Bulgarian Drug Agency

Annual report on the activity 2005

“Administrative-legal and economic service” Directorate

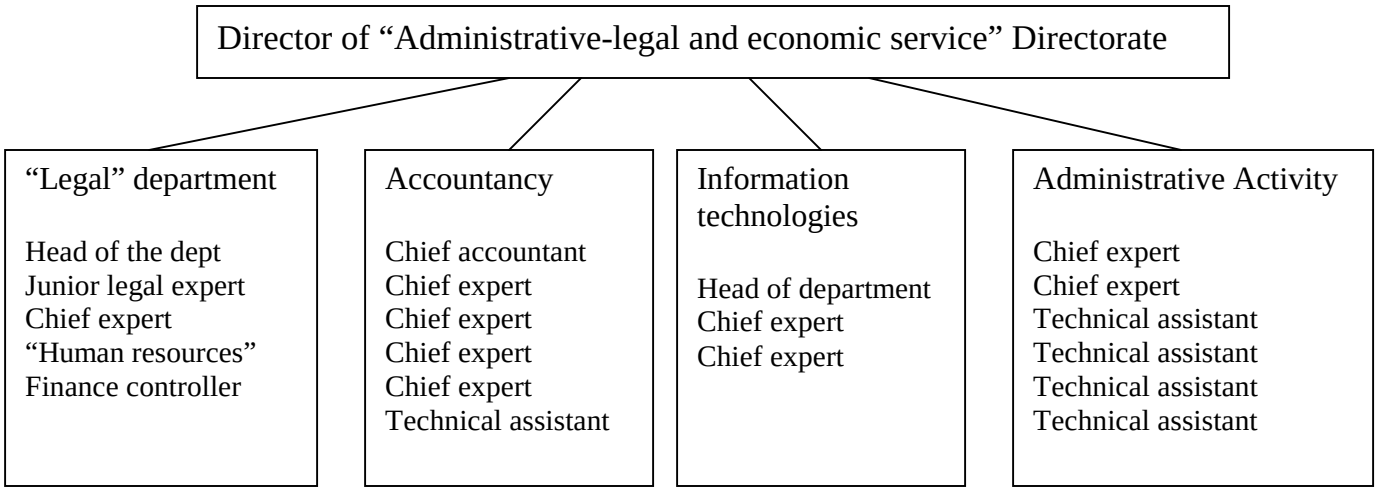
In compliance with the statutory rules of the Bulgarian Drug Agency the “Administrative-legal and economic service” Directorate performs the following activities:

1. prepares a plan for the budgetary funds necessary for the Agency’s activity;
2. organizes the current accounting and exerts control on budget expenditures;
3. prepares the documentation and performs the necessary activities for effecting payments in the Agency;
4. provides legal assistance to the other structural units so that they could perform their functions in compliance with the law;
5. participates in the development of drafts of legislative regulations and makes a statement on their compliance with the law; it also makes a statement on the compliance with the law of drafts of agreements signed by the Agency or proposed by other organizations;
6. Makes a statement on the applications for issuing authorizations under the Pharmaceuticals and Pharmacies Serving Human Medicine Act (PPSHMA);
7. Makes a statement on the compliance with the law of the drafts of the individual administrative acts issued by the General Executive under the Administrative Procedure Act and the penal provisions under the Administrative Violations and Sanctions Act;
8. provides procedural representation before the bodies of the judiciary and performs the necessary legal actions to collect the Agency’s debts;
9. participates via its representatives in commissions for holding competitions under the Public Administration Act and under the Labour Code; it also monitors the compliance with the law of acts related to arising, modification and termination of the employment relationships of the Agency’s staff;

10. prepares the drafts for administrative acts of public appointment and the labour contacts of the Agency's staff and formalizes their termination;
11. is in charge of the correct reporting of the leaves, signs the application submitted for a leave and prepares the documents for business trips;
12. Issues and certifies the work books, prepares the documents necessary for retirement;
13. creates and keeps official files of the staff and keeps the records of the members of the staff that have already left; organizes the selection of candidates for the vacancies;
14. organizes the process of assessment of the Agency's staff;
15. participates in activities related to the planning and organization of the staff training;
16. organizes the records work, affiles, keeps and makes references on the available files under the terms and conditions set by the General Executive;
17. ensures the safety of work in the Agency and draws up acts for occupational accidents;
18. monitors the observance of the admittance regime of outsiders in the Agency's building;
19. assists in organizing the protocol presentations of the General Executive;
20. takes care of the duly issuance of orders for business trips abroad, as well as of the issuance of passports and visas for the people on business trips;
21. organizes and carries out the information and technical service and the access to Internet; provides the integration of the Agency's information system with the information systems of the other public administration units;
22. provides the computer technology and the maintains the information data base in the Agency;
23. establishes public relations.

The “Administrative-legal and economic service” Directorate has 23 members at its disposal – 15 state employees, 8 working under an employment contract, 16 of which have an academic degree and 7 have graduated secondary school.

Table, p.3



Current staff

The staffing level of the “Administrative-legal and economic service” Directorate is 23, 15 of which are state employees, 8 working under an employment contract. There is one vacant full-time job under an employment contract.

The staff in the Directorate have:

An academic degree, master’s degree – 15 people (66% of the total number of people in the directorate);

An academic degree, bachelor’s degree – 1 employee (4% of the total number of people in the directorate);

Secondary education – 7 people (30% of the total number of people in the directorate);

The staff with an academic degree have the following majors:

Lawyers – 3;

Economists – 5, one of which has a second major – Income and pay;

Engineers – 3;

Marketing and management – 1;

Political science – 1;

Social activities – 1.

B. Execution of the assigned activities:

I. Financial activity and results

1. The following financial results were achieved in 2005:

The estimated revenues were 1 600 000 BGN;

The actual receipts in the budget from expert statements and other administrative services amounted to 2 154 045 BGN

The revenues under art.8, par. 3, p.4 of the PPSHMA amount to 60 000 BGN;

The sum total of all revenues in BDA in 2005 was 2 453 479 BGN;

The estimated expenditures in 2005 were 2 721 735 BGN;

The expenditures the Agency has made amount to 1 752 938 BGN;

The money spent on the pay of BDA's staff is 827 473 BGN; 304 835 of which are for fringe benefits of the staff.

II. Legal activity

1. In order to perform the functions assigned to them, the lawyers from the Directorate provided a day-to-day assistance to the other structural units for a legal performance of their activity. Both written and oral statements were made and consultations were prepared on the legal cases that had arisen and other questions in relation to the activity of each one of the Directorates from the specialized and general administration.
2. Participation in working parties for the preparation of regulation drafts:

- a completely new draft of the Pharmaceuticals Serving Human Medicine Act;
- a draft of the Medical Devices Act;
- a draft for a decree on the amendment and supplementation of BDA's Statutory Rules.

In July 2005 Decree 171 of the Council of Ministers was published on the amendment and supplementation of BDA's Statutory Rules, which reflected the amendments made in the functions and tasks of BDA as a result of the amendments in the PPSHMA and the adopted Act on the blood, blood donation and blood transfusion. The Agency's authorities were specified and supplemented in terms of the organization of the expert, monitoring and administrative activity and the staff's level was increased with 11 full-time members.

3. Statements made on the applications for issuing authorizations under the PPSHMA:

During the reporting period the lawyers from the Directorate worked out statements on:

100 applications for issuing authorizations and variations on issued authorizations for wholesale medicines trade;

103 applications for issuing licenses for the registration of drugstores;

2 applications for issuing manufacturing authorizations of medicines;

93 applications for variations in issued manufacturing authorizations of medicines;

7046 files of the "Control of manufacturing and trade with medicines" Directorate

160 files of the "Marketing authorizations of Medicinal Products" Directorate;

263 files of the "Biological Products" Directorate;

19 167 licenses for the authorization of foreign trade transactions with medicines have been coordinated;

Participation in specialized committees under article 21 of the PPSHMA.

- Specialized Committee on the authorization of conducting clinical trials – 24 meetings have been held, at which 490 applications for the authorization of clinical trials with medicines and approvals of variations in already authorized ones were reviewed.
- Specialized Committee for determining the belonging of the products – 13 meetings were held, at which 49 applications for determining the belonging of the products and the documentation of 147 products were reviewed;

- The joint committee on the prices of medicines – 36 meetings;

4. Statements on individual administrative acts under the Administrative Procedure Act and administrative-penal correspondence under the Administrative Violations and Sanctions Act – statements made and coordinated:

- orders for suspending the activity of manufacturers, wholesales of medicines and pharmacies – 23;
- orders for blocking and withdrawing medicines – 20
- orders for the disposal of medicines – 58
- all other individual administrative and inner-departmental acts of the General Executive.

In 2005 the lawyers made statements on 61 acts for establishing administrative violations during the manufacture, retail and wholesale trade with medicines, the clinical trials and the advertisements of medicinal products.

44 penal court rulings were coordinated for imposing fines and penalty payments on physical and legal entities under the PPSHMA and the Administrative Violations and Sanctions Act.

5. In 2005 BDA was a party of 19 administrative penal procedure cases and 2 administrative cases. There have been 33 appearances in court (procedural representation). 12 penal court rulings with imposed sanctions and fines amounting to 14 200 BGN have been irrevocably confirmed and have come into force after a first and second instance court decision.

The appealed penal court rulings pending a court decision are 8.

2 penal court rulings have been lifted at first instance and appealed.

2 first instance cases have been appointed at appealed penal court rulings.

III. Human resources management and activities on the arising, modification and termination of employment relations.

1. After the publication of decree 171 on the amendment and supplementation of BDA’s Statutory Rules the structure of the Directorates from the general

and specialized administration was fully changed in order to comply with the European requirements. The new staff timetable of BDA's structure was prepared.

Thirty-four competitions in total for filling in vacancies in compliance with the State employee Act were announced and held in 2005. They took place in March, July and October, respectively. As a result of the competitions 12 state employees were appointed.

2. Activities related to arising, modification and termination of employment relations:

During the reporting period 513 orders for state employees and supplementary agreements related to arising, modification and termination of employment relations and for indexation of the basic monthly payments have been prepared.

12 employment relations were terminated in 2005, 7 of which were retired employees.

175 orders for business trips of employees in the country were prepared. Throughout the whole year regular references and reports were worked out for the Ministry of Healthcare, the National Statistics Institute, the National Insurance Institute, on the registration of Employment contracts, references to the Register of the state employees.

The experts in the Directorate organized the activity of the evaluation of the performance at work and assessment of the BDA staff for 2005.

IV. Administrative and book-keeping activity.

1. In 2005 the administrative servicing of the citizens and legal entities was improved. There was no case of not observing the legally established time limits on the correspondence.

So as to execute the Government's strategy to service the citizens "at one counter" a restructuring of the Directorate was carried out and a separate unit for administrative servicing was established via which a unified entry-exit of the greater part of the documentation for the Specialized administration is

carried out. The latter includes accepting applications and documentation, sending and receiving correspondence under the established procedure, submission of the final act – authorization, license, registration or any other administrative act.

Yet much effort is still necessary to build a system of servicing "at one counter" and improving the access to the administrative services provided by the Agency.

2. The book-keeping activity may be reported via the following figures:

The table reflects the comparison with previous years:

Year	Import licenses	Entry-exit correspondence	Applications for authorizations, variation and renewal of the marketing authorizations
2001	9850	5600	-
2002	12600	7796	-
2003	15305	8200	-
2004	18039	10470	-
2005	19167	10857	3921

V. Information and technological servicing activities.

BDA's information system is in service of the Agency's basic activities, related to issuing marketing authorizations for medicinal products and medical devices, licensing wholesalers, manufacturers of medicines, drugstores, registering adverse drug reactions, etc.

Via the web-page of the Agency a free access to a great amount of information related to the Agency's activity is provided. The registers of the authorized medicines are updated weekly, and the scanned summaries of products characteristics and packaging are added. The registers of the authorized in vitro medical devices and drugstores are up-dated monthly. A bulletin of the newly

registered medicinal products is published every month. The “Medicinal bulletin” and “Adverse Drug reactions” bulletin are published duly after they have been compiled.

Reports regarding pharmacovigilance are added to the page, including those made by EMEA, as well as the orders for blocking and withdrawing from the market of medicines batches which have not met the quality requirements.

Apart from them legislative regulations which regulate the activities with medicinal products, different directions on the procedures performed by the Agency were published on the web-page. The computer network is maintained daily and the Agency’s work did not stop for more than a couple of hours and if it did, this was due to problems with electricity cuts and other reasons outside our competence, the basic one of which is the old computer technology.

The 26 new computers purchased in 2004 partially solved the problem with the old technology but they are insufficient to a large extent.

BDA’s data base was in constant operation. Whenever necessary or upon assignment references with the data base of the registered medicines are made. All bulletins are entered on the Agency’s web-page after being processed in advance by the experts from the “Information technologies” department.

Throughout the year the computer network was attacked by different types of viruses and the specialists from the department managed to cope with them duly. 26 new licenses for anti-virus programs were purchased, yet there is still no full system for anti-virus protection of BDA’s corporate network.

Particularly significant to the Agency’s work is the development and implementation of a completely new information system, computer network, technical means – servers, computer systems, systematic and applied software, printers, copy machines, with view to the requirements set before BDA for joining the information system of the European Medicines Agency and the telematic network of the EU member states regulatory bodies.

VI. Participation in international events.

Two employees from the Directorate were nominated as active observers in EMEA's scientific committees and working parties – in the Eudranet TIG working party and EMEA's managing board and they actively participated in the regular meetings of the latter.

CHEMICAL-PHARMACEUTICAL EXPERTISE OF MEDICINES DIRECTORATE

The CPEMD is comprised of two departments:

"Evaluation of chemical-pharmaceutical documentation" and "Analysis of medicines".

The major activities are:

Evaluation of chemical-pharmaceutical documentation under authorization procedures, renewal and variations of the medicinal products of synthetic, herbal and homeopathic origin;

Analysis of the medicinal products after they have been granted marketing authorizations after an alert on not meeting the quality requirements, upon the request of the National Investigation Service, etc.;

Participation in inspections;

Participation in the activity of the European control laboratories network related to the monitoring of the market and tests on the suitability of laboratories;

Participation in the activity on developing the Bulgarian pharmacopoeia on the basis of the European pharmacopoeia.

EVALUATION OF THE CHEMICAL-PHARMACEUTICAL DOCUMENTATION

512 applications and chemical-pharmaceutical documentations have been submitted under the marketing authorizations for medicinal products procedure. 324 expert statements have been approved, 58 of them are made by Bulgarian

applicants, 219 are under the national procedure, 27 are under the centralized procedure, and 31 – under the decentralized procedure. 72 documentations have not been read yet which are transferred to the year 2006 and there are 116 letters still awaiting answers.

650 applications and chemical-pharmaceutical documentations have been submitted under the procedure for renewal of the marketing authorizations of medicinal products. 490 of them have been approved and statements made. 137 of them are submitted by Bulgarian applicants and 353 of them – by foreign ones. 74 documentations have not been read yet which are transferred to the year 2006 and there are 86 letters still awaiting answers.

After the critical assessment of the documentation under the authorization and renewal procedures, 459 letters have been written demanding extra information.

16 expert statements have been approved under the re-registration procedure.

1669 applications and documentations have been submitted under the variation of the authorization procedure. 1478 have been assessed and notification letters have been written for approving the variations. There are 167 documentations which have not been read yet which are transferred to the year 2006 and there are 24 letters still awaiting answers

After the critical assessment of the submitted variation data 78 letters have been written demanding for information.

With respect to the authorization procedure 202 BETX methods have been assessed.

ANALYZED SAMPLES

551 samples have been analyzed after the marketing authorization. 18 of them have been analyzed after an alert on not meeting the quality requirements, an alert by the National service for Fighting Organized Crime. 6 of them do not meet the requirements (BENALGIN tablets, x20, Balkanpharma, Dupnitza, batch numbers 158602 and 071504, six samples taken form different cardboard boxes). 8 arbitration analyses have been made. 41 letters have been written related to the

non-compliance between the analytical licenses of the presented samples and the approved specifications of authorized medicinal products.

The BETX analyses made on marketing authorizations are 13, after the marketing authorization – 171 (2 of which for non-compliance, Glimed 1 mg, 2 mg, tablets, Ecopharma with batch numbers GLT 5001), after a alert on not meeting the quality requirements of the National Investigation Service – 17 (3 of which are for non-compliance – Sustnon sol. Inj., Trenabol sol. Inj. and Boldabol, sol. Inj.)

The Directorate has participated in inter-lab trials, organized by EDQM:

MSS 075, MSS 023

PTS 072

CRS 1 – Calcipotriol monohydrate

CRS 1 – Fludarabine phosphate

CRS 2 – Allopurinol

Trials for uniformity of dose units according to the new monograph of the European pharmacopoeia.

PARTICIPATION IN INSPECTIONS, COURSES, SPECIALIZATIONS AND OTHERS

Two chief experts from the Directorate have participated in inspections in our country (Sofia and Kardzhali) and abroad (Macedonia, Romania, Turkey). Eight chief experts have attended courses in English and have been granted certificates for successfully covering the respective level.

One expert has participated in a conference on the procedure for certifying the compliance with the monograph of the European pharmacopoeia, organized by the European Directorate on the quality of medicines in Istanbul.

Three chief experts have participated in a BETX seminar, organized by Agilent Technologies in Sofia.

Ten chief experts have participated in a seminar “Medicinal regulation in the European Union” in Sofia.

Two chief experts have attended a training course for the implementation of the system for quality OMCL, Strasbourg, France and a seminar on chromatography in Sofia.

Other two chief experts have attended a course on “Requirements set before the systems for managing the quality in compliance with the Bulgarian State Standard (BSS) EN ISO 9001 and ISO/lec 17025:2005”, Sofia.

One chief expert has participated in a seminar “Struggle against fake medicines” in Strasbourg, France and the annual meeting of the European OMCL network, Rome, Italy.

One chief expert has participated in CHMP’s (EMEA) workshop in London.

Chief experts in CPEMD take part in working parties on the preparation of the Bulgarian pharmacopoeia and the preparation of lists with the Bulgarian names of active substances and excipients, for which there are monographs in the European pharmacopoeia.

Three SOPs have been prepared.

STAFF

In 2005 the number of people working in the Directorate was between 25 and 14 taking into account the fact that many people resigned, were retired and appointed. For a long period of time about 14 chief experts worked on the evaluation of the documentation (including the head of the “Evaluation” department and Director of the Directorate). This number is absolutely insufficient to perform the assessment activity within the time limits determined. The number of documentations submitted is increasing, while at the same time the number of evaluators is decreasing, therefore the number of documentations still not reviewed and transferred to the year 2006 is 313 (for authorizations, renewals and variations) – a fact which worries us a lot.

Another disturbing fact is that in the present pre-accession period the increased amount of current work does not allow us to master and practically apply

EMEA's and ICH's directions which are constantly being renewed and which guarantee the quality of the assessment work.

The assessment work is highly specialized and it takes a long period of training for each newly-appointed expert to be able to participate independently and fully in the work. This also necessitates undertaking urgent measures to increase the number of evaluators so that we could successfully cope with the increased amount of work and the new challenges we will be facing in 2006.

LABORATORIES AND EQUIPMENT

The Directorate has three 3 rooms for the evaluation of the documentation at its disposal and 2 for laboratory analysis. The basic problems are:

- there is no room to store the constantly increasing documentation which is used currently;
- there is an insufficient number of computers providing access to a data base;
- insufficient funds for purchasing new apparatuses – the available analytical apparatuses are old and cannot be qualified with regard to the future attestation.

The mixture of different types of documentation is also a problem.

PROPOSALS FOR THE SOLUTION OF CPEMD'S AND BDA'S PROBLEMS

Our forthcoming EU membership requires serious preparatory work in terms of amount and quality. Apart from that, the current work in the Directorate has increased in amount and new obligations have been assumed. Therefore it is necessary to:

- provide more staff for the evaluation of the documentation, the stipulated number of evaluators in the statutory rules is insufficient.
- To provide funds to purchase new analytical apparatuses, chemicals and reactives, computers.

- To continue the work on BDA's new premises which will solve the Agency's territorial problems as a whole. This will also solve CPEMD'S increasing difficulties to store the documentation and apparatuses.

A COMPARATIVE TABLE FOR THE EVALUATION OF THE DOCUMENTATION AND THE LABORATORY ANALYSIS IN 2004 AND 2005.

PROCEDURES	2005	2005	2005	2004	2004	2004
	SUBMITTED	APPROVED	NOT READ	SUBMITTED	APPROVED	NOT READ
AUTHORIZATION	512	324	72	434	372	
RENEWAL	650	490	74	207	196	
VARIATIONS	1662	1478	167	1371	1317	
TOTAL	2824	2292	313	2012	1885	88

	2005	2004
ANALYZED SAMPLES	551	603
ANALYSIS BETX	201	113

"MARKETING AUTHORIZATIONS OF MEDICINAL PRODUCTS" DIRECTORATE

1. Activity of the "Marketing authorizations of medicinal products" Directorate.

The basic activity of the "Marketing authorizations of medicinal products" Directorate (MAMP) is related to accepting, processing and assessment of the documentation of the medicinal products of different origin - chemical, herbal, homeopathic medicinal products, galenicals as well as issuing marketing authorizations, variations and renewals under the meaning of chapter 2 of PPSHMA.

In compliance with Decree 171 of 22 June 2005 of the Council of Ministers, published in state gazette No. 62 2005 for the amendment and supplementation of the BDA's statutory rules, adopted by virtue of Decree No.80 of the Council of Ministers of 2000 (publ. SG No.40, amend. No.89 of 2001), the MAMP Directorate:

- processes the documentation on the marketing authorizations of medicinal products, the renewal and variations of the marketing authorizations;
- fills in and maintains a data base of the medicinal products under procedure and a data base of the medicinal products having marketing authorizations;
- assesses the administrative, pharmaco-toxicological and clinical data from the dossier when authorizing the medicinal products, the summary of products characteristics and the packaging and leaflets of the medicinal products;
- organizes the work of the specialized committees under art. 21 of the PPSHMA; makes expert statements on marketing authorization, renewals and variations of the medicinal products;
- maintains and updates the register under art. 28 of PPSHMA;
- maintains the dossier registers of the medicinal products;
- approves the advertisements of the authorized medicinal products and controls their distribution;
- maintains and fills in a data base of the medical devices; evaluates the documentation required when granting a marketing authorization of medical devices;
- coordinates the import and makes proposals for issuing sales authorizations of medical devices.

The Directorate's duties also include:

- a preliminary evaluation of the documentation on the different types of procedures for marketing authorizations of medicinal products. After establishing deficiencies and incomplete information of the presented

documentation written directions are prepared for eliminating the latter within a 14-day time period.

- A final assessment of the marketing authorizations of MP documentation, which includes an expert assessment of the administrative, pre-clinical and clinical documentation and an assessment of the risk/benefit balance of the concrete medicinal product or medical device;
- Determining the belonging of the products;
- Participation in establishing a system for the registration, analysis and summary of incidents arising while taking the medicines and for undertaking the respective measures respectively;
- Taking part in the control of the manufacturers' and wholesalers' of medical devices activities, of the pharmacies and drugstores.
- Active participation on an expert level in working parties together with the Ministry of Healthcare and the Ministry of Economy for working out legislative regulations and secondary legislative regulations so as to bring the national legislation in line with the European one in the sphere of medicinal regulation and the Directives on medical devices;
- Participation in the work of the technical committee 69 "Medical devices" at the Bulgarian Standardization Institute related to the translation of standards. Participation, as active observers, in the activity of working parties at the European Commission and EMEA.

II. Current staff

The staffing level at the Directorate, according to an Annex to art.7, par.3 from the BDA's Statutory Rules is 26 full-time members. The activity of the Directorate is practically carried out by 18 employees (approximately 70% of the full-staff members).

The number of jobs under an employment contract – 2

The number of jobs under contracting arrangements – 17

The number of lead jobs – 1 for a director of directorate, 2 for head of a department, 2 – for head of sectors

Number of employees with an academic background – 19, 17 of which have a master's degree:

Medical doctors – 6

Master-pharmacists – 6

Engineer-chemists – 3

Chemists – 1

Biologists – 1

Specialists – 2.

DISTRIBUTION OF THE PLACES IN DEPARTMENTS ACCORDING TO THE EDUCATIONAL DEGREE

Director of MAMP

	Evaluation of documentation under the national procedures Department	Evaluation of documentation under the simplified procedures nCadreac department	Medicinal products department	Advertisement	Secretariat
Educational degree					
Medical doctors	2	1	1	1	

Master pharmacists	1	2	3		
Engineer - chemists			1		1
Biologists					1
Chemists					1
Specialists	1			1	

The jobs in the Directorate are distributed in 3 departments and 2 sectors:

- "Evaluation of documentation under the national procedures" department – 7, 4 of which actually function;
- "Evaluation of documentation under the simplified procedures nCadreac" department – 6, 3 of which actually function
- "Medical devices" department – 6, actually functioning – 3
- "Advertisement" sector – 3, 2 of which actually function;
- "Secretariat" sector – 3, 3 of which actually function;

During the reporting period one employee resigned – head of the "Evaluation of documentation under the national procedures" department.

One employee is in a continuous leave with the permission of the administration and two are in maternal leave.

The average age of in MAMP is approximately 40 years.

III. Activities.

Accepting and reviewing documents:

During the period 1 January 2005 – 30 December 2005, 3513 applications were submitted in MAMP:

-3134 of which are medicinal products, including medicinal plants, galenicals, homeopathic products, and applications (38) for the approval of packages under the terms and conditions of decree 7;

- 330 medical devices and groups;

- 49 products for determining their belonging, which were assessed in advance and distributed for a final assessment of their quality, efficacy and safety.

In the 14-day legally established time limit they were inspected for compliance with the legislative requirements, in accordance with the forms for inspection, applications for marketing authorizations, for the renewal of marketing authorizations, for variations in the marketing authorizations.

During the reporting period all submitted applications for marketing authorizations were inspected and when deficiency and incomplete information were established letters were sent to the applicant for their removal, which terminate the procedure.

The total number of the procedures for issuing marketing authorizations of MPs, terminated within the 14-day time limit, was 120; there were 44 for medical devices;

The evaluation of the applications started after the letters on the established deficiencies and incomplete information had received a satisfactory answer.

Forms for the check of the applications for the renewal of marketing authorizations and variations in the marketing authorizations (type I and II) were introduced as well. After establishing incompleteness in these procedures written directions for their removal were given.

During the reporting period after checking the applications for renewal of the marketing authorizations 60 letters with notes were sent.

After checking the applications for variation type I, 85 letters were sent and after checking the applications for variation type II – 20 letters.

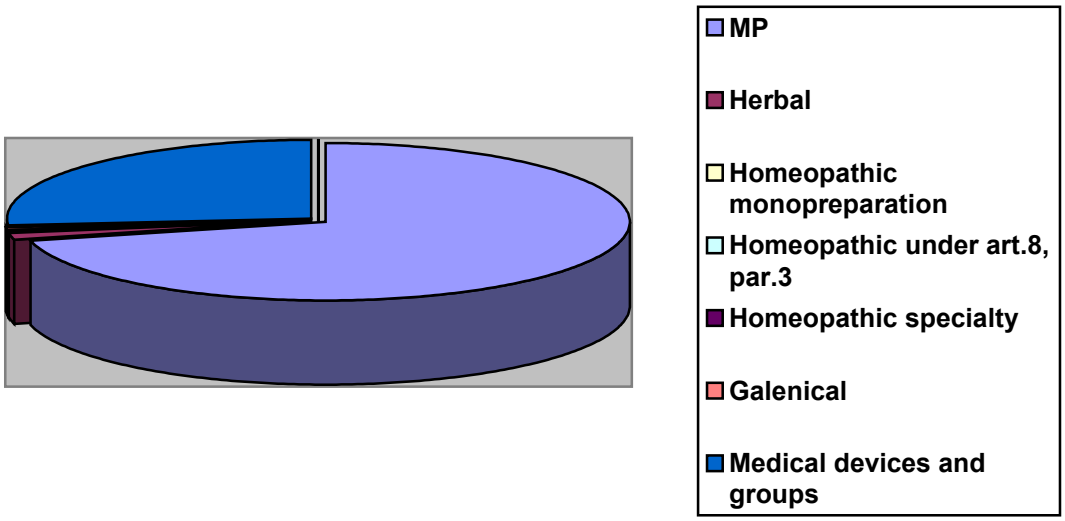
The employees in the Directorate sent to the applicants 74 letters with notes under the procedure for approving a model for secondary packaging. During the reporting period the following have been submitted to the directorate:

TYPE OF APPLICATION	TYPE OF PRODUCT	NUMBER	% of the total number of applications

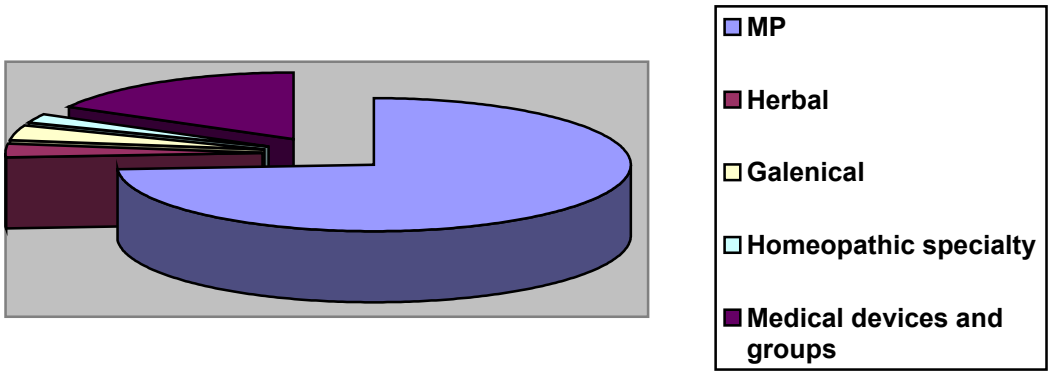
			(under a type of application)
Marketing authorization	Medicinal product	411	71%
	Herbal MP	8	1.4%
	Homeopathic monopreparation	0	
	Homeopathic MP, under art.8, par.3	0	
	Homeopathic specialty	2	0.4%
	Galenical	4	0.7%
	Medical devices and others	152	26.3%
Total number of applications for marketing authorizations		577	16.7%
Renewal of marketing authorizations	Medicinal product	550	74%
	Herbal MP	23	3.1%
	Homeopathic monopreparation	0	
	Homeopathic MP, under art.8, par.3	0	
	Homeopathic specialty	17	2.3%

	Galenical	28	3.8%
	Medical devices and groups	125	16.9%
Total number of applications for renewal of Marketing authorizations		743	21.5%
Variation of Marketing authorizations	Medicinal product	2047	95.5%
	Herbal MP	42	1.95%
	Homeopathic monopreparation	0	
	Homeopathic under art.8, par.3	0	
	Homeopathic specialty	2	0.09%
	Galenical	0	
	Medical devices and groups	53	2.5%
Total number of applications for variation of marketing authorizations		2144	61.8%
Total number of applications		3464	

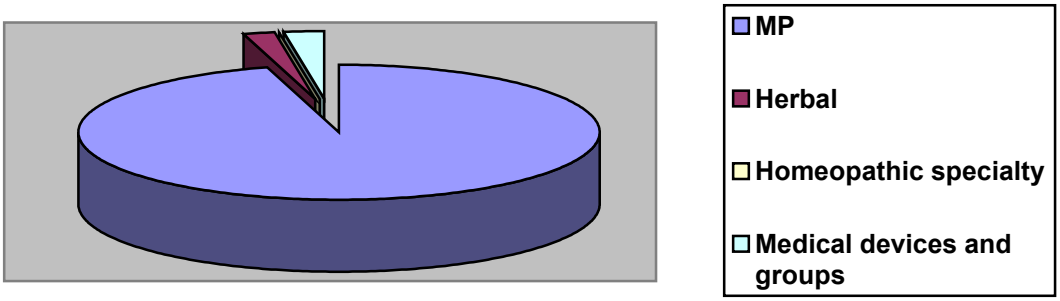
Graphic representation 1 Distribution of the applications for marketing authorizations according to the type of product



Graphic representation 2 Distribution of applications for the renewal of marketing authorizations according to the type of product



Graphic representation 3 Distribution of applications for variation of marketing authorizations according to the type of product



Part of the indicated applications for procedures follow the simplified nCadreac, centralized and mutual recognition procedures:

	NATIONAL		**CENTRALIZED**		**MUTUAL RECOGNITION**	
	number	%	number	%	number	%
Marketing authorization	236	73.6% of the applications for marketing authorizatio n	29	9.05% of the applications for marketing authorization	56	17.5% of the applications for marketing authorization
Renewal of marketing	500	90% of the applications	50	9% of the applications	-	-% of the applications

authorization		for marketing authorization		for marketing authorization		for marketing authorization
Variation of marketing authorization	1362	66.7% of the variation applications	579	28.4% of the variation applications	106	5.2% of the variation applications

Note: the application for renewal is a retrospective inclusion in the mutual recognition procedure

During the reporting period 292 applications in total for approval of advertisement materials have been submitted in MAMP.

Out of the total number of applications (292) – 140 are for advertisements intended for the population (39 audio-visual, 21 audio and 80 printed), while the rest 152 are to be published in specialized medical editions.

Out of the total number of applications (292):

- 45 for variation of an already approved advertisement (not included in EU)
- 247 new advertisements, 11 of which are reminders

During the reporting period 49 applications for determining the belonging of the products were submitted in MAMP.

During the reporting period the following letters were submitted to MAMP: 98 for medicinal products, 75 for medical devices with questions set before the BDA or related to the marketing authorization procedures.

Evaluation of the documentation

In compliance with art.13, p. 3, 8 and 10 of BDA’s statutory rules, MAMP:

Submits and processes and evaluates the documentation on the medicinal products and medical devices entering for marketing authorization;

Establishes a link with the specialized committees under art. 21 of the PPSHMA and with expert councils;

Approves and controls the distribution of the advertisements of medicines intended for both the specialized and mass editions.

During the reporting period an evaluation of the documentation on 1406 applications was done and in approximately 92% of the cases the documentation was returned for corrections.

Expert Council/chamber	**Meetings held**	**Products reviewed**	**returned for corrections**
chamber		743 out of which: 286 for marketing authorization 261 for renewal 24 for re-registration 172 for variations	
Expert Council on phyto-galenical products and homeopathy	22	119 (medicinal plants, galenicals, homeopathic products), out of which: 28 for marketing authorization 71 for renewal 3 for variations 17 reviewed and approved homeopathic products	
Council on marketing authorizations of	13	297, out of which: 149 for marketing authorization	

MP under art. 3, par. 3 and 5 of PPSHMA (Medical devices)		46 for variations in the marketing authorization 102 for renewal of the marketing authorization	
Expert Council on the approval of advertisements	24	247 evaluated advertisements 2 received refusals (under art.8. p. 16 of Decree No. 13) 2 acts for illegal advertisement of MP 0 orders for stopping the advertisement of MP 20 terminated procedures (due to expiry of the term under art. 11, par. 4 and art. 16, par.4 of Decree No. 13) 8 intended for the population 12 intended for medical specialists	

Evaluation of documentation in the Specialized committees

Specialized Committee	Meetings held	Products reviewed
SC for evaluation of the therapeutic efficacy and safety of medicinal products	21	1524, out of which: 243 for marketing authorizations under the national procedure 41 for marketing authorizations under the centralized procedure 35 for marketing authorizations under the mutual recognition procedure 19 for re-registration 311 for renewal of the marketing authorizations 452 for variation type I in the marketing authorization 328 for variation type II in the marketing authorization 3 refusals for variation type II (prescription status) 87 reviewed twice
SC for evaluation of the	11	101, out of which:

therapeutic efficacy and safety of medicinal products – phyto-galenicals and homeopathic		34 for marketing authorizations 48 for renewal of the marketing authorizations 19 for variation type in the marketing authorization 2 for variation type I in the marketing authorization 17 for variation type II in the marketing authorization
SC for evaluation of the medical devices	3	24 devices/groups, out of which: 6 for marketing authorizations 6 for variation in the marketing authorization 12 for renewal of the marketing authorizations
SC for determining the belonging of the products	13	147 evaluated documentations for determining the belonging of the products: 36 determined as

		medicines in compliance with the PPSHMA 41 products not determined as medicines in the meaning of PPSHMA 70 returned for providing additional information 3 letters – answers to questions

Marketing authorizations:

ISSUED ADMINISTRATIVE ACT	TYPE OF PRODUCT	NUMBER	% of the total number of administrative acts (according to the type of application)
Marketing authorization	Medicinal product	286	59.5%
	Herbal MP	16	3.3%
	Homeopathic MP	3	0.6%
	Galenicals	18	3.7%
	Medical devices/groups	156	32.5%
Total number of issued marketing		479	28.9%

authorizations			
Renewal of marketing authorization	Medicinal product	261	67.6%
	Herbal MP	20	5.2%
	Galenicals	23	5.9%
	Medical devices/groups	82	21.2%
Total number of renewed marketing authorizations		386	23.3%
Re-registration	Medicinal product	24	100%
	Herbal MP		
	Galenicals		
Total number of re-registrations		24	
Variation of a marketing authorization	Medicinal product	699	91.6%
	Herbal MP	20	2.6%
	Medical devices/groups	48	6.3%
Total number of issued marketing authorizations with variations		767	46.3%
Total number of issued administrative acts	1656		

Issued authorizations during the reporting period under the centralized and mutual recognition procedures

ADMINISTRATIVE ACT	CENTRALIZED		MUTUAL RECOGNITION	

	Number	% of all administrative acts (247)	Number	% of all administrative acts
Marketing authorization	38	15.4%	32	45.7%
Renewal of marketing authorization	37	14.8%		
Variation of marketing authorization	172	68.8%	38	54.34%

Refusals for granting marketing authorizations of MP – 3 (variation in the prescription status)

Termination of the marketing authorization of a MP at will and letters by the marketing authorization holder, for medical devices – 2.

Letters for corrections in the directions for use of the medical devices – 74

Letters for the suspension of the procedure on issuing a marketing authorization of medical devices – 2

Coordinated licenses for the import of medical devices – 3891

Issued sales authorizations - 409

Participation of experts from the “Medical devices” department in inspections – inspections of manufacturers (0), storehouses and pharmacies (51).

Check of alerts on not meeting quality requirements of the medical devices -1

Entering a data base

During the reporting period the data base is updated with information from the submitted applications for marketing authorizations, renewal of the marketing authorizations for use and for variations in the marketing authorizations. It is also updated with the issued marketing authorizations for use, for renewal, re-

registration and variation in the marketing authorization. The following data have been entered:

3134 applications for MP in total/330 for medical devices and groups

Keeping a register and record

2. In compliance with art.13,p.6 and 7 from BDA'a statutory rules the "Marketing authorizations of medicinal products" Directorate maintains and updates the register of the medicinal products authorized for use.

The register of the medicinal products, the biological products, the medical devices and the in vitro diagnostic devices is kept by one employee from the directorate who is responsible for storing the documentation in the record.

During the reporting period the following items were entered in the register:

Type of product	Marketing authorization	Renewal	Variation
MP	319	311	780
Phyto-galenical MP	28	71	3
Medical devices	156	82	48
In vitro medicinal products	80		6
Biological products	18	20	75

Participation of employees in the work of Expert Councils (EC) on phyto-galenicals and homeopathies – 2

Council on medical devices – 5

EC on advertisement approval – 3

Participation of employees from the directorate in Specialized Committees (SC)

SC on the assessment of the therapeutic efficacy and safety of medicinal products – 1, as secretary of the Committee.

SC on the assessment of the therapeutic efficacy and safety of medicinal products - phyto-galenicals and homeopathies – 1 employee, as secretary of the Committee and 1 employee as its member.

SC on determining the belonging of the product – 1, as secretary of the Committee.

SC on assessment of medical devices – 1 as secretary of the Committee and 1 employee as its member.

SC on clinical trials – 1 employee as its member.

Participation of employees from the directorate in working parties for the preparation of drafts of legislative regulations.

In compliance with art. 5, par. 2, p.26 of the BDA's statutory rules, MAMP performs expert and consultation activities in the sphere of medicinal regulation and control.

Regarding the latter experts participate in:

Working out an amendment in DECREE No. 17 OF 19 APRIL 2001ON THE REQUIREMENTS THE DATA INCLUDED IN THE DOCUMENTATION ON THE MARKETING AUTHORIZATION FOR USE OF MEDICINAL PRODUCTS SHOULD MEET – 2 employees;

The working out of a draft of a PHARMACEUTICALS AND PHARMACIES SERVING HUMAN MEDICINE ACT – 2 employees;

The working out of a draft of MEDICAL DEVICES ACT - 2 employees;

The work of the technical committee 69 "Medical devices" at the Bulgarian Standardization Institute, related to the translation of standards - 2 employees;

Participation of employees from the directorate in working parties of the European Commission

Standing Committee on medicinal products for human use
Advisory committee on the approximation of the laws of the member states relating to medical devices
Pharmaceuticals and medical devices
Market Surveillance Operation Group (MSOG)
Market Surveillance Operation Group (MSOG) + Notified Bodies Operation Group (NBOG)
Notified Bodies Operation Group (NBOG)
Notified Bodies Operation Group (NBOG) + Market Surveillance Operation Group (MSOP)
Medical Devices Expert Group (MDEG) – Classification and Borderline
Medical Devices Expert Group (MDEG) Vigilance
Medical Devices Expert Group (MDEG)

IX. Participation in compiling lists and references for the Ministry of Healthcare

During the reporting period employees from the directorate took part in working out lists of medicinal products for suspension of marketing authorizations for use, lists of medicinal products, the term of authorization of which has expired, as well as in the working out of references for the registration status of medicinal products.

X. Improving the qualification

Training course at Institute on Public Administration and European Integration: "European technical legislation (New approach Directives) introduction and readiness for implementation in Bulgaria" – 4 employees

English language course at the British Council – 11 employees

November 2005 – Grand Hotel Sofia – Medicinal regulation in the EU – requirements and standards for biological products – 5 employees

April 2005 – Grand Hotel Hilton – Medicinal regulation of generic products in South-east Europe – 2 employees

Specialization on “Clinical pharmacology and therapy” – 1 employee

June 2005 – report by BDA at the Fourth National Conference on Homeopathy - 1 employee

XI. International events

In compliance with art.5, par.2, p.26 of the Statutory Rules, BDA internationally cooperates with the World Health Organization (WHO), the European Commission – “Entrepreneurship and Enterprises” Directorate, with the regulatory and control bodies of other states and with the organizations working in the sphere of medicinal regulation and control.

BDA participated via its representatives, as active observers, in the work of the European Commission, in the following groups: Medical Device Expert Group (MDEG), Market Surveillance Operation Group (MSOG), MDEG Vigilance, MDEG – Classification and Borderline etc. Due to the complete change in the regulatory procedures that the new Medical Devices Act will impose, BDA’s participation in the work of the European Commission – working out and changing the practical directions for action, will provide the opportunity to attune the present experience to the new requirements.

Name	Event
Ivanka Atanassova	April 2005 – Skopje, Macedonia – GMP inspection – “Alcaloid” plant May 2005 Vienna, Austria – participation in a conference under the heading “Bioavailability, bioequivalence and dissolution” June 2005 – Rome, Italy, training of EU evaluators of the Heads of medicines Agencies “The evaluation of the clinical

	part of the dossier: focus on trial methodology and conduct" September 2005 – Edinburgh, Scotland – participation in the EMACOLEX meeting on regulatory problems September 2005, EMEA, London – participation in a meeting of EMEA on negotiating the PHARE program
Maryana Todorova	February 2005 in Strasbourg – Symposium on homeopathy "Quality of homeopathic products in the new European legislative framework" April 2005 in Zurich, Switzerland – Course on the topic "Introduction to European Regulatory Affairs to meet Drug Registration Procedure Guidelines" June 2005 in Rome, Italy. Training of EU evaluators of Heads of medicines Agencies "The evaluation of the clinical part of the dossier: focus on trial methodology and conduct" September 2005 – 60th meeting of COMP
Tzvetomir Delyiski	March 2005 in Erevan – Meeting of the WHO for the compilation of monographs of the most frequently used

	plants in the Black Sea region countries June 2005 in Colombo – Medicinal plants and other natural products – guidelines and development. September 2005 in London – meeting of Database & tracking TIG in EMEA December 2005 in Istanbul – GMP inspection of the "Mustafa Nevzad" plants in Turkey
Bilyana Georgieva	November 2005 – plenary workshop and training in London in the "Quality review of documents at EMEA" group
Detelina Ivanova	April 2005 – Grand Hotel Hilton - medicinal regulation of the generic products in south-east Europe April 2005 - in Zurich, Switzerland – Course on the topic "Introduction to European Regulatory Affairs to meet Drug Registration Procedure Guidelines" October 2005 – Iash Romania – GMP inspection – "Fabiola" plant, "Mark International" October 2005 regular workshop in London COMP November 2005 - regular workshop in London of PEG (pediatric committee).

Elena Chobanova Vessela Budinova	July 2005, Brussels – Meeting of the Medical Devices Expert Group (MDEG)
Elena Chobanova Vessela Budinova Maryana Kovacheva Todor Darakchiev	September/October 2005 in Nikosia – Workshop on Medical Devices: Best practices, market surveillance and vigilance, conformity assessment, classification and borderline issues
Vessela Budinova Maryana Kovacheva Todor Darakchiev	June 2005, Prague – Workshop on Medical Devices

Business trips in the country

Tzvetomir Delyiski – July 2005 – inspection of 37 pharmacies

Todor Darakchiev – inspections of 51 storehouses and pharmacies

Maryana Kovacheva – inspection of pharmacies

Problems in the Directorate

Insufficient staff. Necessity to fill in the vacancies with specialists with the appropriate qualification for expert work on the evaluation of the documentation.

Necessity of:

On-going training and specializations of employees from the directorate in the sphere of medicinal regulation in the medicines agencies from the CADREAC states and in the European Agency for the evaluation of medicines;

Participation in EU training projects on harmonizing the activities related to the surveillance of the market of the medical devices, assessment of the people evaluating the compliance of the medical device with the requirements they should meet, building a system for reporting, summary and analysis of incidents related to enforcing the provisions of the Medical Devices Act.

BDA’s joining a Twinning project with the European Agencies with the aim of exchanging useful information and experience with respect to the implementation of the European legislation on medicinal products and medical devices.

Providing a suitable equipment. The present premises of BDA does not allow for opening new jobs. Therefore it is necessary to speed up the process of housing in the new BDA premises.

Providing technical means – 6 computers, 2 printers, network equipment, in compliance with the requirements for access to the European data bases.

Urgently providing a room for storing the documentation:

- till an administrative act is issued;
- after an authorization is issued, for the records;

The establishment of an up-to-date record is a prerequisite for good storage of the documentation and a possibility to make quick references.

An up-dated assignment for changes in the electronic database, imposed by the new requirements set by the legislative and secondary legislative regulations. The pending changes in PPSHMA and the draft for a new Medical Devices Act necessitate a subscription so as to maintain an adequate and up-to-date data base.;

The “Biological products” Directorate should enter a database, “Medical Devices” module with the data for the in vitro diagnostic medical devices.

Still not developed by the “Import of medicines” department at the “Control of the manufacture and trade with medicines” department are the “Import and Sales” Module, and “Sales Authorizations” in data base – Medical devices module which does not provide the opportunity to make quick electronic references of the imported and authorized for sale types and quantities of medical devices

MEDICINAL INFORMATION AND PHARMACOVIGILANCE DIRECTORATE

Organizes and maintains a system for the registration, analysis and summary of adverse drug reactions and when necessary undertakes the respective measures;

Prepares an expert statement of the submitted periodical reports on the safety profile and other summarized data on adverse reactions of the medicinal products after they have been granted a marketing authorization for use;

Assesses the identified risk alerts and the related benefit – risk balance when taking medicinal products;

Proposes and carries out measures for communication and decreasing the risk when taking medicinal products;

Controls the activity of the marketing authorization holders under the pharmacovigilance system;

Issues specialized medicine-regulatory bulletins;

Checks and answers alerts by citizens and medical specialists regarding pharmacovigilance;

Coordinates and participates in the activities related to the European pharmacopoeia and the working out of the Bulgarian pharmacopoeia;

Maintains, stores and up-dates an information system of the European legislation on medicinal regulation;

Provides and up-dates information for the medicinal community on the issues related to rational pharmacotherapy;

Submits information falling under its competence to the governmental, non-governmental and other institutions;

Prepares summarized analysis of medicine consumption in the country;

Maintains and up-dates a list of the medicinal products which are prescribed OTC;

Performs coordination of the Directorates' and Agency's activities, related to European integration, the participation in activities related to the work of the international bodies, organizations and agreements, to which Bulgaria is a party;

Cooperates with the regulatory and control bodies of other states and with the organizations working in the sphere of medicinal regulation and control.

Full-time staff of the Pharmacovigilance Directorate:

By 31 December 2005 there were 13 full-time jobs in the directorate. All of them are for state employees. There is one department and two sectors within the structure of the directorate with the following names: “Medicinal information and euro-integration” department and the “Pharmacopoeia” and “Adverse drug Reactions” sector.

Staffing level by the end of the reporting period:

The reported activities are carried out by 7 employees with an academic degree (four medical doctors, two pharmacists and a bachelor).

Reports on adverse drug reactions (ADR)

A. During the reporting period 125 spontaneous reports on adverse drug reactions throughout the country were submitted to the Agency (Annex 1). Out of them: spontaneous reports sent to medical specialists – 70 – including 7 submitted on-line.

Via a printed copy of the Internet form of the Agency’s web-page – 15;

Via yellow cards – 22, Regional Inspectorate on protecting and control of public health, Ministry of Healthcare, National Center for contagious and parasite diseases – 26

Enhanced activity has been observed after decree No.2 on immunization and obligatory reports of adverse reactions related to immunizations by BDA’s Regional Inspectorate on protecting and control of public health and the Ministry of Healthcare came into force (in 2004 – 11 reported cases).

There are 60 reports on serious ADR, two of the validated reports are on unexpected ADR.

Spontaneous reports submitted by marketing authorization holders – 55

Indicator	2005	2004	2003	2002	2001	2000
Reports on ADR form	125*	172	111	120	80	95

Bulgaria – total number						
Spontaneous reports by medical specialists	70	123	69	101	70	90
Spontaneous reports by marketing authorization holders	55	49	42	19	10	5

The majority of the reports (the reports submitted by medical specialists from the country and by Bulgarian manufacturers have priority) *are included in the register* on adverse reactions within five working days on average. There is some delay regarding the reports by the marketing authorization holders from outside the country because of the presence of incomplete data in the reports.

15 *letters confirming the receipt* of the reports by medical specialists were sent – within the period of five working days on average.

The validation of the reports by the medical specialists regarding the obligatory minimum of data was made within a period of ten working days on average. When necessary *supplementary information* was required (in writing or via telephone), necessary to validate and/or analyze the case. There was delay in 24% of the cases submitted by the marketing authorization holders because the presence of incomplete data.

The valid reports were coded and *filled in the module* on ADR in BDA's data base.

The reports were classified according to the *criteria for serious* adverse reactions within the period of ten working days after the receipt of the minimum data.

The marketing authorization holder(s) of the suspected medicine was/were *informed* about 10 (in 2004 – 6) spontaneous reports on ADR submitted by medical specialists within the period of 10 calendar days after the validation of the report.

All reports, meeting the requirements for *submission to WHO* are sent within the periods set in the agreement – every three months.

B. Registered reports on serious and unexpected ADR observed in *other countries* –

982 letters were received by approximately 70 marketing authorization holders (for 2004 the letters were 749 by approximately 70 marketing authorization holders).

Enhanced activity has been observed after decree No. 26 came into force.

Periodical reports on pharmacovigilance:

Priority was given to the assessment of the periodical reports on pharmacovigilance as summaries of the whole information on the observed ADR for the individual products within the specified periods. The tendency registered in the last years of an increase in the number of periodical reports submitted to the department continued – there were 785 reports by 100 marketing authorization holders (Annex 3).

Indicator	2005	2004	2003	2002	2001	2000
Submitted periodical pharmacovigilance reports	785	705	594	497	89	150
marketing authorization holders	100	78	47			
Letters –	21*	47	30	48	13	7

according to INN on the requirement for variations after assessment of periodical safety report						
Submitted variations within a year's period	6	15	8	68		2

The assessed periodical safety reports for the reporting period are 548 (together with the 63 non-assessed reports left over from the previous period their number increases to 611). 237 periodical reports submitted in 2005 have not been assessed yet.

The assessment made by the periodical safety reports on 70 medicinal substances necessitated up-dating the approved information of the product.

*Consequently 21 letters have been sent to the marketing authorization holders and 6 respective procedures for variation within the same year have been initiated.

The periodical pharmacovigilance reports *are entered* in BDA's data base within a period of five working days after the receipt. This provides access to up-dated information on all submitted periodical safety reports of the experts using the data base before the assessment of the report by the experts from the department is made.

Up-dating the information for the medical specialists on the issues related to rational pharmacotherapy.

The data on the approved therapeutic indications of the medicinal products, newly-authorized in the country, containing unfamiliar active substances and combinations were prepared and sent to the medical specialists (by April 2005).

An explanation on the ATC coding was prepared for the same medicines. The data on all variations in the marketing authorizations, presenting a variation of the approved indications – elimination of certain indications or defending a new indication for the same period – were prepared and sent. Two summary articles presenting new opinions on the treatment, worked out according to the principles of independent medicinal information (ISDB), more specifically a comparative and critical view on all alternatives, were prepared. Also information on the national tendencies in the use of medicines was prepared, there were no advertisements.

The editions in which the information is published are financed only by BDA and are distributed for free to about 2500 addressees only after showing a feedback ticket. During the reporting year two bulletins were issued, 8 pages A4 format each. The first issue of these bulletins dates back to 1 May 1994. There is an electronic version of these bulletins which has been published on BDA's web page since 2001 to which there is free access.

Materials were prepared for 2 editions of bulletins on ADR (4 pages format A4 each) addressed to 2500 addressees in the healthcare network. The two bulletins are not only sent but also published on the Agency's web page with a free access.

Information for the medical specialists on topical problems of pharmacovigilance is also published – 12.

Year	2005	2004	2003
Number of reports on internet	12	5	12

A list of the authorized for use OTC medicinal products is kept. It is up-dated periodically (every month) and is provided at free access on the web page.

Issuance of specialized bulletins on medicinal regulation.

Electronic versions of the hard copy bulletins on newly-authorized medicinal products and regulatory changes were published on the Agency's web page at free access every month.

Year	2000	2001	2002	2003	2004	2005
Frequency of publication	-	-	monthly	monthly	monthly	monthly
Hyperlink for the indications and ATC for the new substances	-	-	-	+	+	+

Answers to alerts made by citizens on pharmacovigilance problems:
Answers to all (14) questions (for 2004 -11) put in writing by patients and medical specialists on pharmacovigilance problems were provided.
Upon the request of marketing authorization holders 36 references (for 2004 -30) on spontaneous ADR reports of 154 medicines (for 2004 -93) submitted to BDA were prepared for a period of up to 5 years.

Indicator	2005	2004	2003	2002	2001	2000
References sent to MAH on submitted ADR	36	30	11	11	12	15
Number of the medicinal products in the references	154	93	43	46	31	

Other correspondence and references on pharmacovigilance problems – 52 letters of notification and those requiring an answer were received in total (in 2004 -24).
Working out annual analyses of the pharmaceutical market for 2005:

- Analysis of the dynamics of the medicinal products authorized for use
- Analysis of the import and the local manufacture of the Bulgarian pharmaceutical market in value and number of packages for products, manufacturers and pharmacological groups.
- Analysis of the 100 international names of the least administered medicines belonging to them.
- Consumption of medicines data in Bulgaria presented in compliance with the DDD/1000/per day methodology. A reevaluation is made only in the JO1 group with respect to our duties to EARSS.
- Publication of the part of the annual analysis for 2004 of the pharmaceutical market:

A. Ratio between the sales of Bulgarian vs the sales of imported products – analysis in value

B. Ratio between the sales of Bulgarian vs the sales of imported products – analysis in sales volume

C. Ratio between the sales of prescription medicines vs those administered free – Bulgarian and imported, analysis in value

D. Ratio between the sales of prescription medicines vs those administered free – Bulgarian and imported, analysis in sales volume.

Year	2000	2001	2002	2003	2004	2005
OTC Medicines	-	-	+	+	+	+
Medicines which have dropped out from a marketing authorization				+	+	-
Realization of the medicinal products on the Bulgarian market by local			+	+	+	+

manufacturers – monthly and annual data						
Addresses of the recipients of the “Medicinal Bulletin” and “Adverse Drug Reactions” bulletin	+	+	+	+	+	+
Questions put forth before the recipients of the “Medicinal Bulletin” and “Adverse Drug Reactions” bulletin	+	+	+	+	+	+

Working out of references, answers to letters and inquiries.

Answers to 96 inquiries in writing have been prepared out of which

21 via e-mail.

17 to the Ministry of Healthcare

45 answers of letters form agencies, medical specialists and citizens were provided.

An answer to a questionnaire required by the WHO regarding information on the whole spectrum of the regulatory activity was provided. The task was fulfilled via coordinating the answers provided by all directorates in BDA.

Answers were provided to questions raised by citizens, medical specialists and others working in the pharmaceutical sector; assistance was provided falling under its competence to the press center of the Ministry of Healthcare – 8 inquiries a day on average.

Coordination and participation in the activities related to the European pharmacopoeia and the development of the Bulgarian pharmacopoeia (pharmacopoeia secretariat):

Getting acquainted with the current documents received by the Secretariat of the Commission of the European pharmacopoeia regarding the working out of pharmacopoeia standards (more than 3 000 documents in 2005) and where necessary – assessment and delivery of the required information, as well as storage of the necessary documents.

Informing the interested departments in BDA on approved monographs, methods of analysis, standard terms, standard substances and tendencies when working out the pharmacopoeia standards.

Participation in two joint surveys of the European pharmacopoeia and the Quality Working Party (QWP) at EMEA on the level and qualification of admixtures present in medicinal products on the Bulgarian market related to establishing the respective criteria for the receipt of admixtures in the pharmacopoeia monograph.

Participation in surveys on the inclusion or deletion of monographs or methods of analysis in the work plan of the European pharmacopoeia or for the development of new standard terms of the European pharmacopoeia – 18;

Translation and coordination within BDA, the expert group on standard terms at the pharmacopoeia committee and the Institute for control of the veterinary-medicinal substances of the new standard terms and their definitions, as well as the combination of standard terms for human and veterinary medicine, approved by the Commission if the European pharmacopoeia in 2005 were made. Current consultation of BDA experts, manufacturers and companies related to the adopted new standards. Up-dating the list of standard terms for pharmaceutical forms, route of administration and packaging for human and veterinary medicine: in alphabetical order, intended for the internet web page of the Agency; depending on the route of administration of the pharmaceutical forms accompanied by explanatory notes of definite standard terms – to be published in the Bulgarian pharmacopoeia.

Compiling lists with the names of active substances and excipients and preparations (in English, Latin and Bulgarian), for which there are monographs in

the fifth edition of the European pharmacopoeia (up to supplementation 5.5). The Bulgarian names of the substances are also necessary with respect to the requirement of art. 63 of the 83/2001 Directive of the EU "*all obligatory data on the packaging and leaflet of the medicinal product, including the names of the substances should be in the official language of the respective member-state*", in which the product is sold.

The lists were prepared by a working party, the major participants in which were: from the "Chemical-pharmaceutical expertise of medicines" directorate (Dafina Marinkeva, Diana Dimitrova, Violeta Lyuleva, Sonya Ivanova, Margarita Georgieva), from the "Biological products" directorate (Elena Zhelyazkova), and from the Pharmacopoeia sector (Lyuba Kostova), chief editor was Lyuba Kostova.

Updating of texts translated by the European pharmacopoeia for the Bulgarian pharmacopoeia (10 texts and monographs);

Translation of monographs and general texts for the Bulgarian pharmacopoeia (6); correspondence on pharmacopoeia issues with the Ministry of Healthcare, the secretariat of the European pharmacopoeia, the Institute for the control of veterinary preparations, other pharmacopoeia committees – 65 letters and reports.

Publication of the information on BDA's web page in the "pharmacopoeia" section on standard terms, a schedule for entry into force of the supplementation to the fifth edition of the European pharmacopoeia with the respective orders for its introduction on the territory of Bulgaria etc. BDA's subscription for the European pharmacopoeia, Pharmeuropa, USP 29/NF 24 and BP 2005.

Activities related to European regulatory acts (up to September 2005).

Current up-dating of the available regulatory acts related to the quality of medicines, published on the web page of EMEA, the European Commission, the International Conference on harmonizing the technical requirements (ICH), FDA/CDER, the Medicines Agency of Canada etc, which includes:

Direction of the QWG and other directions of SWP, IWP etc. related to the quality;

Notice to applicants – volumes 2A, 2B, 2C;

Current EU directives and decree;

Materials and symposia of the European pharmacopoeia;

1. New revised directions of the Medicines Agency of Canada related to the quality of medicines.
2. Up-dating the lists with the current regulatory acts and directions.
3. Preparing short reports related to the new European documents for BDA's information board:

Information on EMEA's new documents – 7

Information on new documents of the European Commission – 5;

4. Current references to the European regulatory acts and consultation with BDA's employees related to the current activity and working out of legislative and regulatory acts;
5. A coordinated translation of the harmonized samples of EMEA for the summary of the products characteristics, packaging and leaflet of the medicinal products and the respective reference documents, related to the pre-accession linguistic check of the medicinal products, authorized for use under the centralized procedure of the European Union. This check started in relation to the forthcoming membership of Bulgaria in the European Union.

Activities related to the working out of Bulgarian regulatory acts.

Participation in the working parties on the working out of a PPSHMA – 4 employees;

Participation in the working parties on the working out of a the law on blood, blood transfusion and blood donation – 1 employee;

Decree No. 26 on reporting ADR - 2 employees;

Decree on the terms and conditions of authorizing medicinal products for the treatment of rare diseases (correspondence table) - 1 employee;

Decree on the amendment and supplementation of Decree 7/2000 on the obligatory data on the packaging and leaflets and to the directions for the use of medical devices – 2 employees;

Decree on the amendment and supplementation of Decree 17/2001 on the requirements set to the data contained in the documentation for granting marketing authorizations for medicinal products - 1 employee;

Decree 34/25 November 2005 on the terms and conditions of covering the cost by the central budget of the medical treatment of Bulgarian citizens for diseases beyond the scope of mandatory health insurance - 1 employee.

Other activities performed by the Pharmacovigilance directorate

Preparation of statements related to the implementation of Decree No. 2 – 289 statements for the reporting period.

Year	2000	2001	2002	2003	2004	2005
Number of statements issued	-	-	153	98	123	289

Coordination of import of homeopathic medicinal products

22 import authorizations for medicinal products have been coordinated with experts from the department during the reporting period.

Participation of the experts from the directorate in the assessment of medicinal products in the course of the procedures on authorization, renewal and variation. All but one employee in the directorate, the latter having a degree in information technologies, participate throughout the whole year in the assessment of medicinal products in the course of the procedures on authorization, renewal and variation. The specialists with a medical degree are included in the assessment of the chemical medicinal products, the phyto-galenicals and herbal products, as well as in the chemical-pharmaceutical part. For instance, from the pharmacovigilance sector 323 dossiers of medicinal products have been assessed by three experts

under different procedures (herbal, galenicals and homeopathic products are included).

Participation in committees and other advisory structures:

- Committee on the prices of medicinal products - 1 employee.
- Committee on the assessment of the therapeutic efficacy and safety - 1 employee.
- Committee on the assessment of the therapeutic efficacy and safety - phyto-galenicals and herbal products - 1 employee;
- Committee on determining the belonging of the products - 1 employee;
- Committee on the positive medicinal list - 1 employee as a member and one performing expert functions;
- Pharmacopoeia committee – scientific secretary, head of an expert group on standard terms and member of the chemical, technological and pharmaco-diagnostic expert group at the Pharmacopoeia committee - 1 employee;.
- Expert Council on phyto-galenicals and herbal products – 3 employees, one of which is the head (after June, there will be two, because Toncheva, MD will take a maternal leave).

Specializations.

- Completed qualification course at WHO in Upsala, Sweden on pharmacovigilance - 1 employee from the pharmacovigilance sector;
- Participation in a meeting with an expert from WHO, with the aim of assessing how the program on the elimination of measles and inborn fire measles is worked out - 1 employee from the pharmacovigilance sector;
- Completed English language course at the British Council with a certificate – 2 employees form the Pharmacovigilance sector (One of the two employees completed an English language course at the BBC with a certificate)

- Participation in a seminar – “Pharmaceutical regulation in the European Union – requirements and standards for the biological products” – 6 employees
- Participation with a report in Albena in the 4th National Conference on Clinical Homeopathy - 1 employee from the Pharmacovigilance sector.

Participation in the work of international regulatory bodies, conferences and other international and national forums

- Participation (as active observers) in EMEA’s working parties – 4 employees

1. Pharmacovigilance working party (PhVWP) - 2 employees

Quality Review of documentation working party (QRD) - 1 employee;

Pre-clinical pharmacovigilance working group -1 employee;

Quality Working Group – by June 2005 -1 employee;

- Participation (as a member) in the work of the European Pharmacopoeia Commission -1 employee (3 meetings)
- Participation in the annual meeting of the national Pharmacopoeia committees’ secretaries - 1 employee;
- Presented report at the World annual congress in Prague under the heading “Internet and Medicine” - 1 employee form the Pharmacovigilance department;
- Presented report at a seminar (certificate) Herbal Medicine, Phyto-pharmaceuticals and other natural products: Trends and advances, Colombo, Sri Lanka – 1 expert from the Pharmacovigilance sector
- Participation in a conference on Environmental Risk Assessment
- Participation in a conference on Quality of homeopathic products in the new European legislative framework, Strasbourg, France - 1 employee from the Pharmacovigilance sector

- Participation via providing data on the usage of antimicrobial medicines, expressed as DDD/1000/per day on the participation of Bulgaria in the EARSS system (European antimicrobial resistance surveillance system).
- Assistance was provided related to the activities on signing the PALC2 agreement.
- Cooperation is provided when necessary on international events.
- Presentations at the annual meeting of manufacturers – 2 employees.
- Delivery of a lecture on the topic of "Advertisement of medicines and ethics";
- Preparation of two lectures on the topic "Medicinal information and information on the treatment of patients: BDA's experience" and "Medicinal usage and rational medicinal usage on a macro-level";

Necessary actions in order to optimize the directorate's activity

- Profiling the experts-evaluators from the Pharmacovigilance Directorate to assess especially the procedures on variation type II and renewal, which are related to a large extent with the assessment of the safety profile.
- Establishing cooperation with the Bulgarian Union of Medical Doctors in the working out of directions on the ongoing medical qualification under Decree No. 30 of the Ministry of Healthcare on including the submission of ADR reports in the possible forms of maintaining qualification.
- Consultations with the Ministry of Healthcare on including the frequency of submitting ADR reports in the attestation criteria of the medical activity of medical institutions.
- Cooperation with the National Health Insurance Fund on supplementing the protocol for prescribing expensive medicines on a form for reporting ADR which have led to a change in the therapy.

- Participation of experts from the department in training on the problems of pharmacovigilance for students from the Medical University in Sofia and in the courses organized by the National Institute on Contagious and Parasite Diseases on the issues of reporting ADR related to vaccines.
- Establishing closer contacts with medical specialists submitting ADR reports and developing motivational tools.
- Translating in Bulgarian and approving the form for reporting ADR with the aim of providing assistance to Bulgarian manufacturers.
- Participation in inspections controlling the fulfillment of the monitoring the safety of medicines requirements in compliance with art. 91, par. 3 of the PPSHMA – the Bulgarian marketing authorization holders have priority.
- Up-dating the ADR module in BDA's data base, including reaching compliance with the international standards on electronic exchange of information – ICH E2B (M).
- Regarding the necessity to implement the new MEDRA terminology which presupposes using the 10^{th} international classification of diseases (we are now using the 9^{th}), as well as working out an electronic data base on the serious and unexpected ADR from abroad and their electronic filing it is necessary for us to have access to an IT specialist – it is possible to have a specialist from outside the Agency working under a contract. It is necessary to improve the qualification of the employees in training courses on MEDRA.
- Experience exchange with other agencies;
- We need assistance in order to attract academic clinical specialists in the process of working out and edition of the "Medicinal bulletin".
- It is necessary to provide information sources on medicinal products consumption on the territory of Bulgaria in the future medicinal

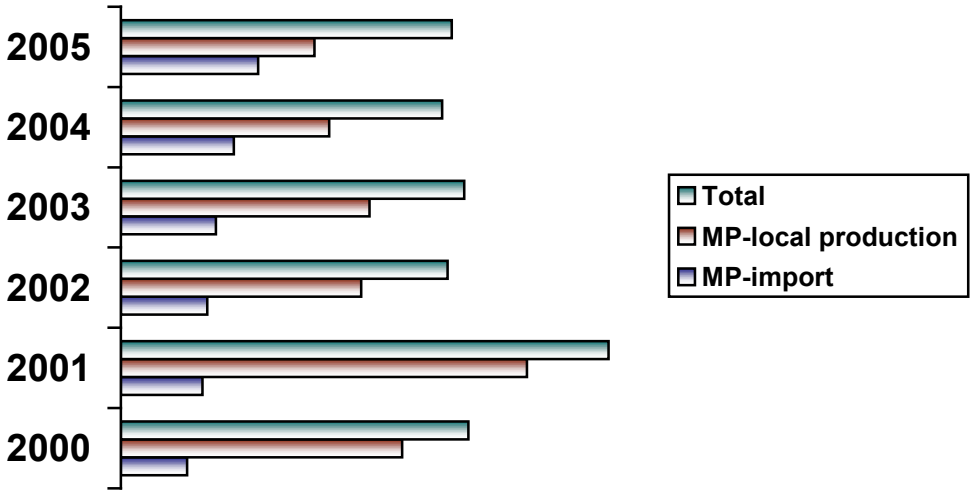
legislation so that BDA can perform its assumed duties according to the statutory rules.

- Financing the work of the Pharmacopoeia Committee and its expert groups;
- We consider it necessary to further cooperate with the Institute on Veterinary – medical substances with the aim of working out some Pharmacopoeia monographs.

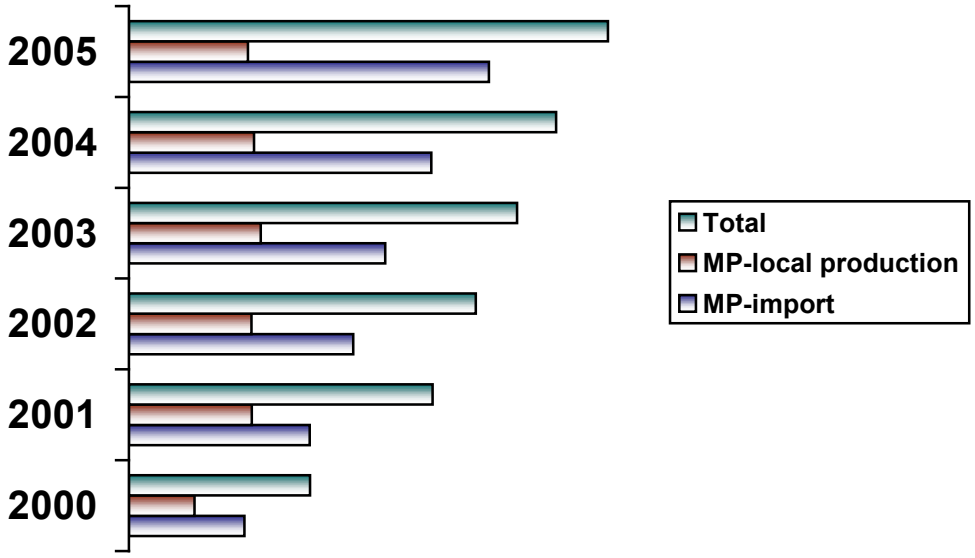
Year	Number of packs from import	Number of packs from local production	Total number of packs from import + local production	Value of the pharm. market from import /BGN	Value of the pharm. market from local production /BGN	Total value of the pharm. Market from import + local production /BGN
1999	27 351 817		27 351 817	160 463 117	128 000 000	288 463 117
2000	31 538 127	133 733 785	165 271 912	185 224 658.7	10 531 3472.7	290 538 131.4
2001	38 815 861	193 195 158	232 011 019	289 861 697.6	197 221 137.7	487 082 835.3
2002	41 089 372	114 344 794	155 434 166	359 661 386.3	196 415 953.4	556 077 339.7
2003	45 133 674	118 232 058	163 365 732	410 920 392	211 213 684.3	622 134 076.3
2004	53 743 511	99 072 950	152 816 461	484 638 822.6	200386700.1	685 025 522.7
2005	65 245 245	92 121 860	157 367 105	577 063 349	190 910 392.49	767 973 741.4

The realization of the Bulgarian manufacturers is based on data from: Sopharma; Balkanpharma Dupnitza; Balkanpharma Troyan; Balkanpharma Razgrad; Unipharma; Bul Bio NICPD; Pharmaceutical enterprises – Milve; Adipharm Institute on hemodialysis and transfusion; Chemical Pharmaceutical Research Institute.

Realization of medicinal products by number of packs in the period 2000-2005 in Bulgaria



Realization of medicinal products according to the value in BGN in the period 2000-2005 in Bulgaria



THE FIRST TEN TRADE NAMES BY NUMBER OF PACKS

Trade name and pharmaceutical form	INN	ATC-code	Manufacturer	State	Prescription status	Number of packages
ANALGIN tabl. 500 mg x 20	Metamizole sodium	N02BB02	SOPHARMA	Bulgaria	Over-the-counter prescription (OTC)	796 1245
ATENOLOL tabl. film. 25mg x 30	Atenolol	C07AB03	BALKANPHARMA-DUPNITZA	Bulgaria	Prescription only medicine (POM)	2148658
CORVITOL 50 tabl. 50mg x 30	Metoprolol	C07AB02	Berlin-Chemie AG Menarini Group	Germany	POM	2004420
NATRIUM CHLORATUM sol. Inf.0.9% - 500 ml-pl.	Sodium chloride	B05CB01	BALKANPHARMA-TROYAN	Bulgaria	POM	1829410
ANTISTENOCARDIN tabl. 25mgx60	Dipyridamole	B01AC07 C01DX00	SOPHARMA	Bulgaria	POM	1820910
FURANTHRIL tabl. Subling. 60mgx 20	Furosemide	C03CA01	BALKANPHARMA-DUPNITZA	Bulgaria	POM	0687370
RENAPRIL tabl. 5mgx 28	Enalapril	C09AA02	BALKANPHARMA-DUPNITZA	Bulgaria	POM	1507948
VALIDOL tabl. Subling. 60mg x 20	Menthyl valerate	N05CM09	Farmak	Ukraine	OTC	1501739
PARACETAMOL tabl. 500mgX 20	Paracetamol	N02BE01	SOPHARMA	Bulgaria	OTC	1421434
RENAPRIL tabl. 10mgx 28	Enalapril	C09AA02	BALKANPHARMA-DUPNITZA	Bulgaria	POM	1389315

THE FIRST TEN TRADE NAMES IN VALUE

Trade name and pharmaceutical form	INN	ATC-code	Manufacturer	State	Prescription status	Total value
ANALGIN tabl. 500 mg x 20	Metamizole sodium	N02BB02	SOPHARMA	Bulgaria	OTC	8040682.53
PREDUCTAL MR tabl. Modif. 35mgx 60	Trimetazidine	C01EB15	Les Laboratories Servier	France	POM	7809232.50
AMOPEN caps. 500mgx 20	Amoxicillin	J01CA04	BALKANPHARMA-RAZGRAD	Bulgaria	POM	7482804.96
TERTENSIF SR tabl. Prolong. 1.5 mg x 30	Indapamide	C03BA11	Les Laboratories Servier	France	POM	7431058.12
AVANDIA tabl.film 4 mg x 28	Rosiglitazone	A10BG02	SmithKline Beecham Plc.	Great Britain	POM	5484365.84
SEROQUEL tabl.film 200mg x 60	Quetiapine	N05AH04	AstraZeneca UK ltd.	Great Britain	POM	5206074.08
CORVITOL 50 tabl. 50 mg x 30	Metoprolol	C07AB02	Berlin-Chemie AG Menarini Group	Germany	POM	4952374.79
ZYPREXA tabl. coat. 10 mg x 28	Olanzapine	N05AH03	Eli Lilly Export S.A.	Switzerland	POM	4703084.69
ENTEROL powd. 250 mg x 10	Saccharromyces boulardii	A07FA01	Laboratoires Biocodex	France	OTC	4581211.58
VIAGRA tabl. Film. 50 mg x 4	Sildenafil	G04BE03	Pfizer HCP Corporation	USA	POM	4554547.92

Companies – manufacturers/from import/with the highest market shared/in value – in English

F.Hoffmann-La Roche Ltd.	32 242 723.10
Novo Nordisk A/S	31 868 339.07
Les Laboratories Servier	26 037 359.02

Berlin-Chemie AG Menarini Group	25 759 476.01
Novartis Pharma Services Inc.	25 584 226.4
Glaxo Group Ltd.	25 346 803.28
Bristol-Myers Squibb Co.	21 340 053.11
Pfizer HCP Corporation	19 821 914.59
Sanofi-Synthelabo France	17 787 294.18
Janssen-Cilag International NV	16 822 793.25
AstraZeneca UK Ltd	15 675 244.49
Baxter S.A.	14 739 714.25
Eli Lilly Export S.A.	14 006 784.3
Boehringer Ingelheim International GmbH	12 462 008.43
SmithKline Beecham Plc.	11 754 031.47

THE FIRST TEN TRADE NAMES BY NUMBER OF PACKS FROM IMPORT

Trade name and pharmaceutical form	INN	ATC - code	Manufacturer	State	Prescription status	Number of packages
CORVITOL 50 tabl. 50 mg x 30	Metoprolol	C07AB02	Berlin-Chemie AG Menarini Group	Germany	POM	2004420
VALIDOL tabl. Subling. 60MG X 20	Menthyl valerate	N05CM09	Tarmak	Ukraine	OTC	1501739
ASPERAN tabl. Film 325mgx100	Acetylsalicicylic acid	N02BA01	Perrigo Company	USA	OTC	1110648
SIOFOR 850 tabl. Film 850mg x 30	Metformin	A10BA02	Berlin-Chemie AG Menarini Group	Germany	POM	1054955
BERLIPRIL 10 tabl. Aomg x 30	Elanapril	C09AA02	Berlin-Chemie AG Menarini Group	Germany	POM	996442
TERTENSIF SR tabl. Prolong. 1.5 mg x 30	Indapamide	C03BA11	Les Laboratories Servier	France	POM	981538
FERVEX ADULTS gran. X 8	Combination	R05X00	Bristol-Myers Squibb Co.	France	OTC	88061
UPSARIN C tabl. Eff. X 20	Combination	N02BA51	Bristol-Myers Squibb Co.	France	OTC	868579
XYLOMETAZOLIN drops nas. 0.1% x 10ml	Xylometazolin	R01AA07	Ciech Polfa	Poland	POM	857807
CORINFAR 20 RETARD tabl. Prolong. 20mgx30	Nifedipine	C08CA05	AWD. Pharma GmbH & Co. KG	Germany	POM	804028

THE FIRST TEN TRADE NAMES BY NUMBER IN VALUE FROM IMPORT

Trade name and pharmaceutical form	INN	ATC - code	Manufacturer	State	Prescription status	Total value
PREDUCTAL MR tabl. modif. 35mgx 60	Trimetazidine	C01EB15	Les Laboratories Servier	France	POM	7809232.50
TERTENSIF SR tabl. Prolong. 1.5 mg x 30	Indapamide	C03BA11	Les Laboratories Servier	France	POM	7431058.12
AVANDIA tabl.film 4 mg x 28	Rosiglitazone	A10BG02	SmithKline Beecham Plc.	Great Britain	POM	5484365.84
SEROQUEL tabl.film 200mg x 60 (combined package)	Quetiapine	N05AH04	AstraZeneca UK ltd.	Great Britain	POM	5206074.08
CORVITOL 50 tabl. 50 mg x 30	Metoprolol	C07AB02	Berlin-Chemie AG Menarini Group	Germany	POM	4952374.79
ZYPREXA tabl. coat. 10 mg x 28	Olanzapine	N05AH03	Eli Lilly Export S.A.	Switzerland	POM	4703084.69
ENTEROL powd. 250 mg x 10	Saccharromyces boulardii	A07FA01	Laboratoires Biocodex	France	OTC	4581211.58
VIAGRA tabl. Film. 50 mg x 4	Sildenafil	G04BE03	Pfizer HCP Corporation	USA	POM	4554547.92
GUTTALAX drops 7.5 mg/ml – 15ml	Sodium picosulphate	A06AB08	Boehringer Ingelheim International Gmbh	Germany	OTC	4297849.73
SOLIAN tabl. Film 400mg x 30	Amisulpride	N05AL 05	Sanofi-Synthelabo France	France	POM	4201770.11

Companies – manufacturers/form local production/with the greatest market share/in value

1. BALKANPHARMA - DUPNITZA	78 090 040.20
2. SOPHARMA	61 977 893
3. BALKANPHARMA - TROYAN	11 014 782.69
4. UNIPHARM	9 025 767.00
5. BALKANPHARMA - RAZGRAD	17 485 450.71
6. PHARMACEUTICAL ENTERPRISES “MILVE” joint stock company	750 918.00
7. ADIPHARM single person joint stock company	73 355.59
8. INSTITUTE FOR HEMATOLOGY AND TRANSFUSION	435 724
9. CHEMICAL PHARMACEUTICAL RESEARCH INSTITUTE	5697432.30
10. BUL BIO	7109947

THE FIRST TEN TRADE NAMES BY NUMBER OF PACKS FROM LOCAL PRODUCTION

Trade name	INN	ATC – code	Manufacturer	Prescription status	Number of packages
ANALGIN tabl. 500 mg x 20	Metamizole sodium	N02BB02	SOPHARMA	OTC	7961245
ATENOLOL tabl. film. 25mg x 30	Atenolol	C07AB03	BALKANPHARMA-DUPNITZA	POM	2148658
NATRIUM	Sodium	B05CB01	BALKANPHARMA-	POM	1829410

CHLORATUM Sol.inf.0.9% - 500ml - pl	chloride		TROYAN		
ANTISTENOCARDIN tabl. 25mgx60	Dipyridamole	B01AC07 C01DX00	SOPHARMA	POM	1820910
FURANTHRIL tabl. 40mg x12	Furosemide	C03CA01	BALKANPHARMA-DUPNITZA	POM	1687370
RENAPRIL tabl. 5mgx 28	Enalapril	C09AA02	BALKANPHARMA-DUPNITZA	POM	1507948
PARACETAMOL tabl. 500mgX 20	Paracetamol	N02BE01	SOPHARMA	OTC	1421434
RENAPRIL tabl. 10 mgx 28	Enalapril	C09AA02	BALKANPHARMA-DUPNITZA	POM	1389315
VASOPREN tabl.. 10mg x 28	Enalapril	C09AA02	SOPHARMA	POM	1338846
EFISOL loz. 250mcg x 20	Dequalinium	R02AA02	BALKANPHARMA-DUPNITZA	OTC	1121307

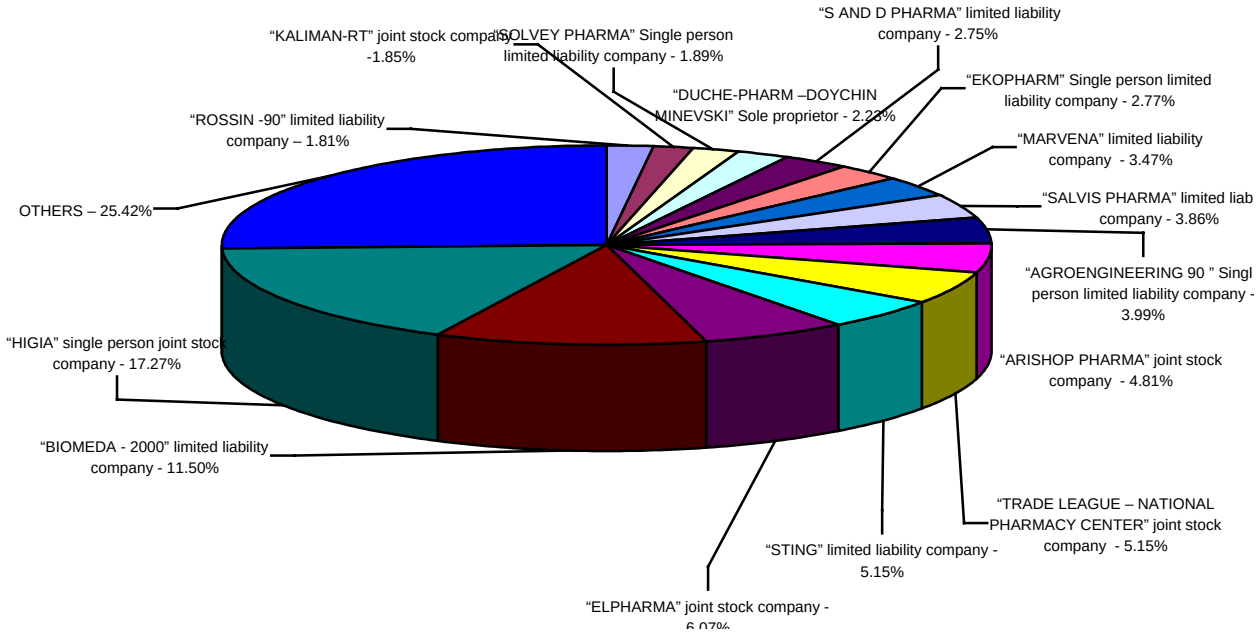
FIRST TEN TRADE NAMES IN VALUE FROM LOCAL PRODUCTION

Trade name and pharmaceutical form	INN	ATC – code	Manufacturer	Prescription status	Total value
ANALGIN tabl. 500 mg x 20	Metamizole sodium	N02BB02	SOPHARMA	OTC	8040682.53
AMOPEN caps. mg x 20	Amoxicillin	J01CA04	BALKANPHARMA-RAZGRAD	POM	7482804.96
ANTISTENOCARDIN tabl. 25mgx60	Dipyridamole	B01AC07 C01DX00	SOPHARMA	POM	
TERCEF powd. Inj. 1g x 5	Ceftriaxone	J01DA13	BALKANPHARMA-RAZGRAD	POM	3499171.3
ISODINIT tabl. Prolong. 20mg x 60	Isosorbide dinitrate	C01DA08	BALKANPHARMA-DUPNITZA	POM	3448334.7
CIPROFLOXACIN tabl. Film 500mg x 10	Ciprofloxacin	J01MA02	BALKANPHARMA-DUPNITZA	POM	3417673.8
ANALGIN sol. Inj. 500mg/ml – 2ml x10	Metamizole sodium	N02BB02	SOPHARMA	POM	3327027.70
VERAPAMIL 120 RETARD tabl. 120mg x 50	Verapamil	C08DA01	BALKANPHARMA-DUPNITZA	POM	3200913.8
CHLOPHADON tabl. X 50	Combination	C02LC01	SOPHARMA	POM	3147986.80
RANITIDIN tabl. Film 150mg x 60	Ranitidine	A02BA02	UNIPHARM	POM	2583092.93

Companies – importers with the biggest market share (number of packages)

IMPORTER	NUMBER OF PACKS	% FROM THE TOTAL NUMBER OF PACKS
1. “HIGIA” single person joint stock company	11 270 086	17.27%
2. “BIOMEDA - 2000” limited liability company	7 502 919	11.50%
3. “ELPHARMA” joint stock company	3 961 618	6.07%
4. “STING” limited liability company	3 361 307	5.15%
5. “TRADE LEAGUE – NATIONAL PHARMACY CENTER” joint stock company	3 359 467	5.15%
6. “ARISHOP PHARMA” joint stock company	3 140 977	4.81%
7. “AGROENGINEERING -90 ” Single person limited liability company	2 606 089	3.99%
8. “SALVIS PHARMA” limited liability company	2 518 942	3.86%
9. “MARVENA” limited liability company	2 262 819	3.47%
10. “EKOPHARM” Single person limited	1 805 518	2.77%

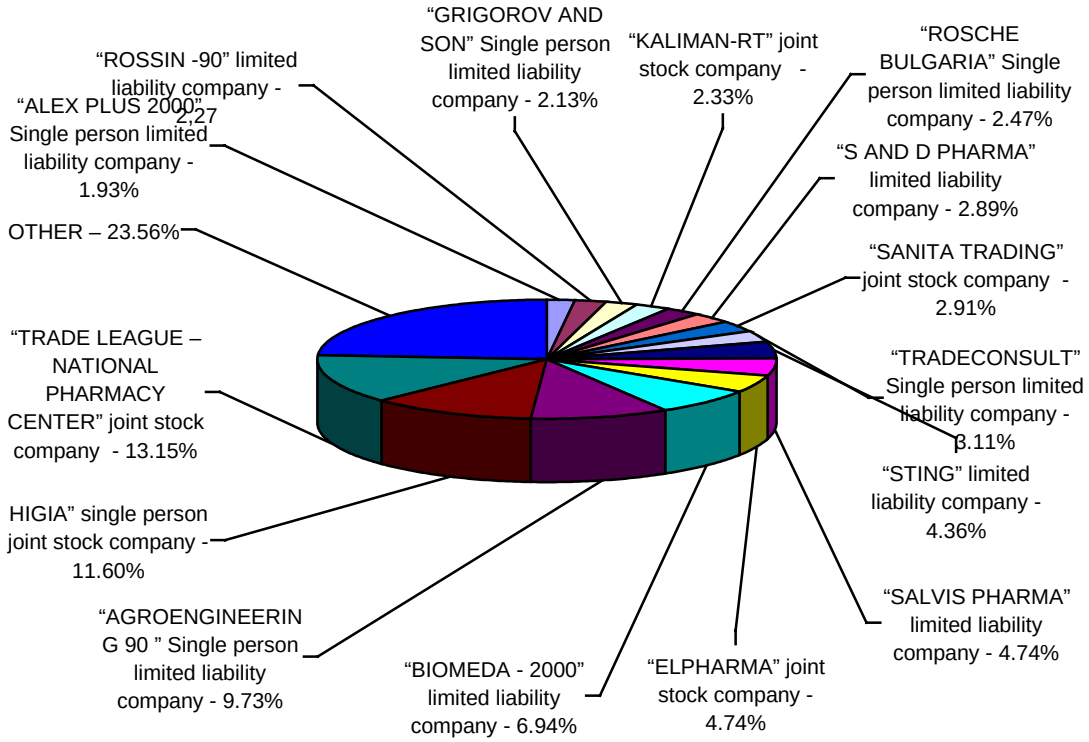
liability company		
11. “S AND D PHARMA” limited liability company	1 795 142	2.75%
12. “DUCHE-PHARM – DOYCHIN MINEVSKI” Sole proprietor	1 457 116	2.23%
13. “SOLVEY PHARMA” Single person limited liability company	1 230 768	1.89%
14. “KALIMAN-RT” joint stock company	1 209 814	1.85%
15. “ROSSIN -90” limited liability company	1 179 182	1.81%



Companies – importers with the greatest market share (in value)

IMPORTER	VALUE	% FROM THE TOTAL VALUE
1. “TRADE LEAGUE – NATIONAL PHARMACY CENTER” joint stock company	78151014.13	13.15%
2. HIGIA” single person joint stock company	68907987.84	11.60%
3. “AGROENGINEERING 90 ” Single person limited liability company	57 797 987.75	9.73%
4. “BIOMEDA - 2000” limited liability company	41 243 969.05	6.94%
5. “ELPHARMA” joint stock company	34 924 096.32	5.88%
6. “SALVIS PHARMA” limited liability company	28 173 495.04	4.74%
7. “STING” limited liability company	25 891 424.87	4.36%
8. “TRADECONSULT” Single person limited liability company	18 470 032.04	3.11%
9. “SANITA TRADING” joint stock company	17 283 143.27	2.91%
10. “S AND D	17 163 225.12	2.89%

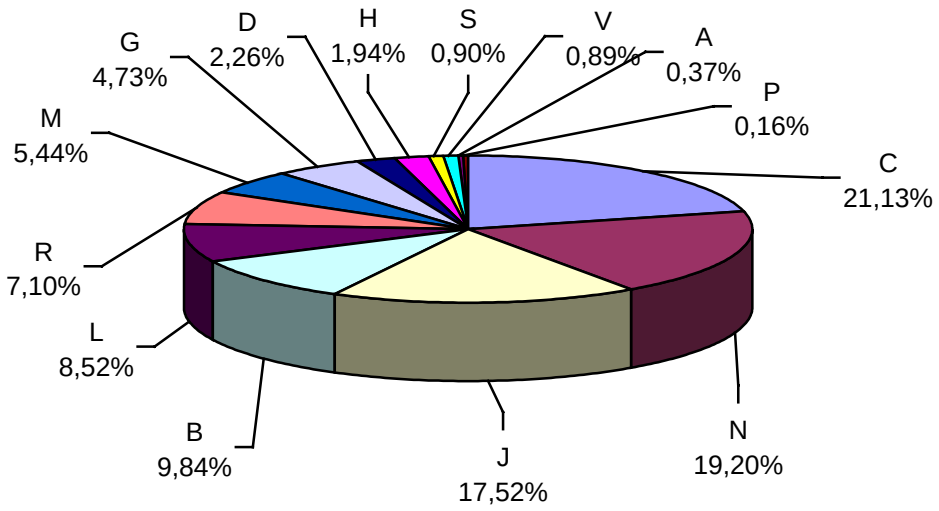
PHARMA” limited liability company		
11. “ROSCHE BULGARIA” Single person limited liability company	14 676 966.68	2.47%
12. “KALIMAN-RT” joint stock company	13 814 589.75	2.33%
13. “ROSSIN -90” limited liability company	13 493 730.04	2.27%
14. “GRIGOROV AND SON” Single person limited liability company	12 668 841.03	2.13%
15. “ALEX PLUS 2000” Single person limited liability company	11 465 082.9	1.93%



The most sold ATC groups in % (in value)

ATC group	Total value/BGN	% of the total value
C	133494084.40	21.13%
N	121271969.50	19.20%
J	110651563.50	17.52%
B	62145575.00	9.84%
L	53823076.78	8.52%
R	44824603.00	7.10%
M	34348030.25	5.44%
G	29856059.00	4.73%
D	14276774.00	2.26%
H	12265893.00	1.94%

S	5694113.14	0.90%
V	5628802.18	0.89%
A	2340809.55	0.37%
P	1016479.00	0.16%



H - HORMONAL MEDICINES FOR SYSTEMATIC ADMINISTRATION – 1.95%

D – DERMATOLOGICAL MEDICINES – 2.26%

G – URINARY – REPRODUCTIVE SYSTEM – 4.73%

M – MUSCULAR-SKELETAL SYSTEM – 5.44%

R – RESPITRATORY SYSTEM – 7.10%

L – ANTINEOPLASTIC AND IMMUNOMODULATING MEANS – 8.52%

B – BLOOD AND SANGUIFACIENT ORGANS

J – ANTI-INFLAMMATORY PREPARATIONS FOR SYSTEMATIC ADMINISTRATION – 17.52%

N – NERVOUS SYSTEM – 19.20%

C – CARDIOVASCULAR SYSTEM – 21.13%

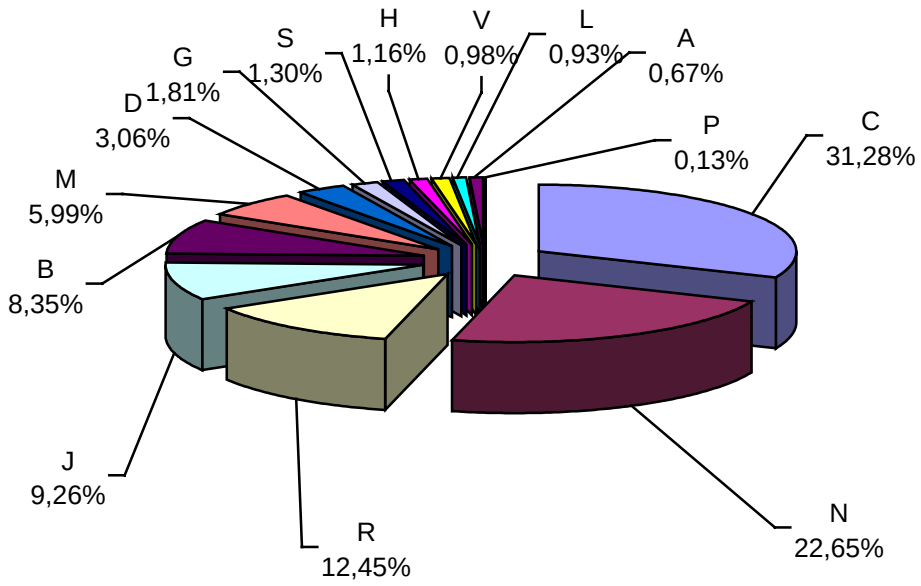
A – DIGESTIVE SYSTEM AND METABOLISM – 0.37%

V – OTHERS – 0.89%

S – SENSORY ORGANS – 0.90%

The most sold ATC groups in % (by number of packs)

ATC group	Total value/BGN	% of the total value
C	36079162	31.28%
N	26118133	22.65%
R	14363248	12.45%
J	10675005	9.26%
B	9627551	8.35%
M	6904002	5.99%
D	3530699	3.06%
G	2093128	1.81%
S	1498831	1.30%
H	1336860	1.16%
V	1127303	0.98%
L	1068482	0.93%
A	767087	0.67%
P	144686	0.13%



S – SENSORY ORGANS – 1.30%

G – URINARY – REPRODUCTIVE SYSTEM AND REPRODUCTIVE HORMONES – 1.81%

D – DERMATOLOGICAL MEDICINES – 3.06%

M – MUSCULAR-SKELETAL SYSTEM – 6.00%

B – BLOOD AND SANGUIFACIENT ORGANS – 8.36%

J – ANTI-INFLAMMATORY PREPARATIONS FOR SYSTEMATIC ADMINISTRATION – 9.27%

R – RESPITRATORY SYSTEM – 12.46%

N – NERVOUS SYSTEM – 22.67%

C – CARDIOVASCULAR SYSTEM -31.31%

A – DIGESTIVE SYSTEM AND METABOLISM – 0.67%

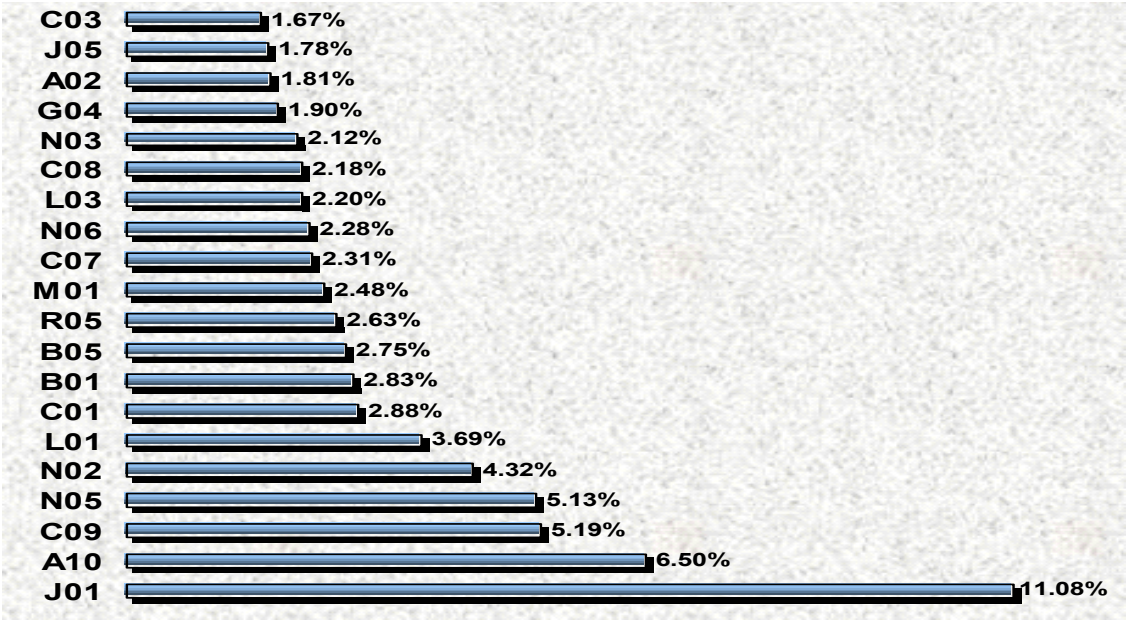
L – ANTINEOPLASTIC AND IMMUNOMODULATING MEANS – 0.93%

V OTHERS – 0.98%

H - HORMONAL MEDICINES FOR SYSTEMATIC ADMINISTRATION – 1%

The most sold ATC groups (level III) in % in value

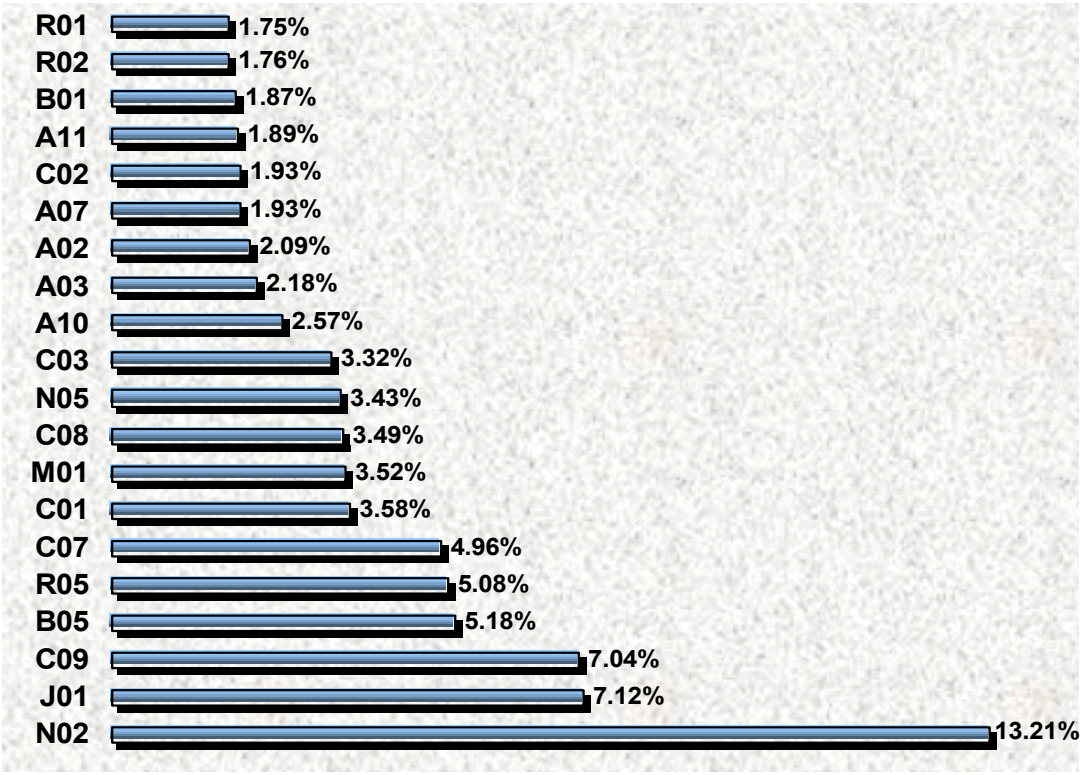
J01	81 455 468.60	11.08%
A10	47 800 143.63	6.50%
C09	38 144 303.27	5.19%
N05	37 720 469.79	5.13%
N02	31 720 447.60	4.32%
L01	27 133 518.91	3.69%
C01	21 194 727.20	2.88%
B01	20 829 979.59	2.83%
B05	20 242 302.05	2.75%
R05	19 305 685.14%	2.63%
M01	18 248 108.07	2.48%
C07	16 976 987.00	2.31%
N06	16 729 585.01	2.28%
L03	16 155 297.77	2.20%
C08	16 002 475.19	2.18%
N03	15 573 418.16	2.12%
G04	13 980 329.23	1.90%
A02	13 269 247.50	1.81%
J05	13 059 495.56	1.78%
C03	12 308 866.68	1.67%



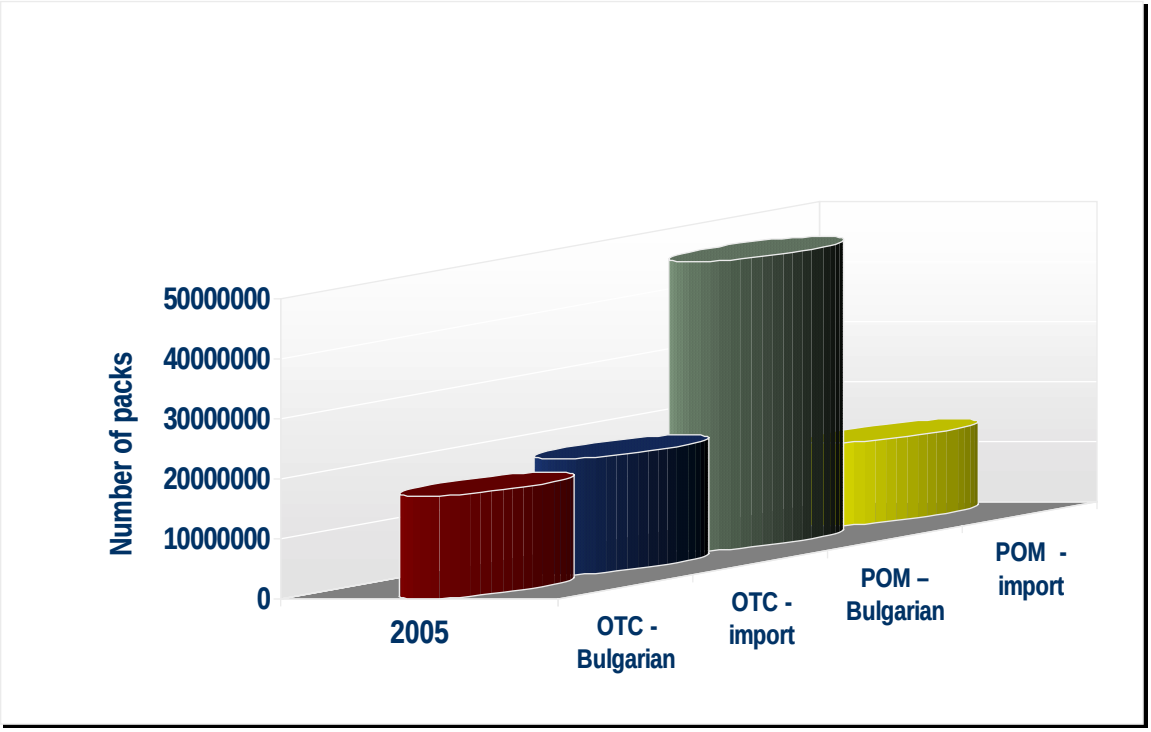
The most sold ATC groups (level III) in % (by number of packs)

N02	17 377 547	13.21%
J01	9 368 958	7.12%
C09	9 259 756	7.04%
B05	6 813 878	5.18%
R05	6 682 641	5.08%
C07	6 518 898	4.96%
C01	4 716 024	3.58%
M01	4 626 386	3.52%
C08	4 594 645	3.49%
N05	4 515 714	3.43%
C03	4 362 019	3.32%
A10	3 378 989	2.57%
A03	2 867 308	2.18%
A02	2 746 513	2.09%

A07	2 540 674	1.93%
C02	2 533 017	1.93%
A11	2 489 918	1.89%
B01	2 464 834	1.87%
R02	2 317 756	1.76%
R01	2 296 169	1.75%



Comparison of the ratio between the medicinal products POM/OTC expressed in quantity of packs



BIOLOGICAL PRODUCTS DIRECTORATE

I. Activity of the directorate

In compliance with the amendments and supplementations of BDA's statutory rules of 22 July 2005 the Directorate's activity includes:

1. Carrying out a chemical-pharmaceutical expertise for the assessment of the quality and safety on issuing marketing authorizations of medicinal products of a biological or biotechnological origin, of medicinal products from human plasma and of in vitro medical devices, including laboratory analyses.
2. Exerts control on the quality and safety of the authorized for use medicinal products of a biological or biotechnological origin, of medicinal products from human plasma and of in vitro medical devices, including laboratory analyses.

3. Coordinates the import of the medicinal products of a biological or biotechnological origin, of medicinal products from human plasma and of in vitro medical devices, including laboratory analyses.
4. Assesses the batch documentation and whenever it considers it necessary, analyses the batches of vaccines and products from human plasma and of in vitro medical devices related to the issuance of marketing authorizations.
5. Works out proposals to the General Executive on issuing licenses for the release of batches of medicinal products in compliance with the license scheme of the World Health Organization.
6. Assesses the safety periodical reports on medicinal products of a biological or biotechnological origin and of medicinal products from human plasma.
7. Participates in inspections of manufacturers of medicines of biological origin.
8. Controls the medical institutions carrying out activities in compliance with the Blood, blood donation and blood transfusion Act.

II. Staffing levels and structure of the Directorate.

In compliance with the amendments and supplementations of BDA's statutory rules of 22 July 2005 the number of the staff in the Directorate was decreased from 29 to 18 full-time members. Therefore the Directorate was restructured into two instead of three departments and one sector in the following way:

- "Medicinal products of biological origin" department – 6 full-time members: head of the department (a medical doctor), 2 chief experts (1 medical doctor and 1 biologist) and 3 junior experts.
- "Medicinal products of human origin and in vitro diagnostic medical devices" department- 6 full-time members: head of the department (a medical doctor), 2 chief experts (biologists), 2 junior experts and one executive.

- “Microbiological and biological analyses of medicinal products” sector – 5 full-time members: head of sector (a biologist), 1 chief expert (a biologist), 1 junior expert and 2 executives.

In October – November one junior expert and one executive from the “Medicinal products of human origin and in vitro diagnostic medical devices” department retired. By the end of the year these full-time jobs remained unoccupied.

At the end of the year the number of employees in the Directorate was 16, out of which:

- with a master’s and bachelor’s degree – 9 (56,25% of the available staff) out of which

4 medical doctors

5 biologists

2 senior research fellows

3 PhDs

a specialist with two majors (in internal medicine and clinical hematology)

3 specialists with a major in microbiology

2 specialists with a major in virology

1 employee without an academic degree and title

According to age:

1 under the age of 30

2 between 30 and 40

4 between 40 and 50

2 above the age of 50

- with an academic degree – specialists – 5
- with secondary education – 2

The ratio between specialists with an academic degree (master’s or bachelor’s) and the remaining specialists is 1:0,77.

III. Activities carried out in 2005.

The employees in the Directorate perform all stages of the assessment of the documentation submitted together with a marketing authorization application, variation and renewal of the authorizations of medicinal products of biological and human origin and in vitro diagnostic medical devices, carried out in BDA – inspections, chemical-pharmaceutical expertise for assessment of the quality and safety, as well as the technical provision of the work of the respective specialized committee.

Work was done on the documents submitted to BDA together with applications in 2005 throughout the year, as well as on incomplete procedures with applications from the previous year – 11 for marketing authorizations, 15 – for variation, 1 for the renewal of medicinal products and 13 for authorizing in vitro diagnostic medical devices.

Applications submitted in 2005 Table 1

Type of application	Type of product	Number	% of the total number of applications (according to the type of application)
Marketing authorization	Medicinal product	35	9,72%
	in vitro diagnostic medical device	77	21,38%
total number of applications for marketing authorizations		112	31,11%
Renewal of	Medicinal product	26	7,22%

marketing authorizations	in vitro diagnostic medical device		
Variation of marketing authorizations	Medicinal product in vitro diagnostic medical device	216 6	60,00% 1,66%
total number of applications for renewal of marketing authorizations		222	61,66%
Total number of applications		360	

In relation to the inspection and assessment of submitted documents for marketing authorizations, variation or renewal of the marketing authorizations, 189 letters with directions for the elimination of deficiencies and incompleteness were written.

The Directorate finalized chemical-pharmaceutical expertise and statements on 80 applications for marketing authorizations and 6 for renewal of in vitro diagnostic medical devices and 251 applications for medicinal products, as follows:

Finalized procedures on medicinal products in 2005.

Table 2

Type of procedure			National procedure	Centralized procedure
Medicinal product	Total number		Number %	Number %
Marketing authorization	17	6,77%	13 76,47%	4 23,52%

Renewal of marketing authorization	28	11,15%	22 78,57%	6 21,42%
Variation of marketing authorization	206	82,02%	105 50,97%	101 49,02%
Total	251		140 55,77%	111 44,22%

The work on the assessment of the documentation of 24 medicinal products for marketing authorizations is ongoing, 7 of them are for variation, 6 – for renewal and 10 for marketing authorizations of in vitro diagnostic medical devices.

The assessment of 87 submitted periodical safety reports on medicinal products of biological and human origin has been finalized.

2867 licenses for the import of medicinal products and in vitro diagnostic medical devices (IVDMD) have been coordinated.

Together with the "Control of manufacture and trade with medicines" directorate, 585 sales authorizations have been issued, out of which 431 after assessment of the batch documentation.

Together with 189 letters with directions for the elimination of deficiencies and incompleteness in the marketing authorizations for use, variation and renewal documentation, 124 correspondence letters on other occasions have been prepared.

Throughout the year 256 analyses of samples of 196 medicinal products were made in the Directorate. 106 of them were of biological and human origin and 87 with a chemical active substance and 3 – medical devices. Samples from 7 medicinal products were analyzed in relation to marketing authorizations, for the issuance of sales authorizations – 177 products and upon alerts for not meeting the quality requirements– 12 medicinal products. Out of all tested samples deviations

from the requirements were established in 3 of them, deviations from the sterility indicator – in 2 samples, and from the microbial content – in 1.

Analyses of medicinal products

Table 3

Testing according to indicators	Type of medicinal product			Number of analyses
	Of biological origin	With a chemical active substance	Medical device	
sterility	59	27	3	89
microbial content	59			59
Pyrogenicity	15	2		17
LAL test		3		3
Identity of bacterial vaccines	17			17
Distribution of molecular mass	19			19
Volume used	41			41
pH	11			11
Total number of analyses				256

Together with that, samples of 20 medicinal products and 79 in vitro diagnostic medical devices were tested via 133 analyses in laboratories outside the Agency due to the lack of apparatuses and other conditions. These were related mainly to the issuance of marketing authorizations and sales authorizations. When comparing the work done in the Directorate during the last years a tendency for increase of the amount of work on the basic activities was established.

Basic activities in the “Biological products” Directorate

Table 4

Year	Chemical-pharmaceutical expertise/opinions worked out			Coordinated import licenses	Sales authorizations worked out	Export certificates worked out	Assessed periodical safety reports	Prepared files	Analysis made
	medicines	IVDMD	Total						
2000	114	15	129		243	124		71	19
2001	116	118	234	1597	272	166		308	97
2002	153	134	287	1485	338	90	68	326	78
2003	141	91	232	2122	400	192	81	232	18
2004	145	62	207	2431	513	163	60	323	37
2005	251	86	337	2867	585	175	87	263	256

There is a significant increase in the number of submitted applications and the finalized expert statements on the assessment of the quality and safety of medicinal products and in vitro diagnostic medical devices on issuing authorizations for use, variation and renewal. After the procedures the greatest number is that of the variations made for medicinal products – 61,66% of the

submitted applications and 82,07% of the finalized expert statements, out of them 49,02% of the finalized procedures on variations are for products authorized under the EU centralized procedure.

At the end of 2005 the directorate started assessing the quality and safety of another group of medicinal products – insulin.

The amount of work on the post-registration control has also increased – coordination of import licenses, issuance of sales authorizations and making analyses. A great part of the analyses have to do with the sterility trials of the bacterial diphtheria vaccine, tetanus and pertussis vaccine, diphtheria- tetanus vaccine, tetanus- diphtheria vaccine and tetatox vaccine after the preservative tiomersal dropped out.

In relation to the introduction of a system on quality in the activity of "Biological products" directorate the draft on quality directions in compliance with the Bulgarian state standard ISO/IEC EN 17025:2001 was partially prepared, but it is no longer up-to-date due to BDA's new statutory rules. The new job descriptions and the new edition of ISO/IEC EN 17025:2005 will be approved as Bulgarian state standard at the beginning of 2006.

The basic activity on the introduction of the quality system in the "Biological products" directorate in 2005 was related to the inspection and qualification of the technical equipment used in laboratory trials. The activity also concerned the assessment, selection and purchase of materials used in trials and the training of the person in charge of quality in the "Biological products" directorate and his deputy.

They participated in the following events and training courses:

Annual meeting of the European network of official laboratories for control of medicines, 23-27 May 2005, in Rome, Italy – L. Antonov

Course on ensuring the quality in the official laboratories for control of medicines, 19 – 21 April 2005 in Strasbourg, France – E. Zhelyazkova

Course on “The requirements set before the systems for managing the quality in accordance with the BSS EN ISO 9001 and ISO/IEC EN 17025: 2005. The technical requirements set before the trials and the calibration”, organized by the meteorologists union in Bulgaria and the “Club 9000” association, 16-17 November 2005, Sofia - E. Zhelyazkova and L. Antonov.

Course on internal audits – requirements and practices – BSS EN ISO 19011, organized by the meteorologists union in Bulgaria and the “Club 9000” association, 14-15 November 2005, Sofia - L. Antonov, completed and passed a test for an internal auditor of the quality management systems.

The employees from the directorate participated in inspections of the manufacturing conditions of the local biological products manufacturers, as well as on the blood, blood donation and blood transfusion Act.

L. Gaydarova, MD and P. Popova, MD participated in the assessment of pharmacovigilance at procedures of other directorates – 50 and 7 procedures respectively.

P. Popova, MD is the president, L. Gaydarova, MD – secretary, while G. Georgiev, MD – member of the Specialized Commission for assessment of the therapeutic efficacy and safety of medicinal products, which had 4 meetings throughout the year and the documents of 117 applications for marketing authorizations, variation or renewal of medicinal products were revised.

P. Popova, MD is an active observer in the EMEA working party and participates in the work of group 15 at the European Pharmacopoeia, L. Gaydarova, MD is an active observer in the EMEA working party and participates in EU meetings on the control of blood, blood donation and blood transfusion. G. Georgiev, MD, E. Zhelyazkova and L. Antonov are nominated as deputies of the active observers at EMEA’s working parties.

“CONTROL OF THE MANUFACTURE AND TRADE IN MEDICINES” DIRECTORATE

Activities:

1. Carries out the activities, stipulated in the PPSHMA regarding the issuance by the General Executive of manufacturing authorizations for medicinal products, proposals for issuing authorizations for wholesale trade with medicines, registration of drugstores and coordination of draft documentation for the construction and re-structure of outlets related to the manufacture of medicines;
2. controls the manufacture and trade in medicines;
3. Exerts control on observing the Good Manufacturing Practice of medicines;
4. Coordinates the import and authorizes the selling of medicinal products on the territory of the Republic of Bulgaria;
5. keeps a register of the issued manufacturing authorizations of medicines and the issued licenses for the registration of drugstores;
6. Makes proposals to the General Executive to stop the manufacture and ban the usage of medicines related to their quality and safety;
7. Makes proposals to the General Executive to issue licenses for medicines in compliance with Licensing Scheme of the World Health Organization;
8. Processes documents for the clinical trials of medicines, controls the conduction of the trials on the territory of the whole country in compliance with the Good Clinical Practice, establishes links with the respective specialized committee under art. 21 of the PPSHMA, carries out inspections and registers the clinical trails conducted in the country;
9. carries out activities related to the blocking and withdrawal of medicinal products which have shown incompliance with the requirements for quality and safety;

10. Carries out on-site inspections for establishing compliance of the actual conditions of manufacture, control and storage of the medicines with the documentation presented for issuing manufacturing authorizations and with the requirements for the Good Manufacturing Practice (GMP) of medicines;
11. Carries out on-site inspections when in the process of receiving marketing authorizations for imported medicines it is established that there is not sufficient evidence for compliance of the manufacturing conditions with the requirements of GMP.
12. Checks the premises related to receiving, processing and usage of blood and blood products in compliance with the blood, blood donation and blood transfusion Act and PPSHMA. Thus added to the already abovementioned duties, the employees from the "Control of the manufacture and trade in medicines" directorate undertook measures and performed supplementary activities during 2005 in the following areas:

1. The process of issuing marketing authorizations of medicinal products on Bulgaria's territory both via inspecting the sites of manufacturing, control and storage of products for which there have been applications for marketing authorizations and via working out statements related to the submitted applications and the accompanying documents (the data are annexed in the respective section). Compared to 2004 there has been an increase of this activity by about 65% which is due mainly to the statement on the submitted applications for marketing authorizations under the terms and conditions of the PPSHMA;
2. the blocking and disposal of medicinal products that have shown incompliance with the quality requirements both on the territory of

the Republic of Bulgaria and within the European warning system operative in EMEA (the data are annexed in the respective section);

3. the assessment of applications and documents concerning the import and use of humanitarian aid and medicinal products that have not been granted marketing authorizations under the terms and conditions of the PPSHMA;
4. working out drafts for amendments of the legislation related to medicinal products. Employees from the directorate took part in a number of working parties on the preparation of an amendment of the PPSHMA;
5. the assessment of applications and their accompanying documents for the revision and/or usage for other purposes of batches of medicinal products under the terms and conditions of Decree No.28;
6. participation in the supreme pharmacy council;
7. the coordination of draft documentation under the terms and conditions of the PPSHMA on the sites for the manufacture, control and storage of medicines;
8. joint inspections intended to assist the activities of the respective Ministry of Interior (MI) and National Health Insurance Fund services on the issues of medicinal products. Greater participation has been registered in the joint inspections with the National Justice Institute, including the one on court decisions that have become effective;
9. preparing answers to questions related to appeals made by the citizens, organizations and interested parties regarding different medicinal products issues. During 2005 there was a greater interest by citizens that made alerts on which checks have been made by inspectors from the “Control of the manufacture and trade in medicines” directorate;

10. Joint inspections with the National Health Insurance Fund on alerts for violations made by the pharmacy network. A considerably greater number of inspections were carries out together with representatives of the regional health insurance funds. Many references on topics determined by the National Health Insurance Fund were prepared;

The tendency of an increase of the amount of activities related to the control on medicinal products made by employees from the “Control of the manufacture and trade in medicines” directorate was preserved in the calendar year 2005. This was reflected both in the amended statutory rules – the number of employees increased from 18 to 25, and in the number of activities carried out.

Four sectors were established in the directorate which outlined the guidelines in the future activities in the directorate. These are the “Good Manufacturing Practice”, “Control of Clinical Trials”, “Retail trade” and “Wholesale Trade” sectors. It should be emphasized that the increase of staffing level in the directorate is extremely insufficient with respect to the amount of activities performed. Specialists who met the definite criteria took part in the competitions announced.

In 2005 a program on additional qualification of the employees was realized. There were also English language courses.

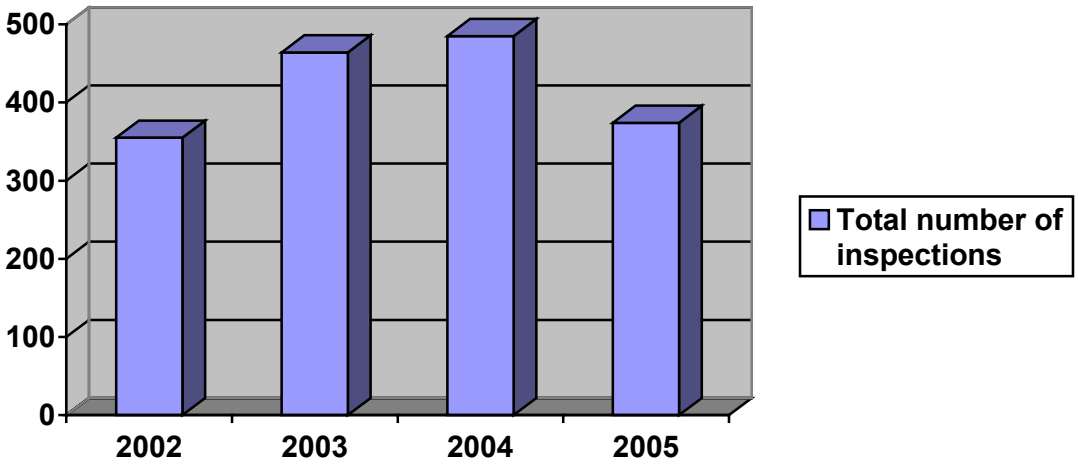
The chief inspectors from BDA’s “Control of the manufacture and trade in medicines” directorate for the reporting 2005 (1 January 2005 to 31 December 2005) period put efforts in fulfilling the determined amount of activities on the control of the manufacture and trade in medicines on the territory of the country.

Compared to 2004 in 2005 there has been an increase in the number of activities and duties in all directions (manufacture, trade in medicines, clinical trials, import, sales etc.)

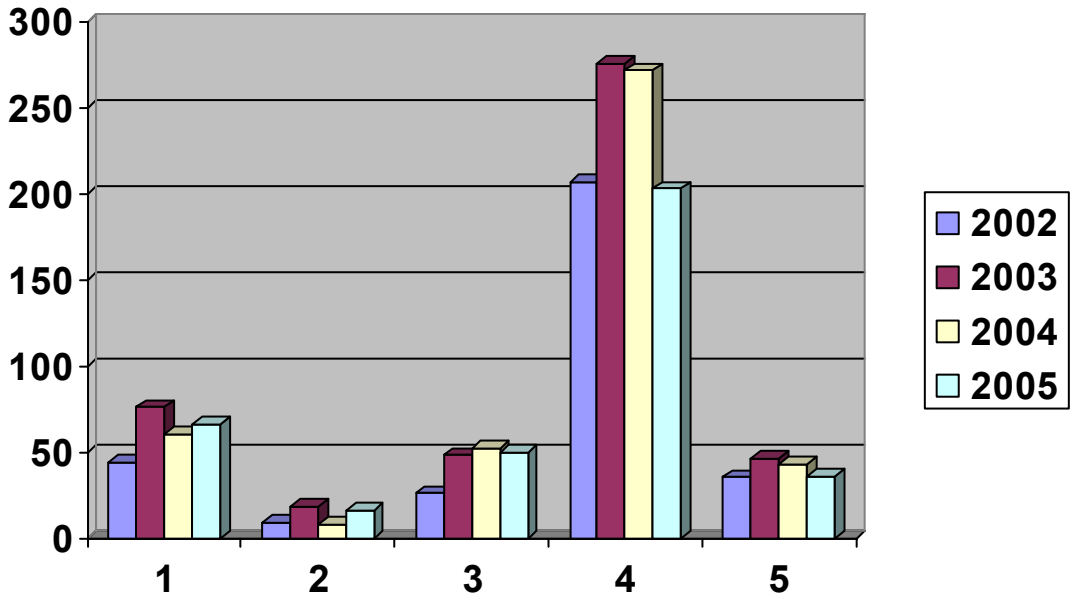
66 inspections in total were carried out during the reporting period (manufacture); 242 inspections (storehouses, pharmacies, drugstores); 50 inspections on the

disposal of medicinal products and 16 inspections of clinical trials were carried out by employees from the directorate.

The graphic representation shows a comparison between the total number of inspections for 2002 - 2005 period.

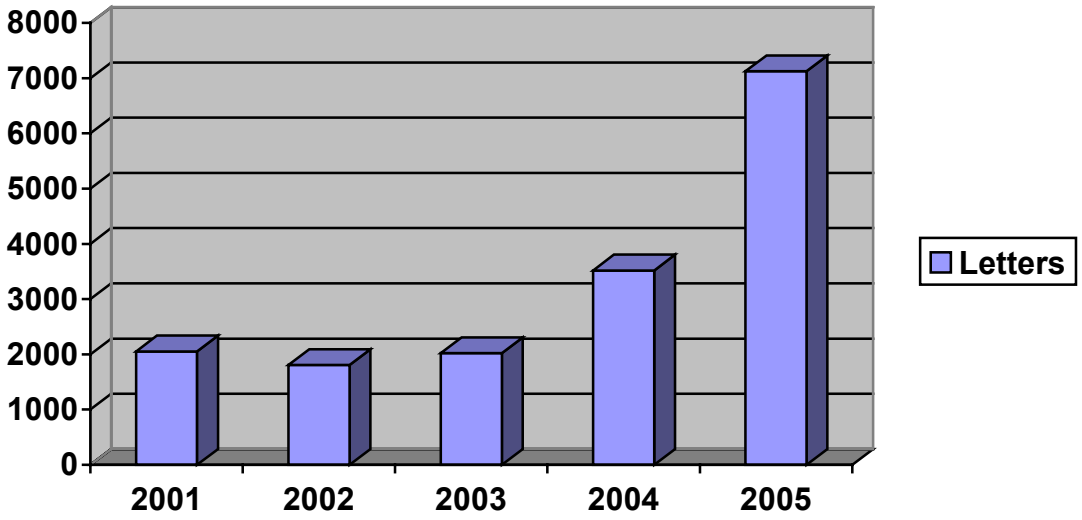


The graphic representation shows the dynamics of the inspections carried in the 2002-2005 period according to the following topics: control of manufacture (1), control of clinical trials (2), control of the activities on the disposal of medicinal products (3), control of retail trade with medicines (4) and control of wholesale trade with medicines (5).



In 2005, 7046 letters (applications, requests) were addressed to the “Control of the manufacture and trade in medicines” directorate.

The next graphic representation compares the administrative service done by the “Control of the manufacture and trade in medicines” directorate for the 2001 – 2005 period. The reference does not indicate the letters and answers addressed to external institutions but only the ones addressed to BDA. It should be mentioned that the basic part of letters is related to issuing sales authorizations, as well as to providing supplementations on submitted documentation on conducted clinical trials.



Employees from the Directorate participated, in compliance with orders of the Ministry of healthcare, in working parties on preparing drafts for amendments of the regulatory framework. The joint activity with the National Health Insurance Fund on controlling the pharmaceutical market is topical in 2005 as well.

In 2005 a lot of joint inspections with the MI bodies were carried out in compliance with the approved interdepartmental plan. MI served as an authority to submit administrative acts and penal court rulings.

The expert committees operative within the "Control of the manufacture and trade in medicines" directorate were closed in 2005 and the respective standard operating procedures were approved for carrying out the activities. The participation of employees from the directorate in the Supreme Pharmacy Council meetings at the Ministry of Healthcare was in compliance with the approved schedule in 2005 as well.

There was one participation in the working party on Good Manufacturing practice at EMEA and one participation in EudraCT.

I. Control of the manufacture of medicines.

The activity on the control of the manufacture of medicines

1. Carries out the activities stipulated in PPSHMA regarding the issuance of manufacturing authorizations by BDA's General Executive;
2. Controls the manufacture of medicines;
3. Exerts control on the observance of the GMP of medicines;
4. Keeps a register of the issued manufacturing authorizations of medicines;
5. Issues licenses on the origin of medicines in compliance with the WHO scheme.

In 2005 regarding the amendments in BDA's statutory rules the tasks in the sphere of the manufacture of medicines set before the "Control of the manufacture and trade in medicines" directorate were supplemented. The new duties were related to the implementation of the Blood and blood products Act. A new duty of the inspectors was added for the assessment of the draft documentation for restructuring the sites for the manufacture, control and storage of medicines.

The control of the manufacture of medicines was done by three employees in 2005 – two chief experts and the director of the "Control of the manufacture and trade in medicines" directorate. For a definite period of time other employees from BDA were included, depending on the nature of the inspection.

The positive tendency observed in 2004 in the sphere of bringing the manufacturing conditions of medicines in line was preserved in 2005 as well. During the period renovated production facilities and equipment for the manufacture of powders and solutions for parenteral administration were put into operation in "Balkanpharma" – Razgrad Joint Stock Company. The renovated production facilities and equipment of "Sopharma" Joint Stock Company for suppositories and pessaries were also put into operation. New production facilities and equipment of "Chaika pharma – the high quality medicines" Joint Stock Company in Plovdiv and "GlaxoSmithKline" Single Person Limited Liability Company started being used.

Compared to 2004, 2005 shows a decrease in the number of inspected foreign manufacturers of medicines. Five companies from three countries were inspected – Macedonia, Romania and Turkey (in 2004 the companies were 9). The inspections of foreign manufacturers were made in relation to submitted applications for marketing authorizations under the terms and conditions of PPSHMA on the territory of Bulgaria.

Three inspections after alerts were carried out during the reporting period. The latter were for incompliance with the quality requirements 2 (two) and 1 (one) for manufacture without there being an issued authorization.

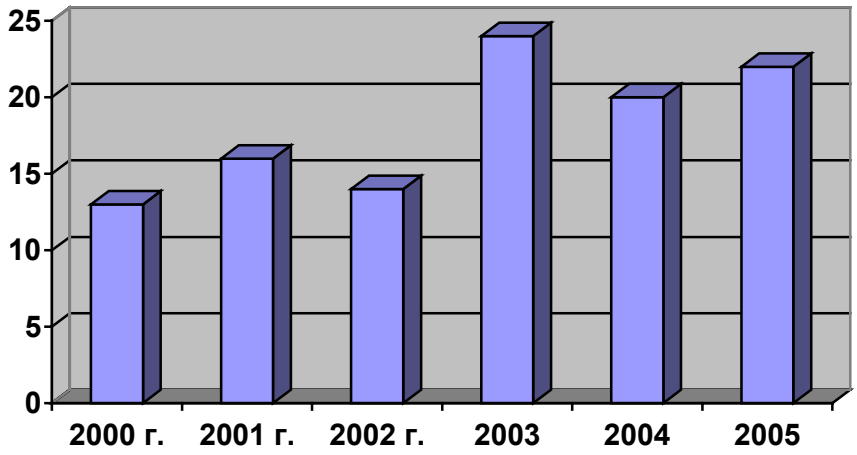
Apart from the already enumerated tasks, activities outside the ones indicated in BDA's statutory rules were carried out in 2005. They were related to the process of issuing marketing authorizations for medicinal products on the territory of Bulgaria. Compared to 2004 there is an increase in the number of statements prepared in relation to applications for marketing authorizations for medicinal products. Twenty-six statements were prepared in 2005 (they were 14 in 2004) on submitted licenses for marketing authorizations of products.

1.1 **Participation in inspections**.

The inspections have been made in compliance with an annual schedule worked out under the terms and conditions of art. 92 of the PPSHMA. Five of these inspections are on the grounds of art. 2, par. 3 of Ordinance No. 12 of the Ministry of Healthcare of 2001.

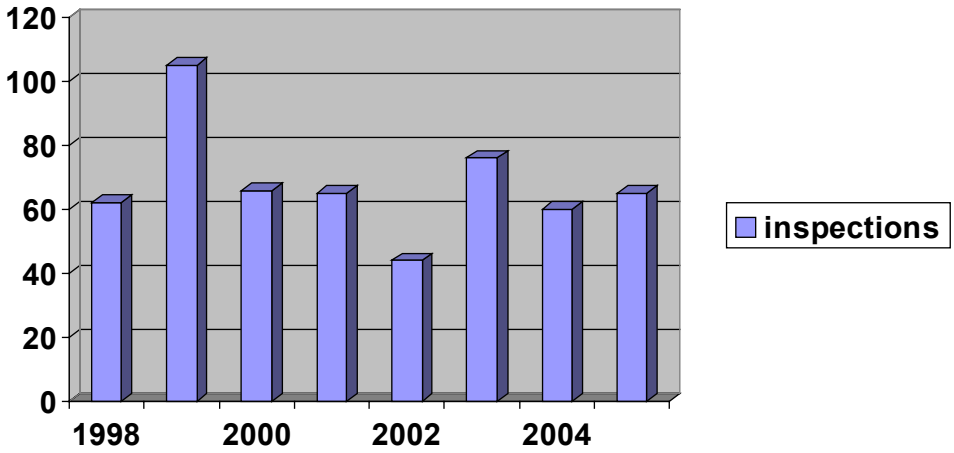
Sixty-six inspections were carried out in companies – manufacturers of medicinal products in 2005 (they were 60 in 2004). There is a 10% increase compared to 2004.

The graphic representation shows the inspectors/inspections ratio for the 2000 - 2005 period.



Apart from inspectors from the "Control of the manufacture and trade in medicines" directorate, employees from other directorates – MAMP, CPEM – also took part in the inspections.

The inspections carried out by the manufacturers of medicines for the 1998 – 2005 period



1.2 **Activity on issuing manufacturing authorizations for medicinal products**.

Seventy-six (76) sets of documents for manufacturing authorizations and 45 supplements to them (121 in total), including the draft documentation were submitted and assessed in 2005. Two (2) were the ones received and assessed for issuing a new manufacturing authorization (they were 4 in 2004) and 93 – for variation of the manufacturing authorization (they were 74 in 2004). For the same period 26 sets of documents (they were 45 in 2004) for coordinating draft documentation for the construction and/or restructure of sites for the manufacture, control and storage were assessed.

The activity of the Expert Council for issuing manufacturing authorizations was terminated in 2005. At present the assessment of the compliance of the drafts is done by inspectors at the directorate in compliance with the approved standard procedure. Thus for instance 39 applications for variation in issued authorizations were revised for a second time (the number was 14 in 2004), and 11 draft documentations were revised for a second or third time (they were 22 in 2004).

The following documents by applicants related to the issuance of manufacturing authorizations or variation were processed in 2005:

- for obtaining a manufacturing authorization of medicines – 2 (4 in 2004);
- for variation of the manufacturing authorization of medicines - 93 (74 in 2004);

The Expert Council on issuing manufacturing authorizations has had 8 meetings (18 in 2004) at which 44 documents by applicants were reviewed:

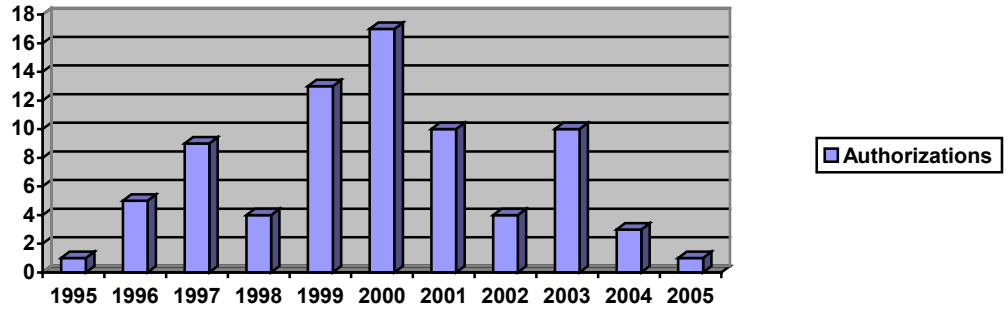
- for issuing manufacturing authorizations – 1 (3 in 2004)
- for issuing authorizations for variation – 32 (69 in 2004)
- for coordinating draft documentation – 11 (30 in 2004)

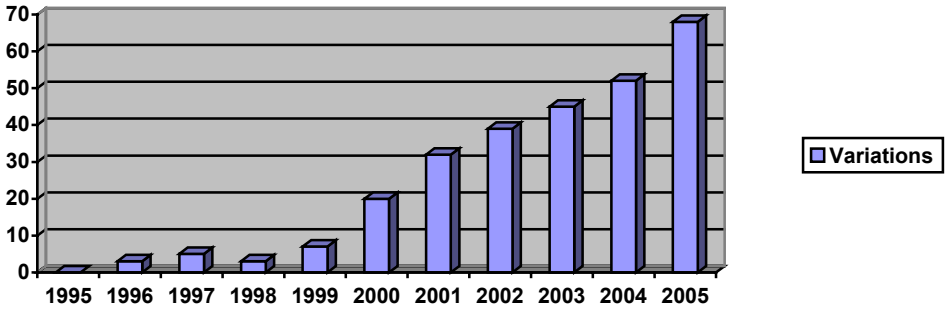
The following statements were prepared by the inspectors:

- for variation of an issued manufacturing authorization – 36;
- for assessment of draft documentation on restructuring a site – 17.

Three committees were established by an order of BDA's General Executive for the assessment of applications and the accompanying documents on re-processing and/or usage of batches of medicinal products for other purposes under the terms and conditions of Ordinance No. 28 of the Ministry of Healthcare.

Fig. 7 shows a comparison of the activities on issuing manufacturing authorizations for medicines. There was one new manufacturing authorization issued in 2005 (in 2004 they were 3). The data indicate a decrease of the issued manufacturing authorizations compared to previous years. At the same time there is a significant increase in the issued authorizations for variation of the issued manufacturing authorizations – 68 variations (they were 52 in 2004).





Comparison between the variations in authorizations for the 1995 – 2004 period.

No variation was denied in 2005. The procedures on issuing manufacturing authorizations of two companies were terminated in 2005.

Three orders were issued in 2005 for corrections in an issued manufacturing authorization due to a technical mistake.

Regarding the draft documentation – 12 drafts coordinated (44 drafts in 2004), the coordination of 3 drafts was denied (1 draft in 2004). A great number of the drafts were not worked out in compliance with the GMP requirements. Therefore 11 drafts had to be reviewed a second time (they were 22 in 2004) after providing supplementary information or their rewriting by the applicants.

1.3. Penalties imposed on the ones violating the provisions of PPSHMA.

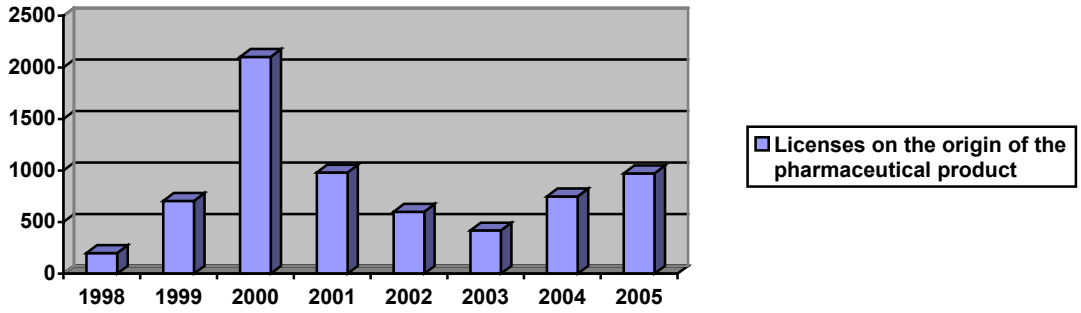
Three penal court rulings to manufacturers of medicines amounting to 7 000 BGN were issued in 2005. At the same time three chief experts on the control of manufacture took part in inspections on the control of the distribution of medicines – this will be indicated in the respective section of the report.

Two orders issued to suspend the exploitation of sites for the manufacture, control and storage of medicines were issued in 2005 (they were 5 in 2004).

1.4. Issuing licenses in compliance with the WHO license scheme

In 2005 the number of issued licenses is considerably greater compared to the previous year. This is due above all to factors related to the renewal of already existing authorizations outside the country as well as to changes in the manufacturing conditions which provide the Bulgarian products with the opportunity to appear on the international market.

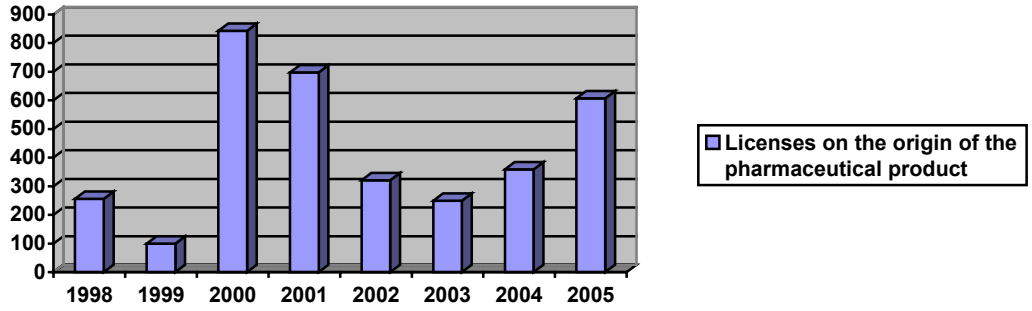
1.4.1. Issuing licenses on the origin of medicines.



977 licenses on the origin of the medicinal products and licenses for trading in medicinal products were issued in 2005 (their number was 748 in 2004). This presents a 30% increase compared to 2004.

1.4.2 **Issuing licenses for medicinal products**.

610 licenses for medicinal products were issued during the period (their number was 359 in 2004). This presents a 40% increase compared to 2004. Comparison with the previous years.



1.5. Participation in international events, seminars and inspections.

The manufacturing conditions of the following foreign manufacturers were inspected: “S.C. Fabiol” S.A.; “S.C. Mark Pharmaceuticals” S.R. L; “Embil Pharmaceuticals” Co., Ltd; “Mustafa Nevzat Ilac Sanayii A.S” and “Alkaloid” Joint Stock Company.

One person participated in a workshop in London on GMP. There should be more active participation in seminars and courses so as to ensure the inspectors' up-dated knowledge and practice in the sphere of the control of manufacture.

The following actions were undertaken in 2005 related to the forthcoming joint inspection of a WHO committee – of the manufacture of vaccines – "Bul Bio – National Centre on Contagious and Parasite Diseases" Single Person Joint Stock Company.

1.3 **Work on BDA's registers**.

In 2005 the register of the issued manufacturing authorizations under the terms and conditions of art. 13 of the Act is kept in the "Control of the manufacture and trade in medicines" directorate. The issued manufacturing authorizations and their variations are duly entered in the register.

At the same time data in an electronic form in the form of electronic tables are entered and they encompass all obligatory attributes indicated in the Act.

The necessary measures regarding the manufacture, import and distribution of medicinal products manufactured in violation of the PPSHMA provisions were undertaken. With regard to the changed conditions in the manufacture of medicines – namely that, on the one hand they have to be brought in line with GMP, on the other – there is a decrease in the number of people employed, measures were undertaken to up-date the number of inspectors engaged in the control of manufacture.

A GMP sector was established.

II. Control of the distribution of medicines.

After the amendments made in BDA's statutory rules the staffing level of the "Control of the manufacture and trade in medicines" directorate was increased. Two sectors were created with a view to the higher efficiency of the activities performed – "Retail Trade" sector and "Wholesale Trade" sector.

The activities related to the control of the distribution of medicines are basically performed by two employees from the "Control of the trade in medicines"

department at the “Control of the manufacture and trade in medicines” directorate. They are assisted in their work by the rest employees in the directorate and the Agency.

In 2005 the employees in the “Control of the trade in medicines” department have performed activities derived from BDA’s statutory rules as follows:

1. Control of the trade with medicines;
2. Working out proposals for issuing wholesale authorizations of medicines and drafts for wholesale authorizations and a register of the issued licenses for the registration of drugstores.

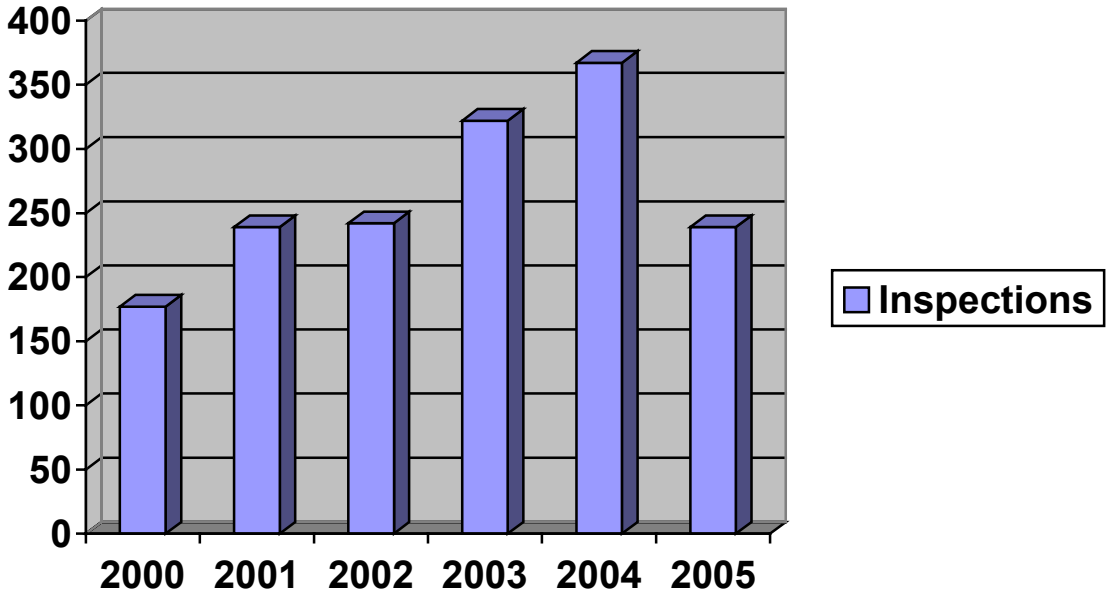
In 2005 the “Control of the trade in medicines” department at the “Control of the manufacture and trade in medicines” directorate was very active in the following respects:

1. the approval, assessment and working out of proposals and authorizations for wholesale trade with medicines;
2. the approval, assessment and working out of licenses for the registration of drugstores;
3. Preparation of drafts for penal court rulings, issued by BDA’s General Executive;
4. actions related to claims lodged in the respective courts against penalties imposed by BDA’s General Executive;
5. Working out of drafts for amendments in the legislation related to the trade in medicines;
6. Participation in the Supreme Pharmacy Council;
7. Joint initiatives with the aim of providing assistance of the respective MI and National Health Insurance Fund services regarding the trade in medicines;
8. Preparing answers on appeals by citizens, organizations and interested parties on different issues related to the trade in medicines;

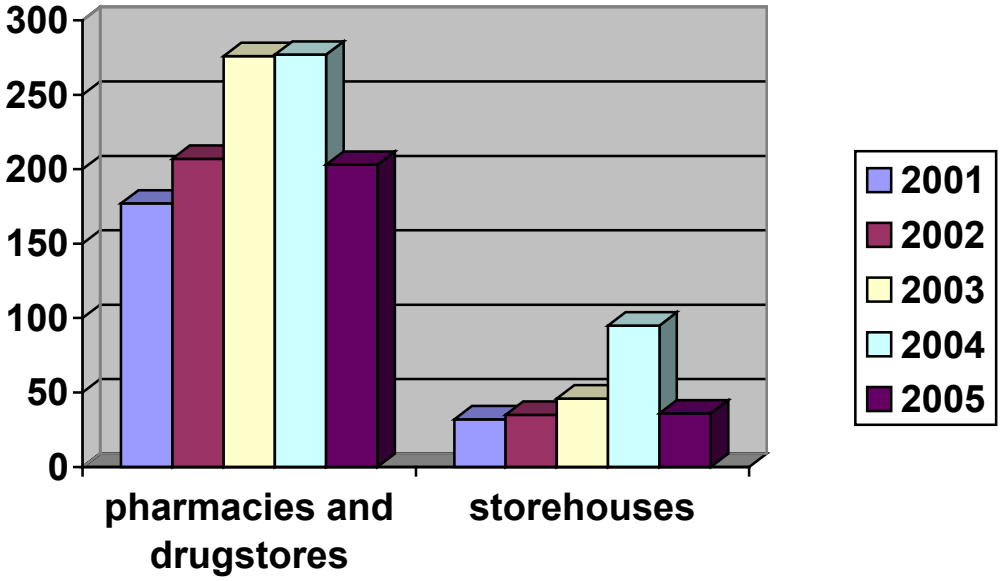
2.1 **Participation in inspections**.

During the reporting year the inspectors from the department and directorate inspected 239 sites (367 – in 2004), out of which 173 pharmacies (261 in 2004), 31 drugstores (11 in 2004) and 36 storehouses (57 in 2004) on the territory of the whole country – 50 towns and villages in total (70 in 2004) at the district cities of Burgas, Blagoevgrad, Varna, Veliko Tarnovo, Razgrad, Lovech, Plovdiv, Stara Zagora, Haskovo, Kardzhali, Pazardzhik, Sofia – district, Targovishte, Gabrovo, Pernik, Russe and Yambol.

Inspections carried out in the 2000-2005 period.



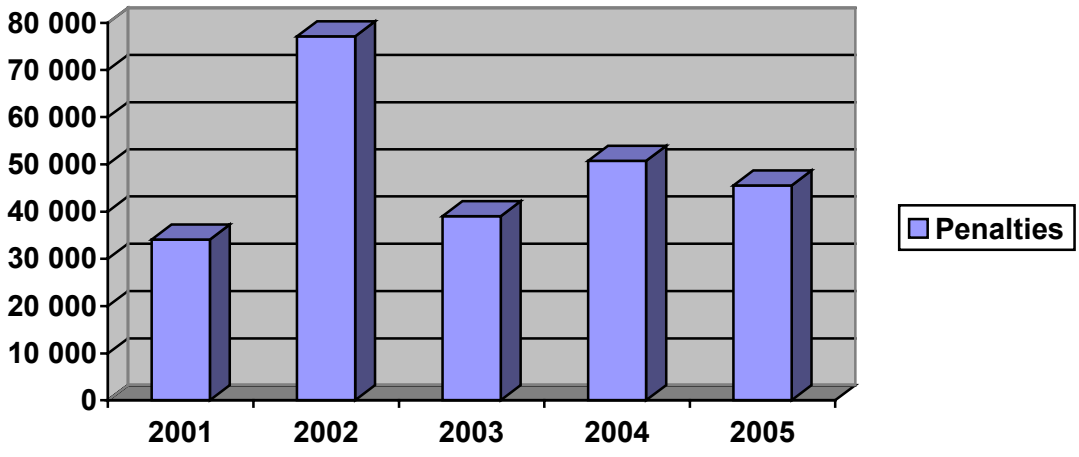
A graphic representation of the comparison of the inspections in 2001, 2002, 2003, 2004, and 2005 regarding storehouses, pharmacies and drugstores.



A considerable increase in the number of inspections in storehouses, pharmacies and drugstores is necessary with regard to their relative share in relation to the functioning properties.

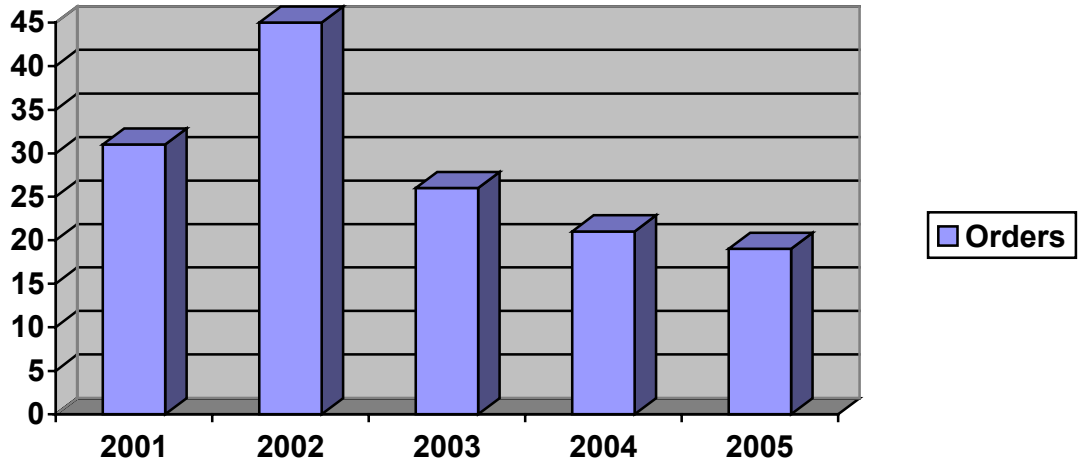
The imposed fines amount to 45 500 BGN (50 700 in 2004). By the time the report was prepared 15 pharmacies were in a procedure for issuing penal court rulings.

Ratio between the imposed sanctions for the 2001 – 2005 period.



Orders for temporary termination of the functioning of sites for the 2001 – 2005 period.

Sites, functioning as pharmacies without an issued authorization by the Minister of Healthcare – 19 pharmacies;



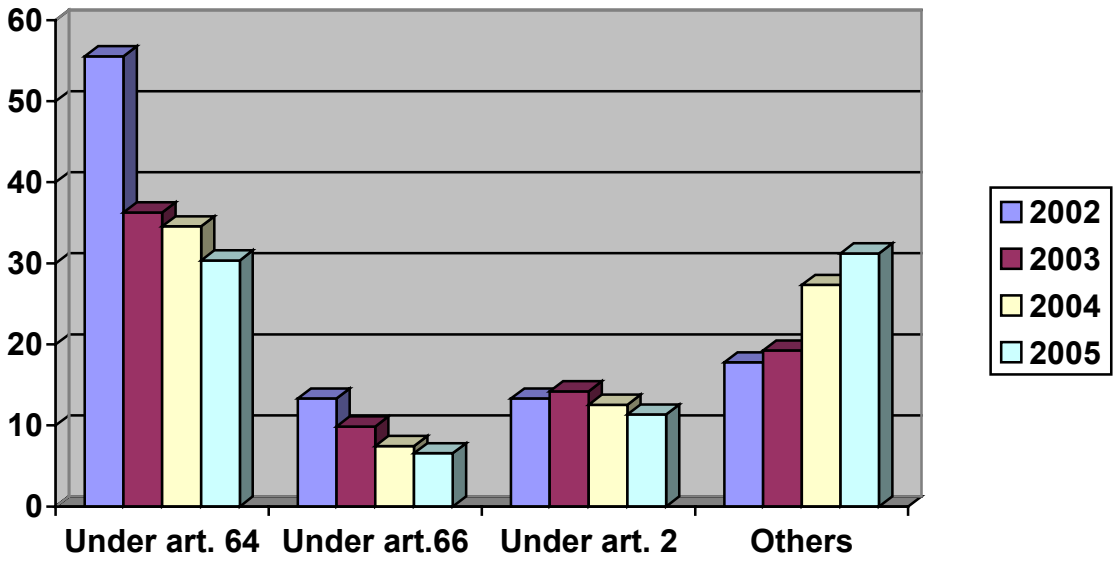
- Sites, in which art. 2, par. 1 of PPSHMA has not been observed – pharmacies which have medicinal products at their disposal without marketing authorizations on the territory of the country in compliance with the provisions of PPSHMA;
- sites, in which art. 66, par. 1 of PPSHMA has not been observed – pharmacies in which the POM medicinal products are given by an assistant-pharmacist.

Established and penalized violations of ordinances by the Ministry of Healthcare:

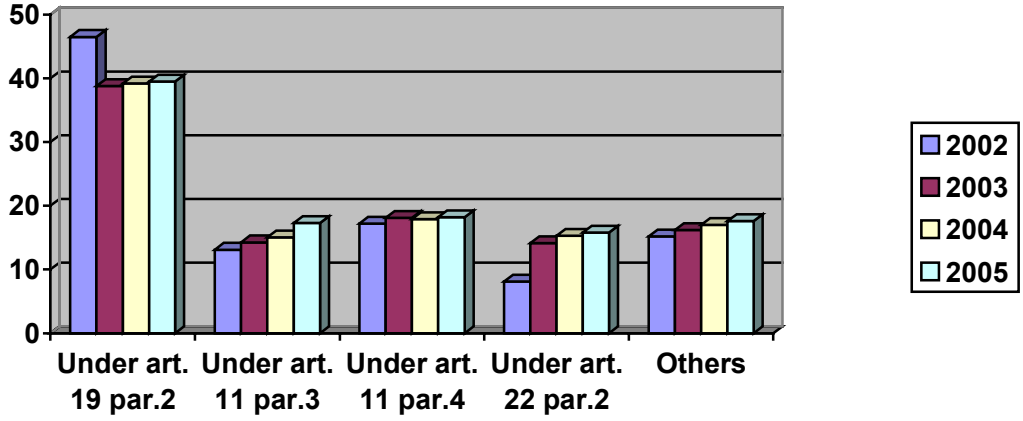
- sites, in which art. 11, par. 3 of Ordinance No. 8 of the Ministry of Healthcare has not been observed – pharmacies in which the medicinal products containing narcotic substances have not been stored in the proper manner;
- sites, in which art. 11, par. 4 of Ordinance No. 8 of the Ministry of Healthcare has not been observed – pharmacies in which the poisonous medicinal products substances have not been stored in the proper manner;

- sites, in which art. 19, par. 2 of Ordinance No. 8 of the Ministry of Healthcare has not been observed – pharmacies in which the thermolabile medicinal products have not been stored in the proper manner;
- sites, in which art. 22, par. 2 of Ordinance No. 8 of the Ministry of Healthcare has not been observed – pharmacies in which medicines of which the shelf life has expired have been stored in the proper manner;

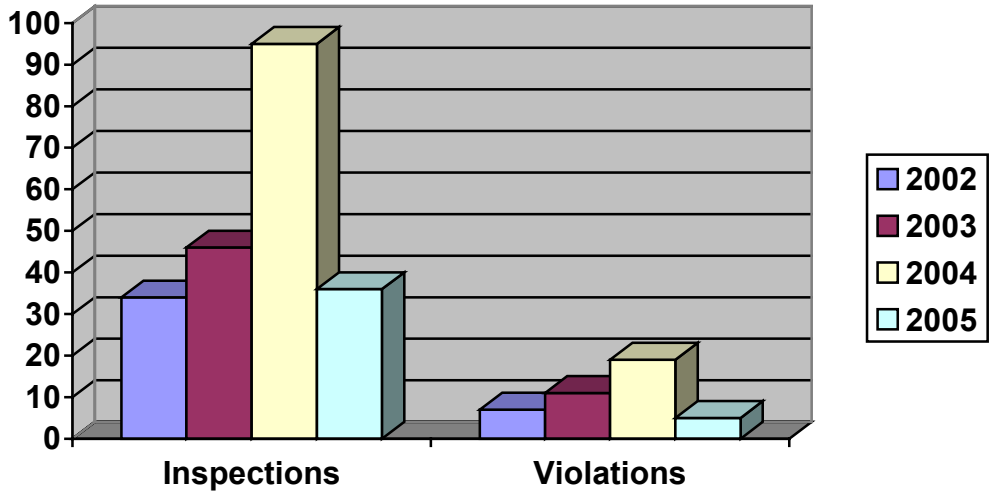
The data on the violations of the PPSHMA for the 2002-2005 period are presented in percentages of the total number of violations. Compared to previous years the share of the pharmacies opened in the country without authorizations in relation to the number of violations has decreased.



The data on violations of the ordinances of the Ministry of Healthcare for the 2002-2005 period are presented on fig. 18 in percentage of the total number of violations. Compared to 2004 a conclusion may be drawn that on the basis of the results of the inspections the share of the inappropriately stored medicinal products compared to the total number of violations has increased.



In 2005, 36 storehouses for wholesale trade with medicines were inspected (95 in 2004). The graphic representation shows the ratio for the 2002-2005 period between inspections and established violations.



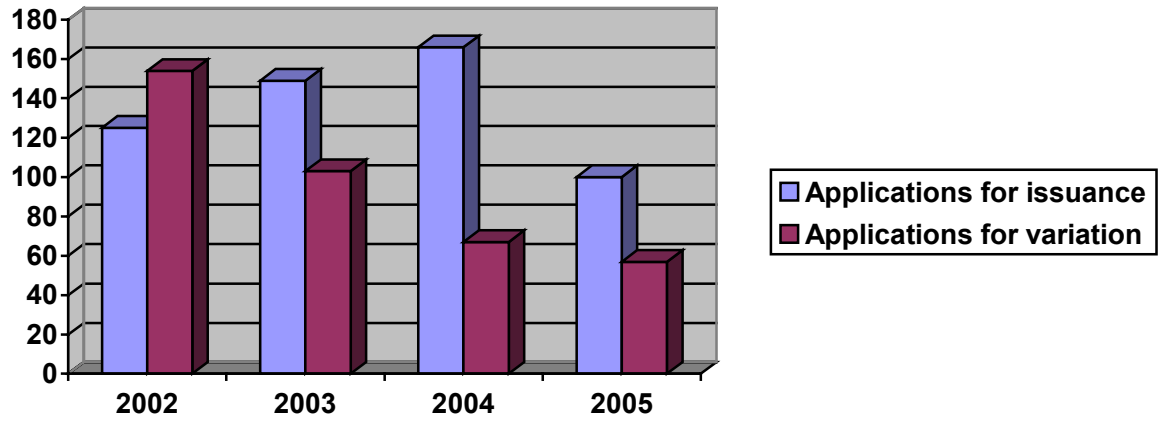
2 400 penal provisions were issued in 2005 (they were 7 500 in 2004). Three storehouses are in procedure for issuing penal court rulings.

In 2005 analogical violations were established in the storehouse network of wholesalers with medicines.

The shortage of a master-pharmacist in the hospital pharmacies is greater in 2005.

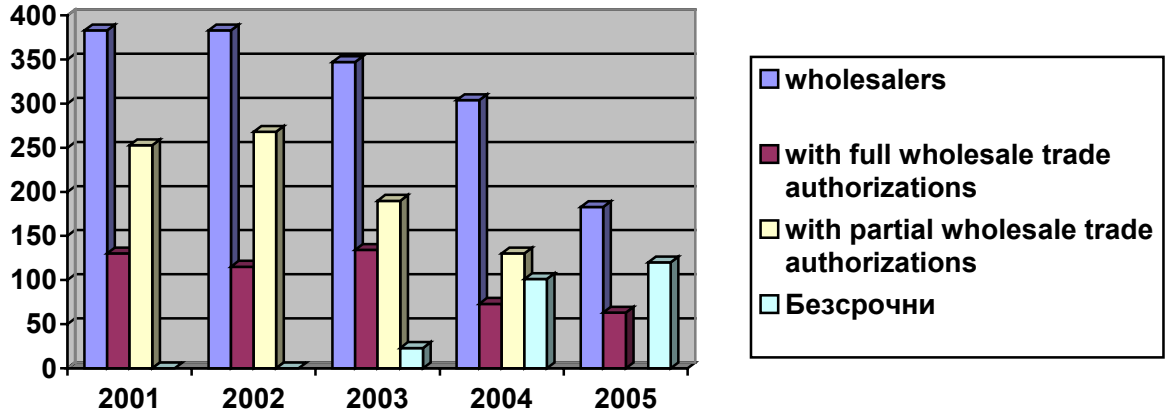
At present 4 master-pharmacists are working as inspectors in the respective Regional Inspectorates for controlling public health – in Lovech, Vratza, Kardzhali, and Sofia-district. In the Regional Inspectorates for controlling public health 8 master-pharmacists are working as inspectors. In the remaining 24 Regional Inspectorates for controlling public health in the country medical doctors are working as inspectors.

2.2. Activities related to the authorization of the wholesale trade in medicines.



In 2005 the chief inspectors from the department assessed 100 applications in total (166 in 2004) for issuing 21 (81 in 2004) authorizations without any limitation and 22 (18 in 2004) applications for issuing wholesale trade authorizations of medicines under art. 3 of the PPSHMA (medical devices). 57 wholesalers of medicines were reviewed and variations made (they were 67 in 2004).

Activity related to the assessment of applications and their accompanying documents for the 2002-2005 period.



During the period 21 wholesale trade authorizations without any limitation of medicines were issued (81 in 2004). Also 22 wholesale trade authorizations of medicines under art. 3, par. 5 of the PPSHMA (medical devices) were issued.

On the territory of the country by 31 December 2005 there were 183 (304 in 2004) companies with wholesale trade authorizations, which have 279 (416 in 2004) storehouses at their disposal. The decrease compared to the previous year is obvious.

Out of them:

- 63 wholesalers (73 in 2004) having 128 storehouses (173 in 2004) have full wholesale trade authorizations of medicines;
- 120 wholesalers (101 in 2004) having 151 storehouses (108 in 2004) have a wholesale trade authorization without any limitation in compliance with the last amendment of the PPSHMA.

Companies - wholesalers with medicines in the 2001-2005 period.

In compliance with the provision of art. 10A from the transitional and concluding provisions of the Act for the amendment and supplementation of the PPSHMA (State Gazette, No. 112 of 2003), the time limit of partial wholesale trade with medical devices authorizations is extended ex officio – 130 wholesalers with 135 storehouses.

New wholesale trade with medical devices authorizations have been issued – 19 wholesalers (42 in 2004) with 19 storehouses (42 in 2004).

2.3 Others.

Inspectors from the department have appeared before official bodies in Sofia, Pazardzhik, Kardzhali, Plovdiv, Pernik, Gabrovo, Veliko Tarnovo and Varna. Inspections were carried out together with the "National Police Service" Directorate and Sofia Directorate of Interior bodies and economy police. 18 alerts submitted to "BDA's green telephone" were processed concerning the activity of the "Control of trade in medicines" department. The employees attended qualification courses in compliance with the approved schedule. The data base with the issued wholesale trade authorizations is regularly filled in. Employees participated in the preparation of PPSHMA amendment and a draft of the Medical devices Act.

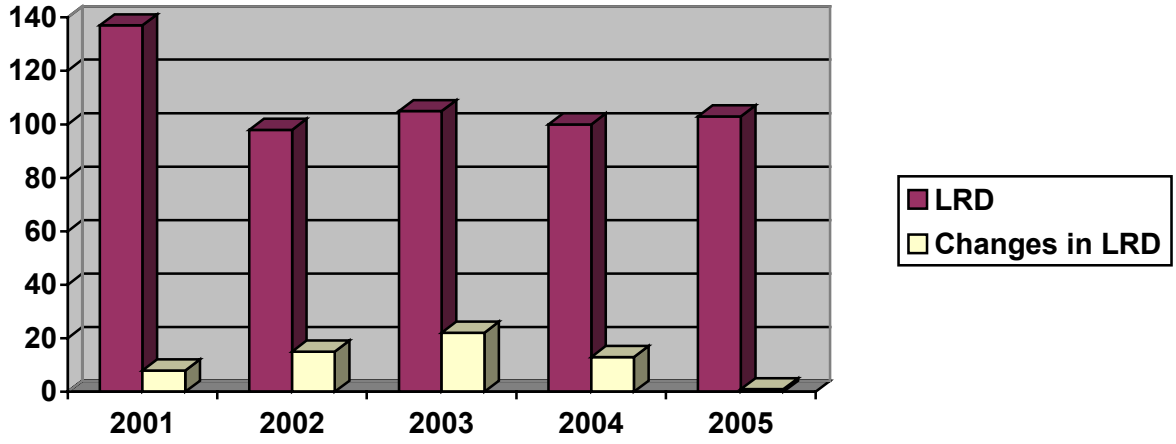
With respect to the professional training of inspectors in the sphere of the control of the distribution of medicines and with the aim of maintaining an up-date knowledge and practice, I consider it necessary that a more active participation in seminars and courses is organized.

2.4. Drugstores

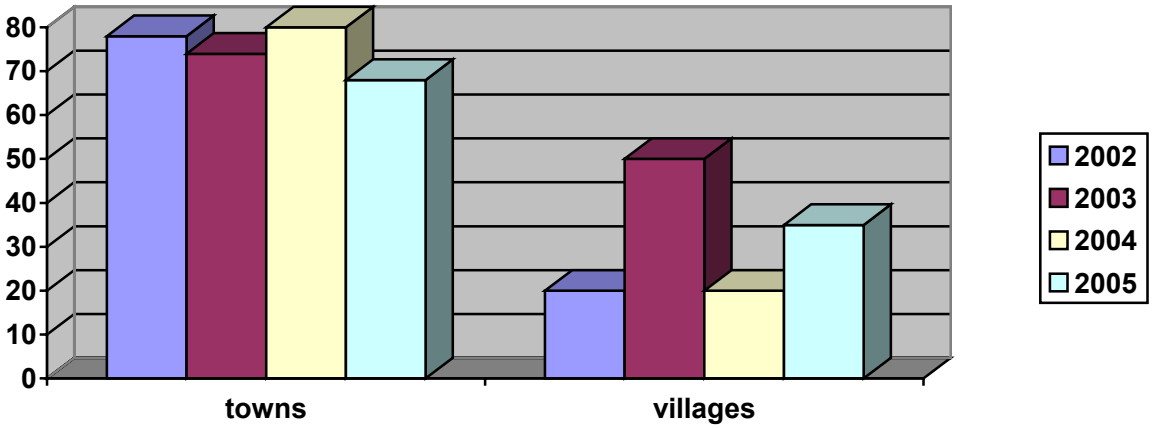
In 2005, 103 licenses for the registration of drugstores were issued (100 in 2004). One license for variations in issued licenses was issued (13 in 2004). One application was denied issuance of registration of a drugstore (1 in 2004).

The register of issued licenses for opening drugstores is regularly filled in. One drugstore was closed (3 in 2004), and 3 have temporarily suspended their activity in 2005 (1 in 2004).

The activity on registering drugstores is presented in the graphic representation. The abbreviation used in the graphic representation is LRD (License for the registration of a drugstore).



In 2005 a considerably greater number of inspections of drugstores were carried out compared to 2004. 31 drugstores were inspected (11 in 2004). The next graphic representation shows the distribution of drugstores in the country according to the town/village criterion for the 2002-2005 period.



III. Post-registration control of medicinal products.

The duties arising from the amended BDA statutory rules which concern the employees from the "Import and sales" department are as follows:

1. Coordinates the import and authorizes the sale of medicinal products on the territory of the Republic of Bulgaria;
2. Performs activities related to blocking and withdrawal of medicinal products which have not met the quality and safety requirements;

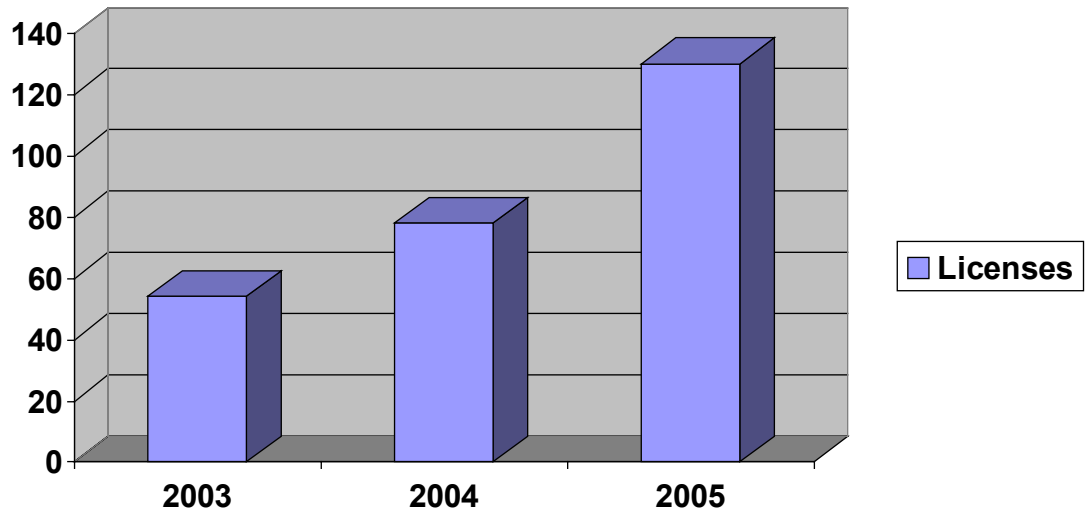
The employees from the “Import and sales” department at the “Control of the manufacture and trade in medicines” directorate participated in:

1. The process of issuing marketing authorizations of medicinal products on the territory of the Republic of Bulgaria via activities in the post-registration control stage;
2. blocking and disposal of medicinal products which have not met the quality requirements of the European warning System within EMEA (the data are annexed in the respective section);
3. working out answers on appeals of citizens, organizations and interested parties regarding different issues related to medicinal products;

Within their duties on coordinating the import of medicines,

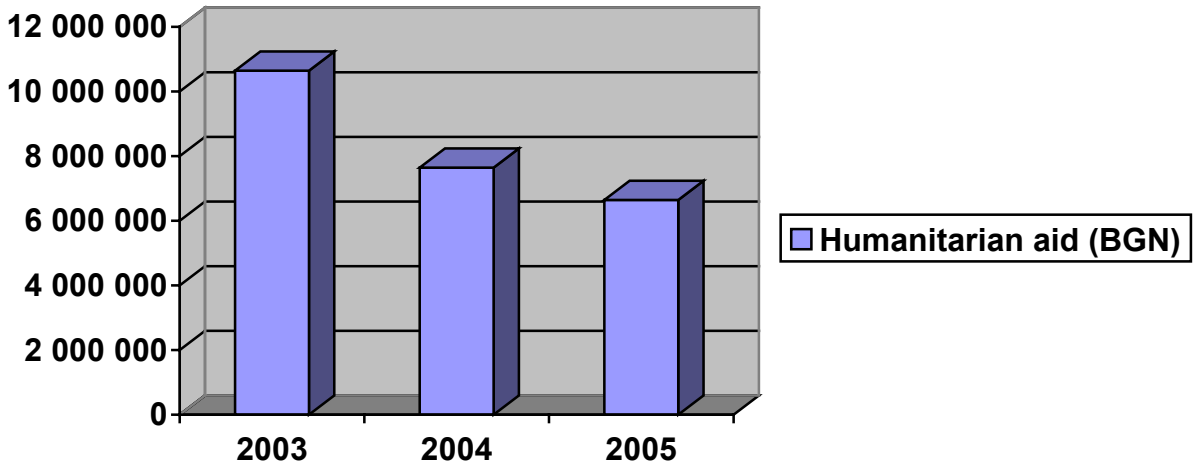
the employees from the “Import” department have processed a considerable number of documents, related to the import of medicinal products, as humanitarian aid and those under ordinance No.2 of the Ministry of Healthcare.

The graphic representation shows a comparison for the 2003-2005 period between the applications for the import of medicinal products under the terms and conditions of Ordinance No. 2 of the Ministry of Healthcare.



For the 2003-2005 period a considerable number of documents and applications for importing humanitarian aid were processed.

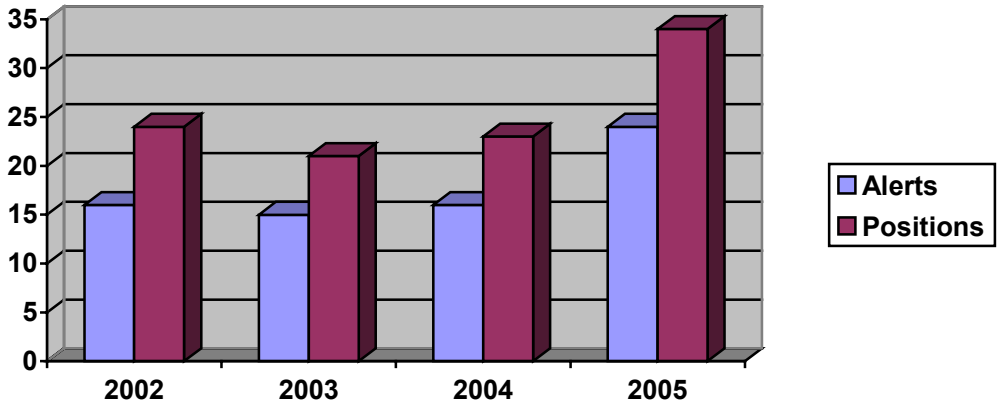
The graphic representation indicates the dynamics in the volume of import.



Activities related to the provisions of PPSHMA and Ordinance No. 5 of the Ministry of Healthcare.

Alerts on problems with the quality of medicinal products.

In the period 1 January 2005 – 31 December 2005, 24 alerts (16 in 2004) with 34 positions (23 in 2004) by the Regional Inspectorate for controlling public health, the medical institutions, citizens and trade representatives were submitted to the "Import" department of BDA's "Control of the manufacture and trade in medicines" directorate. The alerts made by the foreign Agencies for the control of medicines are presented below. The data show that in 2005 the number of alerts made concerning problems in the quality is considerably greater compared to 2004. The graphic representation shows the dynamics in the 2002-2005 period regarding the alerts /positions made throughout the country. The results from the assessment of the obtained information indicate a considerable increase.



The alerts made concerning deviations from the quality of medicinal products may be treated from a number of aspects:

Alerts related to not meeting the quality requirements:

Name	Manufacturer	Pharmaceutical form	Dosage	Risk degree
1	2	3	4	5
Augmentin	GlaxoSmithKline UK	Powd	475 mg/5 ml 70 ml	II
Miacalcic	Novartis Pharma Inc	Nasal spray	200 IU/dose 14 doses	III
Olynth	Pfizer HPC USA	Nasal spray	0.1% 10 ml	III
Xanax	Pharmacia NV/SA	Tabl.	0.5 mg x 30	III
Ibuprom	US Pharmacia	Tabl.	200 mg x 2 x 20 sach	III
Augmentin	GlaxoSmithKline	Tabl.film.	1 g x 14	III
Sortis	Pfizer HCP Corp	Tabl.film.	20 mg x 30	III
Tubocin	Balkanpharma Razgrad	Caps.	300 mg x 100	III
Pyrazinamid	KRKA	Tabl.	500 mg x 6	III
Clinoleic 20%	Baxter AG	Emul.inf.	20 % 500 ml	III
Elixir	Burumpharm India	Sol.	60 ml	III

CopperT CU380	Madex LLC	Dev	x 1	III
Benalgin	Balkanpharma Dupnitza	Tabl.	x 20	III
Puri-Nethol	GlaxoSmithKline	Tabl.	50 mg x 25	III
Sibelium	Janssen Pharmaceutica	Caps.	5 mg x 20	III
Eprex	Janssen-Cilag	Pre-filled syr.	3000 IU/0.3 ml x 6	III
Daktarin	Janssen-Cilag	Oral gel	20 mg/g 40 g	III
Co-Diovan	Novartis Pharma Serv.	Tabl.film.	80/12.5 mg x 14	III
Sedalgin Neo	Balkanpharma Dupnitza	Tabl.	x 20	III

The alerts made have been inspected by conducting the respective trials on the provided samples. Samples of the batches announced by the manufacturers were required. There was a timely response to all alerts. Compared to 2004 no alerts with a risk degree I were made. Throughout the reporting period 44 alerts (41 in 2004) were made by foreign control bodies on failure to meet the quality requirements. The tendency from 2004 is preserved.

Control agency (State)	Number of signals 2002	Number of signals 2003	Number of signals 2004	Number of signals 2005
1	2	3	4	5
France	23	37	11	10
Germany	2	2	1	1
Spain	4	1	2	2
Belgium	2	x	1	2
Norway	1	1	1	2
Canada	1	9	1	x

Sweden	x	1	1	1
USA	x	x	x	x
The Netherlands	x	1	3	1
Great Britain	x	4	3	5
Greece	x	2	1	4
Australia	1	x	x	x
Italy	2	8	2	3
Portugal	2	6	5	3
Ireland	1	1	x	x
Denmark	x	x	1	x
Lithuania	x	x	2	x
Switzerland	x	x	1	x
Slovakia	x	x	2	1
The Czech Republic	x	x	x	2
Finland	x	x	1	1
Poland	x	x	2	6
Total	39	74	41	44

Alerts related to the occurrence of adverse drug reactions when administering medicinal products:

In the “Control of the manufacture and trade in medicines” directorate at BDA 7 alerts were made concerning 10 products (they were 5 in 2004). They are presented in the table below.

Name	Manufacturer	Pharmaceutical form	Dosage	Entity/organization
1	2	3	4	5

Ultracortenol	Novartis Pharma	Drops eye	5 mg/ml 5 ml	“Salvis pharma”
Voyager RX Ballon Dilatation Catheter	Guidant Corp.	Devise	1.5 mm – 3.5 mm	“Medimag MS”
Amaryl	Hoechst	Tabl.	2 mg x 30	Regional Inspectorate for controlling public health
Helnflon	Eastern Medikit	devise		Regional Inspectorate for controlling public health
Glucose	Balkanpharma - Troyan	Sol. Inf.	10% 500 ml	Regional Inspectorate for controlling public health
Natrii Chloridum 0.9% + Glucose 5%	Balkanpharma - Troyan	Sol. Inf	500 ml	Regional Inspectorate for controlling public health
Ringer	Balkanpharma - Troyan	Sol. Inf	500 ml	Regional Inspectorate for controlling public health
Cefazolin i.m./i.v.	Balkanpharma – Razgrad	Powd. Inj.	1 g	Regional Inspectorate for

				controlling public health
Gentamicin	Sopharma	Sol. Inf	80 mg/2 ml	Regional Inspectorate for controlling public health
Penicillin G i.m./i.v.	Balkanpharma – Razgrad	Powd. Inj.	1 MIU	Regional Inspectorate for controlling public health

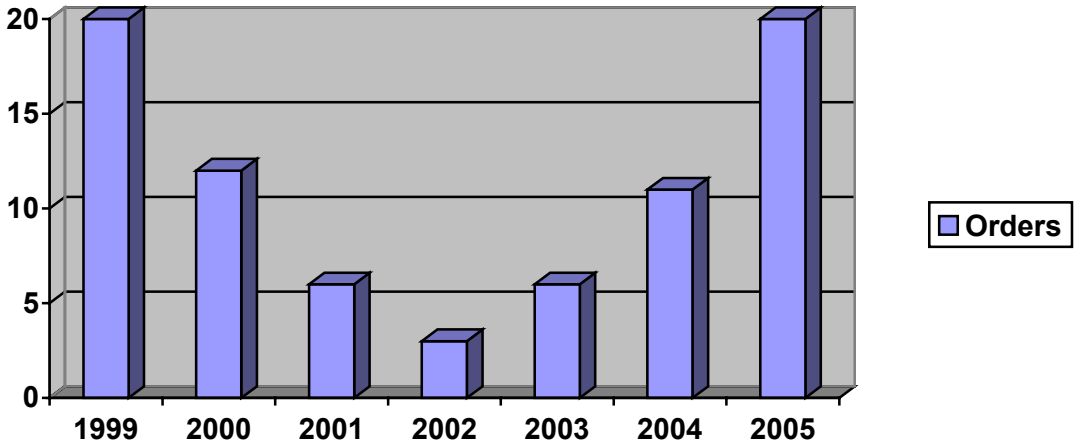
With respect to submitted applications for disposal of medicinal products whose shelf life has expired, 50 inspections under the terms and conditions of Ordinance No. 28 of the Ministry of Healthcare were carried out by the chief inspectors from the department in 2005.

Orders issued related to the quality of medicinal products:

The following orders were issued by the General Executive of BDA in 2005:

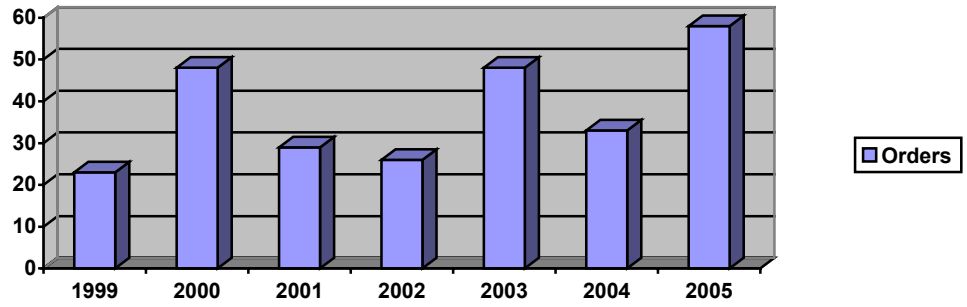
Orders for blocking – 20.

A graphic representation which compares the orders issued for blocking medicinal products under the terms and conditions of Ordinance No. 5 of the Ministry of Healthcare for the 1999-2005 period.



Orders for disposal – 58.

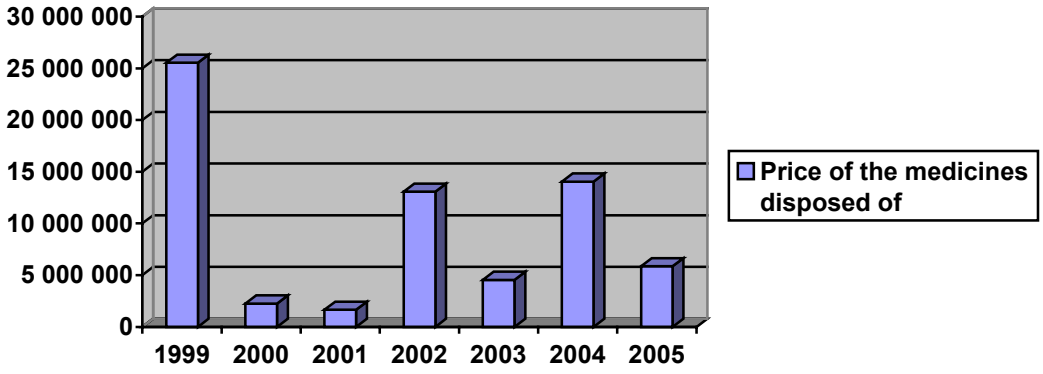
A graphic representation which compares the orders issued for disposal of



medicinal products under the terms and conditions of Ordinance No. 5 of the Ministry of Healthcare for the 1999-2005 period.

The medicines disposed of in 2005 amount to 5 854 111 BGN (14 032 331 BGN in 2004).

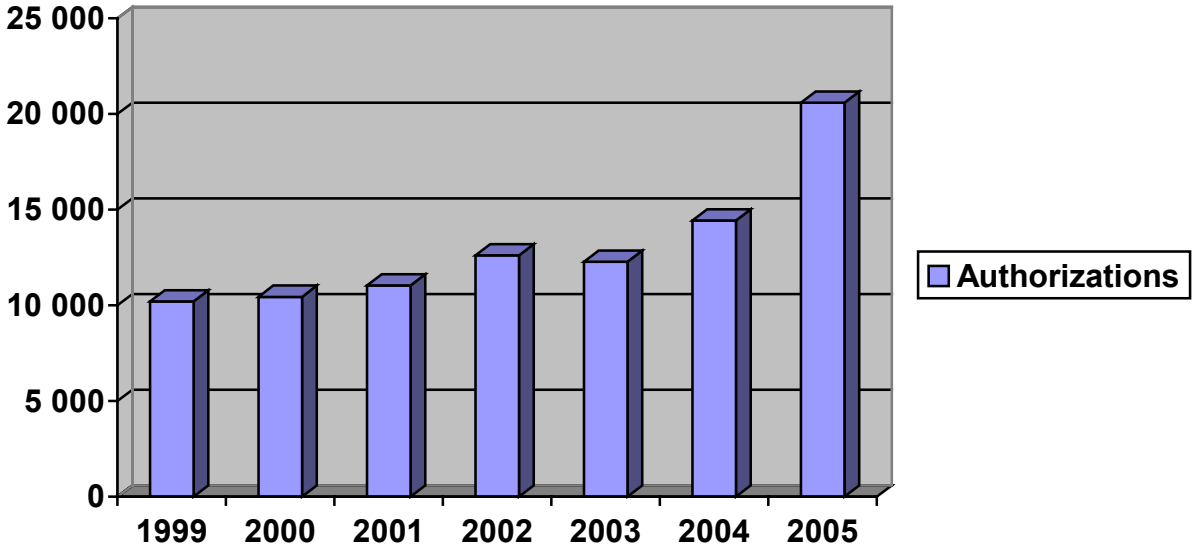
Data on the medicinal products disposed of for the 1999- 2005 period.



In spite of the increase of the number of orders for disposal there is a considerable decrease in the value of the medicinal products disposed of.

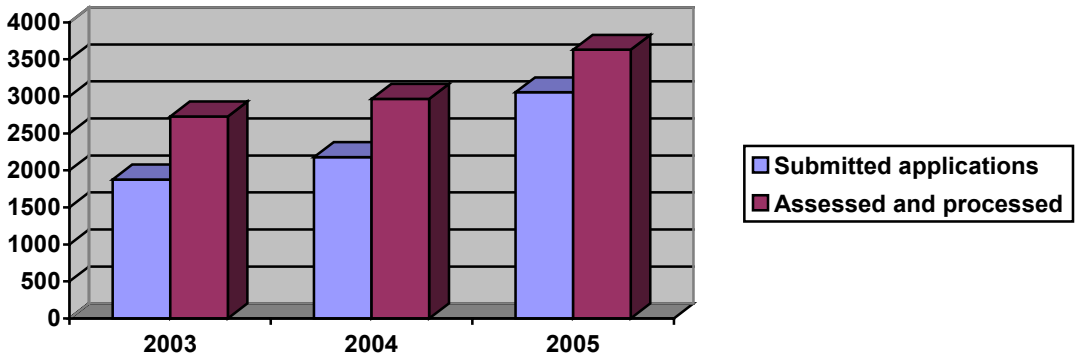
20 592 sales authorizations were issued (14 433 in 2004).

A graphic representation which compares the issued sales authorizations of medicinal products under the terms and conditions of PPSHMA and Ordinance No. 29 of the Ministry of Healthcare for the 1999- 2005 period.



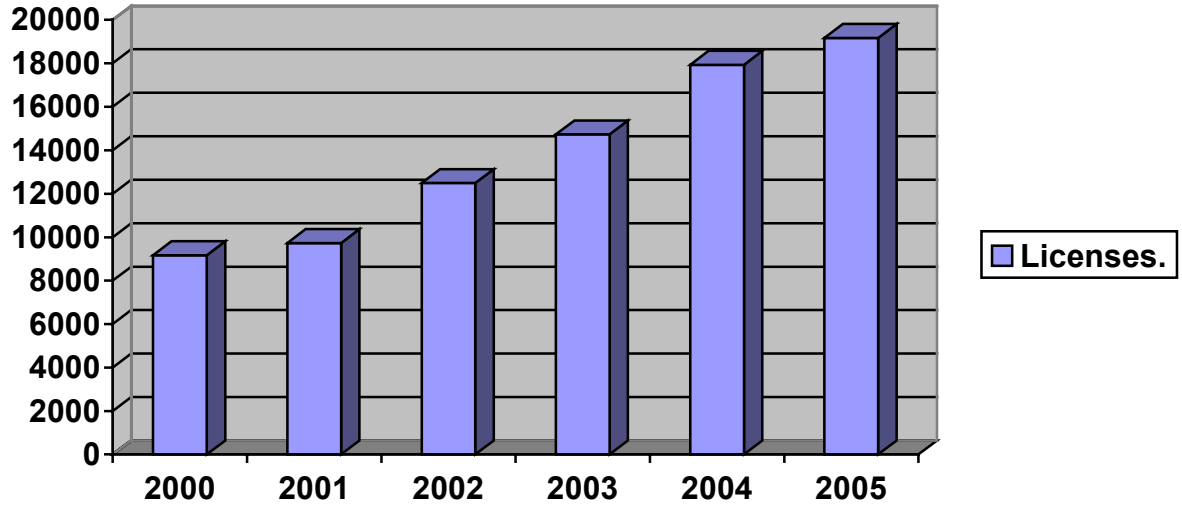
3 055 applications for issuing sales authorizations and their accompanying documents and samples (2 179 in 2004) were submitted and processed in 2005. In compliance with the approved standard operating procedure the samples were returned together with accompanying letters – 3 630 (2 966 in 2004).

The indicated number of issued sales authorizations includes 503 sales authorizations of batches of medical devices and 3 sales authorizations of in vitro diagnostic medical devices. Data for the 2003-2005 period.



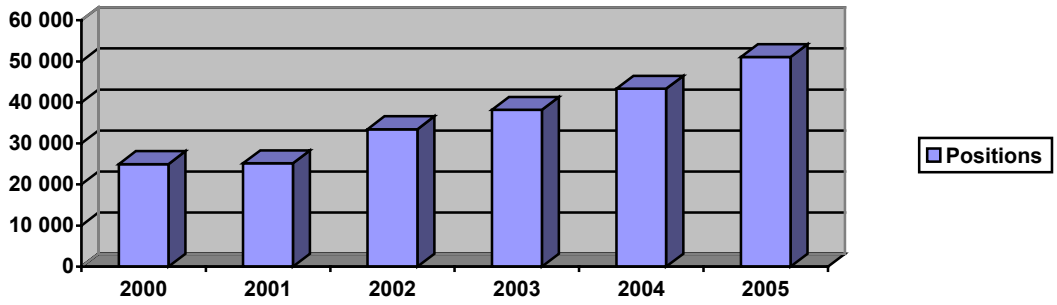
Coordinated licenses for the import of medicines.

19 167 import licenses were coordinated and assessed in 2005 (17 929 in 2004) under the terms and conditions of Regulation No. 233 of the Ministry of Healthcare of 8 November 2000 which include 51 042 positions (43 341 in 2004).



Number of licenses for import for the 2000-2005 period.

The ratio between coordinated positions in the import licenses for the 2000-2005 period.



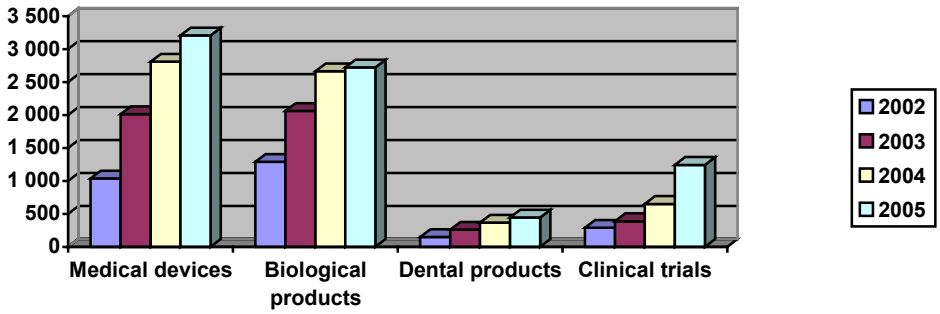
During the reporting period the import licenses indicated not only the typical medicinal products but the following categories as well:

- for medical devices – 3 207 (2 809 in 2004)
- for biological products – 2 723 (2 664 in 2004)
- for dental products – 444 (367 in 2004)
- for clinical trials – 1 243 (650 in 2004)
- for not authorized medicinal products – 130
- for humanitarian aid – 62 (67 in 2004)

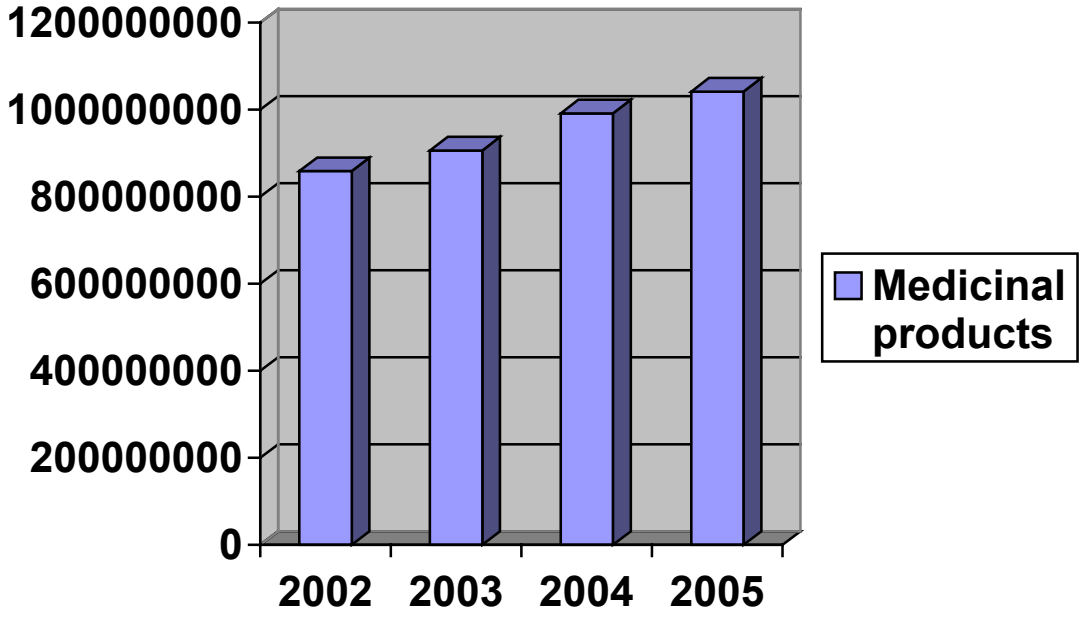
The data on the import of medicines on the territory of Bulgaria for 2005 indicate an **import volume of 1 228 932 654 BGN.**

As a total amount **the import volume has increased by 4.37 % compared to 2004**.

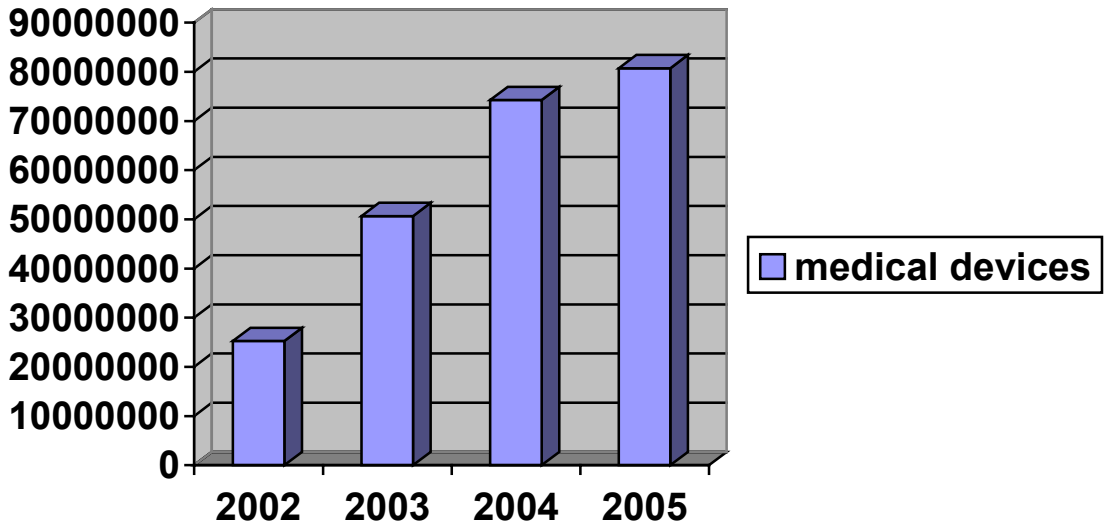
The next graphic representation shows the ratio between the years 2002 and 2005 for some of the products indicated above. It should be taken into consideration that the import volume that will be presented includes the amounts kept in storehouses under customs' control. Practically these quantities are applied for due to the time limit of the import license (three months according to a regulation of the Council of Ministers).



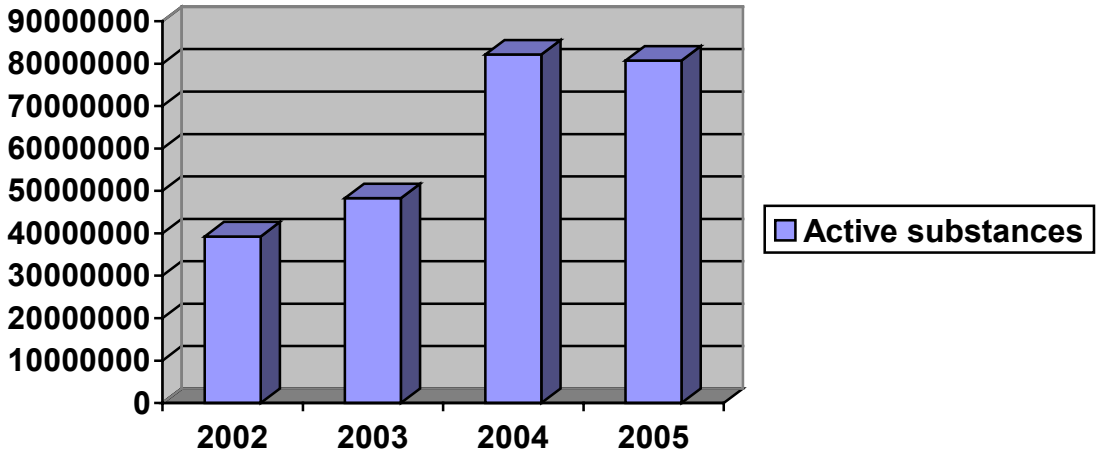
The dynamics of applications for the import of medicinal products for the 2002-2005 period.



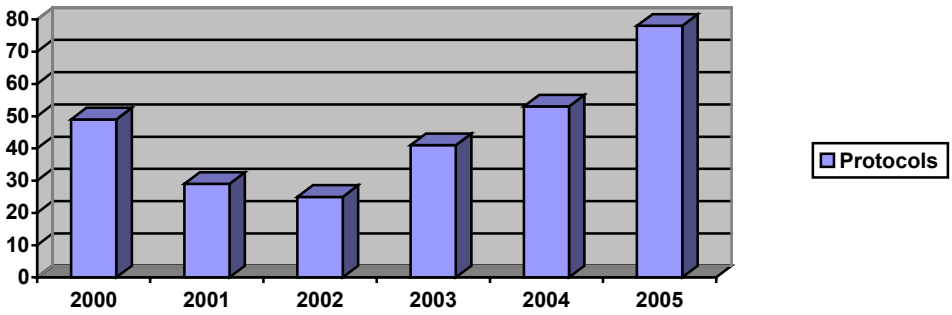
Import applied for of medical devices for the 2002-2005 period.



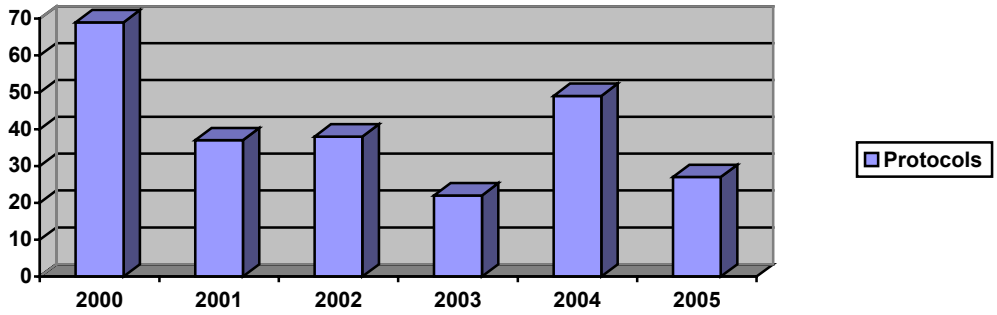
Import applied for of active substances for the 2002-2005 period.



Current control of batches for the 2000-2005 period.



Control of batches after an alert for the 2000-2005 period.



The issuance of sales authorizations was carried out in 2005 via using the developed module in BDA's data base for issuing sales authorizations authorized for use in the country.

The employees from the "Import" department of the "CMTM" directorate took part in inspections of the country's pharmacy and storehouse network as well as in inspections of manufacturers of medicinal products.

The data from 2005 indicate a stable tendency of increasing the activities in the sphere of authorizing the import and sale of medicines.

IV. Control of the clinical trials with medicines.

The control of the clinical trials with medicines is carried out in compliance with the provisions of the PPSHMA and Ordinance No. 14 of the Ministry of Healthcare on Good Clinical Practice of the year 2000.

The activities are performed by Lora Nikolova, MD and master pharmacist Emilia Lambova. The data indicate a considerable increase of the interest in conducting clinical trials in the country in 2005.

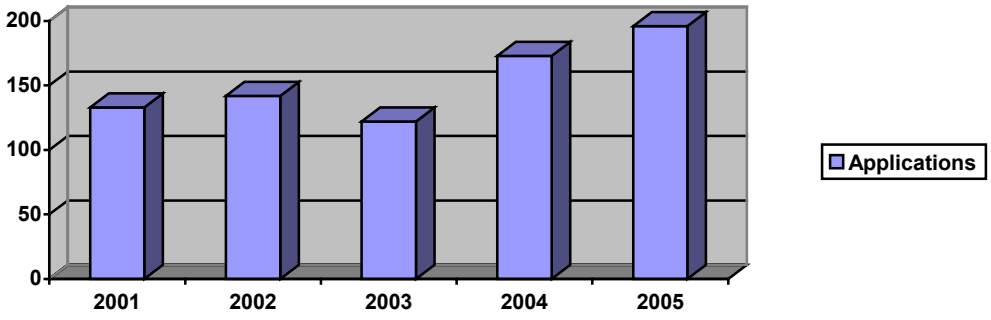
In 2005 a lot of international events in the sphere of clinical trials were organized and specialists from the Directorate took part in them.

The control on the conduction of clinical trials is related to:

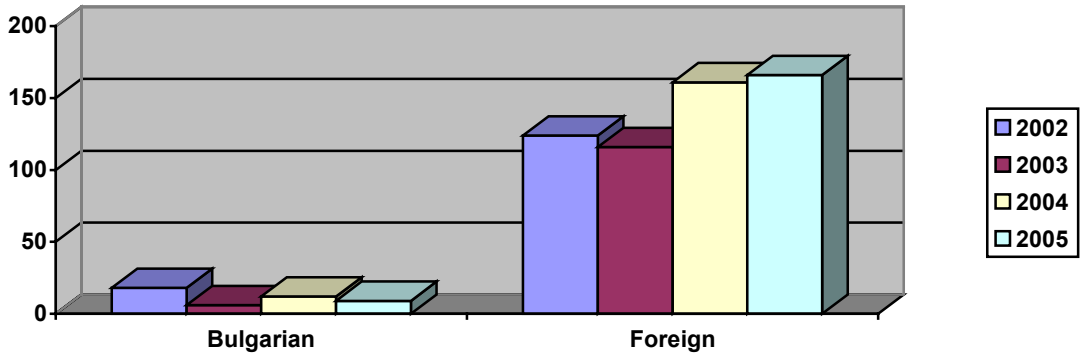
Reception and processing of documentation on conducting clinical trials.

In 2005, 196 applications for conducting clinical trials were submitted to BDA (173 in 2004).

Number of submitted applications in the 2001 – 2005 period



The ratio between applicants in the 2002 -2005 period.

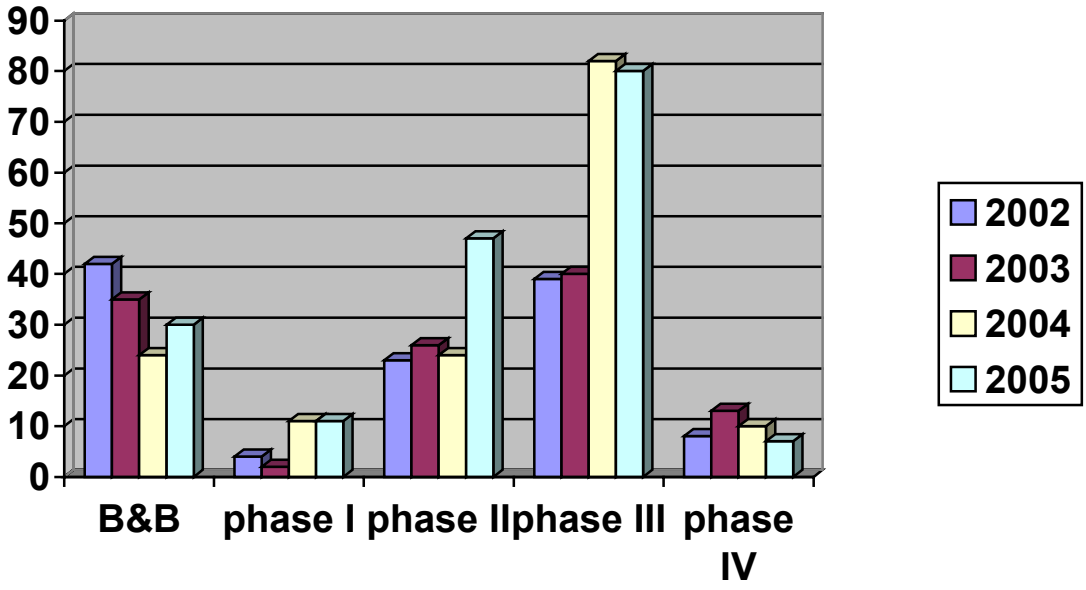


175 clinical trials of medicines were authorized during the period and BDA approved 7 drafts, while 168 were approved by the Specialized Committee for Authorizing Clinical Trials. 9 of the applications (12 in 2004) were by a contracting authority which was a Bulgarian company while the rest 166 – by foreign contracting authorities (161 in 2004).

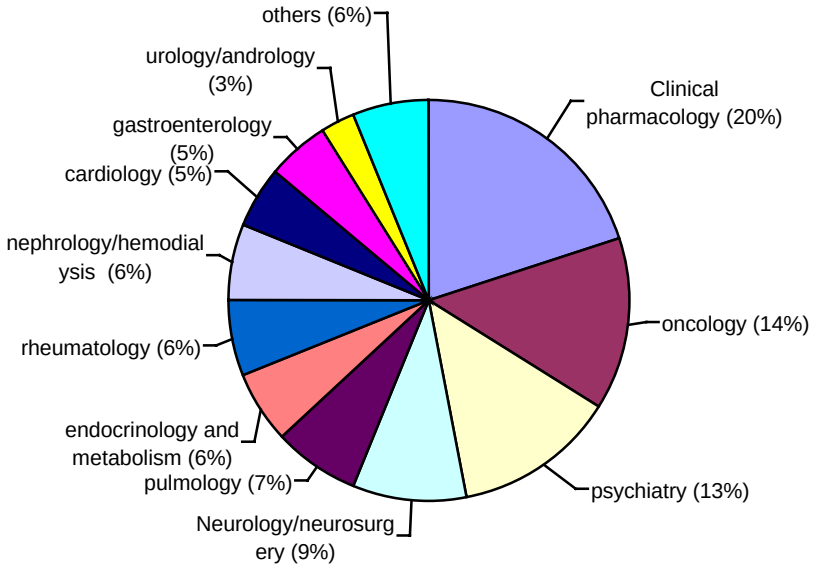
The applications of the contracting authorities are classified as follows:

- 30 for establishing bioavailability/bioequivalence
- 11 for clinical trials phase I/Pharmaco-kinetics
- 47 for clinical trials phase II;
- 80 for clinical trials phase III;
- 7 for clinical trials phase IV.

The data from the clinical trials carried out indicate that the basic part of the foreign contracting authorities refers to conducting clinical trials phase III. The research applied for by Bulgarian manufacturers is directed towards data on bioequivalence of the tested medicinal products.



The authorized clinical trials are classified according to the therapeutic group/medical sphere, as follows:



Out of the authorized clinical trials 48 are one-center, while 126 are multi-center.

24 meetings of the Specialized Committee for Authorizing Clinical Trials were held in 2005 and they took 316 decisions. 175 of them were for conducting clinical trials, 135 are decisions for variation in issued authorizations for clinical trials and 6 are decisions for denying the conduction of clinical trials.

The denial decisions concern two studies for bioavailability/bioequivalence, one study on pharmacology (phase 1), one study in phase II and two studies in phase III.

The decisions for variation include 75 decisions for variation in the protocol of an authorized clinical trial, 52 decisions for adding new centers and 8 decisions for a substitution of a chief researcher, sponsor or research organization on contract of an authorized clinical trial.

A preliminary assessment is made by employees from the directorate of the administrative completeness and compliance with the requirements of the PPSHMA and Ordinance 14 before an assessment is made by experts from the Specialized Committee for Authorizing Clinical Trials of all submitted documentations for variation in authorized clinical trials.

There have been statements prepared on drafts for scientific research on the necessity to authorize a medicine as a clinical trial– 5 drafts.

Control on the conduction of clinical trials.

16 inspections were made in 2005 (6 in 2004). The following inspections were carried out:

- 4 inspections on the activity of the Local Ethics Committees;
- 14 inspections on the manner of conducting the clinical trials.

All inspections have been carried out in compliance with BDA’s approved standard operating procedures. 10 inspections were carried out on the correspondence conditions and quantities of medicinal products used in clinical trials.

In relation to Bulgaria's EU accession and BDA's joining the EMEA groups two employees from the "Control of the manufacture and trade in medicines" directorate – Clinical trials participated in the EudraCT group – a European data base on clinical trials.

Representatives of the "Control of the manufacture and trade in medicines" directorate – Clinical trials participated as lecturers in two forums for the training of researchers, organized by the Bulgarian Association for Clinical Trials.

During the reporting period the following standard operating procedures were up-dated and came in force:

- reception, assessment and movement of the documentation on authorizing clinical trials under art. 37, par. 1,p.1 and correspondence with the applicants.
- Making inspections on the conduction of clinical trials in the Republic of Bulgaria – inspection of a research center.

One employee is attending a post-graduate course on clinical pharmacology.

For the first time in 2005 a full list of the requirements set to the form and contents of the documentation on authorizing clinical trials was published on BDA's web-page. This led to a considerable improvement of the quality of the submitted documentation, facilitated the administrative validation of the applications and led to shortening the time limits for assessment.

The up-dated recommendable SOP for local ethics committees were published on BDA's web-page, as well as the list of data available in BDA on local ethics committees with approved SOP.

One employee took part in a working party on preparing a draft for the PPSHMA.

V. Other activities.

A lot of joint inspections with the MI bodies were carried out in 2005.

A lot of references have been worked out concerning queries made by the regional directorates of the Ministry of Interior on different pre-trial investigations.

Employees from the directorate have participated as experts in different joint inspections with the MI bodies on issues related to the distribution of medicines.

In the “Control of the manufacture and trade in medicines” directorate the following state registers are filled in under the terms and conditions of the PPSHMA:

- register on the issued manufacturing authorizations of medicines - under the terms and conditions of art. 13 of PPSHMA;
- register on the issued licenses for the registration of drugstores - under the terms and conditions of art. 81^{E} of PPSHMA;

At the same time there are registers in the directorate on:

- the issued authorizations for conducting clinical trials - under the terms and conditions of Ordinance No. 14 of the Ministry of Healthcare;
- the issued authorizations for sales of medicinal products - under the terms and conditions of Ordinance No. 29 of the Ministry of Healthcare;
- issued orders for the disposal of medicinal products - under the terms and conditions of Ordinance No. 28 of the Ministry of Healthcare;
- issued orders for the blocking and withdrawal of medicines from the country’s pharmacy and health network - under the terms and conditions of Ordinance No. 5 of the Ministry of Healthcare;

References are worked out on a three-month period regarding the authorizations (licenses) for the import of medicines on the territory of the Republic of Bulgaria. These references are submitted to the Ministry of Healthcare and the Ministry of Economics in compliance with an order issued by the Minister of Healthcare.

In compliance with the Ordinance for the amendment and supplementation of ordinance No. 29 of the Ministry of Healthcare of the year 2000, together with the “Marketing authorizations” Directorate inspections are carried out of the registration status of medicinal products which have been applied for sale in packages on which the information under art. 13, par. 1 of ordinance No. 7 of the Ministry of Healthcare of the year 2000 is not presented in Bulgarian.