ACTIVITY REPORT OF
THE NATIONAL MEDICINES AGENCY, 2006

INTRODUCTORY WORD

Preceding Romania's Accession to the European Union, 2006 has been both the most complex and difficult and the richest and most fruitful year of the entire 8-year history of the institution in its present organisation.

It has been an extremely busy year, characterised by a great workload, compelling to particular collective efforts, higher engagement as both quantity and mostly quality were concerned from every department and involvement of the majority of staff in carrying out professional tasks.

For the National Medicines Agency, the year 2006 represented an important gain in quality, systematically and resolutely prepared by each and every previous step, towards its institutional consolidation as European competent authority in the medicinal product field, whose object is the marketing authorisation of quality, safe and effective medicinal products.

The year 2006 was also a jubilee for the National Medicines Agency, designating 50 years as of the setting up of the regulating authority in the medicinal product field in Romania, named The Institute for Drug Control and Pharmaceutical Research at the time of its foundation (1956), later to become, in 1960, through a change of name, the Institute for the State Control of Medicinal Products and Pharmaceutical Research (ISCMPPR) and finally, in 1999, through ISCMPPR restructuring, the National Medicines Agency.

To celebrate its fifty years as competent authority in the medicinal product field in Romania, on 13 October 2006, the NMA organised a Jubilee Conference at the Rosetti Hall of the Parliament Palace, reuniting more then 600 guests: officials, leading representatives of the faculties of pharmacy, professors, members of the NMA Scientific Council, representatives of the Romanian and foreign medicinal products manufacturers' associations, of Marketing Authorisation Holders, present and former ISCMPPR/NMA staff, the media.

It was an honour to have the participation in the event of Mr. Gheorghe Eugen Nicolăescu, Minister of public health, Dr. Bogdan Marius Chiriţoiu, State Counsellor with the Presidency of Romania, Acad. Prof. Dr. Victor Voicu representing the Romanian Academy, Dr. Vasile Cepoi, General Director representing the National Health Insurance House; the meeting was privileged by the attendance of part of ISCMPPR/NMA leaders along its history as well as of former ministers of health, members of the NMA Scientific Council and Administration Council.

Resuming the activity report, stress should be laid on the fact that, in 2006, the Agency's entire activity as competent authority in the medicinal product field of an Acceding country was placed under the sign of concentrated preparations for Accession, focusing on completion of *acquis communautaire* transposition into national legislation, of improvement and update of national medicinal product legislation as well as intensified evaluation – authorisation activity as imposed by the strategy of authorisation dossier update during pre-Accession and preparation for transition to European procedures.

Following the Agency's participation in the general legislative efforts resulting in the elaboration of the legislative package regulating healthcare reform, a comprehensive and rapid process was necessary to initiate design and adoption of secondary legislation for implementation of Title XVII, The medicinal product of Law 95/2006, set up/update of regulations related to NMA professional activity, and harmonisation with terminology in use in the new legislation and previous legal provisions acting as secondary legislation as well as technical Guidelines in the medicinal product field.

In concrete terms, the legislative endeavour of 2006 for achievement of these goals consisted in elaboration of an unprecedented number of Scientific Council decisions, many of which were approved through orders of the Minister of public health, which has compelled specialised work groups involved in the process to consistent and extensive efforts.

An additional priority direction in 2006 was insuring constant pace of evaluation – authorisation activities. Outstanding labour, commitment, responsibility and professionalism resulted in completion of evaluation of update dossiers for thousands of medicinal products as well as successful finalisation of assessment of authorisation/renewal of the largest ever number of medicinal products.

Every such particularly complex activity was carried out through extremely intense labour, especially because human resources available to the Agency were not significantly increased.

A further noteworthy achievement was NMA connection as of 8 June 2006 to the EudraNet, the European information network of competent authorities in the field of medicinal products of human and veterinary use. Connection was set up following the very favourable closure of the NMA audit by experts of the European Medicines Agency (EMEA) during 07-08.06.2006.

The audit was preceded by the set up to European standards of an area expressly assigned for IT activities and concentrated information exchange on compatibility of NMA available IT equipment with the European system, training of IT staff, implementation in the NMA of the quality management system and insurance of data confidentiality inside the NMA.

NMA connection to the EudraNet represents the successful closure of a very important stage in the complex process of institutional preparation in view of Accession.

An important aspect of 2006 activity is participation of NMA representatives as active observers in EMEA scientific committees and working groups, as well as in other European and international bodies, as the most efficient means to maintain the NMA connected to European/international activities in the field of medicinal products. Given NMA integration as competent authority in the medicinal product field on European and international level, this activity has been turned into a current component of specialised staff current tasks.

Within the same complex process of institutional preparation, the NMA continued its internal restructuring for increased compatibility of operation units and staff structure with requirements for NMA functioning in the European network of competent authorities in the medicinal product field.

Therefore, further measures were successively adopted last year, envisaging regulation of NMA and departmental organisational structure, update of NMA organisation and functioning regulations and NMA internal regulations.

The most important structural changes have been introduced in the Evaluation–authorisation department, for the purpose of preparation of functional subdivisions required for such new activities as the centralised, decentralised and mutual recognition procedures.

In 2006 as well, the NMA top management laid the same stress on the quality management system, largely emphasizing the importance of a process–based approach and monitoring both compliance with standard operation procedures (SOP) in force and identification of new activities and processes as object for further specific SOPs.

The prospect of Romania's status as member state of the European Union staring with the 1st of January 2007 has requested increased professionalism in all NMA activities and consolidated labour relationships between the NMA and its employees.

A new labour collective contract at unit level was negotiated and signed in 2006, complying with legal provisions and combining in mutually convenient manner interests of employer and employees alike.

Special attention was also given to the consolidation NMA human resources and infrastructure.

Goals in the 2006 human resources policy mainly envisaged provision of specialised staff of higher education – specifically in the medical – pharmaceutical field, for adequate coverage of staff deficient positions in specialised departments as well as professional training and improvement of specialised staff in place for preparation of highly qualified specialists able to find solutions to the entire range of tasks and attributions in the NMA scope.

Consolidation of the NMA infrastructure resulted in more adequate labour and environmental conditions for the entire staff, in line with labour legislation in force.

Room has continued to be improved with ongoing refurbishment activities, existing areas have been divided and transformed into offices and a whole number of other actions have been taken to improve arrangement of working areas.

Adequate space has been arranged for secure storage of the NMA archives, in security conditions, in areas such as Demostene and Ilfoveni, in this way clearing the main headquarters and the Schitu Măgureanu area, which has been invalidated starting with the 1st of January 2007, due to improper conditions which physically endangered the documents preserved in that location.

NMA policies also continued in the area of information and extension of the internal computer network, which, as a result of the latest computer purchases, now consists of 6 servers and 195 PCs, together with the necessary additional equipment such as printers, scanners, copy machines etc.

Development of all activities, actions and attainment of goals set for 2006 would not have been possible without an adequate financial policy, based on a strict financial discipline, in compliance with legal provisions on financial execution, well-judged expenditure of allocated financial resources in line with the approved incomes and expenses budget.

From this perspective, every NMA annual incomes and expenses budget has been devised in a balanced manner, the level of expenses not exceeding that of incomes from services performed.

At the same time, tariffs were approved in the past year for a number of activities performed by the NMA departments, which have supplemented the system of financial quantification of NMA services, insuring complete funding of all its activities, in accordance with legal provisions.

The entire progress achieved, mentioned by an exemplificative, non-limitative title, has only been possible through NMA efforts as a whole to adopt and enforce European regulations in the field, in the interest of patients and the general society, according to the mission guiding its activity.

Mention should also be made of the fact that, in addition to its own efforts, NMA achievements are also due to the very good collaboration and counselling permanently established with the Ministry of Public Health, which has contributed to
prompt adoption of orders of the Minister of public health for approval of Scientific Council decisions and their publication in the Official Gazette of Romania.

I. NMA ACTIVITIES DURING 2006

1. Activity of the NMA Scientific Council

NMA Scientific Council activities develop in line with provisions of Section 3 "Scientific Council organisation and functioning" of Government Ordinance No.
125/1998 regarding the setting up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as amended.

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

Meetings of the Scientific Council focus on regulations concerning NMA professional activity, which are discussed and approved as Scientific Council Decisions (SCD).

Decisions of the Scientific Council of ruling character are subject to the approval of the Minister of public health and are published as Minister of public health orders in the Official Gazette of Romania. Its other decisions are submitted to the Minister of public health for approval and enforced within 15 working days after submission, unless the Minister of public health expresses disagreement; following that, they are published in the NMA Informative Bulletin.

Scientific Council decisions transposing European directives are notified to the Ministry of European Integration, posted on the Ministry of Public Health website (MPH) for information; following implementation of relevant notices, they are next approved through Minister of public health order and published in the Official Gazette of Romania.

As far as the name constituency of the Scientific Council is concerned, this underwent a number of changes in 2006, in result of certain members' retirement and assignment of others, in accordance with provisions of Article 10(1) of Government Ordinance No.125/1998.

In 2006, the Scientific Council activity was summoned in 6 working reunions, adopting as many as 59 Council decisions as compared to the average 35/year SCDs adopted during 2002-2005.

Of the mentioned 59, 32 SCDs have a ruling character; out of these, 28 were already approved through Minister of public health order and published in the Official Gazette of Romania, while 4 others are waiting to be approved or published.

The very intense SC activity has mainly consisted in adoption of secondary legislation for the implementation of Title XVII, The medicinal product of Law 95/2006; of these, the following should be mentioned: transposition of 5 European directives, regulations related to marketing authorisation and surveillance of medicinal products for human use, norms for NMA administrative procedure for management of variations, regulations regarding manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and starting materials used in manufacturing of medicinal products for human use, regulations on export of medicinal products for human use, investigational medicinal products included, norms on the procedure for grant of exemption of specific medicinal products label and package leaflet from the obligation that certain particulars shall appear and that the leaflet must be in Romanian, when the product is not intended to be delivered to the patient for self - administration, norms for the resolution of Marketing Authorisation Applications transfer etc.

A large number of decisions have been the result of approximation of older secondary legislation with terminology used in the new legislation as well as of revision and harmonisation of European technical Guidelines in the medicinal product field, previously elaborated by the NMA.

2. Activity of the NMA administration Council (AC)

Activities of the Administration Council develop in accordance with provisions of Section 2 "Administration Council organisation and functioning" of Government Ordinance No. 125/1998 regarding the setting up, organisation and functioning of the NMA, approved as amended through Law No. 594/2002, as amended.

In result of its working sessions, the Administration Council adopts decisions regulating areas set up through Article 8 of Government Ordinance No. 125/1998, i.e.:

- Approval of NMA economic and financial policy;
- Proposal of the organisational structure of the NMA departments;
- Approval of the budget for incomes and expenses;
- Analysis of the opportunity and possibilities to conclude contracts for collaboration and services;

- Proposal of tariffs and emergency tariffs for NMA activities, as well as the value of quota for maintaining marketing authorisations in force, which are published in the Official Gazette of Romania, Part I, after approval through Minister of public health order;

- Approval of the NMA annual activity report;

- Approval of NMA organisation and functioning regulations;

- Approval of NMA internal regulations.

From a procedural perspective, Administration Council decisions of ruling character are approved through Minister of public health order and published in the Official Gazette of Romania, Part I.

In 2006, the NMA Administration Council (AC) carried out 8 working sessions, which has determined the adoption of 44 decisions, 5 of which are of ruling character, approved through Minister of public health order and published in the Official Gazette of Romania, Part I.

The AC regulatory scope has covered the entire range of administration activities in its competence, mainly ruling on administrative issues related to better NMA organisation and functioning, approval of incomes and expenses budget, approval of updated versions of the NMA Organisation and Functioning Regulations and NMA Internal Regulations etc. A number of tariffs have also been approved for use in NMA
departments, which have supplemented the system of financial quantification of NMA services.

3. Regulatory activity

The legislative endeavour initiated with the elaboration of the new "Drug Law", actually Title XVII, The medicinal product of Law 95/2006 on healthcare reform has been carried on at very brisk pace in view of preparation of secondary legislation required for implementation of Title XVII, The medicinal product.

Due to the NMA and its Scientific Council highly constructive cooperation, it has been possible to elaborate, approve through Minister of public health orders and publish in the Official Gazette of Romania the entire secondary legislation required as well as other regulations related to NMA professional activity, in line with community regulations.

Of the 59 Scientific Council decisions, 20 have made up the foundation for secondary legislation required for implementation of Title XVII, The medicinal product of Law 95/2006.

Transposition of the 5 European directives represented an extensive and very rigorous activity in the frame of secondary legislation set up:

- *Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use;*

- *Commission Directive 2003/94/EC laying down the principles and Guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use;*

- *Commission Directive 2005/28/EC of 8 April 2005 regarding Principles and detailed Guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products;*

- *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;*

- *Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products,as amended .*

The five European directives have been transposed, revised and handled in line with the complex notification procedure established by the Ministry of European_Integration (MEI), requiring a great workload and permanent exchange of documents and opinions among bodies involved in transposition of European legislation, the NMA, MPH, MEI and finally the European Commission, respectively.

The consistent activity related to preparation of secondary legislation was also given concrete form through elaboration of certain regulations and norms, of which the following should be mentioned:

- Regulations regarding marketing authorisation and surveillance of medicinal products for human use;
- Norms regarding the National Medicines Agency administrative procedure for management of variations;
- Regulations regarding manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and starting materials used in manufacturing of medicinal products for human use, investigational medicinal products included;
- Regulations concerning attestation by the National Medicines Agency of the qualified person of the manufacturing/importation authorisation holder;
- Regulations relating to the contract-based control of medicinal product quality, as drawn between the manufacturer and a control unit outside the manufacturing site, in case of certain special testing;
- Regulations concerning the export of medicinal products for human use;
- Norms on the procedure for grant of exemption of specific medicinal products on the label and package leaflet from the obligation that certain particulars shall appear and that the leaflet must be in Romanian, when the product is not intended to be delivered to the patient for self-administration;
- Norms for the resolution of Marketing Authorisation Applications transfer;
- Approval of a simplified authorisation procedure for certain homeopathic medicinal products;
- Norms regarding enforcement of provisions of Regulation No. 141/2000/EC of the European Parliament and Council of 16 December 1999 on orphan medicinal products.

An additional extensive activity consisted of the approximation of terminology used in the new legislation that of secondary legal provisions as well as with European technical Guidelines in the medicinal product field, previously elaborated by the NMA.

Mention should be made of the fact that, because of the large number of Guidelines and their extensive contents, revision of Guidelines approved by the NMA
prior to emergence of Law 95/2006 involved a large amount of labour; the grounds for this action were mainly:

- Emergence of new versions of the Guidelines underlying set up of previous Guidelines;
- Adjustments required to highlight Romania's newly acquired status as EU member state;
- Harmonisation with new legal terminology as well as with secondary legislation already in force;
- Improved translation into Romanian.

In addition, a number of new European Guidelines of high interest for both the NMA and Marketing Authorisation Holders have been translated and adapted.

4. Activity of NMA commissions

4.1. Marketing Authorisation Commission

The Marketing Authorisation Commission works based on Decision of the NMA President and according to its own Organisation and functioning regulation, as approved by Administration Council decision.

The constituency of the Marketing Authorisation Commission has been updated through Decision of the NMA President No. 612/2006 and includes the NMA Vice-president, the heads of departments for evaluation–authorisation, raw materials and finished products control, biological products evaluation and control, pharmaceutical inspection as well as the heads of services and bureaus within the Evaluation–authorisation department.

The Commission examines evaluation reports in order to formulate an opinion regarding the marketing authorisation as well as other marketing authorisation-related problems concerning medicinal products for human use.

In 2006, the Marketing Authorisation Commission conducted 73 working sessions concerning the discussion of evaluation reports for 1982 medicinal products for human use and the formulation of opinion in view of marketing authorisation.

Of the above, 1929 medicinal products have been accepted for grant of marketing authorisation, 52 were postponed and 1 medicinal product has been refused.

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

The commission works based on Decision of the NMA President and according to its own Organisation and functioning regulation, as approved by Administration Council decision.

The constituency of the Commission has been updated through Decision of the NMA President No.611/2006 and it is made up of the NMA President and Vice-president, the heads of the departments for pharmaceutical inspection, evaluation–authorisation, raw materials and finished products control, biological products evaluation and control and GMP, GLP, GALP and GCP inspectors within the Department for Pharmaceutical Inspection.

The Commission examines inspection reports drafted by MA inspectors, reports relating to compliance of inspected sites with GMP, GLP, GPAL, GCP rules and/or other problems regarding the activity of the Department for Pharmaceutical Inspection. The Commission mediates in case an inspector's decision is disputed by the inspected unit, the decision belonging to the majority.

In 2006, the Commission for GMP, GLP, GALP and GCL Inspection conducted 10 working sessions for examination of 61 inspection reports.

4.3. Commission for the check of compliance of NMA inspecting staff with the professional ethic and deontology code

The commission works based on Decision of the NMA President and according to its own Organisation and functioning regulation, as approved by Administration Council decision.

The constituency of the Commission has been updated through Decision of the NMA President No.613/2006 and it 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 service.

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 public health No. 160/2004.

No violations of the Ethic and deontology code by NMA staff with inspection tasks have been notified since set up of the Commission.

4.4. Commission for the Coordination of the Romanian Pharmacopoeia

The Commission is set up by decision of the NMA President and includes the NMA President and Vice-president, specialists employed in the Agency, representatives of pharmacy

faculties in university centres of tradition as well as of the Pharmaceutical Directorate in the Ministry of Public Health.

The Commission has continued to coordinate translation and approximation of the general monographs and methods of analysis of the European Pharmacopoeia (EP), in view of their inclusion and formalisation in the Supplements to the Romanian Pharmacopoeia, the 10th edition (RP-X).

To allow them to express their opinion, Commission members were provided the draft of the RP-X 2006 Supplement, including monographs and methods translated from and harmonised with the EP, the 5th edition. Comments received have been analysed and implemented by the Service for Pharmacopoeia (providing secretarial activities for the Commission).

The RP-X 2006 Supplement was published in November 2006.

5. Evaluation-authorisation and related activities

5.1. Marketing authorisation

In 2006, the amount and complexity of evaluation – authorisation activities were particularly increased, in line with the strategy for update of authorisation dossiers during pre-Accession, completion of authorisation of applications already submitted, preparations in view of transition to European procedures as well as with entry into force of provisions of Law No. 95/2006 on healthcare reform, Title XVII - The medicinal product.

In 2006, the NMA was submitted a total number of 1035 Marketing Authorisation Applications, of which:

- 770 applications for authorisation through national procedure;
- 95 applications for authorisation through nCADREAC simplified procedure for medicinal products authorised in the EU through centralised procedure;
- 170 applications for authorisation through nCADREAC simplified procedure for medicinal products authorised in the EU through mutual recognition procedure.

In line with the Guideline on updating and amendment of the authorisation documentation of medicinal products for human use authorised in Romania, in order to comply with the requirements of the European Union, approved through Minister of public health order No. 92/2006, the following have been submitted:

- Statements on compliance of authorisation dossiers with EU requirements for 980 medicinal products with a valid marketing authorisation
- Updated dossiers for 3940 medicinal products for human use

In 2006, marketing authorisations (MA) were granted for 2177 medicinal products for human use, of which:

- 1680 MAs through national procedure;
- 129 MAs through nCADREAC simplified procedure for medicinal products authorised through centralised procedure in the EU;
- 368 MAs through nCADREAC simplified procedure for medicinal products authorised through mutual recognition procedure in the EU.

The authorisation/renewal procedure was suspended for 154 medicinal products, of which:

- 143 on manufacturer’s request;
- 11 on NMA request.

In result of Law No. 95/2006, Title XVII - The medicinal product provisions, decisions were issued for MA withdrawal in the case of 639 medicinal products, of which 416 were medicinal products authorised through nCADREAC simplified procedure for centrally authorised medicinal products.

Based on provisions of Regulation 726/2004, following grant of the European Commission decision, centrally authorised medicinal products are valid in all EU member states

(MS). The document granting them circulation on MS markets is the decision of the European Commission on authorisation through centralised procedure, with the annexes (SPC, package leaflet and labelling) translated into the MS official language.

Given the few months latency between Accession and the publication of annexes to the European Commission decision in the new MS official languages, it has been deemed legal for batches manufactured prior to Accession to circulate for a limited period of time, based on national authorisations granted by the NMA.

Provisions concerning the management of this situation in Romania have been included in Order of the Minister of public health No. 1199/02.10.2006.

A number of 237 linguistic checks were performed in the frame of the PALC II Contract (Pre-accession Linguistic Checks) for centrally – EMEA authorised medicinal products and 75 PALC post-opinion changes of the EMEA Committee for Medicinal Products for Human Use, based on a contract for services between the NMA and EMEA.

Medicinal products authorised for marketing in 2006 have been posted on the NMA website www.anm.ro and are to be published in the annual NMA Index of medicinal products for human use - 2007.

5.2. Approval of variations to marketing authorisation terms

In 2006, the NMA was submitted a total number of 6968 applications for type I and II variations, changes allowed by regulations, marketing authorisations transfers, including the national procedure, European procedures and type II variations regarding changes or additions to therapeutic indications.

A number of 5592 applications were approved, of which:

- 3708 applications for type I variations;
- 1240 applications for type II variations;
- 406 applications for MA transfer;
- 238 applications for other types of changes.

Of the above, for Romanian and foreign medicinal products authorised through *national procedure* or undergoing MA renewal procedure:

- 2896 applications for types I and II variations;
- 393 applications for MA transfer.

For medicinal products authorised in Romania through *European procedures* or MA renewal procedure:

- 2032 applications for types I and II variations;
- 17 applications for MA transfer.

5.3. Approval of clinical trials

In 2006, the NMA was submitted 213 applications for clinical trial approval, of which:

- 8 applications for the approval of phase I clinical trials
- 52 applications for the approval of phase II clinical trials
- 135 applications for the approval of phase III clinical trials
- 18 applications for the approval of phase IV clinical trials.

The following were also submitted:

- 77 applications for approval of bioequivalence studies
- 60 applications for approval of observational clinical trials.

A number of 174 clinical trials were approved by the end of 2006, as follows:

- 7 phase I clinical trials;
- 45 phase II clinical trials;
- 109 phase III clinical trials;
- 13 phase III clinical trials.

58 bioequivalence studies were approved.

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

During 2006, the NMA was submitted 326 applications for approval of advertising material of medicinal products.

In that respect, 238 applications for advertisement approval were approved for OTC (Over the Counter) medicinal products.

The NMA was submitted 88 notifications regarding promotional material meant for specialists.

A number of 6 notifications were issued refusing approval of advertising.

Monitoring and control of advertising medicinal products for human use also materialised in:

- 13 suspensions of advertising material distribution;
- 18 responses to complaints among companies;
- 6 warnings regarding advertising material distributed without NMA approval.

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 and specific European Guidelines.

In 2006, pharmacovigilance consisted in management of safety data coming from spontaneous reporting:

- 351 spontaneous reports of adverse reactions in Romania;
- 10,000 reports in the format of the Council for International Organisations of Medical Sciences (CIOMS);
- 5,500 spontaneous reports of adverse reactions from other countries, transmitted by Marketing Authorisation Holders;
- 935 updated Periodic Safety Updated Reports (PSUR) for imported medicinal products;
- 329 national Periodic Safety Updated Reports (PSUR) for Romanian medicinal products;

The College of Physicians in Romania was informed on 393 spontaneous reports of adverse reactions in Romania, validated by the NMA National Pharmacovigilance Centre.

A number of 214 letters of information were sent to healthcare professionals regarding grant of 856 credits for Continuing Medical Education.The NMA website was added 34 translated EMEA press releases on safety issues of centrally authorised medicinal products.For reasons of advertising among pharmacists issues of adverse reactions to medicinal products, articles continued to be published in that respect in the “Farmacist.ro” magazine.

6. Inspection of GMP, GCP, GLP, GALP, Good Pharmacovigilance practice and market surveillance

Inspection activities in 2006 were significantly increased as compared to 2005, through diversification of types of inspections performed, according to the new attributions generated by Law No.95/2006 on healthcare reform, Title XVII - The medicinal product.

Inspection activities were as follows:

- 43 GMP inspections for authorisation/certification, of which 2 inspections for GMP recertification and 9 inspections for monitoring of implementation of statements in the correction measures plans;
- 13 GMP inspections to pharmaceutical companies of PIC/S non-member countries;
- 17 GCL inspections;
- 1 prior to marketing authorisation inspection on request of the Evaluation-authorisation department (EAD);
- 9 inspections regarding bioequivalence studies;

- 7 pharmacovigilance inspections at MA holders;
- 1,037 consultancy visits on pharmacovigilance problems

Beginning with August 2006, 162 applications for approval of export declaration were submitted and checked, following which export declarations were approved for 747 de medicinal products manufactured in Romania.

A number of 66 Qualified Person Certificates were granted and 37 applications to that purpose were refused.

As far as the activity for quality surveillance of medicinal products authorised for marketing in Romania is concerned, the following were performed:

- Sampling of 71 medicinal products and 25 active substances used in their manufacturing, of which 7 products were non-compliant;
- 464 inspections for monitoring of medicinal product quality in the distribution chain (warehouses, pharmacies);
- 264 inspections for check of quality of oxygen used in hospital units.

For non-compliances found during inspection, 84 manufacturing and distribution units and representations were penalised for violation of regulations.

A number of 47 complaints were received regarding possible medicinal product quality non-compliances, of which 30 were grounded and resulted in withdrawal of 25 medicinal product batches.

59 Rapid Alerts issued in the EMEA and PIC/S Rapid Alert system were received and solved.

7. Quality control of medicinal products

In 2006, the Raw Materials and Finished Products Control Department (RMFPCD) analysed 2,127 batches from both the national manufacturing sector and imports. Of the above:

- 804 medicinal products were obtained through chemical synthesis;
- 1306 were biological medicinal products for microbiological, immunologic and pyrogenic determination (vaccines, immunomodulators, allergens etc.).

For the above products, 3921 analysis bulletins were issued.

There were 84 non-compliant medicinal products, for which inappropriate analysis bulletins were issued, which represented 4% of the total number of analysed medicinal products. Statistic analysis of deficient medicinal products shows the higher incidence of physico-chemical and microbiological types of deficiencies.

As in previous years, in 2006 as well, the RMFPCD continued collaboration with European institutions dedicated to control of medicinal products, an activity presented in more detail in Chapter 11 - International relationships.

RMFPCD specialists also continued evaluation of dossiers for authorisation or renewal of authorisation of Romanian and foreign medicinal products. 210 chemical pharmaceutical dossiers were assessed and the respective quality evaluation reports were devised in view of authorisation/renewal.

A number of 153 reports were elaborated (post-authorisation, validation of certain variations or updated dossiers) and 25 evaluation reports on Drug Master File (DMF) for chemical substances used in manufacturing of finished products, for which authorisation/renewal applications were submitted.

Specialists in the department collaborated in translation and review of certain monographs for the RP-X 2006 Supplement.

In 2006, the Biological Products Evaluation and Control Department (BPECD) analysed 1,580 batches of biological products, of which 1,433 were manufactured in Romania and 147 were imported; of these,

- 1,025 batches were immunomodulators;
- 400 batches were vaccines;

- 2 batches were therapeutic serums;
- 41 batches were IDR antigenes;
- 32 batches were blood derivates;
- 80 batches were allergens.

As in the previous year, for most biological products submitted to the BPECD for testing, determinations performed were physico-chemical and immuno-chemical determinations. One medicinal product batch was refused of the total number of batches analysed, because of con-compliance of laboratory tests with quality specifications.

Post-marketing surveillance was carried on for medicinal products of PIC/S member countries, for which no batch-to-batch testing is performed.

A number of 312 biological medicinal product batches imported from PIC/S member countries were introduced in the BPECD data base in 2006.

As part of dossier evaluation in view of authorisation or renewal for Romanian or foreign medicinal products, 136 biological products were subject to assessment, for which 246 evaluation reports were issued. Support dossiers for 233 variations were also evaluated.

Specialists in the department collaborated in translation review and approximation of certain monographs for the RPh-X 2006 Supplement.

8. Pharmacopoeia related activities

In 2006, elaboration of the RPh-X 2006 Supplement was finalised, following update with latest 5.5 and 5.6 Addenda to the European Pharmacopoeia (published in 2006), implementation of notices from pharmacy faculties and successive revisions.

The RPh-X 2006 Supplement has been approved for publication through order of the Minister of public health, and published by the Medical Publishing House in November 2006.

Elaboration of the RPh-X 2007 Supplement began in 2006, 12 general analysis methods, 5 general texts and corresponding reagents now being in project stage.

New and revised Romanian standard terms/2006 have been elaborated, in line with those adopted by the European Pharmacopoeia Commission, approved through Scientific Council decision and implemented on-line in the EDQM data base of European standard terms.

The *Combined* Romanian standards terms have been established in result of translation of the list related to *Notification of combinations of standard terms by the EDQM*, published in the Pharmeuropa magazine for information of MA applicants and competent authorities. These have also been implemented on-line in the EDQM data base of *Combined* European standard terms.

9. Quality management activity

Through, AC Decision No. 22/2006, the Quality assurance department has been transformed into the Quality assurance bureau, focusing on the same tasks and maintaining the same number of staff.

Reorganisation was imposed by the need to resize this organisational structure according to number of staff as related to specific attributions.

In 2006, quality management activities continued to focus mainly on improvement of the existing system.

In that respect, the quality management system documentation has been completed through the following:

- Elaboration of 2 new general Standard Operation Procedures (SOP);
- Change/review of 3 general SOPs;
- Elaboration of 17 new specific SOPs;
- Change/review of 17 new specific SOPs.

All NMA departments contributed to the set up of SOPs.

The following analyses and evaluations have been performed on departmental and NMA level:

- Annual departmental activity reports;
- Individual activity reports by NMA staff;
- Annual departmental working programs;
- Annual NMA staff training program;
- Annual internal audit program.

Job descriptions and confidentiality commitments have been updated.

Evaluation sheets of individual staff activity have also been set up based on detailed sub-criteria devised for evaluation of professional performance of NMA staff.

In 2006, 8 internal quality audits were carried out, according to the annual internal audit program, approved by the top management. Audit reports were accompanied by plans for improvement drafted by audited departments.

The operation of the NMA system for quality management is presently based on quality documents (mission, quality objectives and policies in the field of quality, established by the top management, the NMA Quality Manual, departmental quality manuals, departmental annual working programs, the annual training program for NMA staff, the annual internal audit program, 500 general and specific SOPs), as well as on good staff training and resolute management involvement in the operation of the system.

10. Insurance of communication and transparency

All during 2006, the NMA continued to be particularly concerned with insuring sound communication with interested parties and transparency in activities developed, in line with provisions of Law No. 544/2001 on free access to information of general interest.

This special concern is also one manifestation of NMA endeavour to comply with European regulations as transposed in Title XVII - The medicinal product of Law 95/2006, i.e. in the issue of transparent activity of competent authorities in the medicinal product domain within the European Union.

10.1. External communication

The National Medicines Agency has continued its good and accurate information of partner institutions regarding activities developed in all domains within its scope.

The NMA has carried on the tradition of quarterly publication of bilingual Informative Bulletins, mirroring the concentrated activity related to transposition of European medicinal product legislation into national legislation. The NMA has been concerned to develop information made available on its bilingual website. Electronic versions of the NMA Informative Bulletins are also posted on the website. At the same time, the NMA elaborated the 2006 edition of the Index of medicinal products for human use has been published, including in brief all medicinal products authorised in Romania, with data on name, International Non-proprietary Name (INN), manufacturer, pharmaceutical form, administration route, packaging, classification for release etc.

The NMA has been concerned to develop information made available on its bilingual website.

In that respect, the NMA web-site published and supplemented the following information and documents:

- Summary of Product Characteristics (SPC) for medicinal products authorised in Romania through CADREAC simplified procedure for products authorised through centralised procedure in the EU;
- SPCs for medicinal products authorised in Romania through CADREAC simplified procedure for products authorised in the EU through mutual recognition procedure;
- Information letters for physicians;
- Press releases related to medicinal product safety.

The following information has been introduced in the Useful information section:

- List of NMA employees assigned as representatives or alternates in scientific committees and working groups of the European Medicines Agency (EMEA);

- Expiry date of the data exclusivity in Romania for medicinal products for human use authorised through EU centralised procedure, which are also authorised in Romania;

- Information on the methodology for approval of export declaration for medicinal products for human use;

- Information on the methodology for approval of partial manufacturing/importation for warehouses storing starting materials used in medicinal products manufacturing;

- List of Over the Counter medicinal products (OTC), in accordance with legislation in force, harmonised with the European legislation.

The following have proved of great interest for external users:

- Medicinal product legislation;

- The Index of medicinal products for human use authorised for therapeutic circulation in Romania;

- Forms and other useful information.

Proof of the manifest interest of parties concerned in information posted on the NMA website has been the large number of visitors, which has been larger than 100,000/year, i.e. a monthly average of 9,000 visitors.

The NMA has also continued its practice of meetings with associations of medicinal products manufacturers, for debates on issues of general interest, mainly related to Accession. NMA partners were timely informed on NMA strategy regarding the submission of authorisation/renewal applications, as imposed by preparations for application of European procedures and the strategy of dossier update during pre-Accession. At the same time, all the above information has been posted on the NMA website.

A new section has been created on the NMA website in support of its users – "Questions and answers", including all answers to questions asked in relation to the Guideline regarding update and change of dossiers for authorisation in Romania of medicinal products for human use for compliance with European Union (EU) requirements, approved through Minister of public health order No. 92/2006.

In 2006 as well, the NMA continued to inform interested parties on its activity through various publications other than its own Informative Bulletin.

To the approval of NMA partners, the NMA report on 2005 activities was again published as a bilingual brochure.

Articles related to various aspects of NMA activity were published in 2006 in Romanian specialised magazines ("Farmacist.ro", "Medical Business"), as well as in the "Parliament Magazine" and "Eurosource" publications of the European Parliament.

NMA representatives made specialised presentations in various conferences and symposia organised nationally and abroad, as well as in the 13th National Congress of Pharmacy, which took place in Cluj-Napoca during 28-30.09.2006.

Presentations approached such topics of general interest as:

- Perspectives of the National Medicines Agency in the context of Accession to the European Union;

- National Medicines Agency mission and goals as mirrored in the development of the pharmaceutical sector in Romania;

- Development of legislation and regulations in the Romanian pharmaceutical sector;

- Medicinal product quality, efficacy and safety – the role of the National Medicines Agency;

- New Romanian medicinal product legislation in the frame of the harmonisation process with the European legislation;

- National Medicines Agency policy related to update of authorisation dossiers of medicinal products for human use;
- Current status of the New CADREAC Agreement;
- Comparative study of the impurity profile in generic and reference medicinal products;
- Comparative study of the dissolution profile for generic and reference medicinal products;
- The history of pharmacy: Monograph presentations of a few personalities in the Romanian medicinal product field.

10.2. Internal communication

For better and faster information of staff on professional and organisational issues, information made available on the NMA intranet was further supplemented and updated in 2006.

As an example of information available to NMA employees on the intranet, the following can be mentioned:

- President's Instructions;
- NMA quality policies;
- Information regarding training courses organised by specialised companies;
- Reports issued by staff participating in training;
- Status of staff training;
- Glossary of quality assurance terms;
- Useful forms;
- NMA Regulations;
- Results of the staff motivation survey;
- Electronic versions of the European Pharmacopoeia and the American Pharmacopoeia (USP).

11. International relationships

In 2006, NMA participations in activities of various European collaborating institutions and bodies continued as follows:

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

As early as September 2003, the EMEA invited the National Medicines Agency to assign its representatives for participation as active observers in scientific committees, working groups and groups for the implementation of technology dedicated to medicinal products for human use.

Starting September 2005, through approval by the European Commission of a new PHARE programme for Romania and Bulgaria, participation in most EMEA scientific committees and working groups has been reimbursed, which has allowed more concentrated participation in such events.

More than 100 NMA representatives took part as active observers in EMEA scientific committees and working groups in 2006.

This participation has represents the most efficient manner to maintain the NMA in line with European activities in the medicinal product field, in view of Romania's accession to the EU in 2007.

11.2. Participation in activities of Heads of Medicines Agencies

NMA representatives also take part in 5 work groups of the European body entitled "Heads of Medicines Agencies".

The working groups are as follows:

- Heads of Medicines Agencies;
- Network of Communications Professionals;
- Transparency Group;
- EMACOLEX;

- Homeopathic Medicinal Products Working Group.

11.3. Participation in European Council activities

In 2006, National Medicines Agency representatives took part in the Working Group for classification for release of medicinal products for human use, the Working Group for medicinal products and medical devices and the Working group for counterfeit medicinal products.

11.4. Participation in activities of the World Health Organization (WHO)

National Medicines Agency representatives took part in various WHO organised events, directed to promotion outside the EU of EU medicinal product standards (Balkan countries in particular), combating counterfeiting of medicinal products and meetings related to WHO consultation on medicinal plants in current use in the New Independent States (NIS).

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

In 2006, the NMA issued medicinal product certificates in WHO format for 284 medicinal products of domestic manufacturers who expressed their intention to authorise these products in other countries as well.

11.5. Participation in activities of the Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries (CADREAC/nCADREAC)

In 2006, the National Medicines Agency provided the Secretariat of the New CADREAC Agreement

After having insured construction of the New CADREAC Agreement website, www.newcadreac.org, operating as of May 2005, the NMA has been in charge of its maintenance and development.

Regular updates of the data base have been performed, including medicinal products authorised through nCADREAC simplified procedure for medicinal products authorised in the EU through mutual recognition procedure.

The NMA has revised CADREAC simplified procedures for adjustment to the new context, now available on the new website www.newcadreac.org.

11.6. Participation in activities of the European Pharmacopoeia Commission

As member of the European Pharmacopoeia Commission, the representative appointed by the NMA took active part in Commission working sessions in 2006 as well as in the annual meeting of secretaries of National Pharmacopoeias in countries member to the Convention for the elaboration of the European Pharmacopoeia.

At the same time, the NMA has continued collaboration with the European Directorate for Quality of Medicines (EDQM), in elaboration and updating of "Standard Romanian Terms" for pharmaceutical forms, administration routes and primary packaging, in compliance with those adopted by the European Pharmacopoeia Commission.

11.7. Participation in PIC/S activities

National Medicines Agency activity as PIC/S member materialised in the following:

- Closure of action towards resolution of deficiencies found during the re-evaluation performed by PIC/S inspectors in April 2005, in the frame of the PIC/S Inspectorates re-evaluation program and their presentation in the meeting of the PIC/S Committee of Officials held in May 2006;

- Elaboration of the draft Guideline related to GMP requirements for inspection of processes related to packaging, labelling, prevention of mix-ups, a fact which further proved the usefulness of the topic selected for the PIC/S Seminar held in Bucharest in 2005.

- Adaptation of Annex 19 of the EU GMP Guideline as Annex to the PIC/S GMP Guideline (the initial draft), presented in the PIC/S Committee of Officials in November 2006.

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

National Medicines Agency representatives participated in the annual meeting of the plenary OMCL Network of May 2006, organised by the EDQM.

On EDQM initiative and under its coordination, specialists of NMA laboratories participated in 7 external analytical studies, as follows:

- 5 studies for the testing of proficiency level among official medicines control laboratories (PTS);
- 2 studies for determination of quality of reference chemical substances (RCS);

At the same time, representatives participated in 3 inter-laboratory LMCS-Proficiency Program studies organised by the Dutch Scientific Pharmaceutical Institute under the auspices of the Laboratory and Medicines Control Section of the International Pharmaceutical Federation (FIP).

The specified studies are performed on an annual basis and their purpose is testing professional capacities of each laboratory of the European network to solve highly difficult aspects encountered in the control of medicinal product quality.

Test results were submitted to the EDQM, in charge of granting a certificate of confirmation of quality of analyses performed and a statistic report on participating OMCL laboratories (about 60 European laboratories).

The NMA laboratory for Physico-Chemical Control is now ranked among the first in all tests performed.

12. Human resources policies

Objectives pursued by the NMA in 2006 in the human resources field mainly envisaged the following:

- Insurance of specialised staff of higher education – specifically in the medical – pharmaceutical field, for adequate coverage of staff deficient positions in specialised departments insuring attainment of the NMA specific goals;
- Professional training and improvement of specialised staff in place for preparation of highly qualified specialists able to find solutions to the entire sphere of tasks and attributions in the NMA scope;
- Motivation of staff by provision of adequate labour conditions, stimulating work environment, access to information, training and professional improvement, stimulation of higher professional achievements of all valuable individual initiatives, better salary packages within the specific financial limits;
- Insurance of smooth communication among organisational structures and access to information handled by the Human resources department;
- Implementation of measures for confidentiality insurance regarding information handled by the Human resources department;

In the transposition of these lines, the Human resources department has been given a large workload, under circumstances created by great instability in the labour legislation, characterised by frequent changes in forms and regular reporting, which compelled to effective identification and in-process assimilation of regulatory acts, adjustment to software and proper registration of personal, salary, contributions and other data.

13. Economic and investment policies

In 2006, the NMA managed an income and expense budget of 16,300,000 RON, for both incomes and expenses.

As far as incomes are concerned, an amount of 21,927,000 RON was achieved, of which 14,256,000 RON were produced from services to internal partners whereas 7, 671,000 RON came from services to foreign partners.

The expenses chapter included 12,289,000 RON, distributed as follows:

- 9,958,000 RON staff expenses;
- 1,866,000 RON material expenses;
- 465,000 RON capital expenses.

Due to compliance with legal economic-financial discipline provisions, no expense exceeded the approved level specified in the 2006 income and expense budget.

The above date show a balanced financial exercise, developed in respect of budget principles and regulations provided in Law No. 500/2002 on public finance.

From an organisational viewpoint, economic activities were developed through the Economics Department and the Patrimony and contracts service of the European Integration, Pharmacopoeia, Legal Issues and Legislation Department and, after approval of the new NMA organisational structures through Minister of public health order No. 1248/2006, through the Economics Department and the General Administration and Patrimony Department, respectively.

Reorganisation was determined by the emergence of new legislation in the matter of public purchases, which has imposed creation of a single organisational structure able to manage the entire activity field, as well as by the need for separate functioning of administration and financial–accounting activities, thus insuring higher efficiency of these support activities.

In 2006, the Economics Department has granted the proper accomplishment of the established objectives – financial-accounting activities, various arrangement activities and the removal of the central archive in Demostene and Ilfoveni, clearing of the Schitu Măgureanu headquarters, the reopening of the Ilfoveni farm, following the retrocession of the Cernica farm to the present owner and other current activities.

A number of tariffs have also been approved through Minister of public health order for activities performed by the NMA departments.

As concerns the investment chapter, the most important goals attained in 2006 were:

- Purchase and installation of the digital telephonic central;
- Achievement of infrastructure required for compatibility of NMA and EMEA IT systems;
- Acquirement of current IT equipment and software;
- Acquirement of equipment for control departments.

14. Encountered difficulties

The main problem that ANM encountered in 2006 has been the insufficient number of pharmacists and doctors employed as professional evaluators, problem which has been partly generated by the massive departures from the institution during 1999-2002 and partly because the well-salaried working offer in the private sector is still high enough.

15. Priorities for 2007

- Insurance of appropriate achievement of NMA mission as provided in the law for its organisation and functioning;
- Consolidation of the internal and international standing acquired, through high quality performance in interaction with both Romanian and foreign partners;
- Accomplishment of all obligations undertaken in relation with partners at home and abroad, close collaboration with the specialised directorate in the MPH, the National Health Insurance House and other state competent authorities, dynamic participation in activities developed by the EMEA, PIC/S and other specialised bodies the NMA is affiliated to;
- Insurance of human and financial resources required for efficient development of activities;
- Redistribution of staff, to insure development of priority activities in result of European Accession, taking into account the workload of each specific position;

- Improved wages for and motivation of existing specialist staff for encouragement for continued work in the institution as well as further employment of young specialised staff;

- Continued in service staff training as well in other locations at home and abroad for improved professional competence and preparation for operation within the European system;

- Strict compliance with legal provisions in all areas of activity and implementation of medicinal product legislation, in line with provisions of Law No. 95/2006;

- Ongoing improvement of the quality management system and participation in benchmarking activities, particularly those organised by the EMEA;

- Improvement of communication with interested parties and transparency of activities.

CONCLUSIONS

The fruitful activity of the National Medicines Agency during 2006 is the outcome of the constant and resolute efforts of most of its staff as well as of leadership permanent availability for cooperation and communication, for the creation of conditions required for human resources development to their best professional capacities.

As a competent authority in the Romanian field of medicinal products for human use, the NMA has accomplished a quick progress towards the European standards, by its own efforts and thanks to the support received from the analogous institutions of the EU member states and from the European bodies.

The NMA is regarded by the European bodies and the analogous institutions of the EU member states as an institution thoroughly prepared in order to meet the challenges of the EU accession, perception mirrored in the results obtained due to various tests that it has undertaken.

At the time being, the NMA is a well-developed institution, fully capable of meeting the activities derived from its new status of competent authority in an EU member state.