NATIONAL MEDICINES AGENCY REPORT ON 2005 ACTIVITIES

INTRODUCTORY WORD

As in every other start of a new year, according to quality management principles, in the first 2006 meeting of the Administrative Council, the President of the National Medicines Agency presented the report on the previous year's activity providing an outline of activities carried out in 2005.

Presentation of a report also meets a communication demand consisting of highlighting, for both staff and external partners, of achievements and difficulties faced by the institution, as a foundation for the set up of a general line and a realistic and enduring development strategy for the following year.

The context for the elaboration and presentation of the current report is essentially defined by the ever closer perspective of accession to the European Union, which has for some time influenced the entire activity of the National Medicines Agency.

Priorities for 2005 were set by the Agency stepping into the stage of pre–accession to European structures.

For the National Medicines Agency, the year 2005 represented an important gain in quality, systematically and resolutely prepared by each and every previous step, towards its institutional consolidation as a specialised public institution whose object is marketing authorisation in Romania of quality, safe and effective medicinal products.

In line with the legislative programme in support of the process related to Romania's accession to the EU and with commitments taken up in the Position Document on the Chapter "Free Movement of Goods", the Agency has undertaken significant tasks in harmonization of national with European legislation under such circumstances as determined by the fact that, on European level, the medicinal product field is one of the most regulated and dynamic sectors.

The entire activity of the Agency as competent authority in an acceding country has been developed under the sign of intense preparations for Accession, focusing on transposition and implementation of the *acquis communautaire* into national legislation, of improvement and updating of national drug legislation as well as enhancement of the thus achieved legislative frame through introduction of a range of complementary aspects.

During 2005, the Agency mainly focused on carrying out its specific tasks, attributions and responsibilities at improved quality parameters, chiefly directing its efforts towards regulatory activities as well as to the internal and external events it is connected to.

In compliance with commitments expressed in the Position Supplementary Document to transpose new European directives provisions into national drug legislation before the end of 2005, the NMA, in collaboration with the General Pharmaceutical and Medical Devices Directorate within the Ministry of Health have elaborated the draft drug law, which is a full and integrated transposition of present provisions of European legislation.

The Agency therefore contributed to the general legislative effort finalised in drafting of the regulatory package on healthcare reform, which has received the Parliament vote of confidence and the President of Romania promulgated on 13.04.2006.

Implementation of the frame law requires initiation of a comprehensive and prompt process for drafting and endorsement of secondary legislation to be materialised in decisions of the NMA Scientific Council and approved through orders of the minister of health, which will require constant and ample efforts from specialist departments in our institution.

A further priority line for 2005 for Agency specialised departments was insuring constant pace for basic activities of the institution. The joint action of everybody involved has led to significant reduction of the number of authorisation files yet to clarify and will carry on

in such a way that, by the end of the year, the NMA will be able to observe the 210 days deadline provided in the drug law according to European practices.

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

An important aspect of 2005 activity is participation of NMA representatives as active observers in EMEA scientific committees and working groups, as the most efficient means to maintain the NMA connected to European activities in the field of medicinal products, in view of Romania's adequate preparation for Accession.

One should also not fail to make primary reference to the special event of the annual PIC/S seminar, which the Agency organised in Bucharest, in September 2005.

Participants met the sessions with particular interest and appreciated both the scientific level of presentations and NMA organisation of the session.

According to the accession strategy for 2005 and 2006 further on, there were special requests concerning strict approach of the regime of the institution's set up of revenues. In result, during 2005, the Agency succeeded in covering most of the income chapter from dues for services provided during the year, which allowed the closure in excess of the financial year.

That is why, in addition to highest efficiency in the use of financial resources, one of the important lines for 2006 activity will be to engage new resources. Depending on opportunities, perspectives along this line are optimistic and provide us reason to estimate that no financial problems will be encountered.

Steps taken in 2005, when a system for the evaluation of staff performance was successfully set up, which is closer to individual contribution and the importance of the specific activity carried out by each member of staff, should be continued in 2006 as well and so should restructuring through elimination of certain inefficient activities.

More appropriate staff policies are intended for 2006, and the main activity along that line will be staff rearrangement depending on institutional present and future interests, going even as far as resizing of staff.

I. NMA ACTIVITIES DURING 2005

1. ACTIVITY OF THE SCIENTIFIC COUNCIL OF THE NATIONAL MEDICINES AGENCY (NMA)

According to provisions of Government Ordinance No.125/1998 regarding the setting up, organisation and functioning of the NMA, approved with changes and completions through Law No.594/2002, with further changes and completions, the Scientific Council establishes the scientific policy of the NMA, according to its attributions.

Meetings of the Scientific Council discuss regulations concerning NMA professional activity, which are approved as Decisions of the Scientific Council.

Decisions of the Scientific Council of ruling character are subject to the approval of the minister of health and are published as minister of health orders in the Official Gazette of Romania. The other Decisions of the Scientific Council are submitted to the Minister of Health for approval and applied within 15 working days after submission, in case the Minister of Health does not express disagreement; following that, they are published in the NMA Informative Bulletin.

The Decisions of the Scientific Council transposing European directives are notified to the Ministry of European Integration, approved through minister of health order and published in the Official Gazette of Romania.

The name composition of the Scientific Council, as established through minister of health order and in accordance with provisions of Government Ordinance No.125/1998, consists in the following: 4 NMA members, one representative of the Academy for Medical Sciences, one representative of the National Sanitary–Veterinary Agency, 4 representatives of medicine faculties, 4 representatives of pharmacy faculties; 4 experienced physicians of various specialisations, an immunologist, an epidemiologist, a dentist, proposed by the specialised commissions of the Ministry of Health, a hospital pharmacist proposed by the Ministry of Health, a representative of the Ministry of Economy and Commerce, a representative of the Ministry of Education and Research, a representative of the College of Pharmacists in Romania, a representative of the College of Physicians in Romania, a representative of the Association of Romanian Medicines Manufacturers in Romania and a representative of the Romanian Association of International Medicine Manufacturers.

The mandate of the NMA Scientific Council is 3 years.

The mandate of the NMA Scientific Council nominated through Minister of Health Order No. 30/15.01.2002 expired on 15.01.2005. The minister of health order for the set up of the new NMA Scientific Council was issued in May 2005 and therefore the NMA Scientific Council was unable to operate during January–May 2005.

The NMA Scientific Council resumed its activities in June 2005 and conducted **3** working sessions, the first meeting of which was focused on election of the president, vice president and secretariat of the new Scientific Council and presentation of the NMA Scientific Council President's report on the 2002–2005 mandate.

During 2005, the activity of the NMA Scientific Council has been materialised in adoption of **12** decisions.

Most of the **12** decisions mentioned above have been very complex, involving transpositions of European directives, regulations related to marketing authorisation and surveillance of medicinal products for human use and the Guidelines on updating and change of documentation for authorisation of medicinal products for human use authorised in Romania, for compliance with European Union requirements.

2. ACTIVITY OF THE NMA ADMINISTRATIVE COUNCIL

According to provisions of Government Ordinance No. 125/1998 regarding the setting up, organisation and functioning of the NMA, approved with changes and completions through Law No. 594/2002, with further changes and completions, the Administrative Council carries out the following activities:

- Approves NMA economic and financial policy;
- Proposes the organisational structure of NMA departments;
- Approves the budget for incomes and expenses;
- Analyses the opportunity and possibilities to conclude contracts for collaboration and services;
- Proposes 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 health order;
- Issues the NMA annual activity report;
- Approves NMA organisation and functioning statutes and regulations;
- Approves NMA internal regulations.

The name composition and structure of the Administrative Council is established through minister of health order and, according to provisions of Government Ordinance No. 125/1998 it includes the President, Vice–president and heads of NMA departments, the Director

of the General Pharmaceutical, Pharmacy Inspection and Medical Devices Directorate within the Ministry of Health, the Director of the Budget and Purchases General Department of the Ministry of Health, the Director of the Department of Relationships with the Parliament, Legislation and Claims Office of the Ministry of Health and the General Director of the National Health Insurance House.

During 2005, the NMA Administrative Council carried out **8** working sessions, which has determined the adoption of **34** decisions, **2** of which are of ruling character, approved through minister of health order and published in the Official Gazette of Romania, Part I.

3. REGULATORY ACTIVITY

In line with the legislative programme in support of the process for Romania's accession to the EU, to commitments assumed in the Position Document referring to the chapter "Free Movement of Goods", the NMA Scientific Council has drafted/updated regulations regarding NMA professional activity, in compliance with community regulatory documents.

Consistent with commitments expressed in the Position Supplementary Document to transpose new European directives provisions into national drug legislation before the end of 2005, the NMA in collaboration with the General Pharmaceutical and Medical Devices Directorate within the Ministry of Health have elaborated the draft drug law, which is a full and integrated transposition of present provisions of European legislation.

Stages so far in project development have been:

– Drafting as such (August–September 2005);

– Evaluation and inclusion of applicable comments of interested parties after public consultation;

– Evaluation and inclusion of applicable comments of the Ministry for European Integration, authorising ministries, the Legislative Council;

– Inclusion of the draft drug law as Title XVII, The Medicinal Product, into the Law for Healthcare Reform.

The draft drug law is a transposition of Directive 2001/83/CE, updated through: Directive 2002/98/CE, Directive 2004/24/CE, Directive 2004/27/CE and introduces a range of new aspects such as:

– Change of the "medicinal product" definition;

– Introduction of the "generic medicinal product" definition;

– Introduction of the "reference medicinal product" definition

– Introduction of the "similar biological medicinal product" definition.

– Introduction of a new approach in data exclusivity issues:

  – the 8+2+1 formula for data exclusivity for all reference products;

  – 1 year of data exclusivity for new therapeutic indications of medicinal products authorised with bibliographic documentation;

  – 1 year of data exclusivity for change of status, based on clinical trials, from prescription medicinal product to OTC;

– Introduction of the Bolar provision;

– Introduction of special provisions applicable to traditional herbal medicinal products;

– Provision on single renewal of marketing authorisation five years after issuance, the authorisation acquiring unlimited validity afterwards;

– Provision on cessation of marketing authorisation validity in case of lack of use for 3 years;

– Introduction of Braille writing in labels;

– Introduction of special provisions on medicinal products derived from human blood and plasma;

– Introduction of the 210 days deadline for resolution of applications for marketing authorisation;

– Introduction of authorisation under exceptional circumstances;

– Introduction of conditional authorisation;

– Inclusion of provisions concerning decisional transparency of the competent authority, commercial confidentiality and public access to information pertaining to the medicinal product specific information.

In 2005, **three** of the **12** decisions endorsed by the NMA Scientific Council were approved through Minister of Health Order and published in the Official Gazette of Romania.

Two of the decisions endorsed by the NMA Scientific Council in 2005 are transpositions of European directives in the medicinal product field, namely:

– *the Annex to Directive 2003/63/CE of 25 June 2003 on Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products,* amending Directive 2001/83/EC

– *Directive 2003/94/CE 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.*

The above decisions are to be approved through minister of health orders and enter into force 90 days following publication in the Official Gazette of Romania of the Law of Healthcare Reform.

4. ACTIVITY OF NMA COMMISSIONS

4.1. Marketing Authorisation Commission

The Commission is set up through Decision of the NMA President and includes the NMA Vice–president, the heads of the 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 offices 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 2005, the Marketing Authorisation Commission conducted **77** working sessions for discussion of evaluation reports for **1058** medicinal products for human use and formulation of opinion in view of marketing authorisation.

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 is set up through decision of the NMA President and is made up of the NMA President and Vice–president, the heads of 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 NMA 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 is competent to confirm or invalidate decisions made by inspectors as mentioned in the inspection report.

In 2005, the Commission for GMP, GLP, GALP and GCL Inspection conducted **10** working sessions for examination of **45** inspection reports.

4.3. Commission for the Coordination of the Romanian Pharmacopoeia

The Commission is set up by decision of the NMA President and includes the President and Vice–president of the NMA, representatives of traditional pharmacy faculties, of the General Pharmaceutical and Medical Devices Directorate of the Ministry of Health as well as NMA specialists.

The Commission has continued to coordinate translation and harmonization 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 (RPX).

To allow them to express their opinion, Commission members were provided the draft of the RPX 2005 Supplement, including monographs and methods translated from and harmonized with the EP the 5th edition and Addenda 5.1–5.5 as well as reagents needed for determinations provided for in the respective texts.

Comments are to be analysed and implemented by the Service for Pharmacopoeia (providing secretarial activities for the Commission) and Commission members will further discuss divergent opinions.

5. EVALUATION–AUTHORISATION AND RELATED ACTIVITIES

5.1. Marketing Authorisation

In 2005, the NMA was submitted **1153** applications for marketing authorisation, of which:

– **85** applications for authorisation through CADREAC simplified procedure (Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries) for products authorised through centralised procedure in the European Union (EU);

– **156** applications for authorisation through CADREAC simplified procedure for products authorised through mutual recognition procedure in the EU;

– **909** applications for authorisation through national procedure.

In 2005, the NMA issued **1034** marketing authorisations (MA), of which:

– **80** MAs through CADREAC simplified procedure for products authorised through centralized procedure in the EU;

– **94** MAs through CADREAC simplified procedure for products authorised through mutual recognition procedure in the EU;

– **858** MAs through national procedure.

Medicinal products authorised for marketing in 2005 have been made available on the NMA website (**www.nma.ro**) and published in the annual NMA Index of medicinal products for human use, at the beginning of 2006.

The total number of medicinal products authorised for circulation on 31.12.2005 was **5292,** corresponding to **976** International Non–Proprietary Names (INN).

Of the above:

– 1**468** are Romanian medicinal products

– **3824** are imported medicinal products.

Of all medicinal products entitled for circulation, **831** are medicinal products to be released without prescription (Over the Counter = OTC).

5.2. Approval of variations to marketing authorisation terms

In 2005, the NMA received **5706** applications for type I and of type II variations, changes allowed by regulations, transfers of marketing authorisations.

A number of **4035** applications were approved, of which:

– **3139** applications for type I variations;

– **693** applications for type II variations;

– **65** applications for transfers;

– **138** applications for other types of changes.

5.3. Approval of clinical trials

In 2005, the NMA received **182** applications for the approval of clinical trials, of which:

– **2** applications for the approval of **phase I** clinical trials;

– **54** applications for the approval of **phase II** clinical trials;

– **2** applications for the approval of **phase II/III** clinical trials;

– **112** applications for the approval of **phase III** clinical trials;

– **12** applications for the approval of **phase IV** clinical trials.

220 applications were also submitted for approval of bioequivalence studies.

Before the end of 2005, the following clinical trials were approved:

– **2 phase I** clinical trials;

– **54 phase II** clinical trials;

– **2 phase II/III** clinical trials;

– **110 phase III** clinical trials;

– **12 phase IV** clinical trials.

220 bioequivalence studies were approved.

5.4 Approval of advertising material

Approval of advertising material for medicinal products for human use is carried out according to Regulations regarding advertisement of medicinal products for human use, approved through Minister of Health Order No. 263/25.03.2003 published in the Official Gazette of Romania, which are a transposition of *Title VIII – Advertising,* of *Directive 2001/83/EC of the European Parliament and Council, of November 6, 2001, on the Community Code regarding medicinal products for human use.*

During 2005, the NMA was submitted **204** applications for approval of advertising materials of medicinal products and approved **203** advertising materials.

5.5. Pharmacovigilance

The activity of the National Pharmacovigilance Centre operating within the NMA is conducted according to Pharmacovigilance Regulations transposing *Title IX – Pharmacovigilance* of *Directive 2001/83/CE,* approved through Minister of Health Order No. 411/2005, as well as the Guidelines on procedure to be followed by competent authorities in pharmacovigilance activities, Guidelines for the management of clinical safety data/the Regular updated report on the safety of marketed medicinal products, approved through orders of the minister of health and published in the Official Gazette of Romania.

In 2005, pharmacovigilance consisted in management of the following reportings:

– **418** spontaneous reports in Romania;

– **5500** reports in the format of the Council for International Organisations of Medical Sciences (CIOMS);

– **593** updated Periodic Safety Update Reports (PSUR) for imports;

– **169** Romanian Periodic Safety Update Reports (PSUR).

In result of measures taken to revigorate pharmacovigilance activity conducted by practitioners, the number of adverse reactions reported by physicians increased by 152% as compared to 2004.

24 EMEA press releases – public statements have been posted on the NMA web–site, on safety issues of medicinal products Authorised through centralised procedure.

For reasons of advertising among pharmacists issues of adverse reactions to medicinal products, **9** articles have been published in the „Farmacist.ro" magazine.

6. INSPECTION OF GMP, GCP, GLP, GALP, GOOD PHARMACOVIGILANCE PRACTICE AND MARKET SURVEILLANCE

In 2005, inspection activities were as follows:

– **39 GMP** inspections, of which **22** were performed at local manufacturing sites and 17 abroad; inspections abroad on solicitation from interested companies are conducted by the NMA as a member of the Pharmacy Inspection Cooperation Scheme (PIC/S) and a participant in the International Medicines Inspectorates Database (IMID);

– **16 GCP** inspections;

– **1 GLP** inspection;

– **1 GALP** inspection;

– **2** prior to marketing authorisation inspections;

– **53** inspections following complaints on the quality of certain medicinal products;

– 1204 inspections within the annual plan of market surveillance;

– **5** authorisation inspections for operation of medicinal products manufacturing sites;
– **3** pharmacovigilance inspections at MA holders;
– **1220** consultancy visits on pharmacovigilance problems.

7. QUALITY CONTROL OF MEDICINAL PRODUCTS

During 2005, the Raw Materials and Finished Products Control Department (RMFPCD) analysed **2819** series of imported and domestic products. Of these:
– **1317** were chemical products;
– **92** were radiopharmaceutical products;
– **1410** were biological products.
For the above products, **5207** analysis bulletins were issued.

As of April 2005, RMFPCD specialists have been involved in activities related to the evaluation of documentation for Authorisation and reAuthorisation of Romanian or foreign medicinal products. So far, **128** evaluation reports have been finalised.

In 2005, the Biological Products Evaluation and Control Department (BPECD) analysed **1539** series of biological products, of which **1472** series were internally produced; of these:
– **414** were vaccines;
– **1020** were immunomodulators;
– **64** were antigens;
– **37** were blood derivates;
– **3** were therapeutic serums.
67 biological products were subject to evaluation for marketing authorisation; **109** evaluation reports were drafted for the respective biological products assessed as well as for **77** variations.

Specialists in both departments collaborated in translation and review of certain monographs for the RPX 2005 Supplement.

8. PHARMACOPOEIA RELATED ACTIVITIES

Through Romania's accession to the European Pharmacopoeia Convention of the European Council and therefore acquisition of full membership status on 24.09.2003, quality standards of the European Pharmacopoeia have become mandatory for all raw materials and medicinal products for human use both imported by and manufactured in Romania.

In 2005, drafting was finalised of the 2005 RPX Supplement; the approximately 400 pages of the volume provide 23 general methods of analysis, 12 general monographs, 5 general texts, 3 individual monographs, 4 monographs of homeopathic preparations, 190 reagents and new and revised Standard Romanian Terms complying with EP 5 and Addenda 5.1–5.5.

Through draft and publication of the 2005 RPX Supplement, the NMA supports users by provision of a Romanian official version of the general part of the European Pharmacopoeia, harmonized with specific Romanian terms in the field, as well as with Romanian standard terms approved for pharmaceutical forms, administration routes and primary packaging.

9. QUALITY MANAGEMENT ACTIVITY

In 2003, within the program of the PanEuropean Regulatory Forum (PERF), the NMA system of quality management was evaluated by a team of Member States and candidate countries auditors.

The conclusions of the evaluation were the following:

"The National Medicines Agency has a well established system of quality management which is based on ISO 17025 in the field of laboratory control and ISO 9001 for the regulatory activity. The Quality Handbook and other documents of the quality management system are drafted and it is obvious that within the organisation the process–based approach is implemented. The management at the highest level is deeply involved in activities related to the system of quality management and the whole staff is motivated and understands clearly the mission and objectives of quality. The employees are well trained in the problems of the quality management system".

In 2005, quality management activities mainly focused on improvement of the existing system.

In this respect, the documentation of the quality management system was completed in 2005 through the following:

– Elaboration of **2** new general Standard Operation Procedures (SOP);
– Change/review of **6** general SOPs;
– Elaboration of **38** new specific SOPs;
– Change/review of **28** new specific SOPs.

Detailed sub–criteria were drafted for evaluation of staff professional performance and an evaluation was conducted on activity carried out during the first half of 2005.

The following have been drafted:

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

In 2005, **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

According to provisions of Law No. 544/2001 on free access to information of general interest, the NMA continued to be particularly concerned in insuring good communication with interested parties and transparency all along 2005.

This special concern is also one manifestation of NMA's endeavour to comply with European regulations, one notable change resulted from revision/updating of Directive 2001/83/EC being transparent regulation of medicinal product activities.

Special mention should be made of the fact that, in result of prompt application of Law No. 161/2003 on measures for insured transparency in the exercise of public dignities, i.e. Title II – Transparency in management of public information and services through electronic means, the NMA has been included into the "National Electronic System", contributing to the "system of electronic governance" as of 2004.

In addition, the NMA promptly met requests for implementation on the Government site (www.e–guvernare.ro) of forms made available to users, also posted on the NMA site: www.nma.ro.

10.1. EXTERNAL COMMUNICATION

The NMA has carried on the tradition of quarterly publication of bilingual Informative Bulletins, mirroring the intense activity related to transposition of European drug legislation into national legislation. The electronic version of the Informative Bulletins is posted on the web–site.

The NMA has been concerned to develop information made available on its bilingual web–site.

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

– Summaries of product characteristics (SPC) for medicinal products authorised in Romania through CADREAC simplified procedure for products authorised in the EU through centralized procedure or mutual recognition procedure;

– SPCs for medicinal products authorised in Romania through CADREAC simplified procedure for products authorised through mutual recognition procedure in the EU;

– Information letters for physicians;

– Press releases related to medicinal product safety.

The following have been of great use to external users:

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

– Medicinal product legislation;

– Useful information.

The proof of increased interest from concerned parties for information placed on the NMA website is the large number of visitors, a double figure in 2005 as compared to the previous year, going as high as **85347** visitors/year, a monthly average of **7112** visitors, respectively.

In order to debate problems of wide interest, especially related to problems of European integration, the NMA also continued organising meetings with marketing authorisation holders and associations of medicinal product manufacturers. Participants received timely information on the NMA strategy regarding submission of applications for authorisation/re–authorisation, as determined by preparations for transfer to European procedures as well as on the strategy for update of documentation for authorisation during pre–Accession. Such information has also been posted on the NMA web–site.

In 2005, the NMA continued to inform interested parties on its activity through other publications as well, other than its own Informative Bulletin.

To the approval of NMA partners, the Agency report on 2004 activities was again published as a brochure.

Articles related to various aspects of NMA activity have been published 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 specialist presentations in conferences and symposia organised at home and abroad. Presentations have approached such topics of interest as:

– Stage of the Transposition into Member States and Acceding Countries National Legislation of New Medicinal Product European Legislation (1 presentation abroad);

– Record of Main New Provisions Introduced in Recent Medicinal Product European Legislation (1 presentation abroad and 2 presentations in Romania);

– Difficulties Encountered by Competent Authorities and Pharmaceutical Industry in Implementation of European Pharmaceutical Standards in Central and Eastern Europe (1 presentation abroad);

– Synergies and Harmonizations of Romanian Medicinal Product Legislation in View of Accession – Presentation of NMA Activity (1 presentation abroad;

– Globalisation of Clinical Trial Markets: Analysis of Regulations, Risks and Opportunities (1 presentation abroad);

– Synergies and Collaborations to Be Built in Europe for Better Patient Protection (1 presentation abroad);

– Romanian's Preparation of Accession, Implementation of European Legislation (1 presentation abroad);

– History of pharmacy: Iconographic Presentations of Personalities of the Romanian Medical–Pharmaceutical Field (2 presentations abroad and 3 presentations in Romania).

Last but not least, mention should also be made of participations in the recently set up "Meetings of the Professional Communication Network of Medicines Agencies in the European Union", for joint approach in communication, improved and more efficient communication activities among Medicines Agencies in the European Union and coordination of communication risks and crisis management.

10.2. INTERNAL COMMUNICATION

In 2005, for better and faster information of staff on professional and organisational issues, information available on the NMA intranet was supplemented and updated.

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 of staff participating in trainings;
- Status of staff training;
- Glossary of quality assurance terms;
- Useful forms;
- Results of the staff motivation survey;
- NMA Regulations;
- Electronic versions of the European Pharmacopoeia and the American Pharmacopoeia (USP).

11. INTERNATIONAL RELATIONSHIPS

In 2005, NMA participations in activities of various European collaborating institutions and bodies continued as follows:

11.1. Participation in European Medicines Agency (EMEA) activities

Following the provisional closing in the year 2003 of Chapter 1 "Free Movement of Goods ", subchapter 1.1 "Pharmaceutical products", the NMA received EMEA's invitation in September 2003 to nominate its representatives for participation as active observers in the **26** scientific committees, working groups and groups for implementation of information technology dedicated to medicinal products for human use.

Starting with September 2005, through approval by the European Commission of a new PHARE programme for Romania and Bulgaria, participation in most scientific committees and

work groups has been reimbursed, which allows for more concentrated participation in such events.

Participation of the NMA 26 representatives as active observers in EMEA scientific committees and working groups in 2005 has been the most effective and efficient way to carry on NMA connection to European drug related activities in view of preparation of Romania's Accession in 2007. NMA representatives also take part in **5** work groups of the European body entitled "Heads of Medicines Agencies" as wel as activities organised by the Council of Europe and the World Health Organization.

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

NMA organised the annual 2004 CADREAC meeting in Bucharest, which was particularly successful in both importance of topics and organisation.

According to provisions of the agreement, the NMA has taken over the CADREAC secretariat.

The NMA has also taken the initiative to set up the New CADREAC agreement, an undertaking of maximum interest for new candidate countries as well as for other Central and South–East European countries interested in European standards related to medicinal products.

In result of NMA constant effort and determination, the New CADREAC Agreement (nCADREAC) became effective as of 01.05.2005, according to Article 8 (2).

The 6 signatories of the New CADREAC Agreement are competent authorities of such Member States as the Czech Republic, Slovakia and Hungary and competent authorities of candidate countries (Bulgaria, Croatia and Romania).

Prior to the first annual meeting, the National Medicines Agency of Romania provides the Secretariat of the New CADREAC Agreement.

The NMA has also been in charge of construction of the New CADREAC Agreement web–site, www.newcadreac.org, operating as of May 2005.

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

11.3. Participation in activities of the European Pharmacopoeia Commission

After ratification of the European Pharmacopoeia Convention of the European Council, Romania has gained full membership starting with 24.09.2003. As member of the European Pharmacopoeia Commission, the representative appointed by the NMA took active part in Commission working sessions in 2005.

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 the 5th edition of the European Pharmacopoeia.

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

During 11–16 September 2005, Romania acted host to the annual 2005 session of the International Seminar developed under the Pharmaceutical Inspection Cooperation Scheme – PIC/S.

The seminar was organised by the National Medicines Agency as active PIC/S member since 1982.

90 representatives of 38 countries attended the seminar.

The topic of the seminar was: "Primary Packaging Materials, Labelling and Prevention of Mix–ups".

Participants met the sessions with particular interest and appreciated both the scientific level of presentations and NMA organisation of the session.

Such appreciations have resulted from conclusions presented in the closure of the session, when participants voiced their opinion that "through the National Medicines Agency, lead by President Magdalena Bădulescu and the GMP team led by Simona Raicu, Romania has organised a "perfect 10" PIC/S 2005 Seminar, in the same way as Nadia Comăneci and Romania's team were successful in scoring a "perfect 10" in the Olympic Games. The seminar has been well <packaged, validated and with no packaging errors>".

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

NMA representatives participated in the annual meeting of the plenary OMCL Network of May 2005, organised by the European Directorate for the quality of medicines (EDQM) on "Quality Control of Medicinal Products: Place and Role of the European OMCL Network within the Regulatory Framework in Europe".

Specialists of NMA laboratories participated in **4** studies for testing competence level among official laboratories for medicinal products control (PTS) organised by the EDQM and **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 (LMCS–FIP).

Agency representatives also took part in **3** studies related to determination of quality of reference chemical substances (RCS) initiated by the EDQM.

According to the statistic report on results of all OMCL laboratories submitted by the EDQM fro certain studies, the NMA laboratory for Physico–Chemical Control is now ranked 1–2 among the approximately 60 participating laboratories.

12. STAFF POLICY

Objectives pursued by the NMA in 2005 in the human resources field were as follows:

- Provision of specialised staff with university degrees, competent, appropriately trained, endowed with adequate abilities and experience, able to contribute to carrying out the NMA mission;
- Stimulation of individual employees for self training;
- Delegation of responsibilities on each management level in order to ensure individual contribution to the achievement of quality objectives;
- Establishment of competences/tasks, responsibilities and communication thereof to agency staff;
- Planning of human resources for best achievement of organisation tasks;
- Promotion of staff involvement in achievement of quality related objectives and better organisational efficacy and efficiency;
- Provision of staff training according to job (position) requirements;
- Provision of access for various organisational and management structures (departments, services, offices, compartments) to specific Human Resources Department (HRD) information required for ongoing improvement of activities;
- Provision of an adequate working climate stimulating motivation, satisfaction, development and performance of organisational staff;
- Insuring confidentiality of information handled by the HRD.

13. ECONOMIC AND INVESTMENT ACTIVITY

The NMA revenues and expenditure budget for 2005 was 14,500,000 RON.

As far as revenues are concerned, their amount was 13,683,843 RON, of which 8,609,258 RON represented fees and tariffs from services provided to Romanian medicinal products and 5,077,584 RON from services performed for foreign medicinal products.

Payments amounted to 10,626,839 RON, distributed as follows: 8,549,789 RON staff costs, 1,597,142 RON material costs and 479,908 RON capital costs.

The budget exercise presents an excess of 3,057,004 RON and the NMA complied with every expenditure chapter as assigned by the annual budget, in respect of all legal provisions.

As activities standing out among current performance one should mention calculation of tariffs for services provided by the NMA through its departments for authorisation–evaluation, raw materials and finished products control, biological products evaluation and control, pharmaceutical inspection. This specific activity has resulted in endorsement of decisions of the NMA Administrative Council No. 5/15.03.2005 and No. 18/12.07.2005, approved through Minister of Health Orders No. 407/19.04.2005 and No. 1.454/28.12.2005, respectively, related to updating of tariffs according to present levels of general administration and other elements in price calculation.

Investments in 2005 were made in areas of maximum interest for NMA preparation for Accession:

– Completion of NMA endowment with high–quality IT equipment, thus ensuring a network of 180 quality computers, compatible with the European computer system;

– Upgrade of the NMA Internet connection through band–width extension through optical fibre connection, as required by the intense NMA information exchange with European bodies and similar agencies in Member States, during pre–Accession;

– Purchase of sowftware for security of the Internet and e–mail server as well as for controlled access to and use of SMTP–type services (protection against unauthorised access to and use of the e–mail server for sending mail).

II. DEFICIENCIES IN ACTIVITY CONDUCTED

In spite of ongoing efforts to eliminate delays in finalizing the evaluation of the documentation submitted by applicants for marketing authorisation, delays have happened in 2005 as well, mainly generated by delayed applicant payment of authorisation fee and tariff and/or delay in submission to the NMA of requested completions.

III. DIFFICULTIES

The main problem the NMA has encountered during 2005 has been the insufficient number of quality evaluators specialised un pharmacy, situation in part determined by the massive leaves from the institution between 1999–2002 and, on the other hand, by the fact that well paid labour demand in the private sector is still comparatively high.

IV. PRIORITIES FOR 2006

– Improved wages for and motivation of existing specialist staff to continue work in the institution as well as further employment of young specialised staff;

– Further reorganisation of NMA for achievement of compatibility between operational units and staff structure with requirements for NMA operation in the European network of competent authorities in the area of medicinal products;

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

– Further improvement of NMA infrastructure and particularly of its information system for compatibility with requirements of operation in the European system;

– Improved organisational structure to insure optimal operation and compatibility with the European system, with special stress on reorganisation of the two control departments;

– Increased efficiency of organisation manner, mainly aiming at reduction of the time required for resolution of targeted goals;

– Steady continuation of drafting/updating regulations regarding NMA professional activity, in accordance with the new drug law now in process of approval, transposing Directive 2001/83/EC as amended by Directive 2002/98/EC, Directive 2004/24/CE and Directive 2004/27/EC;

– Improvement of communication with interested parties and transparency of activities;

– Provision of financial resources necessary for participation in international activities, thus contributing to permanent contact with similar institutions and European institutions of the same type;

– Provision of human and financial resources appropriate for good activity development;

– Provision of European quality professional training to staff, thus contributing to facilitated NMA integration into the European system after Accession.

CONCLUSIONS

The fruitful activity of the National Medicines Agency during 2005 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.