2008 NATIONAL MEDICINES AGENCY ACTIVITY REPORT

INTRODUCTION

The National Medicines Agency rounded up a year (2008), at the beginning of which it launched upon an ambitious priority plan for fulfilment of its mission as a European drug competent authority. In a responsible and determined manner, it has met its commitments as well as its additional tasks. Successful accomplishment of its duties, positively appreciated by internal and external auditing experts are a confirmation of its status as a consolidated, mature European institution carrying out its activity with no hesitation or failure.

The year 2008 has confirmed that the NMA is a team displaying an outstanding combination of professional competence, top management qualities and commitment or its members in order to reach high performance in its field.

Activities of NMA departments was particularly complex in 2008 and focused on operations related to marketing authorisation. Establishment proper of such activity, consolidated in the efforts made during the previous years is confirmed by the large number of marketing authorisations granted this year as compared to the past year – a number of 868 medicinal products being authorised for marketing as compared to the 504 authorised in 2007.

The number of applications for authorisation through European procedures in 2008 was almost double in comparison to 2007 (1045 in 2008/592 in 2007).

In 2008, Romania received 790 applications for decentralised procedure and 255 applications for mutual recognition procedure, only acting as Concerned Member State. As of November 2008 Romania also acts as Reference Member State (RMS) in this type of procedures.

The recognition and confidence the NMA holds among its beneficiaries is also shown in the large number of applications for authorisation through European procedures with Romania as Reference Member State (150).

The number of applications for marketing authorisation through national procedure was preserved at a level comparable in size to that of 2007 (845 applications in 2008 vs. 842 applications in 2007).

The NMA contributed to the activities carried out by the network of drug competent authorities in EU member States through its representative to the EMEA Paediatric Committee (PDCO) set up by the middle of 2007, who evaluated 44 Paediatric Investigation Plans (PIP) as both Reporter (25) and Peer-reviewer (19) and took part in 11 Committee meetings and 10 teleconferences on issues related to Paediatric Investigation Plans. The NMA has become more visible through its special involvement in evaluation of Paediatric Investigation Plans, placed 5th in the hierarchy of European countries in this type of activity.

According to provisions of Regulation 1901/2006 on medicinal products for paediatric use and in result of the EMEA request to all member States to collect data on use of medicinal products in the paediatric population, the NMA has integrated and organised reports from paediatric hospitals in the country, thus setting up a database in the EMEA requested format and structure.

NMA involvement in activities of the network of EU Member States drug competent authorities materialised in participation in inspections for verification of good clinical practice (GCP) and good manufacturing practice (GMP) for EMEA centrally authorised medicinal products. Within the same context, the NMA also took part in sampling and testing of medicinal products authorised through the same procedure.

Amendment of Law 95/2006 on healthcare reform has added to the object of NMA activities the supplementary task of granting function authorisations to medicinal products wholesale distribution units as well as their inspection.

This newly added task has required set of Norms on the set up, organisation and functioning of wholesale distribution units as well as of the Guideline for medicinal products Good Wholesale Distribution Practice, both approved through order of the minister of health.

For improved coordination of activities related to surveillance of the safety of medicinal products on the Romanian pharmaceutical market, the NMA management has created the Commission for management of medicinal product quality, safety and/or efficacy determined crisis situations. The Commission was set up in April 2008, through the NMA President decision and was instrumental in prompt resolution of certain alerts or communications on quality non-compliances issued by both the EMEA and other competent authorities or marketing authorisation holders.

The year 2008 also meant a time of active participation in EMEA scientific committees and working groups, in workings of the Heads of Agencies as well as activities carried out by the European Council and the European Commission, the Council of Europe, the PIC/S, the European Pharmacopoeia Commission and the Official Medicines Control Laboratories (OMCL) (173 participations).

At the same time, the NMA attended a large number of scientific events such as congresses, conferences, seminars both at home and abroad.

Not least, 2008 activity also involved audits performed at the Raw Materials and Finished Products Control Department and the Biological Products Evaluation and Control Department, by European Directorate for Medicinal Product Quality (EDQM) nominated auditors.

Mention should be made here of the fact that, for best results in the audit process, the NMA began preparations as early as 2007, making significant investments and reorganisations of internal space and personnel, in order to meet standards of institutions in the field in EU Member States.

Reunited in a joint effort and mobilising to accomplish the set goal, the NMA team has "passed" the test of the EDQM audit and the expert auditing report showed appreciation to activities carried out in the audited departments.

Yet another achievement in 2008 was implementation of integrated electronic system for management of medicinal product marketing authorisation procedures and related activities according to recent European requirements. The system is provided with compatibility facilities for electronic data reporting to the EMEA, flows of medicinal product marketing authorisation procedures and related activities now being finalised by the developer and the application ready for use in the NMA.

The second part of the same project, i.e. the system for management of the Index of Medicinal Products authorised for marketing in Romania is currently under development.

Note should also be made of the fact that implementation of this integrated system facilitates admission to the NMA of documentation authorisation in eCTD (Electronic Common Technical Document) format.

Particular attention should be paid to insurance of communication and transparency, constantly developed and improved. The NMA website has posted extensive useful information for both healthcare professionals and the general public.

Communication with the mass-media was also strengthened and improved, in approach of issues of general interest such as safe use of medicinal products. At the same time, application of provisions of Law 95/2006 – Title XVII – The medicinal product has continued with regard to transparency in activities pertaining to European drug competent authorities through the following:

- Preparation of versions for public availability of agendas and minutes of the Marketing authorisation commission and the Commission for the Inspection of Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), Good Analytic Laboratory Practices

(GALP), Good Clinical Practices (GCL) and Pharmacovigilance as well as public versions of Medicinal Product Assessment Reports.

The NMA management gave particular attention to the quality management system, therefore laying stress on Process based approach, aiming at update of quality documents in line with newly entered into force norms applicable to the NMA as well as with changes in the NMA organisational structure, observation of Standard Operation Procedures (SOP) come into force as well as Identification of new processes and activities to become the object of new specific of interdepartmental SOPs.

Special care has been given to strengthening of the NMA human resources and infrastructure.

In 2008, objectives of human resources policies were mainly to ensure employment in staff deficient specialised departments of university graduates, particularly in the medico-pharmaceutical field, as well as training and professional improvement of existing personnel for creation of highly trained specialists able to manage the entire range of tasks and attributes in the NMA activity goals.

The NMA continued to provide optimum working conditions and an appropriate work environment for its entire staff, according to labour legislation in force.

The following were also carried on:

- Actions in view of working area improvement, through refurbishment, cleaning, resizing of rooms in view of their transformation into offices as well as an entire range of works for preparation of working posts.
- Policies for introduction of the information systems and enlargement of the internal computer network.

All activities, actions and goals planned for 2008 could only be carried out with suitable financial policies, based on strict financial discipline, observance of legal provisions on budget execution and thoughtful expenditure of allocated resources, in line with the approved income and expenses budget.

In that respect, the annual NMA income and expenses budget was balanced, with expense levels not exceeding incomes achieved by means of activities provided.

In 2008, new tariffs were approved for a number of activities carried out by NMA departments, which have added to the system of financial quantification of services carried out in the institution, which ensure thorough funding of all activities, according to legal provisions.

All progress achieved became possible due to the entire NMA efforts to adopt and apply European regulations in the field, to the best interest of patients and society at large, according to the mission guiding its activity.

Mention should be made of the contribution to NMA achievements, besides its own efforts, of its very good ongoing collaboration and counselling with the Ministry of Health, which has aided in adoption of orders of the minister of health for approval of NMA Scientific Council decisions as well as in their publication in the Official Gazette of Romania.

NMA ACTIVITIES IN 2008

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 on the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as amended.

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

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

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

In 2008, in result of cessation of the 3-year mandate of the Scientific Council constituency, approved through successive orders of the minister of health during 09.05.2005–30.11.2007 as well as due to NMA proceedings, Minister of Public Health Order nr. 1027/22.05.2008 has been issued for approval of the new Scientific Council constituency. With one exception only, the SC constituency has been preserved which has had a positive effect on continuation of activities of this scientific body. Closure of the mandate of the President in exercise at that time was carried out with presentation of the SC President Report to SC members, report approved by the latter and then submitted for approval by the minister of health.

The report highlighted SC scientific and organisational activity and demonstrated the NMA is provided with all regulations required for performance of activities in line to European standards.

In 2008, the Scientific Council was reunited in **3** working meetings, adopting as many as **25** Council decisions, of which **3** have been approved through minister of health order whereas the remaining 22 have received minister of health approval and are posted on the NMA website. Of the 3 approved minister of health orders one has already been and two are about to be published in the Official Gazette of Romania. All Scientific Council decisions are published in the NMA bilingual informative bulletins.

The Scientific Council activity mainly consisted in adoption of contributing to improved activity of the National Medicines Agency.

Twelve scientific or procedure guidelines were discussed and approved through translation and adaptation of European Commission guidelines.

Guidelines approved involve important aspects of National Medicines Agency work and the following should be mentioned in that respect: Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function, guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population**,** Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population; Guidance on invented names of medicinal product for human use; Romanian specific „blue box" requirements for packaging of medicinal products for human use authorised through centralised procedure; requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials; set up of risk based planning for inspections of pharmaceutical manufacturers. Other SC decisions centred on approval of new Romanian standard terms for certain pharmaceutical forms, primary packaging closure and administration systems, according to those approved by the European Pharmacopoeia Commission.

Other very important aspects in the medicinal product field were discussed in the Scientific Council as well, such as analysis of scientific grounds for change of medicinal product classification for supply (availability on prescription only or not), manufacturer suggested changes.

The Scientific Council discussed and finally approved the Scientific Council Organisation and Function Regulation, modified as requested by the need to introduce a new SC working procedure allowing SC members to be consulted in certain emergency

circumstances, when the plenary session cannot be summoned. EMEA and European Commission scientific committees make use of a similar procedure.

In 2008, on SC members' request, meetings agenda also included an overview of implementation of SC decisions into ANM activity and a presentation was made of the implementation of SC decisions in activities of the European procedures service of the Evaluation–authorisation department.

2. Activity of the NMA Administration Council (AC)

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

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

In 2008, the NMA Administrative Council (AC) carried out **8** working sessions, adopting of **33** decisions, **6** of which are of ruling character, approved through minister of health order.

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 the NMA job list, of the NMA incomes and expenses budget, of changes in the organisational structure of the Pharmaceutical inspection department (DIF), the Raw Materials and Finished Products Control Department. The AC also agreed on the amount of charges for NMA activities as well as of a range of taxes charged by the DIF, which add to the charging system of NMA performances.

The AC approved the NMA 2007 Annual Report, the NMA staff conduct code as well as the Regulation for the organisation and Functioning of the Commission for the management of crises in medicinal product quality and/or efficacy. At the same time, it approved on the revised version of the NMA Organisation and Functioning Regulation (ROF).

3. Regulatory activity

In 2008 as well, National Medicines Agency regulatory work preserved its focus. This received concrete form in elaboration of norms resulted from amendments to Chapter VII - Wholesale Distribution of Medicinal Products of Title XVII - The Medicinal Product of Law 95/2006, amendments making the object of Emergency Government Ordinance No. 93/24.06.2008, the foundation for elaboration of Norms for the set up, organisation and functioning of wholesale distribution units, approved through Order of the Minister of Public Health No. 1964/2008 and guidelines on good distribution practice, approved through Order of the Minister of Health No. 1963/2008.

Work was carried on elaboration of norms required for complete implementation of provisions in Title XVII - The Medicinal Product of Law 95/2006 and a number of regulatory documents were submitted to Scientific Council approval, of which the following may be mentioned:

- Norms related to management of changes to marketing authorisation during renewal of marketing authorisation procedure, transposed into Order of the Minister of Public Health No. 1732/14.10.2008;
- Guidelines on marketing authorisation of medicinal products for human use based on cooperations, starting from an existing marketing authorisation;

- Guidelines on laboratory testing during marketing authorisation/marketing authorisation renewal procedure and/or market surveillance;

- Delegation of responsibilities for GMP inspections for medicinal products covered under the centralised procedure;

- Procedure for co-ordinating foreign and Community pre-authorisation inspections during the assessment of applications;

- Guideline on the preparation of reports on GMP inspections requested by the Committee for Medicinal Products for Human Use of the European Medicines Agency in connection with applications for marketing authorisations and with products authorised under the centralised system;

- Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products, and grant of the good manufacturing practice certificate to medicinal product/active substance manufacturers.

In the same line of harmonisation of national with EU legislation, 10 European guidelines were devised and submitted for Scientific Council approval, as follows:

- Guidance on invented names of medicinal product for human use;

- Guideline on Direct Healthcare Professional Communications;

- Guidance on requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials;

- Guidance concerning consultations with target patient groups for the package leaflet;

- Guideline concerning consultation with target patient groups - meeting the requirements of article 59(3) of Directive 2001/83/EC without the need for a full test - recommendations for bridging;

- Guidance on Romanian specific „blue box" requirements for packaging of medicinal products for human use authorised through centralised procedure;

- Guidelines on the role of pharmacokinetics in the development of medicinal products in the paediatric population;

- Guidance on evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function;

- Guideline on pharmacokinetics**:** repeated dose tissue distribution studies;

- Guideline on set up of risk based planning for inspections of pharmaceutical manufacturers

4. Activity of NMA commissions

4.1. Marketing Authorisation Commission

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

The constituency of the Marketing Authorisation Commission has been updated through Decision of the NMA President No. 190/2008 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 2008, the Marketing Authorisation Commission conducted **54** working sessions for discussion of **1055** evaluation reports for medicinal products for human use and formulation of opinion in view of marketing authorisation.

Of the above, **964** medicinal products have been accepted for grant of marketing authorisation, decision for **23** has been postponed, whereas discussions were resumed for **68** medicinal products.

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

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

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

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

In 2008, the Commission for GMP, GLP, GALP, GCL and Pharmacovigilance inspection conducted **17** working sessions for examination of **180** inspection reports.

4.3. Commission for verification 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 Administration Council decision.

The constituency of the Commission has been approved through Decision of the NMA President no. 613/2006 and it is made up of the NMA President and Vice-president, the head of the Pharmaceutical inspection department and the head of the Juridical and legislation service.

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

In 2008, no violations of the Ethic and deontology code by NMA staff with inspection tasks were notified.

4.4 Commission for management of medicinal product quality, safety and/or efficacy determined crisis situations

The Commission is set up through Decision of the NMA President no. 395/2008 and includes the following: the NMA President and Vice-president, the heads of professional departments, the head of the European Affairs service and the head of the Clinical trials and pharmacovigilance bureau.

The Commission works based on its own regulations for organisation and function, as approved through decision of the NMA Administration Council.

In 2008, the Commission convened in 11 working sessions to discuss issues related to medicinal products safety, notified through the rapid alert system, EMEA press releases or other

information on certain non-compliances as transmitted by competent authorities in EU Member States or the European Economic Area, the PIC/S, EDQM or marketing authorisation holders.

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

5. Evaluation-authorisation and related activities

5.1. Marketing authorisation of medicinal products for human use

In 2008, activities related to evaluation, marketing authorisation, renewal of marketing authorisation, post marketing authorisation surveillance were particularly complex and was conducted in line with purely national procedure and European procedures (mutual recognition procedure and decentralised procedure and repeat use mutual recognition procedure).

A total number of **1890** applications for authorisation/renewal of marketing authorisation were submitted to the National Medicines Agency in 2008, of which:

- **845** applications for authorisation through national procedure, of which: **321** applications for authorisation and **524** applications for renewal of marketing authorisation;
- **1045** applications for authorisation through European procedures with Romania as Concerned Member State, of which: **790** through decentralised procedure and **255** through mutual recognition procedure;
- **21** applications were approved as line extensions.

A number of **150** letters of intention were received concerning marketing authorisation through European procedures with Romania as Reference Member State, of which **16** have been accepted.

In 2008, marketing authorisations (MA) were granted for **868** products for human use, of which:

- **436** MAs granted national procedure;
- **432** MAs granted through European procedures;

The **868** MAs were granted for **323** Romanian medicinal products (37.2%) and **545** foreign medicinal products (62.8%).

Of the **868** MAs mentioned above, **653** were granted for medicinal products submitted for authorisation and **215** for MA renewal.

There were **45** decisions issued for suspension of **184** MAs on marketing Authorisation Holder (MAH) request or following application of provisions of Law 95/2006 on healthcare reform, with further amendments and supplementations.

Authorisation/renewal was discontinued for **98** medicinal products, as follows:

- **43** on manufacturer's request;
- **24** on NMA request;
- **31** according to provisions of Article 2 (1) c) of Order of Minister of Health No. 1203/2006 for Norms for resolution of applications for transfer of marketing authorisations.

5.2. Approval of variations to marketing authorisation terms of medicinal products authorised through national procedure

In 2008, a number of **5487** applications for variation were submitted for medicinal products authorised through **national procedure**, of which **4584** applications for type I variations and **903** applications for type II variations.

The NMA assessed and approved **4020** applications for variation for medicinal products authorised through **national procedure**, of which:

- **3320** type I variations;
- **700** type II variations;
- **85** applications for MA transfer;
- **1204** applications for other change types.

There were **1337** applications for variation concerning medicinal products authorised through **European procedure**, of which 1071 applications for type I variations and 266 applications for type II variations. A total number of **523** applications were approved.

5.3. Assessment and approval of clinical trials on medicinal products for human use

In 2008, the NMA was submitted **424** applications for clinical trial approval, as follows:
- **6** applications for **phase I** clinical trial approval
- **80** applications for **phase II** clinical trial approval
- **164** applications for **phase III** clinical trial approval
- **16** applications for **phase IV** clinical trial approval**.**

A number of **65** applications for observational studies were also submitted.

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

In 2008, the National Medicines Agency assessed for approval **345** advertising materials for OTC medicinal products, addressing the general public.

Assessment was performed on **34** advertising materials to be used in educational programmes, which were approved.

The content of **121** advertising materials addressing persons qualified for prescription or supply of medicinal products was assessed and approved.

The NMA issued **56** notifications of denial of advertising approval.

Monitoring and control of medicinal products for human use advertising found further concrete form in:
- **19** responses to complaints related to advertising;
- **1** sanction for disregard of legislation on approval of advertising material.

5.5. Pharmacovigilance

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 2008, pharmacovigilance activities materialised in the following:
- Management of safety data from spontaneous reporting;
- **363** Adverse reactions reporting sheets from Romania;
-**7200** reports in the format of the Council for International Organisations of Medical Sciences (CIOMS) – from outside Romania (paper, electronic and CD formats);
- Collection, validation and archiving of **799** Periodic Safety Updated Reports (PSUR) related to safety of imported medicinal products;
- Collection, validation and archiving of **777** Periodic Safety Updated Reports (PSUR) related to safety of Romanian medicinal products.

A number of **219** letters of information were sent to healthcare professionals as well as on grant of Ongoing Medical Education credits.

On the NMA website there were posted **53 EMEA** press releases on safety issues of centrally authorised medicinal products.

Publication has been continued in the "Viaţa Medicală" magazine of articles on pharmacovigilance issues.

5.6. Other activities

Certificates in the format according to the WHO scheme were issued for **308** medicinal products by Romanian manufacturers planning their authorisation in other countries.

Material required for print of the Index of Medicinal Products the 2009 edition was prepared, which, by 31.12.2008, contained **6589** trade names corresponding to **1089** INNs, fixed combinations included. Of the above, 2783 are original medicinal products, 3557 are generics and 249 are medicinal products with well established use.

The NMA carried on activities as derived from its status as competent authority in an EU Member State, i.e.:

- Management of responses received in application of art. 729 and 730 of Law 95/2006 on healthcare reform, that is notification of temporary or permanent discontinuation of manufacturing and notification of actual medicinal product marketing („sun-set clause");
- Management of the database related to EMEA authorised medicinal products based on art. 127a of Directive 2001/83/EC and monitoring of implementation of conditions and restrictions placed on the MAH by the European Commission for 26 medicinal products;
- Provision of information required by certain EU competent authorities on MAs granted by the NMA, in view of granting the parallel import authorisation for certain medicinal products imported from Romania: 83 medicinal products;
- Management of European Commission (EC) decisions on referrals, elaboration of letters to MAHs involved requesting applications for variations in implementation of the EC Decision and of MAH responses on the EC Decision: 86 medicinal products

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

In 2008, the process of introduction into the EudraGMP database of NMA granted manufacturing/import authorisations and GMP compliance certificates was continued.

The following have been set up and granted in the pharmaceutical inspection activity:

- **37** GMP certificates (for Romanian and foreign manufacturers);
- **64** manufacturing authorisations, annexes included;
- **86** import authorisations, annexes included;
- **5** GLP certificates;

The total number of inspections in 2008, except inspection for medicinal products quality surveillance, was **129.**

The following types of inspections were performed:

- **71** GMP inspections in Romania;
- **5** GLP inspections;
- **3** GALP inspections to independent control units;
- **40** inspections for verification of compliance with Good Clinical Practice (GCP) regulations;
- **10** pharmacovigilance inspections at MA holders.

A total number of **37** Qualified Person Certificates were granted.

As far as the activity for quality surveillance of medicinal products is concerned, sampling was performed of **25** finished medicinal products and raw materials; laboratory testing outcomes were as follows:

- **10** samples were confirmed to be compliant;
- **6** samples currently under testing;
- **2** finished medicinal products were confirmed as non-compliant, resulting in their withdrawal from the market;
- **7** samples could not be tested for lack of the reference substance.

A number of **185** targeted inspections were performed for verification of distribution units and **240** inspections for check of quality of oxygen used in hospitals.

In 2008, ANM the NMA decided withdrawal from the market of **46** quality non-compliant medicinal product batches.

During the reported time, **69** Rapid Alerts issued in the system by both EMEA and the PIC/S were received and solved. The NMA issued **5** Rapid Alerts in 2008.

7. Quality control of medicinal products for human use

7.1. Quality control of biological and non-biological medicinal products was process based, according to standards SR EN ISO 9001/2001 and ISO 17025.

In 2008, the Raw Materials and Finished Products Control Department (RMFPCD) tested **1150** medicinal products, of which:

- **297** medicinal products obtained through chemical synthesis;
- **853** biological medicinal products (vaccines, sera).

For the above medicinal products, **2219** test bulletins were issued.

Types of tests performed were physico-chemical, pharmaco-toxicological, microbiological or anatomo-pathological.

Most of the **30** non-compliant medicinal products, representing **2,6%** of the total number of medicinal products tested, for which non-compliance certificates were issued, showed physico-chemical and microbiological non-compliances.

As in previous years, in 2008 as well, the RMFPCD continued collaboration with European institutions dedicated to quality control of medicinal product.

In addition to its control activities, the RMFPCD collaborated with the EAD for assessment of medicinal product authorisation dossiers, elaborating reports on assessment of the Drug Master File (DMF). In that respect, **498** such DMF assessment reports were set up.

At the same time, **9** reports on assessment of the chemico-pharmaceutical documentation were elaborated in the frame of the marketing authorisation/marketing authorisation renewal procedure.

Significant investment was made in 2008 to reorganise the 4th floor of the biology sector, thus establishing an optimum setting, at European level, for pharmaco-toxicological and anatomo-pathological tests. Reorganisation of these activities was presented in the Posters section of the Annual meeting of Official Medicines Control Laboratories (OMCL) network.

In 2008, RMFPCD work was subject to **2** audits, one internal and the other external, the latter carried out by EDQM auditors. The audit was developed in line with the EDQM protocol and envisaged the entire quality control activity carried out within the department.

Activities of the RMFPCD received positive appreciation from the auditing team.

7.2. In 2008, assessment and control of biological products in the Biological products evaluation and control department (BPECD) developed in the context of completion of construction and refurbishment works started in 2007, focussing on improvement of department processes. This was the year when the Department presented itself and its activity in the Annual meeting of Official Medicines Control Laboratories (OMCL) network as well the EDQM audit carried out in September.

The BPECD professional profile underwent no changes in 2008, therefore continuing to cover specific activities.

In 2008, within the European Commission administrative procedure for official batch release by the Official Control Authority Batch Release (OCABR), the following were issued:

- **848** batch release certificates and
- **6** non-compliance bulletins.

In the frame of current control of quality parameters of Romanian and foreign biological products for human use, a number of **732** batches were analysed, which corresponds to **6209** laboratory tests. This resulted in grant of **919** test bulletins. There were **3** occurrences of medicinal product batches rejection and **3** more series were rejected in the RMFPCD control process.

Activities related to post-authorisation surveillance were continued and a number of 116 biological product lots were recorded in the BPECD data base.

As part of dossier evaluation in view of authorisation or renewal for Romanian or foreign medicinal products as well as for approval of type I or type II variations, assessment was performed on **22** medicinal products subject to assessment through national procedure, for which **29** Standard Quality Assessment Reports (SQAR) were issued. Support dossiers were also assessed for **165** variations to marketing authorisations through national procedure.

8. Pharmacopoeia related activities

Romanian new and revised standard terms were elaborated for pharmaceutical forms, administration routes and primary packaging, in line with those adopted by the European Pharmacopoeia Commission in 2008, further approved through Scientific Council decisions and electronically submitted to the EDQM for implementation into the European standard terms database.

The current amended version of the Romanian standard terms was elaborated, including all terms approved so far through Scientific Council decisions.

At the same time, new combinations of European standards terms have been translated, notified to the EDQM by the manufacturers and dispatched on-line for implementation into the European standard combined terms database. The list of Romanian combined standard terms has been regularly updated and made available to NMA specialists in the Evaluation-authorisation department.

9. Quality management

In 2008 as well, special consideration was given to implementation and maintenance of the quality management system on all NMA departments level. S

Activities performed consisted of the following:

1. Set up/Reconsideration of quality management system documents, their implementation and observance in current departmental activities. New versions of the Quality Manual were set in each department, accompanied by elaboration/reconsideration of Standard Operation Procedures (SOPs), work instructions, interdepartmental procedures. Job descriptions and individualised job descriptions were updated and staff training plans were devised.

2. Internal and external audits

Maintenance and ongoing improvement of the quality management system was the main goal of the NMA structure in charge of quality assurance. The internal auditing process developed according to the 2008 Internal auditing plan and included auditing of all NMA departments. Internal quality audit findings and conclusions aimed at ascertaining of compliance with audited processes specific SOPs were recorded in internal quality audit reports, also including improvement action plans set up by audited departments.

An external EDQM audit of the RMFPC and the BPEC departments took place during 23-25.09.2008.

An auditing mission from the Ministry of Health visited the NMA during 18.08 – 19.09.2008.

In view of better and strengthened management of the NMA quality management system, the NMA resorted to nomination, through NMA President Decision.

3. Participation of NMA specialists in specialised quality management training sessions

In 2008, NMA management staff took part in the quality assurance training on ISO 9001/2000 Quality management provided by the QUASARO specialised company.

10. Communication and transparency

The National Medicines Agency ensures sound communication with interested parties and the 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 NMA ensures good and accurate information of partner institutions regarding activities developed in all domains within its scope.

The NMA publishes its quarterly bilingual Informative Bulletins, mirroring its regulatory activity in the medicinal product field, in line with European legislation as well as other NMA priority activities.

NMA quarterlies include:

- Laws, ordinances, Government decisions in the area of medicinal products for human use or other fields of NMA concern;
- Orders of the Minister of health for approval of NMA Scientific Council decisions or other fields of NMA concern;
- NMA Scientific Council decisions;
- NMA Administration Council decisions;
- The quarterly list of medicinal products newly authorised by the EMEA through centralised procedure, for which the European Commission has issued decisions in Romanian;
- The quarterly List of medicinal products authorised for marketing by the NMA;
- The quarterly List of applications of marketing authorisation/NMA granted marketing authorisation renewal;
- The quarterly List of medicinal product batches withdrawn by the NMA on quality non-compliance grounds

Electronic versions of the NMA Informative Bulletin are also posted on the Agency website.

The NMA also prepares and publishes the annual Index of medicinal products for human use, including in brief all medicinal products authorised for circulation in Romania and mentioning their trade names, International Non-Proprietary Names (INNs), manufacturer, pharmaceutical form, administration route, packaging, classification for supply etc.

The NMA regularly updates information posted on the Agency's bilingual website, which provides the following data and documents:

- Press releases related to medicinal product safety;
- Communications to healthcare professionals;
- Notifications to MAHs or other interested parties on issues of interest;

- 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;

- On prescription medicinal products authorised for circulation in Romania;

- Over the Counter medicinal products (OTCs) authorised for circulation in Romania;

- Approved orphan medicinal products;

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

- NMA nominated EMEA experts.

In support of its external partners, the National Medicines Agency provided for two new additional headlines on its website, dedicated to the following procedures:

- < The centralised procedure>

- <MRP and DCP> (the mutual recognition procedure and the decentralised procedure, including information on contact persons and a number of useful data for marketing authorisation through the above procedures, i.e.: legislation acts, required forms, bank accounts, NMA notifications and warnings to MAH involved in European procedures. All such information has been improved and updated in both the Romanian and the English version, adding recent information distributed on topics.

Of great interest for NMA website users are sections on:

- medicinal product legislation;

- useful information on European procedures;

- forms and useful information etc.

Proof of the manifest interest of parties concerned in information posted on the NMA website has been the large number of visitors, i.e. 152,000 visitors/year, which means a monthly average of 12,650 visitors.

As far as insurance of transparency is concerned, the NMA carried on and developed application of Law 95/2006 - Title XVII – The medicinal product on transparency of activities of EU medicines competent authorities, through the following:

- Set up of NMA commissions own rules of procedure, publicly accessible on request;

- Preparation of versions for public availability of agendas and minutes of the Marketing authorisation commission and the Commission for the Inspection of Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), Good Analytic Laboratory Practices (GALP), Good Clinical Practices (GCL) and Pharmacovigilance;

- Elaboration of public versions of medicinal product Assessment reports.

In 2008 as well, the NMA continued to inform interested parties on its activity through various publications other than its own Informative Bulletin

Therefore, the Agency report on 2006 activities was again published as a brochure, which has been appreciated by NMA partners.

Articles related to various aspects of NMA activity were also published in 2008 in Romanian specialised magazines („Pharmacist.ro", „Medical Business", „Viaţa Medicală").

NMA representatives made specialised presentations in various conferences and symposia organised nationally and abroad:

- Pharm. Magdalena Bădulescu, PhD, NMA President;

- Sr. Pharm.Rodica Bădescu, NMA Vicepresident;

- Pharm. Robert Ancuceanu, PhD;

- Sr. Pharm. Daniela Enache;

- Pharm. Simona Raicu, PhD;

- Sr. Pharm. Daniela Vasilescu;
- Sr. Pharm. Gabriela Ruja;
- Sr. Pharm. Mihaela Sebe;
- Sr. Pharm. Maria-Gabriela Suliman;
- Sr. Pharm. Andreea Toma;
- Laurenţiu Chiţimia, Specialist MD;
- Adina Pîrvu, Specialist MD;
- Mirela Tavakol, Specialist Biologist.

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 2008 as well.

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

- NMA President's Instructions;
- NMA quality policies;
- NMA Regulations;
- Glossary of quality assurance terms;
- Activity plans of the various NMA departments;
- Useful forms;
- Information on training courses organised by specialised companies;
- Reports of staff participating in training both at home and abroad;
- Staff training status;
- Outcomes of the staff motivation survey;
- Useful information;
- Useful addresses etc.

11. International relationships

In 2008, NMA specialists' participation in activates of the various collaborating European institutions and bodies continued as follows:

11.1. Participation in European Medicines Agency (EMEA) activities

Since as early as 2003, when 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, NMA representatives were an active presence.

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

Full members in EMEA scientific committees, working groups and groups, as of 2007, in 2008, NMA experts took part in more than 100 meetings of these structures.

EMEA scientific committees and working groups are as follows:

- The Committee for Human Medicinal Products;
- The Paediatric Committee;
- The Committee for Orphan Medicinal Products;
- The Committee for Herbal Medicinal Products;
- The Committee for Advanced Therapies;
- The CHMP Biotechnology Working Party;

- The CHMP Efficacy Working Party;
- The CHMP Safety Working Party;
- CHMP Pharmacovigilance Working Party;
- The CHMP Blood and Plasma Working Party;
- The CHMP Vaccine Working Party;
- The Joint CHMP/CVMP Quality Working Party;
- The CHMP Working Party with Patients and Consumers Organisations;
- The GMP/GDP Inspectors Working Group,
- The (EudraGMP Database Sub-working Group);
- The GCP Inspectors Working Group;
- The Pharmacovigilance Inspectors Working Group;
- The GLP Inspectors Working Group;
- The EudraPharm EU Authorised Medicinal Products Database Working Group (EudraPharm TIG);
- The EudraVigilance Adverse Reactions Database Working Group (EudraVigilance TIG);
- The EudraCT Clinical Trials Database Working Group (EudraCT Clinical trials TIG);
- The European Information Network Working Group (EudraNet);
- The e-Submission Working Group (e-Submission TIG);
- The TMC Working Group on Dictionaries;
- The Product Information Management Working Group (PIM);
- The Quality Review of Documents Working group (QRD);
- The Invented Name Review Group (NRG).

11.2. Participation in activities of the Heads of Medicines Agencies

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

The working groups are as follows:

- The Heads of Medicines Agencies;
- The CMD-h (The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human);
- The EMACOLEX (The European Medicines Agencies Co-ordination group on legal questions);
- The Communication Professional Woking Group;
- The Transparency Working Group;
- The Working Group of Enforcement Officers;
- The Clinical Trials Facilitation Group;
- The Homeopathic Medicinal Products Working Group;
- The Quality Managers Working Group.

11.3. Participation in activities of the European Council and the European Commission

National Medicines Agency experts took part in **6** meetings of the working group for medicines and medical devices of the European Council.

In the frame of meetings organised by the European Commission, NMA experts took part in **3** assemblies of the Standing Committee on Medicinal Products for Human Use, and 1 meeting each of the Pharmaceutical and the Notice to Applicants committees as well as in the

meeting of the ***ad hoc*** group for the development of implementing guidelines for Directive 2001/20/EC on clinical trials.

11.4. Participation in World Health Organisation (WHO) activities

The National Medicines Agency has been a member of the WHO Scheme for quality certification of medicinal products on international markets.

In 2008, the NMA the NMA issued medicinal product certificates in WHO format for **308** medicinal products by domestic manufacturers who expressed their intention to authorise their products in other countries as well.

11.5. Participation in Council of Europe activities

In 2008, National Medicines Agency representatives took part in 2 meetings of the Group for classification for supply of medicinal products for human use and the Ad hoc working group for counterfeit medicines.

11.6. Participation in activities of the European Pharmacopoeia Commission

In 2008, the National Medicines Agency representative assigned 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 a European Pharmacopoeia.

At the same time, 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 Pharmaceutical Inspection Cooperation Scheme (PIC/S)

National Medicines Agency activity as PIC/S member materialised in active participation in **2** meetings of the PIC/S Committee of Officials and training sessions following meetings and the annual PIC/S seminar on „Good Distribution Practices as one of the key elements for quality of medicinal products" and the working group on „Manufacture of Sterile Medicinal Products".

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 June 2008, organised by the EDQM, also attending the session on shelf life extension for medicinal products in state strategic stocks, involvement of competent authorities and Official Medicines Control Laboratories and the annual meeting for medicinal products authorised through mutual recognition/decentralised or centralised procedure, organised by the EDQM at CombiStats training session.

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

- **4** PTS (Proficiency Testing Scheme) studies, analytical studies undertaken at EDQM initiative and coordination, performed on an annual basis to test 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 consisting of testing medicinal products authorised in Romania through national procedure by comparison to a standard product provided by the EDQM.

Following Romania's accession to the EU, the NMA has also been involved in studies for verification of quality of medicinal products authorized by the EMEA through centralized procedure, therefore taking part in such a study in 2008. NMA specialists also carried out **3** inter-laboratory studies under the International Pharmaceutical Federation.

12. Human resources policies

Objectives pursued by the National Medicines Agency in 2008 in the human resources field mainly envisaged the following:

- Insurance of specialised staff of higher education – specifically in the medical – pharmaceutical field, for adequate coverage of staff deficient positions in specialised departments insuring attainment of the NMA scope. Efforts to this purpose materialised in employment of 15 members of university graduates.
- 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;
- Training and improvement of NMA personnel develops in line with yearly plans well established on each department level, depending on each employee's activity and training. Mention should be made of both on-hiring and ongoing training provided both internally and outside the NMA, by institutions specialised in various fields, such as: management of quality assurance (ISO 9001:2000), training on specific pharmaceutical inspection matters, on accounting-financial issues etc. To the afore-mentioned, active participation is added in various symposia, congresses on medicinal product topics and the participation of NMA specialists in working parties of international bodies in the field of medicines.
- Motivation of staff by provision of adequate labour conditions, stimulating work environment, access to information, training and professional improvement, stimulation of higher professional achievements of all valuable individual initiatives, better salary packages within the specific financial limits;
- Insurance of fluent communication among organisational structures and access to information handled by the Human resources department;
- Implementation of measures for confidentiality insurance regarding information handled by the Human resources department.

13. Economic activity

In 2008, the Economic department prepared and managed an incomes and expenses budget of 26.900.000 lei, not requiring further budget rectifications.

In 2008, the NMA incomes amounted to 50.317.000 lei, from performances to internal partners.

The expenses chapter amounted to 18.550.000 lei, of which:

- 15.005.000 lei personnel expenses;
- 2.714.000 lei expenses for goods and services;
- 831.000 lei capital expenses.

All expenses were within the approved incomes and expenses budget for 2008, in full compliance with economic-financial discipline legal provisions.

The above date show a balanced financial exercise between NMA incomes and expenses, developed in respect of budget principles and regulations provided in Law no.500/2002 on public finance, also corroborated with specific legislation in force.

From an organisation standpoint, all economic activities were developed through the Economic department, therefore ensuring optimum and efficient carryout of payments and cashing on unit level.

Order of the Minister of Public Health 1038/2008 approved adjustment o tariffs for performances provided by professional departments.

14. General administration and patrimony

The General administration and patrimony department elaborated the 2008 Annual purchase plan, running **370** purchases of products and services, at the same time preparing and completing **42** public purchase files and drawing **102** contracts.

Efficient coordination of activities on all department levels reflected itself on good progress of all other NMA departments.

15. Internal audit activities

According to the Annual auditing plan, the Internal audit bureau finalised **2** audit reports in 2008, 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 the preceding year.

16. Difficulties encountered

In what concerns addition to the personnel establishment of university graduate new personnel, the main obstruction encountered by the NMA in 2008 as well was the insufficient number of doctors and pharmacists employed in professional departments.

17. PRIORITIES FOR 2009

- Insurance 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;
- Insurance of human and financial resources required for proper performance;
- Redistribution of staff, to insure development of priority activities in result of European Accession, taking into account the workload of each specific position;
- Improved wages for and motivation of existing specialist staff for encouragement for continued work in the institution as well as further employment of young specialised staff;
- Continued in service staff training as well in other locations at home and abroad for improved professional competence and 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 on healthcare reform, as amended;
- Ongoing improvement of the quality management system;
- Improvement of communication with interested parties and transparency of activities.

CONCLUSIONS

The particularly fruitful activity of the National Medicines Agency in 2008 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.

Joint efforts by both the NMA management and personnel received positive appreciation on the two audits performed on the NMA in 2008.

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.