THE NATIONAL MEDICINES AGENCY
2007 ANNUAL REPORT

INTRODUCTION

„The National Medicines Agency has reached institutional maturity and is currently fully able to cope with activities derived from its new status as competent authority in a EU Member State. The NMA is perceived by the European bodies and fellow institutions in the EU Member States as an institution well prepared to cope with challenges brought about by accession as of 1 January 2007".

The above concluding statement was made in full confidence and relied on the extensive efforts made in the previous year in view of concentrated preparations for Accession, focusing on the strategy of authorisation dossier update and preparation for transition to European procedures.

The outstanding NMA activity in 2007 that is the object of the present Report fully proves the truth of NMA statements as expressed at that time.

During the first year after Accession (2007), NMA activity focused on strengthening its institutional capacity meant to ensure progress of medicinal product marketing authorisation process through European procedures: Mutual Recognition Procedure and the Decentralised Procedure, with Romania as concerned Member State.

The respective process started on the very first day of 2007 and the NMA had to cope with a large number of applications from the very beginning.

In addition to preparations made as early as 2006, the NMA concentrated on improvement and strengthening staff structure of the Evaluation authorisation department (EAD) in charge of European procedures implementation. Staff has also been redistributed within the Raw materials and finished products control department (RMFPCD) for the purpose of adding to the existing personnel and thus allow compliance with the very strict timetable characteristic to these procedures.

In 2007, activities carried out by NMA specialist departments and particularly EAD work increased in complexity by incorporation of new tasks requiring an impressive amount of labour, such as:

- Authorisation of medicinal product importers;
- Approval of medicinal product exports;
- Certification of the Qualified person for batch release.
- Management of European Commission decisions in the matter of various types of referral;
- Coordination of activities resulting from application of provisions mentioned in Art. 729 and 730 of Law No. 95/2006 on healthcare reform, requiring recording of marketing authorisation holder (MAH) notification of the date of actual marketing as well as of any temporary or permanent cessation of placement on the market of a medicinal product ("sunset clause");
- Coordination of activities resulting from application of legal provisions on parallel import of medicinal products for human use for which marketing authorisations have already been granted;

The year 2007 further brought about use by the NMA of the European Commission administrative procedure for official batch release by the control authority – the Official Control Authority Batch Release (OCABR).

Fulfilment of these multiple tasks required putting to work al resources in set up of secondary legislation compliant with Law No. 95/2006 on healthcare reform and Directive 2001/83/EC. NMA regulatory efforts materialised in a large number of Scientific Council

decisions, some of which have been approved through Minister of Public Health Order. A large number of procedure or scientific guidelines have also been approved, which has involved a large amount of labour and outstanding commitment of all teams engaged in their development.

In the same effort toward compliance with European standards, the NMA has adopted a complex programme of institutional development through internal restructuring for increased compatibility with fellow competent authorities. From this point of view, 2007 represented the year of new and very important material investments. The organisation of the new site of the Raw materials and finished products control department (RMFPCD) has been ceased, activity which has involved a high degree of workforce and spendings mobilisation.

The year 2007 was also the time for completion of Biological products evaluation and control department (BPECD) relocation to an area in former need of arrangement and endowment with effective equipment, meant to result in increased accuracy of all analyses performed.

In 2008, the NMA will be subject to an EDQM inspection for the accreditation of NMA control laboratories.

Another important aspect of NMA labour in 2007 was active participation of NMA experts 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 activities in the field of medicinal products. As a follow-up to the coming into force of Regulation 1901/2006 on medicinal products for paediatric use, the EMEA has founded the Committee for Paediatric Medicinal Product which has the purpose of assessing efficacy and safety of medicinal products with paediatric indication, committee in which all Member States have their representatives.

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In 2007, depending on medical specialisation, the NMA has assigned its representative Romanian experts for work in relation to the EMEA.

One of the first Paediatric Committee initiatives has been to start a European survey on all existing uses of medicinal products in the paediatric population through screening all medicinal products authorised on each Member State level. Romania has started the screening process setting up a data base on paper initially, analysing over 5000 medicinal products. Screening results started to be introduced in an electronic data base at the end of 2007.

Special attention has been paid to ensuring communication and transparency. A large volume of information has been posted on the NMA website addressing both professionals in the medico-pharmaceutical field and the general public as well.

Communication with the mass media also intensified, approaching such aspects of general interest as medicinal product safety. The NMA was constantly preoccupied with improving specific communication with the mass media, setting up a communication procedure for most explicit and accurate information of the public. This procedure has been posted on the NMA website for mass media notification.

In 2007 as well, the NMA top management laid due 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.

Romania’s accession to the EU as of 1 January 2007 has requested increased professionalism in all NMA activities.

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

Goals in the 2007 human resources policy mainly envisaged provision of specialised staff of higher education – specifically in the medical – pharmaceutical field, for adequate coverage of understaffed positions in specialised departments as well as professional training and improvement of existing specialised staff 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 Resultsd in more adequate labour and mediumal conditions for the entire staff, in line with labour legislation in force.

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

NMA policies went further in the IT area and increase of the internal computer network; in that respect, the software has been purchased and installed for dossier electronic submission in the process of marketing authorisation (e-submission), in preparation of the year 2009 set as deadline for electronic documentation submission (e-CTD).

Development of all activities, actions and attainment of goals set for 2007 would not have been possible without an adequate financial policy, relying on strict financial discipline, 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 brought in by services performed.

At the same time, tariffs were approved in 2007 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, according to legal provisions.

The entire progress achieved 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 established with the Ministry of Public Health, which has contributed to prompt adoption of orders of the ministry of public health for approval of Scientific Council decisions and their publication in the Official Gazette of Romania.

National Medicines Agency activity in the first year after Accession was especially successful and all efforts made and particularly its achievements have been repeatedly highlighted and commended on NMA management and experts' participation to working groups organised by European bodies.

The NMA also holds the same prestige and is met with similar appreciation at home, telling proof to that being NMA award of the "Prize of Excellence in governmental activities" in the Administraţie.ro 2007 Prizes of Excellence-Gala.

NMA ACTIVITIES IN 2007

1. Activity of the NMA Scientific Council (SC)

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 with changes and completions through Law No. 594/2002, with further changes and completions.

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 Decisions of the Scientific Council (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, in case the minister of public health does not express disagreement; following that, they are published on the NMA website and in the NMA Informative Bulletin.

As far as the name constituency of the Scientific Council is concerned, this underwent a number of changes in 2007 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 2007, the Scientific Council was convened in 3 working reunions, adopting as many as 27 Council decisions.

Of the mentioned 27 decisions, 3 SCDs are of ruling character and are accordingly to be approved through Minister of Public Health Orders and published in the Official Gazette of Romania, and the remaining 24 have already been approved by the Minister of Public Health, have been posted on the NMA website and will be also published in the NMA bilingual informative bulletins.

SC activity has mainly consisted in adoption of regulations for improved National Medicines Agency activity. Nineteen scientific and procedure guides have been discussed and approved after translation and adaptation of European Commission guidelines, two of which have been revisions of previously approved guidelines. Guidelines approved involve important aspects of National Medicines Agency work, very useful to marketing authorisation holders (MAH) as well, such as: parallel importing of medicinal products; quality systems framework for Good Manufacturing Practice (GMP) inspectorates; GMP inspectors' training and qualifications; handling of suspected medicinal product quality defects reports; handling rapid alerts and recalls arising from quality defects; definition of a potential serious risk to public health in the context of Art. 29(1) and (2) of Directive 2001/83/EC; Braille requirements for labelling and the package leaflet; use by the National Medicines Agency of European Commission administrative procedure for official control authority batch release; implementation of provisions mentioned in Art. 729 and 730 of Law No. 95/2006 on healthcare reform, Title XVII - The medicinal product a.o.

Scientific Council meetings also focused on other very important aspects for the medicinal product field, such as analysis of scientific grounds for change of medicinal product classification for supply (availability on prescription only or not), manufacturer suggested changes or features related to metamizol or nimesulid containing medicinal products safety.

2. Activity of the NMA Administrative Council (NMA)

Activities of the NMA Administrative Council develop according to provisions of Section 2 "Administrative Council organisation and functioning" 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.

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

In 2007, the NMA Administrative Council (AC) carried out 9 working sessions, adopting of 36 decisions, 2 of which are of ruling character, approved through Minister of Public Health Order, one having been 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 and its rectification, approval of updated versions of the NMA Organisation and the structure of the Biological products evaluation and control department. At the same time, the AC has approved the revised list of NMA representatives to the various scientific committees and working groups within the EMEA, the European Commission, the Council of Europe, the European Council, EDQM and PIC/S. A number of tariffs have also been approved for use in NMA departments, which have added to the system of financial quantification of NMA services.

3. Regulatory activity

In 2007 as well, National Medicines Agency regulatory work has preserved the same brisk pace in elaboration of secondary legislation required for complete implementation of Title XVII - The Medicinal Product of Law 9/2006 on Healthcare Reform set up in compliance with Directive 2001/83/EC.

A number of amendments to previously approved norms were set up as draft decisions and submitted for Scientific Council approval, as imposed by changes resulting from Romania's new status as EU member state as well as from implementation of certain articles of Law 95/2006 as of 1 January 2007, as for instance SCD No. 11/31.03.2006 regarding Regulations on marketing authorisation and surveillance of medicinal products for human use approved through Minister of Public Health Order No. 895/20.07.2006, SCD No. 35/2004 approved through Minister of Public Health Order No. 406/2005 on pharmacovigilance, the change consisting in addition of new chapters or correction of others and SCD No. 28/2004 approved through Minister of Public Health Order No. 1141/2004.

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 on parallel imports of medicinal products for which marketing authorisations have already been granted as well as the procedure for grant of parallel import of medicinal products for human use;
- authorisation for medicinal products for human use;
- Training and qualifications of GMP inspectors;
- Content of the manufacturer's batch certificate for medicinal products exported to countries under the scope of a mutual recognition agreement;
- Approval of the procedure for handling rapid alerts and recalls arising from quality defects;
- Handling of reports of suspected quality defects in medicinal products;
- Definition of a potential serious risk to public health in the context of Article 29 (1) and (2) of Directive 2001/83/EC;
- Implementation of legal provisions on Braille requirements for labelling and the package leaflet;
- Marketing Authorisation Holders on pharmaco vigilance procedure;
- Requirements for pharmacovigilance systems, monitoring of compliance and pharmacovigilance inspections;
- Exchange of information on manufacturing and wholesale distribution authorisations between competent authorities in the European Economic Area;
- Use by the National Medicines Agency of European Commission Administrative Procedure for Official Control Authority Batch Release;
- Simplified authorisation procedure for traditional herbal medicinal products;

- Implementation of provisions mentioned in Art. 729 and Law No. 95/2006 on Healthcare Reform, Title XVII – The medicinal product;
- Conduct of inspections of pharmaceutical manufacturers;
- Community format of the GMP Inspection reports;
- GMP certificates issue and update procedure;
- verificarea statutului de BPF al fabricanţilor din terţe ţări;
- Co-ordinating the verification of the GMP status of manufacturers in third countries;
- Rapid alert and non-urgent information system in pharmacovigilance;
- Collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products.

Mention should be made of the fact that, because of the large number of guidelines and their extensive contents, elaboration of guidelines approved by the NMA Scientific Council involved a large amount of labour. A number of grounds have required revision of SC previously approved guidelines:

- the apparition of new editions of the guidelines which which represented the starting point for the guidelines in the previous years;
- 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.

4. Activity of NMA Commission

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 Administrative 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 2007, the Marketing Authorisation Commission conducted 40 working sessions for discussion of 488 evaluation reports for medicinal products for human use and formulation of opinion in view of marketing authorisation.

Of the above, 461 medicinal products have been accepted for grant of marketing authorisation and 27 have been deferred.

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

The commission works based on Decision of the NMA President and according to its own Organisation and functioning regulation, as approved by Administrative 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 Vicepresident, 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 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 mediates in case an inspector's decision is disputed by the inspected unit, the decision belonging to the majority.

In 2007, the Commission for GMP, GLP, GALP and GCL Inspection conducted 13 working sessions for examination of 153 inspection reports.

4.3. Commission for the check of compliance of NMA inspection 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 Administrative 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 Vicepresident, 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 Health No. 160/2004.

No violations of the Ethic and deontology code by NMA staff with inspection tasks were notified in 2007.

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 (Ph.Eur.), in view of their inclusion and formalisation in the Supplements to the Romanian Pharmacopoeia, the 10th edition (RPh-X).

5. Evaluation-authorisation and related activities

5.1. Marketing Authorisation

During 2007, the assessment activity, marketing authorisation, marketing authorisation renewal, post-authorisation surveillance has been extremely complex, the stress being placed on the implementation of European Procedures (Mutual Recognition and Decentralised Procedures).

A total number of 1434 applications for authorisation/renewal of marketing authorisation were submitted to the National Medicines Agency in 2007, respectively:

- 842 applications for authorisation through national procedure, of which: 341 applications for authorisation and 501 applications for renewal of marketing authorisation;
- 592 applications for authorisation through European procedure, of which: 394 through decentralised procedure;
- 198 through mutual recognition procedure (of which: 73 through "repeat-use" procedure).
- 23 applications have been accepted as line extensions.

In 2007, marketing authorisations (MA) were granted for 504 medicinal products for human use, of which:

- 406 MAs through national procedure;

- 98 MAs through European procedures;

The 504 MAs were granted for 277 Romanian medicinal products and 227 foreign medicinal products.

The 504 authorisations were granted for 335 medicinal products submitted for authorisation and 169 for MA renewal.

A number of 2099 MA changes were performed.

In 2007, there were 123 decisions issued for suspension of 277 MAs.

The authorisation/renewal procedure was suspended for 288 medicinal products, of which:

- 66 on notification by the manufacturer;
- 222 on NMA request.

5.2. Approval of variations to marketing authorization terms (excepting clinical variations) of medicinal products registered through national procedure

In 2007 the NMA was submitted a total number of 5760 applications for variation, of which 5283 applications for type I variations and 477 applications for type II variations.

A number of 4619 applications have been approved, of which:

- 3739 type I variations;
- 312 type II variations.
- 110 application received for MA transfers, 326 applications approved;
- 250 applications for other types of changes, 242 applications approved.

5.3. Approval of clinical trials

During 2007, the NMA has received applications for the approval of clinical trials, as follows:

- 3 applications for the approval of phase I clinical trials
- 53 applications for the approval of phase II clinical trials
- **97** applications for the approval of phase III clinical trials
- **13** applications for the approval of phase IV clinical trials**.**

The NMA has also received**:**

- **54** applications for observational clinical trials.

Until the end of 2007, 166 clinical trials were approved:

- **3** phase I clinical trials
- **53** phase II clinical trials
- **97** phase III clinical trials
- **13** phase IV clinical trials

Medicinal product certificates have been issued in the format issued in accordance with the WHO scheme for 320 medicinal products of romanian manufacturers who intend to authorise these in other countries.

The material needed for the printing of theMedicinal Products Nomenclator, 2008 edition which comprised on 31.12.2007 - 6170 non-proprietary names corresponding to 1136 INNs, including fixed-dose combinations.

As a consequence of Romania's change of status from a candidate country in an EU Member State within the evaluation-authorisation department, the activity has been diversified, comprising:

- the management of answers received by applying Art. 729 and 730 of Law No. 95/2006 on healthcare reform, respectively the announcement concerning temporary/permanent cessation of the manufacturing process, and the announcement concerning the effective marketing of medicinal products ("sunset clause");
- the preparation of correspondence containing the information for answering resulting from the marketing authorisation of medicinal products for human use for which the

European National Authorities have sent applications in view of approving parallel imports, for 27 medicinal products;

- management of EC decisions concerning „Referrals" and applications for transmission of variation applications or answers received from the MA holder regarding the implementation of the European Commission Decision for the medicinal products corresponding to 41 INNs.

5.4. Publicity monitorisation and control for medicinal products for human use

In 2007, 279 publicity materials for OTC medicinal products, designated to the public have been assessed in view of approval.

14 publicity materials for educational programs have been assessed and approved.

106 publicity materials for persons qualified to write or release medicinal products have been assessed and approved.

14 repelling addresses of the publicity visa have been released.

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

- 13 instances of stoppage of advertising material broadcasting;
- 16 responses to complaints from companies;
- 209 various answers to questions related to advertising.

5.5. Pharmacovigilance activity

The activity of the National Pharmacovigilance Centre operating within the NMA is conducted according to Title XVII - The Medicinal Product of Law No. 95/2006 and specific European guidelines.

In 2007, pharmacovigilance consisted in management of safety data coming from spontaneous reporting:

- 360 spontaneous reports of adverse reactions in Romania;
- 10700 reports in the format of the Council for International Organisations of Medical Sciences (CIOMS) – outside Romania (paper, electronic and CD formats);
- 990 updated Periodic Safety Updated Reports (PSUR) for imports;
- 470 Periodic Safety Updated Reports (PSUR) for medicinal products manufactured in Romania.

The College of Physicians in Romania was informed on 313 spontaneous reports of adverse reactions in Romania, validated by the NMA National Pharmacovigilance Centre.

A number of 207 letters of information were sent to healthcare professionals regarding grant of 313 credits for Continuing Medical Education.

The NMA website was added 19 translated EMEA press releases on safety issues of centrally authorised medicinal products.

Publication has been started in the "Viaţa Medicală" magazine of a number of articles on pharmacovigilance issues.

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

Inspection activities in 2007 were significantly increased through involvement in new activities such as: authorisation of medicinal product importers, authorisation of medicinal products export, certification of qualified person for batch release.

In 2007, the data base of qualified persons granted a qualified person certificate in medicinal product for human use manufacturing/import units was completed. As of 1.05.2007, all manufacturing/importing authorisations and GMP compliance certificates granted by the NMA have been introduced into the European Eudra GMP data base via the named persons.

The following have been granted and released:

- GMP certificates (for Romanian and foreign manufacturers): 51;

- Manufacturing authorisations, annexes included: 96;
- Importing authorisations, annexes included: 86;
- GLP certificates: 4;
- Qualified person certificates: 129;
- Authorisations for independent control units: 3;
- 30 Romanian manufacturers valid GMP certificates were turned into manufacturing authorisations.

The total number of inspections in 2007, apart from inspections for medicinal products quality surveillance) was 153, including 10 inspections for checks on importer's qualified person's activity relating to batch release of imported medicinal products.

The following types of inspections were performed:
- 68 GMP inspections in Romania;
- 16 GMP inspections to pharmaceutical companies of PIC/S/EU member countries;
- 8 inspections regarding bioequivalence studies;
- 10 GLP inspections to control units;
- 2 joint inspections with EU inspectors;
- 34 GCP inspections;
- 11 pharmacovigilance inspections at MA holders.

As of January 2007, 734 export declarations have been approved for medicinal products manufactured in Romania.

129 certificates attesting the qualified person status have been issued.

As far as the activity for quality surveillance of medicinal products is concerned, sampling was performed of 58 finished medicinal products and starting materials; laboratory testing outcomes were as follows:
- 42 compliant samples;
- 15 samples under testing.
- 2 finished medicinal products were non-compliant, which has Resultsd in their recall;

A number of 199 inspections were performed for verification of 4976 distribution units.

290 inspections for check of quality of oxygen used in hospitals were performed.

In 2007, the NMA decided recall of 27 medicinal product batches.

During the reported time, 94 Rapid Alerts issued in the EMEA and PIC/S Rapid Alert system were received and solved.

7. Quality control of medicinal products

A. In 2007, the Raw Materials and Finished Products Control Department (RMFPCD) analysed 1391 Romanian manufactured and imported medicinal products, of which:
- 454 medicinal products were obtained through chemical synthesis;
- 937 were biological medicinal products for microbiological, immunologic and pyrogenic determination (vaccines, sera, immuno modulators, allergens etc.)

For the above products, 2665 analysis bulletins were issued.

There were 10 non-compliant medicinal products, for which inappropriate analysis bulletins were issued, representing 0.72 % of the total number of analysed medicinal products, respective non-compliances being mainly physical-chemical and microbiological in nature.

As in previous years, in 2007 as well, the RMFPCD continued collaboration with European institutions dedicated to control of medicinal products, an activity presented in more detail in the Chapter on International Relations.

RMFPCD specialists also continued evaluation of dossiers for authorisation or MA renewal of Romanian and foreign medicinal products. By the end of the year 106 chemical-pharmaceutical dossiers had been assessed and the respective quality evaluation reports had been devised in view of authorisation/renewal.

A number of 146 reports were elaborated (post-authorisation, validation of certain variations or updated dossiers) and 210 assessment reports on Drug Master File (DMF) for chemical substances used in manufacturing of finite products, for which authorisation/renewal applications were submitted as well as an additional 52 reports for DMF supplementation.

Distribution of the 210 DMF assessment reports was as follows:

- 101 reports in the National procedure frame;
- 32 reports in the Mutual recognition procedure frame;
- 77 reports in the Decentralised procedure frame.

B. The novelty brought about by 2007 to the Biological products evaluation and control department (BPECD) was appropriation and implementation of the European Commission administrative procedure for official batch release by the Official Control Authority Batch Release (OCABR), annually updated and published by the European Directorate for Quality of Medicines (EDQM).

- As of OCABR procedure first application - 3.09.2007, 214 batch release certificates and 21 non-compliance bulletins have been issued.
- In the frame of current control of quality parameters of Romanian and foreign manufactured biological products for human use, a number of 761 batches have been analysed, which corresponds to 6219 laboratory tests;
- No product batches have been rejected in 2007.
- 1013 analysis bulletins have been issued in 2007 within the BPECD.
- Within the control activity in view of obtaining an MA or an MA reauthorisation, 2 batches for which 18 laboratory testings were carried out were taken.
- Post-marketing surveillance was continued for medicinal products, introducing 161 biological product batches into the BPECD data base.
- As part of dossier evaluation in view of authorisation or renewal for Romanian or foreign manufactured medicinal products as well as for approval of type I or type II variations, assessment was performed on 46 medicinal products (35 manufactured abroad and 11 in Romania) were subject to assessment, for which 48 Standard Quality Evaluation Reports (SQER) were issued, 11 SQER were solicited completions and 37 were proposed for MA release/renewal.
- Support dossiers for 87 variations were evaluated;
- 19 products were evaluated through mutual recognition procedure and 38 through national procedure.

8. Pharmacopoeia related activities

8.1. Issuing and drafting of the FR X supplements, by adopting the European Pharmacopoeia (Ph. Eur.) provisions.

Activities focused on translation and approximation of general analysis methods and general monographs included in the European Pharmacopoeia in force in
frequent use and by and necessary for both NMA specialists and external users (e.g. impurities control, chromatography, spectrophotometry, chromatographic separation techniques, uniformity of even dose preparations, intrinsic dissolution etc.)

8.2. Elaboration and update of Romanian Standard Terms

The consolidated version of Romanian standard terms was set up, including all terms approved so far through Scientific Council decisions, in line with those adopted by the European Pharmacopoeia Commission.

New combinations of standards terms have been translated, notified to the EDQM by the manufacturers and implemented on lint into the EDQM data base of combined European standard terms.

Moreover, the list of Romanian combined standard terms has been regularly updated and made available to Evaluation-authorisation department specialists.

9. Quality management activity

In 2007 quality management activities of the Quality assurance bureau continued to focus mainly on improvement of the existing system.

Within the process of general Standard Operation Procedures (SOP) revision, operational to the entire institution, the following procedures were documented, set up and distributed:

- One new general Standard Operation Procedure (SOP)
- SOP and Quality Manual continuous monitoring (QM);
- NMA staff training;
- Communication;
- NMA quality internal audit;
- Set up of the MC;
- Monitoring of non-compliant product (service);
- Implementation of corrective and preventive action for ongoing improvement of the Quality Management System;
- Monitoring of NMA staff applications and/or proposals for improvement of the Quality Management System;
- Analysis by the management;
- Process management;
- Analysis of client complaints;
- Documents monitoring;
- Records monitoring.

Quality internal audits were performed in 8 NMA departments.

The following analyses and assessments were achieved on department and NMA levels:

- Annual department reports;
- Annual NMA staff individual reports;
- Annual work timetables for each department;
- Annual NMA staff training schedule;
- Annual quality internal audit timetable.

Staff individual work assessment sheets have been devised based on sub criteria set up for assessment of NMA staff professional performance.

10. Ensurance of communication and transparency

All during 2007, the NMA continued to be particularly concerned with insuring sound communication with interested parties and mass-media, in line with provisions of Law no. 544/2001 on free access to information of general interest and of Law 95/2006 - Title XVII – The medicinal product on transparency of activities of EU medicines competent authorities.

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 and posting on its website of bilingual Informative Bulletins, mirroring the concentrated activity related to transposition of European medicinal product legislation into national legislation. The electronic versions of those Informative Bulletins are also published on the website.

At the same time, the NMA elaborated 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 supply etc.

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

In that respect, the NMA website published and regularly updated the following information and documents:

- Summary of Product Characteristics (SPC) for medicinal products authorised through Centralised procedure;
- SPCs for medicinal products authorised in Romania through Mutual recognition procedure and Decentralised procedure;
- SPCs for medicinal products authorised in Romania through National procedure;
- The public versions have been devised of Marketing Authorisation Commission agendas and minutes, made available to the public, on request;
- Specific procedure rules have been set for NMA commissions, made available to the public, on request;
- The list of approved orphan medicinal products;
- Medicinal products authorised for circulation in Romania available on medical prescription only;
- Over the Counter medicinal products (OTC), according to legislation in force;
- Press releases related to medicinal product safety;
- Information letters for physicians;
- NMA employees assigned as representatives or alternates in the Administrative Council as well as scientific committees and working groups of the European Medicines Agency (EMEA);
- Notifications of MAH or other interested parties on issues of interest.

In support of its external partners, the National Medicines Agency provided for two new additional headlines on its website to provide useful information and contact persons related to the new marketing authorization procedures, as follows:

- Centralised procedure
- Mutual recognition procedure
- Decentralised procedure

The following have proved of great interest for users:

- Medicinal product legislation;
- Useful information on European procedures;
- 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 more than 160,000/year, i.e. a monthly average of 13,400 visitors.

In 2007, as well, the NMA continued to inform interested parties on its activity through various publications other than its own Informative Bulletin.

Therefore, to the appreciation of NMA partners, the Agency report on 2006 activities was again published as a bilingual brochure.

Articles related to various aspects of NMA activity were published in 2007 in Romanian specialised magazines (“Pharmacist.ro”, “Medical Business”, “Viața Medicală”), 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 follows:

- Sr. Pharm. Magdalena Bădulescu, President;
- Sr. Pharm. Rodica Bădescu, Vicepresident;
- Dr. Pharm. Robert Ancuceanu;
- Dr. Adina Pîrvu;
- Sr. Pharm. Daniela Enache;
- Sr. Pharm. Mioara Suliman.
- Pharm. sp. Andreea Varvara;
- Sr. Pharm. Daniela Vasilescu;
- Sr. Pharm. Mihaela Sebe;
- Eng. Crînguţa Brăiescu.

10.2. Internal Communication

For better and faster information of staff on professional and organisational issues, information made available on the National Medicines Agency intranet was further supplemented and updated in 2007 as well.

The following can be mentioned among information available to NMA employees on the intranet:

- NMA President's Instructions;
- NMA quality policies;
- Information on training courses organised by specialised companies;
- Reports of staff participating in training both at home and abroad;
- 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 United States Pharmacopoeia (USP).

11. International Relations

In 2007, 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.

This participation has represented the most efficient manner to maintain the NMA in line with European activities in the medicinal product field.

Starting with 2007, NMA experts have become full members in EMEA scientific committees, working groups and groups, taking active part in 106 meetings of these structures.

11.2. Participation in activities of Heads of Medicines Agencies

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

The working groups are as follows:

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

- Work Group on Counterfeit Medicines.

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

National Medicines Agency experts took part in 9 meetings of the working group for medicines and medical devices of the European Council, focusing on completion of the Draft regulation for advanced therapy medicinal products.

Participation in European Commission meetings involved NMA experts' attendance of reunions of the Standing Committee, of the Pharmaceutical Committee, of the Working Group "Notice to Applicants" and assemblies of the Working Group on set up of Directive 2001/20/EC on clinical trials implementation guidelines.

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 of EU medicinal product standards.

This was the frame for participation in the WHO International Conference: Developing Effective Legislation to Combat Counterfeit Medical Products (December 2007).

NMA experts also took part in a working session with the Ministry of Public Health, organised by the latter, along with the WHO, on the topic of preparedness in case of avian influenza epidemic.

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

In 2007 the NMA issued medicinal product certificates in WHO format for 320 medicinal products of domestic manufacturers who expressed their intention to authorize their products in other countries as well.

11.5. Participation in Council of Europe activities

In 2007, National Medicines Agency representatives took part in the Group for classification for supply of medicinal products for human use and the Ad hoc working group for counterfeit medicinal products.

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

The National Medicines Agency performed regular updating of the data base containing information coming from Croatia concerning medicinal products authorised through nCADREAC simplified procedure for medicinal products authorised through mutual recognition procedure in the EU.

11.7. Participation in activities of the European Pharmacopoeia Commission

The National Medicines Agency assigned representative as member of the European Pharmacopoeia Commission took active part in the latter's working sessions as well as in the annual meeting of national pharmacopoeias secretaries in member countries of the Convention on the elaboration of European Pharmacopoeia.

Collaboration was also continued 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.

11.8. Participation in activities of the PIC/S

In 2007 National Medicines Agency activity as PIC/S member materialised in the following:

- participarea activă la clarificarea unor aspecte tehnice privind interpretarea RBPF, revizuirea unor capitole, anexe ale acestuia, revizuirea unor proceduri de operare elaborate de PIC/S;

- active participation in clarification of certain technical aspects on interpretation of GMP regulations, revision of certain chapters and annexes, reconsideration of PIC/S standard operation procedures;

- participation of NMA representatives in the JOINT Visit Group 73 training programme;

- participation in the 2007 meeting of the Committee of Officials and the PIC/S 2007 Seminar "GMP inspection of dosed solid forms" of November 2007.

11.9. 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 2007 organised by the EDQM.

Specialists of NMA laboratories participated in 6 studies:

- 4 PTS studies (Proficiency Testing Scheme), analytical studies undertaken at EDQM initiative and coordination. The specified studies are performed on an annual basis and their purpose is testing professional capacities of each laboratory of the European OMCL network to solve highly difficult aspects encountered in the control of medicinal product quality.

- 2 market surveillance studies – for determination of quality deficient medicinal products.

12. Human resources policies

Objectives pursued by the National Medicines Agency in 2007 in the human resources field mainly envisaged the following:

- Ensurance of specialised staff of higher education – specifically in the medical – pharmaceutical field, for adequate coverage of staff deficient positions in specialized departments ensuring 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 medium, 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;

- Ensurance of fluent communication among organizational 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.

Transposition of these lines has imposed a large workload to the Human resources department, amending software in use for accurate introduction of human resources data and wages particulars, contributions etc.

13. Economic policies

In 2007, the National Medicines Agency coordinated a balanced total incomes and expenses budget of 19.700.000 RON.

As far as incomes are concerned, an amount of 24.942.653 RON was achieved, of which 16.591.891 RON were produced from services to internal partners whereas 8.350.762 came from services to foreign partners.

The expenses chapter amounted to 14.751.200 RON, distributed as follows:

- - 11.484.000 lei staff expenses;
- 2.154.300 lei material expenses;
- 1.112.900 lei capital expenses.

All expenses were within the approved incomes and expenses budget for 2007, in full compliance with economic-financial discipline legal provisions. 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, also corroborated with specific legislation in force.

Speaking in organisational terms, economic activities were developed through the Economic department.

During 2007, the Economic Department has ensured the the accurate fulfilment of the established objectives through: financial-accounting activity, certain arrangement actions of the NMA site, Demostene and Ferma Ilfoveni sites, while observing an economy of expenses compared to those planned.

A number of tariffs have also been approved through order of the Minister of Public Health for new activities performed by the NMA departments.

14. General administration and patrimony

On approval of the new NMA organisation structure through Order of the Minister of Health No.1248/2006, General administration and patrimony activities were separated from the Economic department, therefore becoming a department in itself.

This structure elaborated the 2007 Annual public purchase programme, performing 60 direct purchases, at the same time setting up 50 dossiers for public purchases through the request for supply and Public Purchase Electronic System (SEAP) publication procedure, finalised in 78 contracts.

Efficient coordination of activities on all department levels reflected itself on good progress of all other NMA departments. Mention should be made of the set up an electronic record of all NMA patrimony.

As concerns the investment chapter in 2007, an important achievement was relocation of the physical-chemical control section of the Raw materials and finished product control department to a new especially designed area, whose rearrangement consisted of large and extensive investments such as:

- repartition of sites, the revision of water and electric installations, hygienisations, furnishings, the purchase of 2 niches, validation and qualification of equipment and laboratory appliances.

Moreover, the biochemical determination laboratory has been rearranged cu by own means within the Laboratory of Toxicology and Pharmacology.

An important investment is represented by the installation of a parameter monitorisation system within the Microbiology Laboratory, the purchase of 7 electric thermohygrographs with OPUS 10 TSE external sensors, of various pieces of furniture, the qualification and validation of equipment and devices.

In 2007, mutarea DECPB has been settled at the new site on Demostene Street; this relocation has involved a number of changes of the existent space which has also led to spendings from the institution's budget. The site repartitions were, therefore, necessary, as well as the projection and purchase of laboratory furniture, new lab equipment, service ensurance for devices which needed to be checked as a consequence of moving from a site to another, the verification of the thermic central and of the air-providing one.

An ELISA line was also purchased for improved determinations accuracy, within the DECPB, as well as exchange pieces for laboratory equipment and other objects needed in order to conduct the activity.

Concerning other departments, investments consisted of acquisitioning personal computers, printing machines, photocopiers, refrigerators, air conditioning appliances, various pieces of furniture etc.

15. Internal Audit Activities

According to the Annual auditing plan, the Internal audit bureau finalised 3 audit reports in 2007, all approved by the NMA management.

Reports included recommendations remitted for implementation to the management of audited departments.

In line with legal provisions, a report was sent to the Ministry of Public Health on activities of the Internal Audit Bureau in 2007.

16. Difficulties occured

The main issue that the NMA had to deal with during 2007 was the insufficient number of assessors (pharmacists and physicians), this situation being determined by the massive leavings from the institution during 1999-2002 and, on the other hand, by the fact that the well paid working offer in the private sector is still large enough.

17. Priorities for 2008

- Ensurance of appropriate achievement of National Medicines Agency 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;
- Ensurance of human and financial resources required for efficient development of activities;
- Redistribution of staff, to ensure 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 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 particularly fruitful activity of the National Medicines Agency during 2007 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.

The year 2007 was exceptionally difficult, requiring outstanding efforts for achievement of new tasks facing the National Medicines Agency in result of changed Romania's status from candidate to EU member country.

The NMA is committed to resolute and perseverant continuation of its efforts to cope with tasks as competent authority in the domain of medicinal products for human use.