ACTIVITY REPORT
for the year 2003

INTRODUCTION

The present activity report tries to point within it is definitely lines the year 2003, extremely important for the National Medicines Agency's life. It was a year rich in events, problems but also with important achievements.

On the other hand, even if in general the results were closed to expectations, there were also hesitation moments, which showed us that there is, still enough work by the maximum possibilities level.

It should be mentioned the fact that the followed up objectives obliged the National Medicines Agency's personnel to alert working rhythms, reactions and adaptation.

For achieving these objectives, it was imposed as mandatory a new managerial approach, characterized by dynamism, perseverance, great availability to effort, courage in assuming responsibility, capacitating to the maximum level of a bigger number of institution employees. It can be said that on the fly it should followed both the objective achievements as well as the modeling of a new working mentality. In addition, if from statistical balance points of view there are dissatisfaction reasons, regarding the changing of the mentalities the thinks are more complicated and far from an optional functioning.

The analysis of conducted activity during the year, which was finished, we should take into account the concrete circumstances under which the activity was conducted in 2003 by the Agency:

1. A deficient structure of human resources both at the professional experience, situation due in principle to the difficulty to attract university degree specialty personnel to equilibrate the looses due to leavings or retirements, determined by the absence of attractiveness of the salaries from the Agency compared to the ones offered in the private sector, as well as regarding the mean age. This situation determined the overloaded/person of the activity in certain important sectors.

2.The disproportionate report university degree personnel/ medium and general degree personnel compared to the unit necessities and which determined personnel expenses that could have been directionated more efficiently.

3.Limited stimulation possibilities and personal interest of the personnel due to the wage system.

4.The complexity and volume of activities increased compared to previous years.

It should be mentioned the fact that at the previous year achievements concurred besides the own effort also the excellent collaboration and established counseling between the National Medicines Agency and the Ministry of Health.

Going to the more detailed analysis of the activity conducted in 2003, we will structure as such:

I. Participation of the National Medicines Agency to normative activity;
II. External activity conducted by the National Medicines Agency;
III. Development policy of the National Medicines Agency;
IV. Activity performed by the National Medicines Agency's departments;
V. Conclusions;
VI. Perspectives 2004.

I. PARTICIPATION OF THE NATIONAL MEDICINE AGENCY TO NORMATIVE ACTIVITY

Regarding the superior level of legislation, 2003 brought the National Medicines Agency's activity domain changes and completions to the framing normative acts, which were inscripted in the normality of the legislative consolidation process.

There were amended, in the way of changes and completions, both the Government Ordinance no. 125/1998 regarding setting up, organization and functioning of the National Medicines Agency as well as the Emergency Ordinance no. 152/1999 regarding the medicinal products for human use.

The first normative act was modified and completed by Government Ordinance no. 66/2003, while the second had two corrective interventions– Law No. 351/2003, respectively Government Ordinance no. 72/2003.

The Law for organization and functioning of the institution followed in principle, the finishing of previous dispositions related to the optimization of the organizational system and to the managerial act, requests imposed by the institution evolution.

The changes brought by the GEO no. 152/1999, far more substantial, followed, regarding what the NMA is interested in, technical aspects related to the definition and classification of the regulatory object, organizational procedures, sanctions apparatus as well as the put of the competencies given

by the National Medicine Agency as specialty institution subordinated to the Ministry of Health.

The participation of the specialist of the NMA to three normative acts mentioned above was active, the Ministry of Health consulting the Agency regarding all initiated changes.

The changes to the two laws are useful and welcome, these representing the legislator and executive interest for chasing the initial regulations in the context of the necessities imposed by reality and international assumed obligations.

More rich and diverse was the own normative activity of the National Medicines Agency, conducted by the intermediate the Scientific Council and Administrative Council.

During the year 2003 was adopted a number record of Decisions of the Scientific Council – 44 – covering the entire spectrum of the institution scientific activity, from organizational problems to the diverse procedures, good practice regulations and to the regulatory acts for harmonization of the Romanian legislation to the European one.

It should be remarked regarding the decisions with normative character the substance change operated by the GO no. 66/2003 – special approval procedure by Minister Order and publishing in the Official Monitor.

The activity of Administrative Council was concretized during 2003 in a number of 27 decisions (ACD), out of which one decision with normative character regarding the approval of new tariffs for new activities performed by the Evaluation- Authorization and Pharmaceutical Inspection Departments.

In addition to the regulatory activity it should be signalized the active participation of the specialists of the institution to the activities of the national organisms coordinating the negotiation processes for accession to the European Union.

II. EXTERNAL ACTIVITY CONDUCTED BY THE NATIONAL MEDICINES AGENCY

The external component of the institution activity for 2003 was very rich. It should be underlined that Romania adhered at the Convention regarding Elaboration of European Pharmacopoeia of the European Council and became member with full rights starting with 24.09.2003.

The presence of the NMA representatives to the actions of the international specialty forums became a current fact, their activity being well appreciated by external partners of the Agency. It should be remarked also the

benefic effect for the Agency, related to external experience valorization, quantified in consistent working documents and regulatory documents at the level of European exigencies.

Statistically, in 2003, there were achieved a number 49 meetings to external activities, with a number of 25 persons. These data signify, in addition to the external dimension ampleness of the institution activity and the pleasant and not at all neglected fact of the outline of a specialist's nucleus, able to assume important responsibilities at a level of high performance.

In 2003, an important part from the financial effort related to participation to these actions was supported by the European Union by PERF III Program. Another part was supported by the National Medicines Agency through its own revenues.

For 2004, the level of participation to external actions will significantly increase, by acceptance of the NMA's representatives as active observers to the working groups and to the scientific committees of EMEA and directly proportional the value of financial effort. At a first evaluation, the participation to the planned meetings can be appreciatively of 400,000 Euros.

For the current year, the meetings were evaluated based on criteria cost/efficiency, considering the importance from professional point of view of the respective activity.

In 2003, within the planning of PERF III, our institution was evaluated by an external auditor's team from Germany, Poland, Slovakia and Lithuania regarding the level of implementation of the quality management system, the conclusion being the following:

"The National Medicines Agency has a well established quality management system based on ISO 17025 in the field of laboratory control and ISO 9001 for its regulatory activity. The Quality Manual as well as other QMS documents are present and it is clear that the process approach is implemented within the organization. The top management is deeply involved in QMS related activities and the whole staff is well motivated and clearly understands the mission and objectives of the organization. The employees are well trained in amps issues".

It should be remarked that this evaluation placed the Romanian National Medicines Agency within the countries group with a score of 3 out of 5 possible.

III. DEVELOPMENT POLICY OF THE NATIONAL MEDICINE AGENCY

The development policy of the Agency in 2003 considered a series of principles established following the conclusions from the fields, of institution necessities and of concrete possibilities for solving them. Succinct enumerated, these are:

a) The assurance of a strict legacy of all activities of the National Medicines Agency;
b) The achievement of all assumed capacities and objectives by the institution object of activity;
c) The assurance of the financial recourses corresponding for a good performance of activity;
d) The reorganization of the institution organizational structure for assurance of the optimal functioning;
e) The passage to a new personnel waging system; assurance of decent incomes at the maximum level of institution possibilities;
f) The continuation and finalization of started and unfinished investments;
g) The increase of the institution prestige, internally and internationally.

The above enumeration has an orientative character, all objectives being in the first place of the National Medicines Agency's administrative management attention.

Chronologically speaking, the starting was done by reorganization of the institution departments; in 2003 the structure was the following:

-Evaluation-Authorization Department;
-Raw Materials and Finished Products Control Department;
-Biological Products Control Department;
-Pharmaceutical Inspection Department;
-European Integration, Pharmacopoeia, Juridical, Legislation Department;
-Quality Assurance Department;
-General Administration and Patrimony Department;
-Economic Department;
-Human Resources Department.

Following the organigrame, it can be observed that the specialty departments have the same constitution, the reorganization affecting administrative departments.

The Juridical, Legislation, Relations with Other Institution Department disappeared, merged together with the Pharmacopoeia Service in a new department. This measure was imposed by the necessity of existence of a special structure European integration to better monitor the activities related to the problematic in domain.

To a greater extend was the reorganization of the General Administrative Department. Here, the reorganization necessity was imposed for at least four reasons:

-Activity objects very vast;

-Excessive dimensions of the department;

-The existence of a legislative frame that individualize the economic activities and human resources as distinct activity sectors;

-The need to optimize the activity.

Even correct, this measure created a series of dysfunctions in the current activity being necessary measures in order to harmonize the tree new departments.

Another important organizational operation was the completion of the institutional frame at the highest level of management by establishing the vice-president function of the National Medicines Agency. Regulated by the GO no. 66/2003, the function of vice-president of the institution represents a necessity considering the problematic very complex of the institution and its dimensions.

It also should be mentioned the finalization of the territorial unit's reorganization, in the way of transforming the last seven territorial units which still conducted the control activities with object of activity exclusively of inspection. The measure was determined by the necessity to efficiencies the activity by reduction of the over plus expenses.

The following step followed objective was the assurance of the financial resources corresponding to an efficient institution activity.

Regarding financing, the NMA has a particular statute within the Ministry of Health system, financing being realized exclusively by own incomes.

By own law of organization and functioning, the Agency benefits by a large economical-financial autonomy, having exclusively administrative competence.

This statute is determined by the European exigencies and practice in the fields, undergoing a responsibility extremely important from the entire managerial body.

Characterized in the initial version as public institution with mix financing, the National Medicines Agency succeed – de facto – to assure for it only from the incomes obtained from labor conscription to third parties the financial resources for a functioning in good and very good conditions, achieving also year-by-year financial over plus. These elements as well as the necessity of adaptation of the institution to European practice imposed the

change of juridical regime and the transformation of the National Medicines Agency in the biggest public extra budgetary institution from sanitary system.

For consolidating the financial autonomy it was continued the identification action of all financial resources possible to be attracted, during 2003 were established a series of tariffs for activities performed by the Evaluation-Authorization and Pharmaceutical Inspection Departments, including in emergency regime, as well as the subscription for maintaining the Marketing Authorization paid by the holder for each medicinal products for human use.

Another followed up objective which was under the attention of the administrative management was the corresponding internationally representation of Romania.

During the last year, the National Medicines Agency received the visit of an international auditor's team, within PERF III program in order to be evaluated concerning the implementation of the quality management system, the results being very good, and inscribing NMA between the European Agencies with a well established management system.

The very good results were possible only following an exceptional mobilization, taking into account that practically the action started from zero. For the moment, we can say that we have articulated a functional system for coherent management of quality by which will be possible to ensure a corresponding development.

The year 2003 was also the year of finalizing a long awaited investment objective – arrangement of the microbiological laboratory from the Control of Raw Materials and Finished Products Department.

The Agency has presently a modern microbiological laboratory, well equipped, corresponding to the domain standards.

Also in 2003, the NMA had as permanent concern the assurance of material endowment corresponding to the institution level and statute.

One of the most important achievements from last year having a social profound impact is represented by the passing to a new waging system of the National Medicines Agency's personnel.

Even formally, this possibility exists from the moment of validation by Law of the Emergency Ordinance No. 125/1998, the step being done later, at the end of August 2003 by amending the collective working contract at the unit level. Before amendment of the collective working contract more steps were passed in order to change the personnel mentality regarding waging.

An important managerial signal transmitted to the entire personnel was the one that it is desired to overpass the old thinking mode, the one that all are

equal in rights due to the low level of waging, this despite the fact that at the chapter of responsibilities ones are much more overloaded than others.

In this sense, it was passed to the stimulation, at the beginning symbolic, of those with merits, showing them that their work and devotement are recognized and appreciated. The financing source constituted - the premium fond of 2%, which by common law is given to all. Most of the employees have correctly understood the significance of the taken measure, supporting implicitly by sensitive change of the professional attitude.

For these, but also for showing that the managerial team understand to respect its given promises, it was passed to the put into practice of the new waging system, definitive the radical change of the juridical regime of the institution started since November 2002.

By the simple change of the waging system and by the introduction of a new waging grid not all the existing problems were resolved.

The importance of this step is that it will determine the next ones. The level of the next negotiation of wages will increase more the exigencies of the demands and will constitute the moment of real establishment of the personnel wages based on the professional capacity of each employee, on quantity and quality of the effort put for the institution.

The entire personnel will have to understand that the exit from the budgetary waging system signify that the institution does not have the obligation to pay unconditional salaries. There will be employees who will have very big salaries and employees, which will receive salaries at the minimum economy level, the appreciation criteria being the visible performance standards with which each will be present to the negotiation.

IV. ACTIVITY PERFORMED BY THE NATIONAL MEDICINES AGENCY'S DEPARTMENTS

Regarding the activity of National Medicines Agency's departments in 2003, it can be mentioned the fact that each department contributed more or less to the good progress of the activity, competing together to the results generally good of the NMA.

The activity reports of the departments, annexed to the present report complete the general image of the activities performed during 2003.

The principal statistical data regarding NMA's activity in 2003 are the following:

Personnel structure of the institution.

At 31 December 2003, the total number of personnel was 432, out of which

a. Full time 405, out of which:
-Personnel with university degree 142 (pharmacists 53, doctors 15, biologists, biochemists, chemists 45, economists, engineers, jurists, analysts, librarian, documentarist 29)
-Personnel with short-term university degree 3
-Personnel with post-lyceum degree 70
-Personnel with medium degree 92
-Personnel with general degree 98 (workers 70, servants 28)
b. Part time 27

The activity of Evaluation-Authorization Department

The department has a number of 116 persons, corresponding to a framing of 130 positions.

Out of these, 80 are with university degree and 36 with medium and general degree.

From the organizational structure point of view, the department did not suffer during last year important changes, the replacements being operated for the purpose of a superior coordination and systematization of the activities.

The activity of this department is follow up especially by the managerial team, considering the premise that this department was is and will be the synthesis department of the institution, its weight center and the place where it is realized in principle the object of National Medicines Agency's activity.

The evaluation authorization department was also in 2003 the motor, which stimulated the functioning of the other departments, and benefited in his turn from their services.

In 2003, 1400 applications for authorization/renewals were submitted, out of which 749 applications for authorization and 651 applications for renewal. 1100 Marketing Authorizations were granted out of which 371 were for Romanian medicinal products and 729 for foreign medicinal products; 976 with 5 year validity and 124 with 1 year validity; 599 for products received for authorization and 501 for products received for renewal.

The activity of services and bureaus for evaluation of the documentation was concretized in 1429 evaluation reports out of which 1002 with the recommendation for authorization, 422 with requests for completion of the documentation and for 9 negative reports were given.

The service for variations evaluation received a number of 1317 applications for type I variation, 115 applications for type II variations, 145 applications for other changes admitted by Regulations, 11 applications for transfer of Marketing Authorization, granting approvals for 929 type I

variations, 132 type II variations, 67 changes admitted by Regulations, 34 transfers of Marketing Authorizations.

The service for leaflets, clinical trials, pharmacovigilance evaluated, approved and granted 95 updated annexes to Marketing Authorization for variations regarding therapeutical indications, 79 approvals for type I variations for products authorized by European procedures, 140 changes of Marketing Authorization and annexes as a consequence of variations approval by the evaluation service by European procedures.

91 applications for clinical trials were received and approved; a number of 195 bioequivalence studies were evaluated; 51 final reports for safety evaluations were issued. In addition, it was achieved a sustained pharmacovigilance activity.

A remarkable activity consisted in the peculiar effort conducted for identification and establishment of specific standard operating procedures, of the Department Quality Manual and of those 59 standard operating procedures.

The Evaluation-Authorization Department furnishes the biggest part of active observers to working groups and scientific committees of EMEA.

The activity of Pharmaceutical Inspection Department

The department had at 31 December 2003 a number of 74 employees, including the personnel from the territorial units.

In the headquarters, there were 13 employees, 9 with university degree and 4 with medium and general degree, while in territory there were 61 employees, 24 with university degree and 35 with medium and general degree.

Per total, a number of 35 persons with university degree and 39 with medium and general degree.

Keeping the same organizational structure and employees, the Pharmaceutical Inspection Department covered in 2003 an important volume of activities, achieving a number of 19 inspections for Good Manufacturing Practice, 1 follow-up inspection for solving the deficiencies concluded at SC SICOMED SA; following specialty inspections, a number of 7 manufacturers were certified in Good Manufacturing Practice; there were performed a number of 46 inspections for evaluation of the degree of implementation of Good Manufacturing Practice, 5 inspections for pre-authorization for products submitted for Marketing Authorization procedure, 2 authorization inspections, 2 inspections for Good Laboratory Practice for granting the certificate for laboratories which perform the bioequivalence studies and a

number of 14 GMP inspections requested by the pharmaceutical companies from non PIC/S countries members.

In addition to these actions, it should be remarked the active contribution to the effort for regulating the legislative frame and participation to the internal and external training courses, the efforts for assimilation and completion of the quality management system.

The activity of Raw Materials and Finished Products Control Department

The Raw Materials and Finished Products Control Department constitutes, numerically, the most numerous collective of the institution, having in its functioning statute a number of 155 positions, out of which 114 are occupied.

Out of these, 34 persons with university degree and 80 with medium and general degree.

The department benefited also as last year from the biggest investments volume, the main financial effort of the Agency being concentrated on the finalization of the fitting out working of the microbiological laboratory, work that was finalized with success.

During 2003, the Raw Materials and Finished Products Control Department granted a number of 9742 analysis bulletins out of which 333 at the request of the Evaluation-Authorization Department, 1044 at the request of Pharmaceutical Inspection Department, the difference of 8340 being analysis bulletins for currently samples. Out of 9742 worked bulletins, a number of 104 were for non-conform products.

249 reports for microbiological evaluations and 5 reports for radiopharmaceutical products evaluation were issued.

737 Technical Import Sheets (out of 743 registered) were advised.

The department specialists participated in 2003 to different training courses locally and abroad; special efforts for establishing the Department Quality Manual, revision of a number of 15 administrative procedures and elaboration of a number of 6 others were put down.

The activity of Biological Products Control Department

The Biological Products Control Department is the only one that functions outside the headquarters.

Employment of personnel – a number of 43 positions normed in the functioning statute out of which 30 occupied by 10 persons with university degree and 20 by personnel with medium and general degree.

The department performs in general activities for control of biological products: currently control, control within the authorization or renewal activity, control of recalled products for quality problems. Supplemental, starting with November 2003, the department was given attributions regarding the evaluation of the authorization/renewal dossier for marketing authorization of biological products.

In 2003, 2101 samples accompanied by the corresponding documentation there were registered, 3 times more than in 2002.

In the 4 department laboratories, 2101 product batches were tested, performing 6311 laboratory tests, a working volume above the activity from 2002.

A number of 177 batches for biological products for imported products from PIC/S countries was authorized; 10 dossiers for evaluation-authorization were received out of which there was finalized a number of 3 products.

A sustained activity was done for corresponding implementation of the quality management system (revision of a number of 18 standard operating procedures, establishment of a number of 31 new operating procedures, identification of new processes and sub/processes from the department and establishment of corresponding flow diagrams, writing of the Department Quality Manual).

The activity of Quality Assurance Department

The year 2003 was the year of affirmation for this department, which had an important contribution for preparation of general documentation for quality management system of the NMA, evidenced as being good with the occasion of the visit of the auditor's team designated by the EMEA for establishing the level of implementation of the NMA's quality management system.

The activity of European Integration, Pharmacopoeia, Juridical, Legislation Department

New department, constituted following the necessity to adopt the organizational structure to the actual exigencies and for a better gestation of the problems related to the European integration. In 2003, the department functioned with a number of 13 employees out of which 6 with university degree and 7 with medium degree.

The department activity covered diverse sectors out of which the monitoring of the stage for achievement of the assumed commitments of the NMA to the EU accession legislative Program for 2002/2003 and reporting to the competent authorities; the collaboration to the identification of barriers against the commerce in the harmonized and non-harmonized legislation, respectively in SCD and ACD, monitoring of the European sites for updating the information regarding European legislation, making up and distribution of

4 Informative Bulletins in Romanian and 3 Informative Bulletins in English language.

The Pharmacopoeia Service elaborated the Romanian Standard Terms for pharmaceutical forms, projects for 2003 Supplement (315 pg.) and 2004 Supplement (250 pg.) of the Xth RF, organized 2 meetings of the Commission for Coordination of Romanian Pharmacopoeia, and performed the opinion poll regarding the possibilities for application of European Pharmacopoeia by the Romanian manufacturers of medicines with the mentioning of requested transition period.

The IT Service developed database applications, completed the internet site of the NMA with the English version, improved the intranet site and ensured the maintenance and service of PC's software and hardware.

The activity of Juridical-Legislation Service covered the juridical reports scale, both from the institution and also with other juridical entities and this was concretized by writing up of 172 Decisions of the NMA's President, 27 Decisions of the Administrative Council, 175 letters; it related from juridical point of view to all contracts, proposals for acquiring goods and services, tender dossiers and starting with October also the financial preventive control visa for a number of 473 financial-accounting papers.

Within the department, the management of quality system was established, documented, implemented and improved, with the capacity to realize the defined quality objectives.

The activity of General Administration and Patrimony Department, Economic Department, Human Resources Department

The activity of these departments, which consist in principle in the support activity for professional departments, was in general good, even if there were also observed a series of dysfunctions, which perturbed in a certain degree the good activity of the institution.

For each of these, there are possibilities for improvements, which we are sure that will be valuated.

V. CONCLUSIONS

The results for 2003 can be considered, in general, good, establishing the launch basis for the objectives of 2004.

By what was accomplished in 2003, it is continued the construction process of a new, modern institution, comparable to the similar institutions of the EU.

During 2003, the managerial team of the National Medicines Agency made sustained efforts to ensure the conditions necessary for a high level of professional activity. Unfortunately, not always, the response was concordant, and from here, a series of deficiencies resulted in the institution activity.

The departments had different reactions to the requests of managerial team, generating certain difficulties, which had repercussions on the general function of the Agency.

In addition, the difficulties of communication between departments persisted.

VI. PERSPECTIVES 2004

1. Continuation of organizational consolidation of the National Medicines Agency;
2. Continuous improvement of the quality management system;
3. Increase of activity quality performed by all National Medicines Agency's departments;
4. Further on participation of the National Medicines Agency to the international activities.

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