evaluation Service

At the end of 2009, the organisational structure of the Post-Authorisation Department consisted of:

- National Procedure Variations Service
- European Procedure Variations Service
- Pharmacovigilance and Risk Management Service
- Renewal Service

5.1. Marketing Authorisation of medicinal products for human use

In 2009, activities related to 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 and decentralised procedure, and repeat use mutual recognition procedure).

A total number of **1621** applications for authorisation/renewal of marketing authorisations were submitted to the National Medicines Agency in 2009:

- **794** applications for authorisation through national procedures, of which: **281** applications for authorisation and **513** applications for renewal of marketing authorisations;
- **827** applications for authorisation/renewal of marketing authorisations were submitted through European procedures with Romania as a Concerned Member State, of which: **631** through decentralised procedures, **148** through mutual recognition procedures, and **48** for the renewal of marketing authorisations through European procedures.

A number of **51** applications for marketing authorisation have been received through European procedures with Romania as the Reference Member State, of which **9** have been accepted in order to be enforced in 2010.

In 2009, following the assessment of the documentation concerning quality, non-clinical safety, efficacy, information concerning the medicinal product, 942 dossiers have been issued, leading to the granting of **942 marketing authorisations** for medicinal products for human use, (**589** authorisations and **353** renewals of marketing authorisations), of which:

- **359** applications for authorisation through *national procedure*, of which 118 applications for authorisation submitted until January 2007 (74 authorisations, 44 renewals of marketing authorisation) and **241** applications for renewal of marketing authorisation submitted after 2007 (83 authorisations, 158 renewals of marketing authorisations);
- **583** marketing authorisation applications through *European procedures,* of which **432** marketing authorisations and **151** renewals of marketing authorisations.

It must be emphasised that, in 2009, the first European authorisation procedure has been completed (Decentralised Procedure - DCP), with Romania as the Reference Member State.

51 decisions have been issued for the withdrawal of **134** MAs of which **38** decisions (for **107** MAs) at the request of MAHs and **13** decisions **(**for **27** MAs) following the enforcement of provisions of Law No. 95/2006 on healthcare reform, as amended (authorisation through European procedures of previously authorised medicinal products through national procedure).

The authorisation/renewal procedure for **65** medicinal products was discontinued (**49** through national procedure and **16** through European procedures), of which:

- **63** at the request of the manufacturer;
- 2 by the NMA in accordance with the provisions of Art. 2 (1)(c) from Order of the Minister of Health 1203/2006 for the approval of standards regarding the application for transferring marketing authorisations.

In 2009, a new activity within the Authorisation Department consisted of the receipt and assessment of applications for parallel import authorisations. 14 applications have been received and assessed, 2 parallel import authorisations have been granted.

5.2. Post-Authorisation variation assessment activity (except for clinical variations) of the terms of the Marketing Authorisation (MA)

5.2.1. In 2009, a number of **5270** applications for variation of MA terms were submitted for medicinal products authorised through **national procedure or undergoing MA renewal procedure**, of which **3921** applications for type I variations, **898** applications for type II variations, **212** applications for MA transfer and **239** applications for modification of design and package labelling.

The NMA assessed and approved **4146** applications for variations for medicinal products (received in 2007, 2008, 2009), except for clinical variations, authorised through **national procedure** or undergoing MA renewal procedures, of which:

- **3252** type I variations;
- **575** type II variations;

- **197** applications for MA transfer;
- **122** applications for modification of the design and package labelling.

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 2009:

- **2142** type I variations
- **657** type II variations
- **115** applications for MA transfer
- **39** notifications in accordance with Art. 61 (3) of Directive 2001/83/EC

In 2009, **952** applications for variations for medicinal products for human use authorised through decentralised/mutual recognition/repeat-use mutual recognition procedure were approved, namely:

- **789** type I variations
- **76** type II variations
- **81** applications for MA transfer
- **6** 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 2009, the NMA received **288** applications for clinical trial approval, as follows:

- **9** applications for **phase I** clinical trial approval
- **82** applications for **phase II** clinical trial approval
- **137** applications for **phase III** clinical trial approval
- **21** applications for **phase IV** clinical trial approval**.**
- **39** applications for observational clinical trials

and

- **75** applications for bioequivalence studies

Until the end of 2009, **240** clinical studies were assessed and **223** authorisations were issued for:

- **7** phase I clinical trials
- **70** phase II clinical trials
- **127** phase III clinical trials
- **19** phase IV clinical trials**.**
- **39** observational clinical trials have been assessed and approved

The following were assessed:

- **83** bioequivalence studies of which **73** were approved, and protocol amendments were sent for 10 such studies.

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

In 2009, the National Medicines Agency assessed for approval **370** advertising materials for OTC medicinal products, addressing the general public.

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

The content of **70** advertising materials addressing persons qualified for prescription or supply of medicinal products was assessed and approved.

11 notifications on denial of advertising approval were issued.

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

15 responses to advertising related complaints;

No sanction for disregard of legislation on approval of advertising material has been issued.

5.5. Pharmacovigilance

The activity of the National Pharmacovigilance Centre operating within the NMA is conducted in accordance with Title XVII - The medicinal product of Law No. 95/2006 on healthcare reform, as amended, and specific European guidelines.

In 2009, pharmacovigilance activities materialised in the following:

a) Management of safety data from spontaneous reporting;

- **363** Adverse reactions reporting sheets from Romania;
- **839** works imposed by the monitoring of the single European electronic database of adverse reactions, EUDRAVIGILANCE, for medicinal products used on Romanian territory.
- **81** 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 NMA – the National Pharmacovigilance Centre.
- **397** answers to MAH applications concerning adverse reactions transmitted to the NMA related to medicinal products authorised in Romania; **64** adverse reaction reports were handled.
- **22** response letters on MAH requests concerning pharmacovigilance-related aspects.

b) Collection, validation and archiving of **1913** Periodic Safety Updated Reports (PSUR) related to safety of medicinal products;

- **1088** Periodic Safety Updated Reports (PSUR) related to safety of imported medicinal products;
- **825** Periodic Safety Updated Reports (PSUR) related to safety of Romanian medicinal products.

53 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 **51** EMA press releases of **14** EMA questions and answers documents, **36** Lines to take proposed by the EMA, **22** Direct Healthcare Professional Communications, handling of information letters from the MAHs on safety issues of medicinal products.

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

- 9 NUI replies to applications by EU certain authorities - 7 actions in collaboration with the Pharmaceutical Inspection Department with regards to rapid alerts.
- 3 replies 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:

- **510** 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)
- **444** assessment reports of the summary of the pharmacovigilance system of the marketing authorisation applicant through national procedure.

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.

At Ministry of Health request, the statutes of innovative, original, generic, and first generic were established for **5340** medicinal products included in the successive versions of Canamed in 2009. At the end of the year, there were **7288** trade names corresponding to **1239** International Non-proprietary Names (INNs) in the NMA product index.

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

a) Management of responses received in application of art. 729 and 730 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, i.e. notification of temporary or

permanent discontinuation of manufacturing and notification of actual medicinal product marketing ("sunset clause");

- Verification of the **7288** medicinal products included in the product index at the end of 2009;
- of which **2100** authorised through centralised procedure, their handling concerning enforcement of the "*sunset clause*" being the responsibility of the European Medicines Agency (EMA);
- for **5188** medicinal products, the NMA has received marketing reports, of which **400** have been identified as potentially falling under *"sunset clause"* criteria, the final decision to be taken following the centralisation of present data, at the beginning of 2010.

b) 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: 21 new medicinal products have been introduced;

c) Provision of information required by certain EU competent authorities on MAs granted by the NMA, in view of granting parallel import authorisations for certain medicinal products imported from Romania: 164 medicinal products;

d) Management of European Commission (EC) decisions on referrals, elaboration of letters to MAHs involved requesting applications for variations in implementation of the EC Decision and of MAH responses on the EC Decision: 161 medicinal products, corresponding to 7 INNs.

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 2009, 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:

- **34** GMP certificates (for Romanian and foreign manufacturers);
- **57** manufacturing authorisations, annexes included;
- **72** import authorisations, annexes included;
- **2** Good Laboratory Practice **(**GLP) certificates;

- **17** qualified person certificates;
- **1** authorisation for independent control units.
- **225** 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;
- **131** applications for exemption from legal provisions concerning the packaging/labelling of medicinal products have been solved;
- The databases referring to inspection encoding, 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 2009 consisted of:

- **43** GMP inspections in Romania, in view of manufacturing authorisation/import/certification;
- **9** certification inspections of GMP conformity of pharmaceutical companies from third countries;
- **3** inspections were conducted before grant of the MA for Romanian medicines manufacturers;
- **4** GLP inspections;
- **1** GALP inspection at independent quality control units;
- **24** inspections in view of assessing compliance with GCP rules;
- **1** GLP inspection at units performing nonclinical toxicity studies;
- **5** pharmacovigilance inspections at the MAH, of which 2 inspections of Romanian MAHs and 3 inspections of the Romanian representative of the MAH.

Commencing March 2009, on approval of tariffs for PID services, the PID has enforced the regulatory provisions in the field of inspection at wholesale distribution units.

In 2009, within the inspections performed in view of Good Distribution Practice (GDP):

- **307** inspections in view of authorisation were performed;
- **283** wholesale distribution authorisations were granted;
- **4** authorisations issued by the Ministry of Health were recalled, in accordance with previous legislative regulations, following the finding of critical deficiencies which occurred during inspections in view of authorisation;
- a database concerning wholesale medicinal products distributed was organised;

- the documentation for 335 export declarations was examined, following which export declarations were approved for **863** medicinal products manufactured in Romania.

The documentation for 27 requests to issue a Qualified Person certificate was examined and evaluated, and 17 such certificates were issued.

The monitoring activity of medicinal products and the handling of rapid alerts was objectified by:

a) Carrying out the sampling plan on monitoring the quality of medicinal products:

- From the **30** products proposed, **24** were sampled, and 6 were not found in the distribution network; - The results issued from laboratory analysis have been the following:
- **19** samples have been declared compliant;
- **4** products are under analysis;
- **1** product had unproductive testing parameters; the manufacturer was requested to modify the quality specifications of the product, which the manufacturer did (pending variation).

In addition to the sampling plan, the following samples were provided in 2009:

- **5** 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.
- **4** medicinal products have been sampled in view of solving a finding concerning the medicinal product quality, of which **3** have been declared noncompliant with quality standards and have been withdrawn from the territory;
- **3** 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):

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

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

- **236** 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 20 hospitals still comes from unauthorised manufacturers).

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:

- **25** common actions with specialised local bodies, carried out by territorial inspectors (13 Cluj, 2 Satu Mare, 8 Târgu Mureş, 2 Bacău).

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

- from 116 resolved complaints, 64 have resulted in withdrawal from the territory of the respective medicinal product.

f) withdrawal from the market of medicinal products showing quality non-compliances: in 2009, the NMA requested the withdrawal of **64** medicinal products, of which:

- **7** medicinal products were identified to have intrinsic quality nonconformities;
- **57** medicinal products had nonconformities with the inscriptions on the packaging/leaflet.

g) Rapid Alert system:

- in 2009, 78 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Co-operation 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:

- 6 cases reported (1 by Romania) on non-compliance with GMP rules by active substances or medicinal products manufacturers from third countries, for which the steps followed were in accordance with the joint decisions made by authorities;
- 11 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 NMA website and introducing in the EudraGMP database the information concerning the NMA activities of manufacturing authorisation/import/GMP certification.

In September 2009, the PID was audited by inspectors from European competent authorities (France and Greece), who carried out an evaluation of conformity of GMP inspections legislation, GMP inspection methods and the quality system implemented by the PID towards the legislation and the European requirements in this field (”pre-MRA audit”).

In their report, the audit team found that the inspection system applied by the PID functions according to the same principles and regulations as in the other EU member states and that the inspectorate in Romania is prepared for the

inspection performed by the regulatory authority in Canada, for the Mutual Recognition Agreement (MRA) of Romania with MRA member states.

In November 2009, one of the PID inspectors, nominated on the list of the auditors for the BEMA benchmarking programme, participated in the audit of the quality system of the French Agency for the Safety of Health Products (AFSSAPS).

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 assuring 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 standard requirements SR EN ISO 9001/2001 and standard SR EN ISO 17025/2005.

The NMA Medicines Quality Control Department is integrated into the European network of Official Medicines Control Laboratories (OMCL), coordinated by the EDQM and participates in all related activities.

7.1. Quality control of non-biological and biological medicinal products

The main types of analysis performed by the Medicines Quality Control Department (MQCD) are as follows: physicochemical analysis, pharmaco-toxicological analysis, immunogenetics and pathological anatomy analysis, micro-biological analysis and radio-pharmaceutics analysis.

Core activities in 2009 dealt with:

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

In 2009, **636** medicinal products were analysed, of which:

- **201** obtained through chemical synthesis;
- **435** biological medicinal products (vaccines, sera), the majority of which manufactured by the "Cantacuzino" Institute

Analysis of the 636 medicines necessitated 1970 physicochemical, pharmacological, immunological and microbiological determinations. To this, 868 internal analyses were added of environmental checks, calibration of equipment, testing of the suitability of the systems and equipment used.

Products with non-compliances, for which inadequate test reports were issued, were 12 in number, these being:

- Counterfeit products (10 in number, in which the following were detected: absence of active substance, presence of active substances other than the stated, concentration of active substance other than the declared value, or presence of impurities over the permissible limit)

- Biological products (2 in number) rejected under the parameter "microbiological sterility" inappropriate.

b) Evaluation of chemical documentation (DSSA, clinical studies, finished product).

In 2009, the DCCM was assessed for 1185 chemical products, namely:

- 838 Assessments for authorisation of medicinal products undergoing the procedure;
- 347 Assessments - addition to evaluation reports.

c) External cooperation concerning medicinal product quality.

As in previous years, the DCCM continued in 2009 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)

i. PTS studies (Proficiency Testing Scheme): PTS has participated in four 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 medicines.

ii. Surveillance studies on medicinal products authorised through European procedures: since 2008, the EDQM has applied, active NMA, DCCM respectively, involvement in the analysis of medicinal products approved through European procedures in accordance with Document PA / PH / OMCL (06) 116 7R "Cooperation in the quality of post-marketing surveillance of medicines approved by the mutual recognition and decentralised procedures." The procedure involves consulting the EDQM - MRP database, in which approved medicines have been identified in Romania, as a Member State concerned and analysed by another OMCL laboratory in the European Community.

iii. Studies concerning check of the quality of medicinal products authorised by the EMA through Centralised procedure.

After EU Accession in 2007, the NMA has been involved in other EDQM financed studies as well. Samples forwarded to the laboratories have proven expertise in medicines quality control and meet the requirements of ISO/CN 17025/2005, addressing process-based activities. In 2009, the NMA distributed for review 4 batches of an ophthalmic medicine (three commercial batches, collected by the European Inspection Service from three EU countries and a standard batch).

- The International Pharmaceutical Federation (FIP).

The DCCM is an affiliated member of the FIP, which takes annual part in professional studies of the same level of difficulty as PTS tests initiated by the EDQM. In 2009, they participated in two FIP studies. The accuracy of results and

working techniques used in our laboratories were confirmed by reports from the FIP Central Laboratory.

7.2. Evaluation and control of biological medicinal products

The activity of the Biological Product Control Department (BPCD) in 2009 was marked and influenced by the H1N1 influenza pandemic, officially declared by the WHO on 11 June 2009. Since the Ministry of Health together with the National Institute for Research and Development for Microbiology and Immunology (NIMRD) decided on production of a pandemic vaccine for the local market, the NMA has been involved in intense activities through the BPCD regarding advice for choosing the best solution for this purpose and then evaluating and monitoring the CANTGRIP monovalent, purified, inactivated and fragmented pandemic vaccine.

Also in 2009, renovations were started on the 5th floor – the B building of the NMA headquarters in order to relocate the BPCD. Development of new blank was completed in December 2009; actual relocation will take place in early 2010.

Activity of the department covers the following aspects:

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

a) Control Laboratory:

- 534 sets of products have been analysed corresponding to a number of 3531 laboratory tests;
- 561 test reports were issued, including:
- 528 Bulletins for finished products
- 33 Bulletins for intermediate and bulk products (In 2009, field tests performed in the BPCD were extended to intermediate and bulk products, to comply with EDQM recommendations).

In 2009, new methods of biological control of products were introduced into laboratory practice: determining absence of live micro-bacteria in tuberculin potency in vitro determination by ELISA for anti- B hepatitis vaccine, determination of albumin content in influenza vaccine by ELISA (initiation of method validation).

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. BPCD representatives started sampling in June 2009. Finished, intermediate and bulk products were used.

For the biological products tested, 194 batch release certificates were issued and two bulletins of non-compliance (for two sets of biological product for which the test was rejected by the DCCM).

158 commercial intentions were recorded related to products for which 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 part of resolving complaints, on NIMRD request, a sample testing was performed of samples labelled CANTGRIP pandemic vaccine, delivered by the Criminal Investigation Service Sector 3, Bucharest. Following laboratory testing, this proved to be a counterfeited product.

B. Assessment of documentation submitted for Marketing Authorisation/Marketing Authorisation Renewal through national, mutual recognition and decentralised procedures, as well as in view of variation:

- 29 have been medicinal products evaluated through national procedure, for which 52 reports have been issued;
- 254 MA variations have been assessed through national procedure;
- 33 variations have been assessed through the mutual recognition/decentralised procedure, for which 63 reports have been issued.

C. Post-authorisation surveillance of medicinal products for human use: 146 batches of commercialised and authorised biological products have been registered in the DSCB database.

8. Communication and transparency

The NMA 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 95/2006, Title XVII – The medicinal product on transparency in the work of EU competent authorities.

8.1. External communication

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

On its website, the NMA publishes bilingual quarterly newsletters (BN), 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 following is published within the NMA BN content:

- Laws, ordinances, Government decrees in the field of medicinal products for human use or other areas of NMA interest
- Orders of the Minister of Health for approval of NMA Scientific Council decisions and orders of the minister of health in other areas of NMA interest
- Decisions of the NMA Scientific Council
- Decisions of the NMA Administrative Council

- Quarterly list of marketing authorisation/ marketing authorisation renewal applications submitted to the NMA
- Quarterly List of EMEA newly centrally authorised medicinal products, for which the European Commission issued the decisions on translation into Romanian of medicinal product information
- Quarterly list of medicinal products authorised for marketing by the NMA
- A quarterly list of medicinal product batches recalled because of quality defects.

The NMA 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, active substance, marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, release mode etc. and publishes it on its website. In 2009, implementation began, for each medicine, of electronic versions of the summary of product characteristics (SmPC), leaflet and information on labelling and inscription.

The NMA 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 medicines;
- Direct Health Care Professional Communications;
- Notifications to marketing authorisation holders (MAH) or other interested parties on issues of interest;
- SmPC 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 in Romania which are prescription medicines;
- List of over-the-counter (OTC) products authorised for circulation in Romania;
- List of valid orphan medicinal products;
- NMA employees assigned as representatives or alternates of the Administrative Council;
- NMA employees assigned as representatives or alternates of the Administrative Council, scientific committees and working groups of the European Medicines Agency (EMA)
- list of NMA nominated EMA experts.

To assist external partners involved in EU procedures for marketing authorisation of medicinal products for human use, there are two dedicated categories on the NMA website:

1. CP (Centralised procedure)

2. MRP and DCP (Mutual Recognition Procedure and Decentralised Procedure),

Which include contacts and a series of useful information for marketing authorisation through these procedures, namely: regulations, forms required, bank accounts, notices and warnings to the attention of MAH involved in European procedures. All this information has been improved and updated in both the Romanian and English versions, with up to date information collated by topic.

The following categories have proved of great interest to users of the NMA website:

- 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.

Evidence of increased stakeholder interest for information published by the NMA website has been the large number of visitors, growing by approximately 200,000 visitors / year in 2009, which means an average of 16,670 visitors per month.

Regarding transparency, the NMA has continued and developed, as far as administrative capacity goes, the application of Law 95/2006, in Title XVII – The Medicinal Product, transparency in the work of European medicine authorities by:

- Establishing its own rules of standard operating procedure of NMA committees, which are publicly available upon request;
- Keeping versions of agendas and minutes of the Commission for marketing authorisations and the Commission for GMP, GLP, GALP, BPD, GCP and pharmacovigilance available to the public on request.
- Keeping versions available to the public, upon request, of medicine evaluation reports.

In 2009, the NMA continued to inform stakeholders about its work and publications through means other than its own newsletter.

Thus, the NMA Annual Report in 2008 was again published as a bilingual booklet, highly appreciated by NMA partners.

Also, in 2009, articles were published on various aspects of the NMA in Romanian journals (“Farmacist.ro","Medical Business","Viata Medicala ").

NMA representatives participated in numerous specialised scientific / professional works organised in Romania and abroad.

8.2. Internal communication

In 2009, professional and organisational information on the intranet was continually supplemented and updated, thus enabling NMA employees to stay up to date on matters in a good and timely fashion.

The following information can be found on the intranet by NMA employees:

- the NMA President's instructions;
- NMA policy on quality;
- NMA regulations;
- Glossary on quality assurance;
- Activity plans of the departments;
- Useful forms;
- Information on Pharmacopoeia services
- Information on training courses organised by specialised companies;
- Reports by personnel who have undertaken training courses both in Romania and abroad;
- Staff training situation;
- Staff motivation survey results;
- Useful information;
- Useful addresses etc.

9. Quality Management Activity

In 2009 as well, special attention was paid to implementation, development and improvement of the quality management system across all NMA departments.

Activities covered were:

- Actions to develop/revise quality management system documents, their implementation and assurance of compliance of each department's current work with such management system documents. For some departments, new versions of the Quality Manual have been developed/revised, and new Standard Operating Procedures (SOPs), specific work instructions, and interdepartmental procedures have been developed. Job descriptions and individual job descriptions have been updated, and new plans for staff training were set up.
- Internal and external audits.

The main focus of the NMA structure responsible for quality assurance was maintaining and continuously improving the quality management system.

The internal quality audit process was conducted according to the Internal Quality Audit Programme for 2009 and it included an audit of all the NMA departments. The findings and conclusions of internal quality audits, which aim to establish compliance with SOP of specific audited processes, were recorded in the internal quality audit reports, which included improvement and action plans developed by the audited departments.

From 30.08.-04.09.2009, the Pharmaceutical Inspection Department (PID) was audited by inspectors of the competent authorities in the EU (France and Greece), who conducted an assessment of compliance of GMP legislation, GMP

inspection techniques and of the quality system implemented by PID, compared to European legislation and requirements in the field (Mutual Recognition Agreement pre-audit).

In their report, the audit team found that the inspection system applied by the PID functions by the same principles and regulations as other EU Member States and that the inspectorate in Romania is ready for inspection by the regulatory authority in Canada for Romania's mutual recognition agreement (MRA) with MRA Member States.

In November 2009, one of the PID inspectors, nominated on the list of auditors for the BEMA benchmarking program, participated in the quality system audit of the French Agency of Sanitary Safety of Health Products for (AFSSAPS).

Also, a PID inspector actively participated with two papers on the training of GCP auditors and inspectors, organised by the Drug Information Association (DIA), London.

- Participation of NMA specialists in specialised quality management training.

In 2009, all personnel involved in quality assurance in each department attended the training course in: ISO 9001:2008 Quality management, provided by Quasaro.

9. International Relations

In 2009, NMA specialists' participation in activates of the various collaborating European institutions and bodies continued as follows:

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

Since 2003, NMA representatives have actively participated in the EMA initiative as active observers in the working groups, scientific committees and groups to implement information technology dedicated to medicinal products for human use.

This participation has been and continues to be the most effective way to keep the NMA connected with European activities in the medicinal product field.

Having gained full membership as of 2007, of EMA scientific committees and working groups of, NMA experts participated in 2009 in over 100 of their meetings.

The scientific committees and working groups of the EMA are as follows:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Paediatric Committee (PDCO)
- Committee for Advanced Therapies (CAT)

- CHMP Working Group for Biotechnology
- CHMP Working Group effectiveness
- CHMP Safety Working Party
- CHMP Pharmacovigilance Working Party
- CHMP Working Group for blood and plasma
- CHMP Vaccines Working Party
- Joint working group CHMP / CVMP on quality issues
- CHMP Working Group with patient and consumer organisations
- Working for GMP/GDP inspectors
- Working sub-group for EudraGMP database
- Working Group for GCP inspectors
- Working Group for Pharmacovigilance inspectors
- Working Group for GLP inspectors
- Working Group for the database of medicines approved in the EU (EudraPharm TIG)
- Working Group for the adverse reactions database (EudraVigilance TIG)
- Working Group for the European database for clinical trials (EudraCT Clinical Trials TIG)
- Working Group for the European computer network (EudraNet)
- Working Group for the electronic transmission of documents (E-Submission)
- Working Group for controlled terms (European Union Telematics Controlled Terms - EUTCT)
- Working Group on medicines information management (Product Information Management = PIM)
- Working Group on quality review of documents (QRD)
- Working Group for reviewing the invented names

10.2. Participation in the activities of the Heads of Medicines Agencies

NMA representatives also actively participate in meetings of working groups of the European “Heads of Medicines Agencies” Body.

These are:

- Meetings of Heads of Medicines Agencies
- Co-ordination Group for Mutual Recognition and Decentralised Procedures for Medicinal Products for Human Use (CMD-h)
- EMACOLEX (The European Medicines Agencies Cooperation on Legal and Legislative Issues)
- Working Group for communication professionals
- Working Group on Transparency
- Counterfeiting Working Group
- Working Group to facilitate clinical trials
- Working for homeopathic medicines

- Working Group of Quality Managers

10.3. Participation in the EU Council and the European Commission (EC)

NMA experts participated in 21 meetings of the Working Group on Medical Devices and Medicines of the EU Council, which debated the new draft of the Directive on counterfeiting and pharmacovigilance.

In meetings organised by the European Commission, NMA experts attended meetings of the Standing Committee for Medicinal Products and of the Pharmaceutical Committee and Notice to Applicants, and an ad-hoc EC meeting to develop guidelines for implementing Directive 2001/20/EC on clinical trials.

10.4. Participation in World Health Organisation (WHO) activities

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

In 2009, the NMA issued certificates for medicinal products in the WHO format, for a total of 478 medicinal products by Romanian producers who intended their authorisation in other countries.

10.5. Participation in activities of the Council of Europe

In 2009, NMA representatives attended meetings of the Working Group for classification for the supply of medicinal products for human use and the ad-hoc committee to combat counterfeiting.

10.6. Participation in activities of the European Pharmacopoeia Commission

The NMA designated representative, with membership to the European Pharmacopoeia Commission, actively participated in its working sessions in 2009 and annual meeting of secretaries of national pharmacopoeias for developing countries of the European Pharmacopoeia Convention.

Furthermore, collaboration continued with the European Directorate for the Quality of Medicines (EDQM) in elaborating and updating of "Romanian Standard Terms", in line with those adopted by the European Pharmacopoeia Commission.

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

The activity of the NMA as a member of PIC/S has resulted in active participation in meetings of the Committee of PIC/S Officials and the annual PIC/S seminar on “Inspection of sterile dosage forms”.

10.8. Participation in the European Network of Official Medicines Control Laboratories (OMCL)

In the frame of collaboration with European institutions working in medicinal product quality control, specialists in NMA laboratories took part in 6 studies, as follows:

- 4 PTS (Proficiency Testing Scheme) studies, analytical studies undertaken under EDQM initiative and coordination
- 1 market surveillance study consisting of testing medicinal products authorised in Romania through national procedure
- 1 market surveillance study consisting of testing medicinal products authorised by the EMA through centralised procedure

11. Logistics activity, computer and electronic data management

To optimize the flow of documents within the NMA and for better communication with marketing authorisation holders (MAH) or third-parties, the department was established for Logistics computer and electronic data management.

This department is made up of:

- The Logistics and Information Service;
- The Data and Document Management Service.

The Logistics and Information Service aims to maintain the optimum parameters of communication channels with the EMA and to provide real time information exchange between the NMA and external collaborators (marketing authorisation holders, distributors, healthcare professionals, patients, organisations and associations) ;

In 2009, the database applications programming was continued, namely modifications to 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, statistical data reports were extracted periodically at the request of the Ministry of Health, the National Health Insurance, the NMA President and various NMA departments.

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

The administration of the NMA network was assured, comprising of 9 servers and 250 workstations;

Also, maintenance and troubleshooting of the software and hardware of existing computers was performed, as well as installation and configuration of new computers purchased in 2009.

Internet and intranet NMA websites were maintained and updated, and the following was accomplished: the weekly back-up server data of the NMA, the regular back-up data and daily NMA website, configuring and maintaining antivirus software.

In continuation of good cooperation with the EMA, the forms were sent with answers relating to preparations for the electronic transmission of data and steps have been taken for access to the EMA managed NMA experts database.

IT professionals have participated in the EursIsYours training conducted by Extedo GmbH company representatives at the NMA offices. During the course, participants were informed about a new deadline (January 1, 2010) regarding the ability of competent authorities to receive and manage deposits of non-electronic format files Common Technical Document (Non-eCTD) and/or electronic CTD (eCTD).

The Data and Document Management Service take care of 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 942 drugs approved for authorisation.

Also, the typing of:

- 51 decisions of the NMA president to suspend the MA of 134 medicinal products.
- MA withdrawal decisions issued for medicinal products approved by national procedure, where MA through MRP were issued for the same products.

478 applications were received for WHO form of product certificate, and the same number of certificates were issued

Periodical check was performed of fee payments and tariffs.

The dossiers to be discussed in the Marketing Authorisation Commission were verified.

12. Ensure elaboration and implementation of policies and strategies of the National Medicines Agency

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

- The European Affairs Service
- The Pharmacopoeia Service
- The Communication and Institutional Relations Service

Along with other professional departments, the DPS participated in management of problems relating to the operation of the NMA in the European

network of competent authorities in the field of medicines and to establish the interface between the NMA and stakeholders.

In as far as its administrative capacity, the DPS participated in ensuring transparency in NMA activities, in accordance with the law, consisting of:

- Preparation of the publicly available versions of 30 Agendas and 30 minutes of the Marketing Authorisation Commission;
- Preparation of publicly available versions of 29 national assessment reports for national authorisation procedure and their transmission to the MAH to express consent or certain comments on issues of confidentiality;
- English translation from the public versions of 20 evaluation reports by the European mutual recognition procedure and decentralised procedure, with Romania as Concerned Member State;
- Summing up and management of publicly available versions, developed by the PID, of the agendas and minutes of the Committee on GMP, GDP, GLP, GALP, GCP and pharmacovigilance inspections.

The DPS handled Scientific Council Decisions (SCD), from their design to publication, in accordance with interdepartmental SOP, by:

- Gathering, verifying and managing 22 SCDs/2009,
- Creation of electronic records of the SCDs, from design to publication, dedicated directories of the Scientific Council (SC) meetings;
- Of the 22 SCDs, 6 are pending approval by Order of the Minister of Health, and the other 16 have been posted on the NMA website and published in the NMA bilingual informative bulletins (IB);
- Participation in the preparation of three sessions of the SC, sending members of the SC documents in electronic/paper versions, updating records and contact details of SC members and drafting of minutes of the 3 SC meetings;

Development of the NMA Informative Bulletins (IB) was continued, which were posted on the NMA website, namely: 4 IB in Romanian (No: 4/2008, 1/2009, 2/2009, 3/2009).

Delays, for objective reasons, of IB translation into English were recovered and 7 IB issues were completed (No: 4/2006, 1/2007, 2/2007, 3/2007, 4/2007, 1/2008, 3/2009).

In collaboration with NMA departments, the DPS participated to update and improve the information contained on the NMA website as well as the NMA intranet.

The Brochure containing the NMA Annual Report for 2008 was developed and presented bilingually and with enhanced graphic and illustrative material.

The translations office provided:

- Translation/verification of the translation of 13 European guidelines;

- Checking the translation of 70 evaluation reports and documents in English, the mutual recognition procedures and decentralised procedures;
- Checking/translating 121 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.
- Translation into Romanian of EudraGMP - User Interface files
- Providing advice to check the translation of SmPCs and leaflets, correspondence and communication in English with European institutions.

Of the activities relating to pharmacopoeia:

- Developing new and revised Romanian Standard Terms consistent with those adopted by the European Pharmacopoeia in 2009, which were approved by Scientific Council decisions and were transmitted on-line to the European Directorate for the Quality of Medicines (EDQM), to be implemented to the European standard terms database;
- Elaboration and approval by the Scientific Council of the consolidated version of the Romanian Standard Terms, including all terms approved over time by Council resolutions;
- Translation, also, of the new European standard combination of terms notified by the EDQM and online transmission to the EDQM, to be implemented in the database combined with European standard terms.

Regarding communication, free access was ensured to public information in accordance with Law 544/2001, both to the media, and the general public, providing information on NMA activities, or information on the safety of medicinal products. For this, the translation bureau has worked with all departments to collect and systematize NMA information requested by the media.

The bureau assured management and monitoring of NMA appointed employee participation in scientific committees and working groups of the EMA, HMA, EDQM, European Commission, EU Council, PIC/S, and ensuring communication with the EMA for the nomination of holders/replacements.

More than 450 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 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.

Recording data electronically has been initiated for documents under debate, on topics, from the permanent representative of Romania to the EU and/or the Ministry of Health.

Electronic e-mails containing decisions from the Representation Commission (EC) on conditionally authorised medicinal products (under Art. 127a of Directive 2001/83/EC), suspension/withdrawal/MA modification (based on art. 107 of Directive 2001/83/EC) and decisions as a result of referral proceedings (under art. 20 and art. 30 of Directive 2001/83/EC) were monitored/managed and redirected to the specialists appointed by the NMA for their implementation.

Electronic records have been initiated for 130 European Commission Decisions, received on paper versions from the Ministry of Foreign Affairs/Ministry of Health in 2007-2009.

The activity of the commission secretariat was assured for handling crisis situations and 12 minutes of the commission meetings were prepared, as well as the meetings and the report of the joint session of the Crisis Management Committee and the MA Committee of 25 November 2009, relating to the grant of MA for the Cantgrip pandemic vaccine.

13. Judicial work of the NMA

Developing the legal framework governing medicinal product authorisation, both at national and European level, has imposed a separation of the legal department, and organising it into three services:

- European legislation Service
- National legislation Service
- Administrative Litigation Service

During 2009, 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.

In carrying out its object of activity, the legal legislation service prepared documentation representing drafted legislation and legislative initiatives of the institution, promoted by the Ministry of Health.

Thus, documentation for the promotion of seven Minister orders, a government decision (with the object of updating regulatory provisions of GD 720/2008 for approving the list of common international names for medicinal products benefiting policyholders, with or without a personal contribution, the prescription, the health insurance system), an ordinance amending the Pharmacy Law no. 266/2008, and the draft emergency ordinance amending the Law no. 95/2006 on healthcare reform, were prepared.

Along with other departments, the legal department has contributed, to the action to combat medicinal product counterfeiting and illegal trade of counterfeit medicines, information and warning to the public, and develop relationships with other institutions and bodies involved in this activity.

To better inform the public, a new section, "Counterfeiting", was created on the NMA website, in which reports of counterfeiting through the rapid alert system are uploaded.

The NMA initiated and signed a cooperation protocol with the Directorate for Investigating Organised Crime and Terrorism (DIOCT) to combat medicines counterfeiting and illegal trade with them.

The proceedings create the frame for the future Directive on prevention of penetration in the legal distribution network of counterfeit medicines in terms of identity, history or source, now a draft under EU Council debate including the NMA appointed representative presenting and supporting the views of Romania.

Notice should be made of the fact that, within the Legal Department, the establishment of security structures was proposed and approved, whose organisation is in progress. This was imposed by the complexity of the information managed by the NMA and the need to ensure their protection in compliance with Law no. 182/2002 on protection of classified information, as amended.

14. Human resources department activity

Activity of the Human resources department was strongly influenced by the successive modifications of the NMA organisational structure, as a result of both optimised activities and the impact, as of April 2009, on the Agency's structure and activities of GEO 34/2009 for 2009 budget rectification and then by Law no. 329/2009 on reorganisation of public authorities and institutions.

During 2009, changes in the NMA organisational structure consisted of redistribution of employees according to qualification, competence, professional performance and establishment of control area of management personnel.

Providing human resources in the NMA structures, particularly in areas characterised, according to the analysis, by shortage of qualified staff was obviously hampered by unpredictable external influences. The main external impediment in attracting of both pharmaceutical, medical and administration personnel has been the legal frame established by Ordinance 34/2009 regarding the 2009 budget rectification and regulation of fiscal measures, providing suspension of employment proceedings by examination or contest for vacant positions, the exception to this provision, in duly justified cases, allowing approval of employment of a maximum rate of 15% of all future vacancies after the effective date of the emergency ordinance.

According to the NMA functions status, in April 2009, the maximum 15% percentage of the total vacancies meant that the NMA could hire one person by contest per seven vacancies, thus being unable to cover the lack of personnel.

This impediment, with major impact on human resources management, has been doubled by the unfavourable economic circumstances and Law no. 329/2009 on reorganisation of public authorities and institutions, which changed the

financing regime of the NMA, becoming a public institution fully financed from the state budget, through the Ministry of Health.

Also as a result of application of Law 329/2009, i.e. to "measure the cumulative pension scheme with salary income, to reduce expenditures", resulted in loss of NMA trained and qualified employees.

In conclusion, assuring human resources in deficit areas was not feasible, according to the needs planned, identified and established by the Human Resources Department; more than that, after the law entered into force in 2009, the deficit has grown significantly.

Given the large differences between the pay scales of the NMA medico-sanitary staff and technical administrative staff, the human resources department has proposed equalisation of these two types of grids to the Administrative Council (AC) as well as differentiation only by level of education, qualifications, professional degrees and stages. The proposal was approved in the AC and then by the Ministry of Health, and the new salary scales were annexed to the collective labour contract.

14.2. Human resources policy

In spite of all obstacles encountered in 2009, the top management has always been concerned with implementation of the NMA human resource policy and focused on the following objectives:

- provision of higher education staff, particularly medical and pharmaceutical, to ensure coverage of staff shortage in specialised departments ensuring implementation of the NMA objective.

In spite of all the efforts in this direction, the *dynamics of personnel* for 2009 shows a negative balance:

21 new individual labour contracts were drawn in November, as compared to 36 individual labour contracts termination.

- Improving training of professional staff, to form highly qualified specialists, able to address the full range of NMA attributes and duties;
- The NMA annual staff training and development plans carried out are well-established at departmental level, depending on the activity and training of every employee. Note should be made of training upon employment and further training undertaken both internally and externally by institutions specialised in such fields as quality assurance management (ISO 9001:2000), pharmaceutical inspection activity-specific training, legislation, financial accounting etc. This is complemented by active participation, with papers in various symposia, congresses on medicinal product topics as the extraordinary participation of NMA specialists in working groups of international bodies in the field of medicines.

Motivating staff by providing appropriate working conditions, a stimulating work environment, access to information, training and development, stimulation of professional achievements of all valuable personal initiatives, salary packages within financial possibilities;

- Ensuring of smooth communication between organisational structures and access to information managed under the Human Resources Department;
- Implementing measures to ensure confidentiality of information managed by the Department of Human Resources.

14.3. NMA staff participation in training

Besides participating in activities of various institutions and bodies, the most effective way to keep the NMA connected to European activities in the field of medicines is that NMA specialised staff annually benefit from both continuous training program specifically for professional development at the NMA offices and training sessions organised nationally and internationally:

European Commission/European Medicines Agency:

- Participation of a specialist evaluator from the post-authorisation department (PAD) in the EMA training course for quality evaluation
- Participation of a PAD evaluator in the pharmacovigilance training course organised by the EMA for PSUR evaluation
- The participation of two inspectors of the Pharmaceutical Inspection Department (PID) in the 7th GCP Supervisors training course organised by the EMA
- The participation of two PID inspectors in the Joint Conference organised by the EMA and the Parenteral Drug Association (PDA)

Cooperation scheme in pharmaceutical inspections (PIC/S)

The participation of three PID inspectors in the 2009 PIC/S seminar - "Inspection of sterile dosage forms"

The European Directorate for the Quality of Medicines (EDQM)

Participation of a specialist from the medicines quality control department (MCCD) in the training course for *MRP/DCP database* administrators for products authorised through mutual recognition/decentralised procedure

Participation of a MCCD specialist in the "Annual Meeting of medicinal products authorised through MRP/DCP and centrally authorised medicinal products (CAP)"

Other involvement:

in the field of industrial property:

- Participation of a NMA specialist in the Round Table organised by the State Office for Inventions and Trademarks (SOIT) for industrial

property attorneys on novelties in SOIT business in services, databases and publications;

in information technology:

- Participation of IT specialists in the EursIsYours training, conducted by Extedo GmbH company representatives at the NMA headquarters.

15. Economic activity

In 2009, the economic department has developed and managed a balanced budget of revenues and expenses, amounting to 33,119 million lei from their own income for 11 months and in December 2009 by a revenue and expenditure budget of 3.701 million lei from the state budget.

The expenditure amounted to 19,702,021 lei, of which:

- 16,565,825 lei were staff costs
- 2,498,780 lei to cover goods and services
- Capital expenditure was 637,416 lei.

All expenses were within the approved budget for 2009 with the legal provisions on economic and financial discipline.

The data reveals a balance between NMA 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, all financial activities were conducted in the economic department, ensuring optimal and efficient performance of payments and receipts in the business.

In 2009, through its financial-accounting activities, the economic department provided proper performance of their objectives.

The recalculation of charges for services rendered by professional departments was approved through order of the Minister of Health no. 716/2009.

With the entry into force of order of the Minister of Public Finances no. 3156/2009, regarding approval of the methodological standards on payment to the state budget of revenues by the authorities and public institutions funded wholly or partly from its own revenues, which were reorganised as public institutions financed from the state budget entirely as per law no. 329/2009 on the reorganisation of public authorities and institutions, rationalising public spending, supporting the business framework agreements and ensuring compliance with the European Commission and International Monetary Fund, the NMA has changed its funding system. Thus, the financing of expenditure is entirely the state budget.

Also, pursuant to Art. 7 (2) of Law no. 329/2009 and Order no. 3156/12.11.2009 (art. 1, art. 3), published in the Official Gazette of Romania, Part I no. 787/18.11.2009, public authorities and institutions concerned, the NMA began to transfer all revenues and proceeds to the 50.32 account "available from

amounts collected for the state budget" to the state budget after entry into force of the normative act, to be filed no later than two working days as of receipt.

16. General administration and heritage

During 2009, the Department of General Administration and Heritage (DGAH) managed to meet its targets and respond promptly and effectively to requests from NMA structures.

Due to DGAH structure, namely the various attributes of services/departments located in its structure, DGAH employees were directly involved in the NMA reorganisation proceedings:

- The DGAH participated in rearrangement of the organisational structure of the NMA headquarters;
- The DGAH initiated the relocation of the Department of biological products control, from its headquarters located in Demostene street, to the NMA headquarters, the move to be completed in 2010 and result in creating an optimal environment in laboratory work, and solving the problem of biological samples transportation from the former to the NMA headquarters, the redundant space in Demostene street to be used to expand the NMA archive.

The Public Procurement department organised and supervised the planning, preparation, development and acquisition of products, services and works required for the proper functioning of the NMA business, consistent with its needs and objectives of the approved budget, developing the documentation necessary for all types of procurement.

During 2009, a number of 80 public procurement contracts were completed and a number of 296 reports of necessity were answered.

Another achievement of the DGAH is organisation of the NMA archive by recording and arranging 39,000 volumes of which 29,000 were in the Ilfoveni location and 10,000 in the Demostene location.

Besides participating in physical relocation of the organisational structure of the NMA headquarters, the Administrative Service – the Maintenance and repairs bureau independently built 70 metal shelves necessary for the NMA archives after reorganisation.

To improve the Central NMA Repository, a database has been created that can be accessed via the intranet site, by the NMA staff for viewing existing product inventories.

17. Internal audit activities

According to the annual audit plan, in 2009 the Internal Audit Office concluded three audit reports approved by NMA executives.

Reports were concluded with recommendations communicated to the management of the audited departments for implementation.

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

16. Difficulties encountered

Lack of higher education personnel, 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 "repeat use" procedure with Romania as a Reference member state.

Lack of external experts with different medical specialties to evaluate clinical variations for approval of new clinical indications, for both medicinal products authorised nationally and through the European process.

17. Priorities for 2010

- Ensuring proper performance of NMA objectives, as required by law for organisation and functioning;
- Strengthening the prestige acquired domestically and internationally through high quality performance with both internal external and 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, authorities of the state, active participation in actions and activities of the EMA, PIC / S and other specialised bodies to which the NMA is affiliated;
- Ensuring adequate human and financial resources to run a good business;
- Organising competitions for filling vacancies;
- Reduction in working time by replacing paper with electronic versions, as far as possible, of different types of documents both within the institution and in relation to others;
- Evaluators' computers are equipped with two monitors, efficient and reliable connection to the intranet and internet, so that each evaluator would be able to complete his assessment and prepare the assessment report, providing information on the server view, accommodating rapid access to intranet or databases, as appropriate;
- Producing complete integrated software that is versatile, multi-tasking, to manage medicinal products information throughout their life cycle;
- Improving staff remuneration and motivation of specialist staff in order to maintain existing ones and attract young professional personnel;

- Continuing training of staff at work, at home and abroad in order to improve professionally and better function in the European system;
- Strict adherence to the law in all spheres of activity and implementation of medicinal products legislation, in accordance with Law no. 95/2006 on healthcare reform, as amended
- Continuous improvement of the quality management system
- Improving communication with stakeholders and transparency in business.

CONCLUSIONS

The work of the National Medicines Agency in 2009 was particularly fruitful, thanks to efforts made by the majority of staff, and availability of management for cooperation and communication, to create the conditions necessary for human resources development at their full professional capacity.

The NMA will continue to assume the role of the competent authority in the field of medicinal products for human use in Romania and the statutes of competent authority of a EU member state, fully integrated in the activities of the competent authorities in the field of medicine in the EU and in the activities of committees and work groups in the field of medicinal products in Europe.