STATE AGENCY OF MEDICINES

ANNUAL REPORT 2010

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2010

CONTENTS

ABBREVIATIONS

SAM	State Agency of Medicines
MH	Ministry of Health
CM	Cabinet of Ministers
EMA	European Medicines Agency
EU	European Union
NP	National Procedure
MRP	Mutual Recognition Procedure
DCP	Decentralised Procedure
SAMIS	State Agency of Medicines Information System
ADR	Adverse Drug Reaction
VIC	Vaccine Induced Complication
LIC	Infectology Center of Latvia
CPP	Certificate of a Pharmaceutical Product
WHO	World Health Organisation
MD	Medical Devices
MAH	Marketing Authorisation Holder

STATEMENT FROM THE DIRECTOR OF THE STATE AGNECY OF MEDICINES

In 2010 the structural changes, that were initiated and planned in the previous year, were implemented in the State Agency of Medicines (SAM). The same as in other institutions, work effectiveness is an important indicator in SAM. But particularly important in this time of limited finances and human resources is the work efficiency ensuring that tasks are completed by utilising the available resources as rationally as possible. We are constantly searching for ways of improving work procedures by making them logistically rational and fast. Therefore, in accordance with the December 22nd 2009 Order of SAM No. 1-6/56 a new structural scheme is in effect since 04.01.2010 (see Appendix No. 1).

In essence it is an inner restructuring of SAM and it is based on the analysis of work procedures, staff member work load, effectiveness and efficiency. It mainly affected the Human Medicines Registration Department by formation of 6 functional groups (sectors) whose staff members are united to carry out a collective work assignment with a definite distribution of responsibility and supervision (see Appendix No. 2). The organisation of work procedure flow was also changed to increase work effectiveness.

In February 2010 a client service point was introduced in the Administrative Resource Management and Documents Management Department to provide services for clients at a single place, including submission and acceptance of documents and providing consultations regarding matters where a special meeting with experts or administration is not necessary.

In 2010 changes were made in several legislative norms that affected the functions and procedures of SAM. The approval of advertisement material in SAM for medicines before distribution was abolished (amendments to the Pharmaceutical Law 01.12.2009 came in effect in 01.01.2010). It is justified by the surveillance function that remains pertaining to the Health Inspectorate.

Significant reforms in SAM were related to the implementation of the July 12th 2010 Cabinet of Ministers (CM) Regulation No. 388 “Regarding the Conception “A United State Surveillance of Circulation of Veterinary Medicines”” and the following August 24th 2010 CM Order No. 500 “Regarding the Plan of

Action "On Adoption of Ministry of Health Functions in the Field of Veterinary Medicines"". SAM had to ensure a successful transfer of functions according to the approved schedule. In accordance with this Order the Veterinary Medicines Evaluation Department was eliminated at the end of the year.

In accordance with the 13.10.2010. Ministry of Health Order No. 194 "Regarding the Internal Audit System" the audit structural unit of SAM was eliminated. In the future the internal audits of SAM will be planned and carried out by the appropriate MH department.

From September 6th until September 8th benchmarking was carried out in SAM to evaluate it and to compare it to other Agencies in the European states. Every 4 years the 45 Agencies within the European Medicines Regulatory Network are evaluated and compared with each other according to certain criteria.

It required significant preparation that included composing self-evaluations and sending them to the team of auditors. Already during this preparation we could see our weak points and begin thinking about introducing newly defined procedures.

SAM was also involved in the audit of functions organised by the State Chancellery and carried out following the November 17th 2009 Order No. 487 from the President of Ministers Valdis Dombrovskis "Regarding Audit of Functions Group and Performing Audit of Functions for Surveillance of Merchants". We were actively involved in the discussions regarding the audit report and in the development of suggestions.

As in previous years, we have also carried out client and staff member surveys. The results are analysed and discussed at a collective staff member meeting and are taken into account to improve cooperation, quality of services, as well as satisfaction of staff members.

Significant changes in the financing of SAM activities were related to the amendments to 17.01.2006. CM Regulation No. 61 "Regulations Regarding the State Agency of Medicines Publicly Available Paid Service Pricelist" (15.09.2008. CM Regulation No. 745). Section 4 of this edition of CM Regulations includes an exemption from the post-marketing monitoring fee (Ls 30, 100 or 350 depending on the product), if the gross revenue for the medicinal product during the previous year does not exceed Ls 1500 and the medicinal product is necessary to ensure therapy. We have received very many applications for granting exemption from fee to medicinal products. Basing on the aforementioned section, the total sum that has not been collected in the budget (due to the grant of exemption from fee) is Ls 129 150.

The possibility of receiving this exemption gives support to companies so that they would be interested in maintaining their products in the Drug Register even when the consumption of said products for some reason is small.

SAM budget in 2010 consisted only of our own income from provision of paid services.

I wish to express gratitude to every staff member of SAM for their accomplishments in 2010.

The reward for a work well done, is to have done it.

Inguna Adoviča

1. GENERAL INFORMATION ON THE STATE AGENCY OF MEDICINES

1.1. Legal status of the State Agency of Medicines

SAM is a State institution under the supervision of the Ministry of Health of the Republic of Latvia that carries out evaluation, marketing authorisation, monitoring, control and regulation of distribution of medicinal products in Latvia.

The operation of SAM is regulated by the State Administration Structure Law, Public Agency Law, Pharmaceutical Law, Cabinet of Ministers Regulation No. 1006 "Statutes of the State Agency of Medicines" adopted on December 7th 2004 and other normative acts.

1.2. Functions of the State Agency of Medicines

The operational objective of SAM is to ensure the availability of effective, safe and qualitative medicinal products to the citizens of Latvia.

Functions of SAM:

- ensure that only effective, safe and qualitative medicinal products are included in the Drug Register by performing expertise on marketing authorisation/renewal and variations documentation;
- ensure inspection of compliance, certification and licensing of companies manufacturing and distributing medicinal products;
- monitor the safety of medicines consumption, control the quality of medicines and ensure risk minimisation measures;
- monitor import, export, transit and distribution of medicines in the state by issuing permits and gathering data on consumption of medicines;
- ensure evaluation of clinical trial projects for medicines, issue authorisation for conduct of clinical trials in Latvia and monitor their compliance;
- perform evaluation of compliance, registration and monitoring of safety of medicinal devices;
- provide the society and specialists with objective and thorough information regarding medicines, their use and ensure data exchange;
- operate in the European medicines network by taking participating in work-sharing, complying with the collective standards and procedures and by cooperating with other European and international organisations.

1.3. The main objectives of the year of review

- Develop a long-term strategy for the period 2011-2015.
- Implement the continuously changing and updated legislation, defining the appropriate rational work procedures, clearly defining the holders of the process, distribution of tasks and the responsible persons.

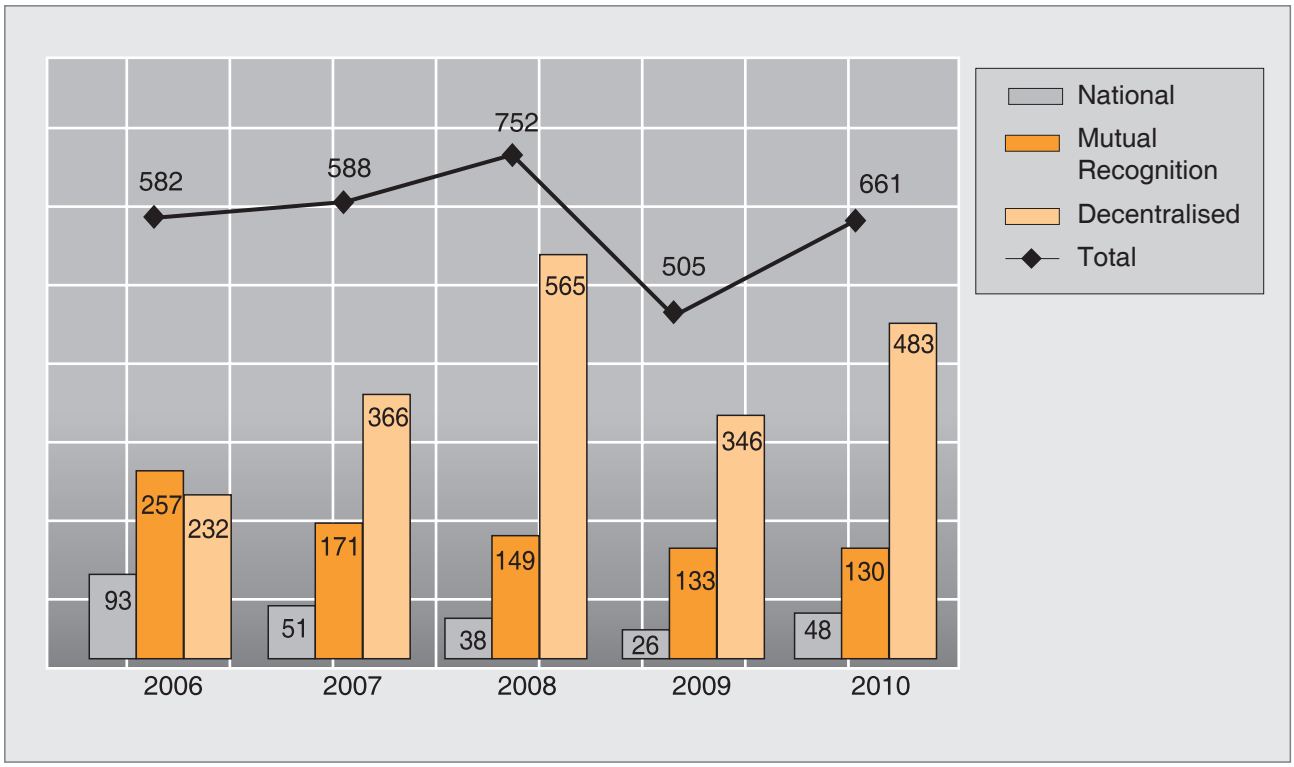
- To full extent ensure the performance of functions adopted during the reorganisation by providing extra training to staff members, developing rational procedures and integrating them in the SAM Quality System, as well as cooperating with the new clients in a constructive manner.
- Take more active part in the mutual recognition and decentralised authorisation procedures of medicines as a Reference Member State.
- Also take active part in other international cooperation projects (evaluation of safety information, quality control of medicines, evaluation of paediatric data, development of guidelines).
- Improve and update SAMIS, within our abilities ensure the completion of special requests from clients and supplement the section of publicly available information.
- Actively participate in the support for implementation of the e-health projects, for example, support the project for development and introduction of e-prescription information system.
- Ensure the submission of marketing authorisation documentation in a definite electronic format (eCTD) for the human sector and in any electronic format for the veterinary sector, as well as broaden the possibilities for clients to submit and receive documentation in electronic format.
- Ensure data exchange with European data-bases for data regarding medicinal products, veterinary medicinal products, medical devices, clinical trials, manufacturers, distributors and tissue, cell and organ centres (undertake the commitments stated by the *Memorandum of Understanding on the Exchange of information in the context of EU Telematics*).
- Ensure inspection of compliance of pharmacovigilance systems after they are defined by law.
- Ensure and coordinate the development of the list of active substances and excipients in Latvian, involving in the process academic forces and the State Language Center.
- Plan on initiating mutual recognition procedure with Canada regarding good manufacturing practice.
- Prepare for and ensure the benchmarking of SAM by representatives of Member States in September of 2010.
- Improve inter-institutional cooperation and communication with professional associations of doctors, veterinary doctors and pharmacists, academic and scientific institutions as well as the society.
- Continue to improve the technical possibilities and content of the SAM website and expand the communication possibilities on the public website.

2. RESULTS OF OPERATION OF THE STATE AGENCY OF MEDICINES

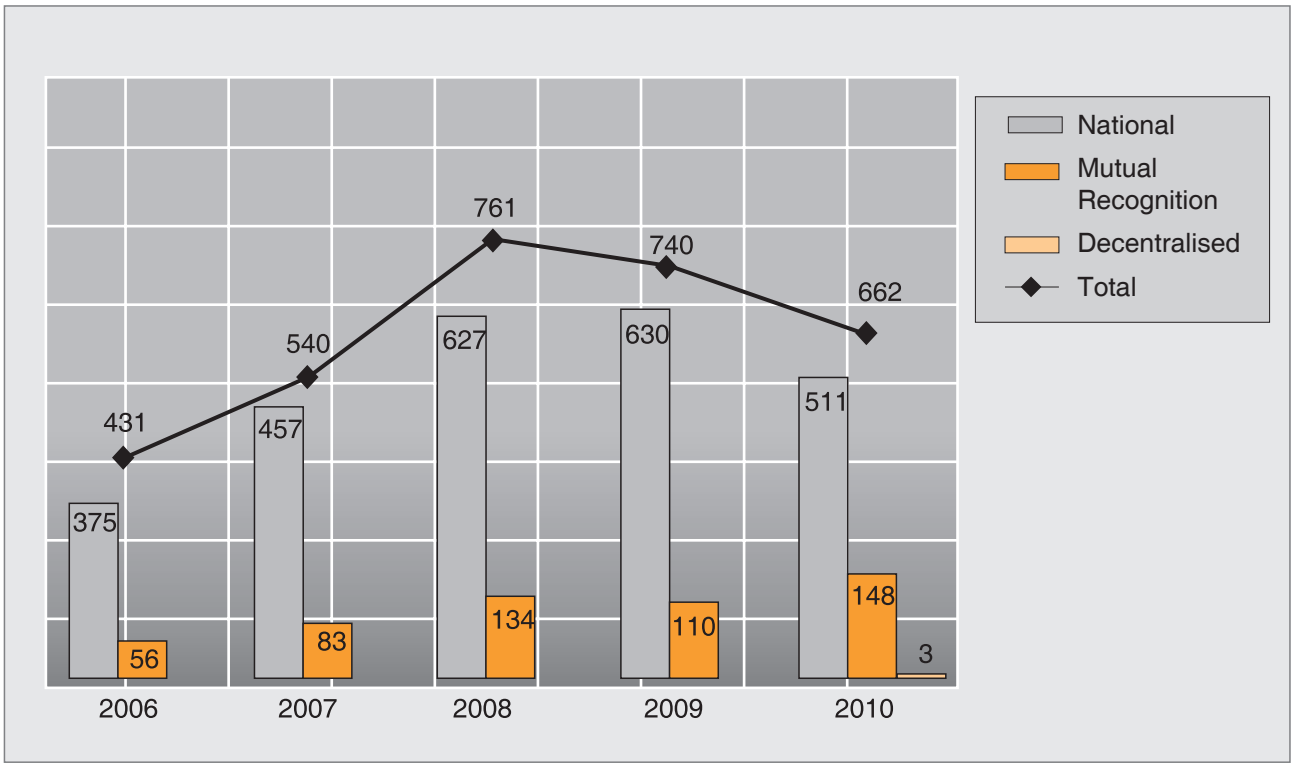
2.1. Authorisation of Medicines

In 2010 by evaluating documentation on quality, safety and effectiveness of medicines SAM has carried out expertise more than 2000 times on general, chemical and pharmaceutical, as well as preclinical and clinical sections of the documentation of medicines. Evaluation reports on 559 medicines have been prepared for the SAM Commission for Registration of Human Medicines for adoption of a decision regarding marketing authorisation and renewal of medicines in the national procedure. In 2010 Latvia has completed one procedure with a positive outcome as a Reference Member State and has initiated three mutual recognition procedures. Last year Latvia has also completed two type II variation procedures as a Reference Member State. In 2010 SAM carried out 661 marketing authorisation procedures and 662 renewal procedures. We have received a total number of 296 applications for marketing authorisation. In comparison with the previous years the number of applications for marketing authorisation has decreased.

Number of marketing authorisation procedures



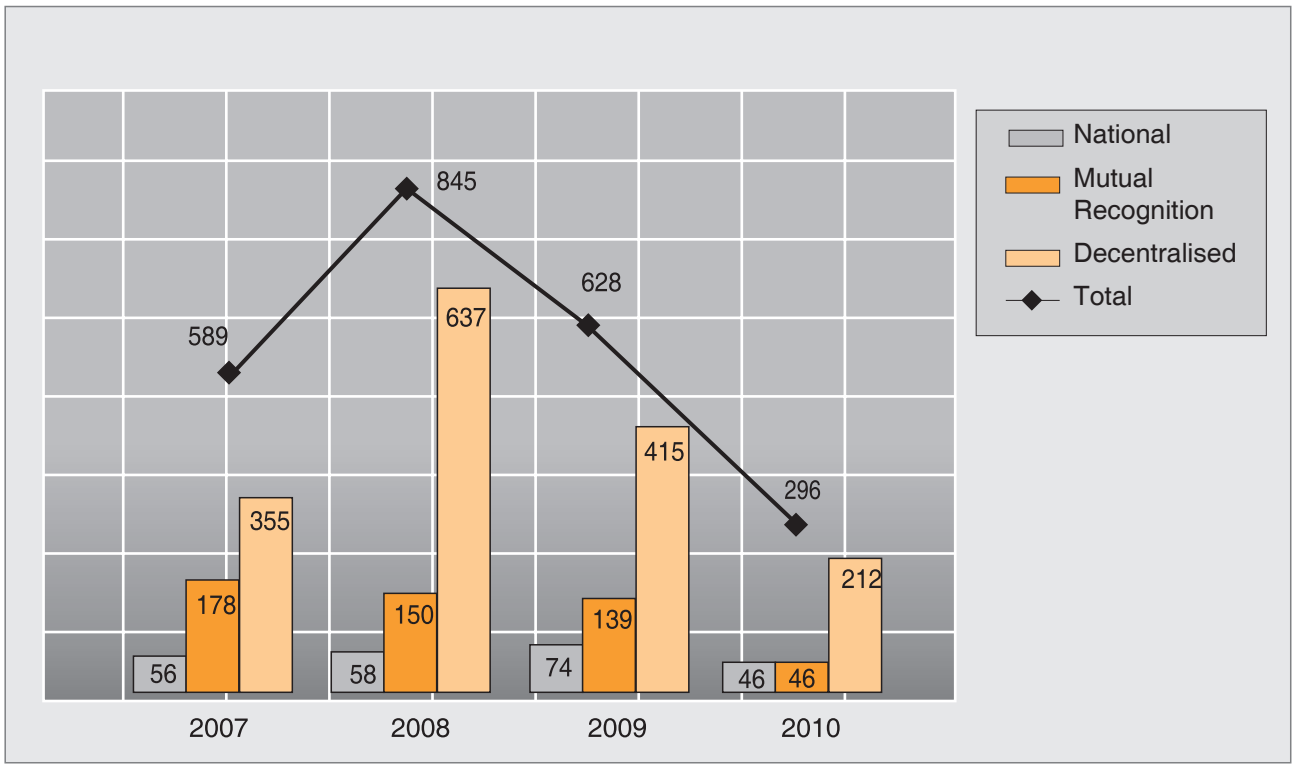
Number of renewal procedures



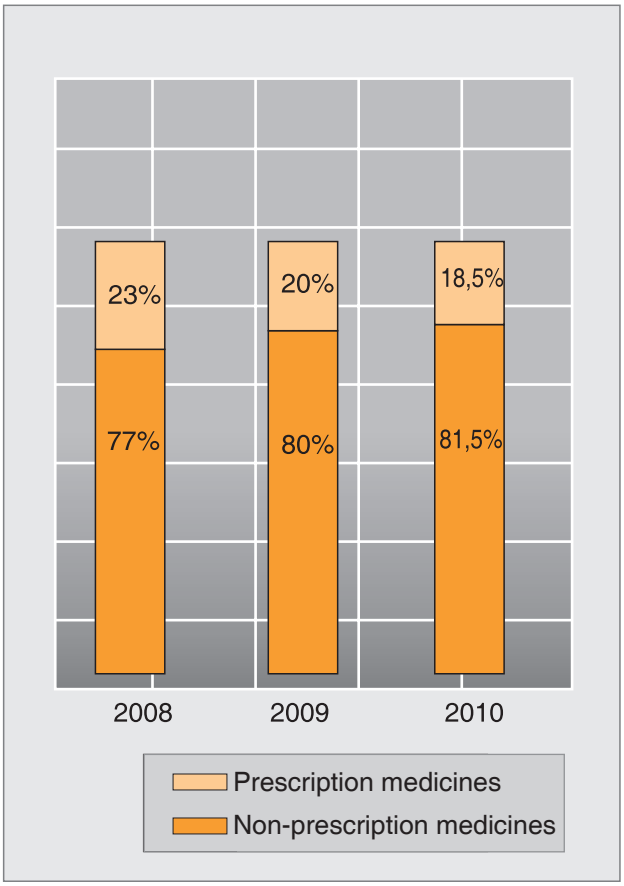
The ratio of prescription and non-prescription medicines in the Drug Register of the Republic of Latvia remains at the usual level with only a 1.5% increase in the number of prescription medicines in 2010.

In January 2010 the new European Commission Regulation 1234/2008 (November 24th 2008) and the new variations classification were introduced accord-

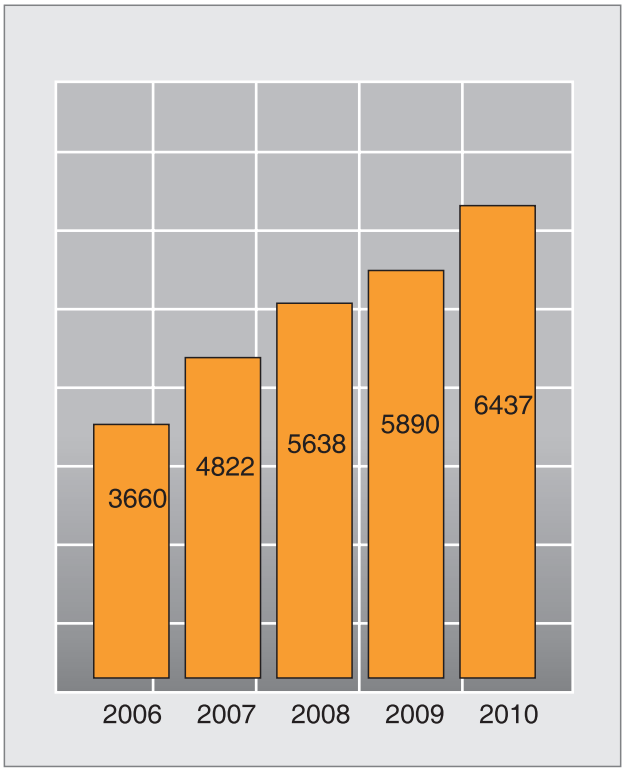
Number of received applications for marketing authorisation



Ratio of authorised prescription and non-prescription medicines



Variations to the marketing authorisation documentation



ing to the guidelines on classification of variations for evaluation of variations to medicines authorised in the mutual recognition and decentralised procedures. The first experience in categorisation of variations has been obtained. 75% of the applications for variations to authorised medicines in the mutual recognition procedure regard several medicinal products.

In 2010 applications for variations to the documentation of 6437 authorised medicines were submitted and reviewed, of these variations 40 % were type I A variations, 24.6 % - type I B variations, 35.4 % - type II variations.

In the year of review there were 30 applications for evaluation of product compliance/non-compliance with the definition of a medicinal product where SAM has given a verdict on the product status.

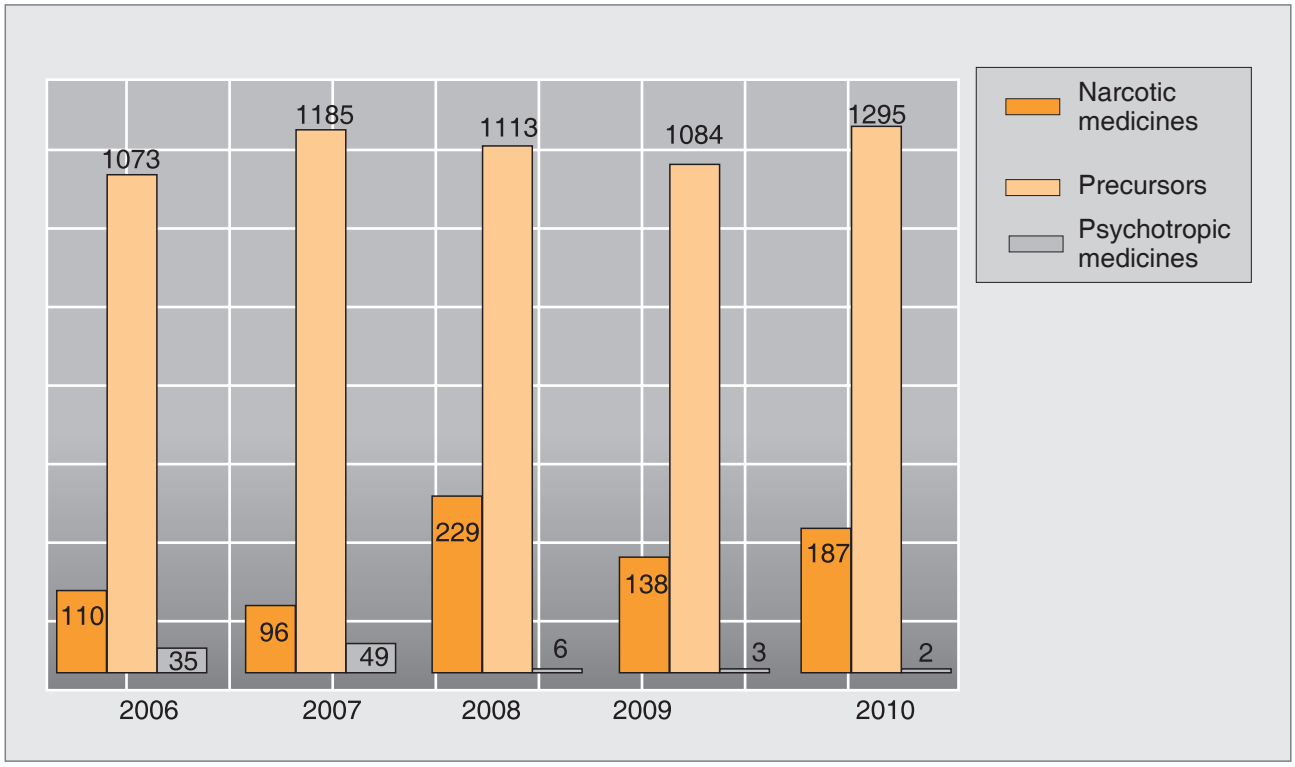
2.2. Issuing Authorisation for Distribution of Medicines

In 2010 SAM issued 3212 authorisations for distribution of unauthorised medicines (including 70 authorisations for distribution of unauthorised veterinary medicines), 76 authorisations for distribution of remaining stocks of medicines after the withdrawal of the medicine form the Drug Register of the Republic of Latvia. 8 authorisation cards were issued to precursor operators, also 5 authorisations were issued for using plants, substances and medicines included in the I, II and III list of narcotic, psychotropic substances and precursors for medical and veterinary medical scientific research or training, as well as determining their physical and chemical properties.

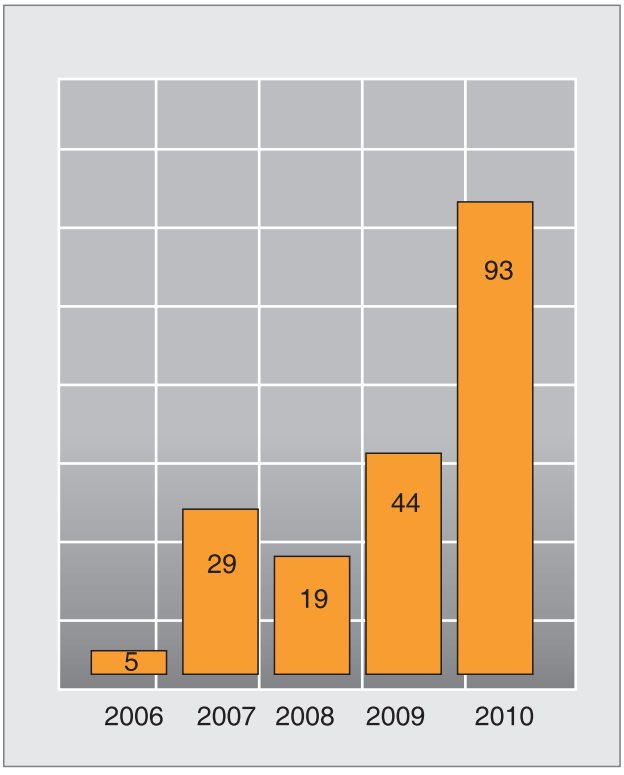
SAM regularly assembles and updates information on the availability and price of medicines included in the Drug Register.

SAM prepares a quarterly review of the import and export of narcotic substances and an annual review of the consumption of narcotic and psychotropic substances within the state and forwards them to the International Narcotics Control Board (INCB). SAM also prepares and forwards to the European Commission a quarterly review of the circulation of illegal precursors and an annual review of the circulation of legal precursors.

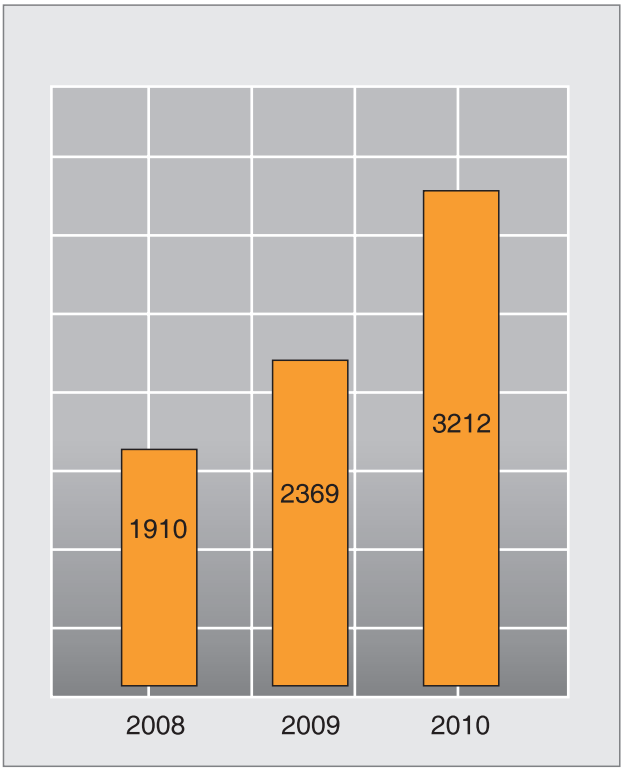
Number of authorisations issued for import and export of narcotic, psychotropic medicines/substances and precursors



Number of authorisations issued for distribution of parallel imported medicines



Number of authorisations issued for distribution of unauthorised medicines (including veterinary medicines)



Every quarter SAM has assembled the statistical information on consumption of medicines submitted by wholesalers and has prepared a publication (in disc format) “Statistics of Medicines Consumption in 2009”.

2.3. Clinical Trials

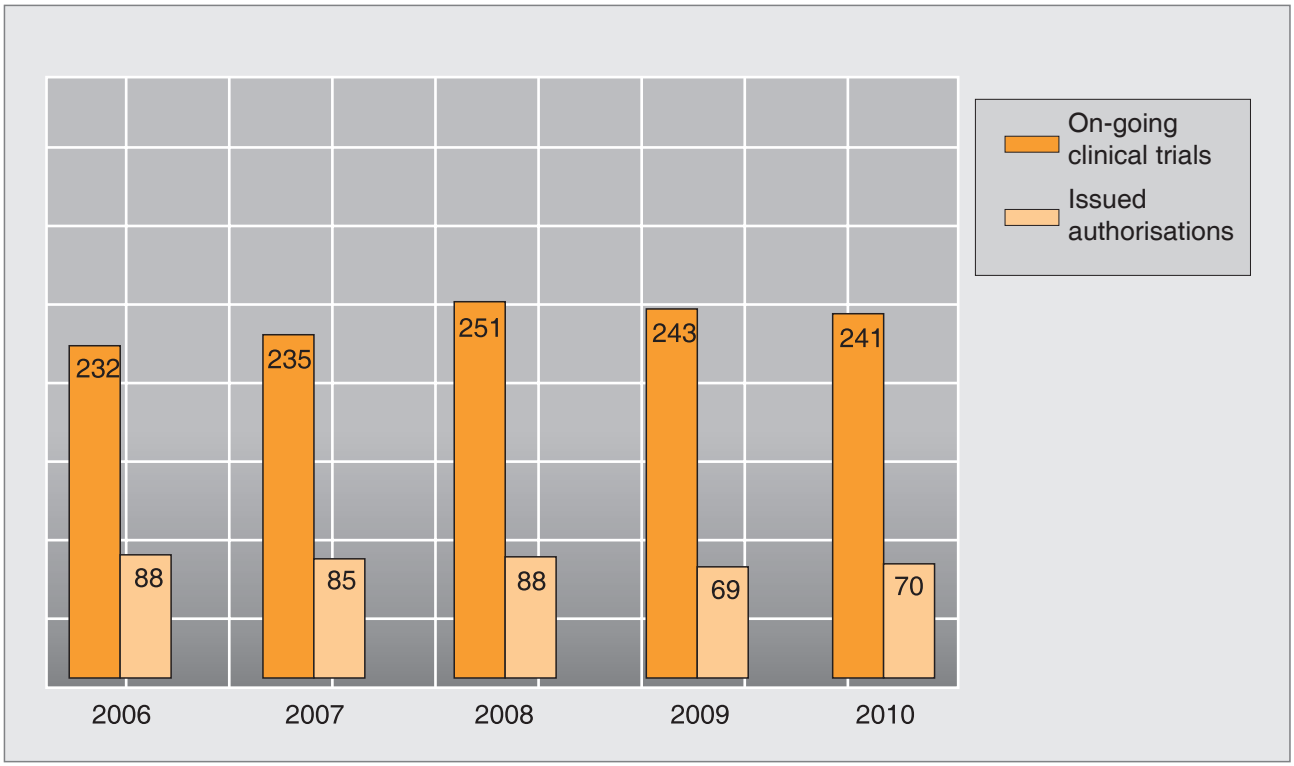
In 2010 SAM received 77 applications for clinical trials of medicines. After carrying out expertise on the application documentation and evaluating the benefit/risk balance for the patient, Clinical Trial department staff members made decisions on the approval of the trials at the department meetings. Altogether 22 Clinical Trials Department meetings were held. Basing on the decisions of the department meetings, in 2010 SAM issued authorisations for 70 clinical trials and 2 post-trial registers. Taking into consideration the safety of patients, on two accounts the authorisation was not granted for conduct of clinical trials at two trial sites chosen by the sponsor. On some occasions the sponsors and/or investigators received an authorisation for initiation of a clinical trial together with additional recommendations relating to the safety of patients.

10 of the clinical trials authorised in 2010 involved children. Paediatric clinical trials were authorised in several medical specialities - pulmonology, neurology, abdominal surgery. Among the authorised trials, 19 clinical trials included biological medicinal products obtained with DNA technology (monoclonal antibodies, interferons, growth factor inhibitors) and were intended for treatment of oncological, rheumatic, neural and other types of diseases.

190 authorisations were issued for substantial amendments in clinical trial protocols or other documentation related to the clinical trial.

Information regarding applications for clinical trials, the time of their authorisation, the dates of approval of substantial amendments, opinions of ethics committees, completion of trials, as well as inspections of good clinical practice was regularly entered into the European clinical trial database *EudraCT*. Due to the preparation of the European Clinical Public Trials Register and the requirements of the European Medicines Agency (EMA), an employee of the department entered supplementary information since 2004 into the *EudraCT*.

Number of issued authorisations and on-going clinical trials



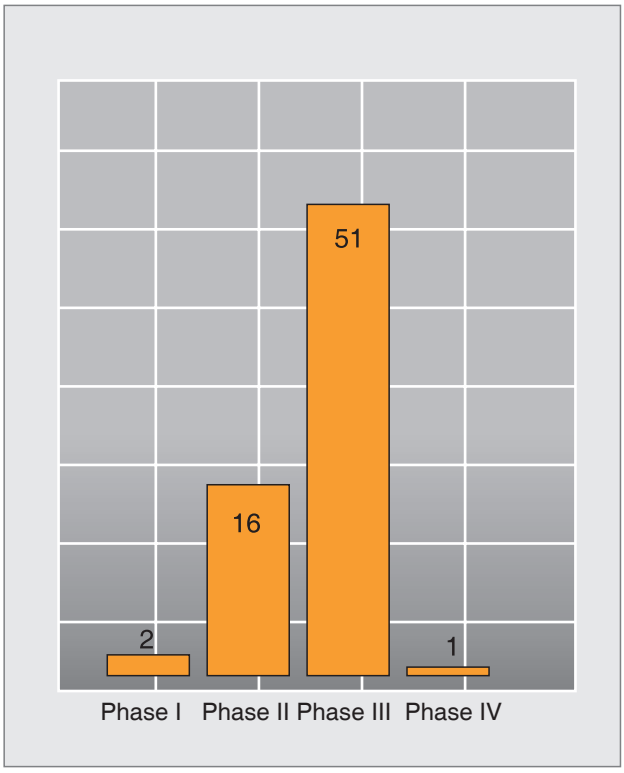
SAM ensured electronic data exchange in the *EudraVigilance* system by forwarding acknowledgements of receipt of safety reports relating to the clinical trials conducted in Latvia to clinical trial sponsors that had submitted safety reports in the Clinical Trial Module of the *EudraVigilance* data base according to European and local normative requirements, indicating the address of Latvia's SAM. The 100 reports that were received in the year of review regarding serious adverse drug reactions observed at trial sites in Latvia were analysed and included in the SAM register.

In cases of some problematic trials SAM coordinated opinions on pharmaceutical-chemical, preclinical and clinical aspects of trial documentation with experts from other Member States via an electronic exchange of information.

20 external experts were involved in the evaluation of documentation of authorised projects. Altogether expertise was carried out on 70 projects in 2010. 4 experts were involved for the first time.

Altogether 241 clinical trials were conducted in Latvia in 2010. 56 projects were completed.

Number of clinical trials authorised in 2010 (distribution according to phase)



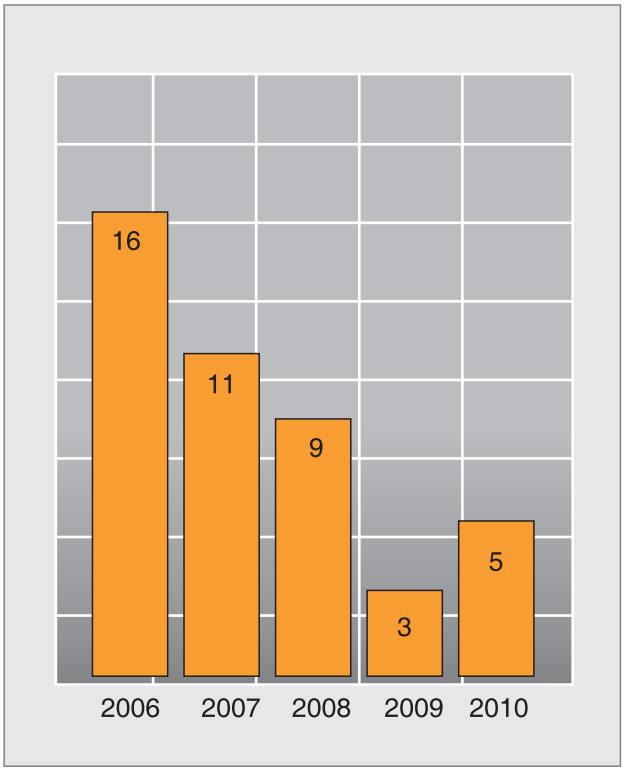
Distribution of clinical trials authorised in 2010 according to the field of medicine

Field of medicine	Number or trials
Pulmonology	11
Oncology	11
Endocrinology	11
Neurology	10
Rheumatology	8
Nephrology	4
Psychiatry	4
Cardiology	4
Ophthalmology	2
Dermatology	2
Surgery	2
Gynecology	1

Clinical trial centres that participated in the clinical trials authorised in 2010

Clinical trial center	Number of trials
P. Stradins Clinical University Hospital	40
Riga Eastern Clinical University Hospital	30
Clinical hospital „Gailezers"	18
Latvian Oncology Center	5
Clinic "Linezers"	7
Daugavpils Regional Hospital	22
Vidzeme Hospital	12
Children Clinical University Hospital	10
D. Teterovskas Doctors Endocrinology Practice	7
"Health Center 4"	7
Liepaja Regional Hospital	7
S. Salenieces Doctors Rheumatology Practice	6
State Limited Responsibility Company "Maritime Hospital"	6
Limited Liability Company „Olvi"	5
Medical Company "Center for Examination and Treatment of Allergic diseases"	5
Dr. Viktorijas Vēveres Doctors Pulmonoly and Allergology Practice	5
D. Saulītes – Kandevicas Cardiology and Rheumatology Private Practice	5
Other clinical trial centers (71 in total)	1 – 4 trials at each center

Number of non-intervention studies registered at SAM



The authorised clinical trial projects were sponsored by a total of 35 foreign pharmaceutical companies.

In accordance with the power of attorney from the sponsors, the following contract research organisations participated in the organisation and ensured the quality of conduct of clinical trials in Latvia: *Quintiles* (10 projects), *ICON* (7 projects), *Amber CRO* (7 projects), *Crown CRO* (6 projects), *Parexel International* (4 projects), *PSI Company* (3 projects) and 12 other contract organisations (1-2 projects each).

7 inspections of compliance of clinical trials with good clinical practice were carried out at trial centres during the conduct and after the completion of the trials. During the inspections some critical, as well as major and minor non-compliances were discovered.

In 2010 a qualified SAM staff member participated in an EMA initiated good clinical practice inspection at 3 trial centres (in Canada and Latvia) relating to the centralised authorisation procedure.

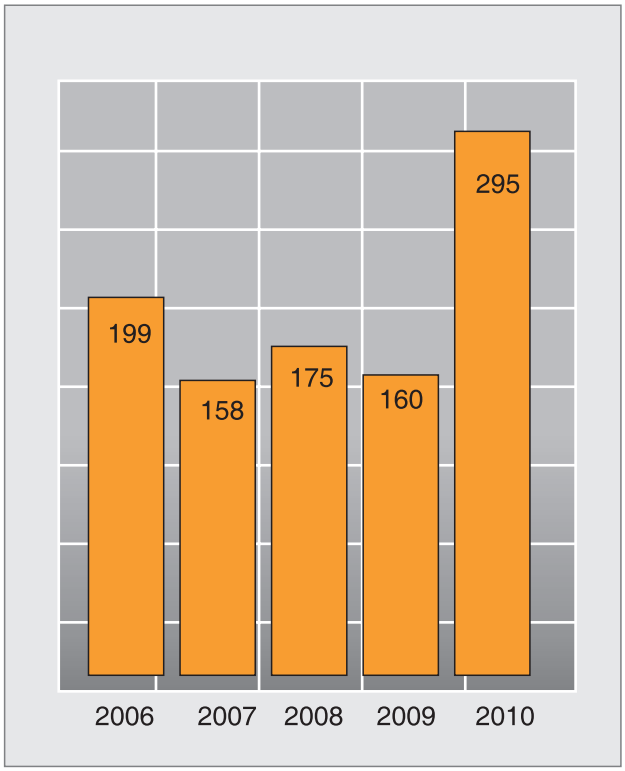
In the year of review SAM received, evaluated and registered 5 applications for non-interventional studies. The list of non-interventional studies that is available on SAM website (www.zva.gov.lv) was accordingly regularly updated.

2.4. Adverse Drug Reaction Monitoring and Risk Minimisation

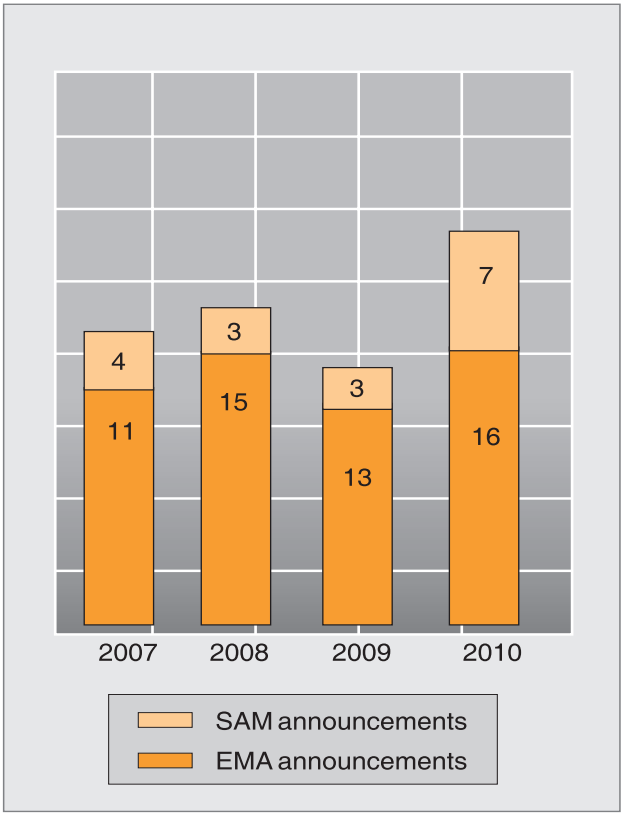
In 2010 SAM received 295 reports of observed adverse drug reactions (ADR). In the period of review a significant increase in the number of received reports could be observed. It is mostly due to the well organised exchange of vaccination induced complication (VIC) data with the Infectology Center of Latvia (LIC). The reporting activity of doctors and pharmacists has also increased. Expertise was carried out on all received reports and according to requirements they were forwarded to the European Union ADR database *EudraVigilance*, as well as to the World Health Organisation (WHO) database *Vigibase*.

SAM continued to improve the evaluation of the pharmacovigilance system developed by marketing authorisation holders (MAH) that is necessary for the authorisation process. In the period of review 101 pharmacovigilance systems were evaluated. This

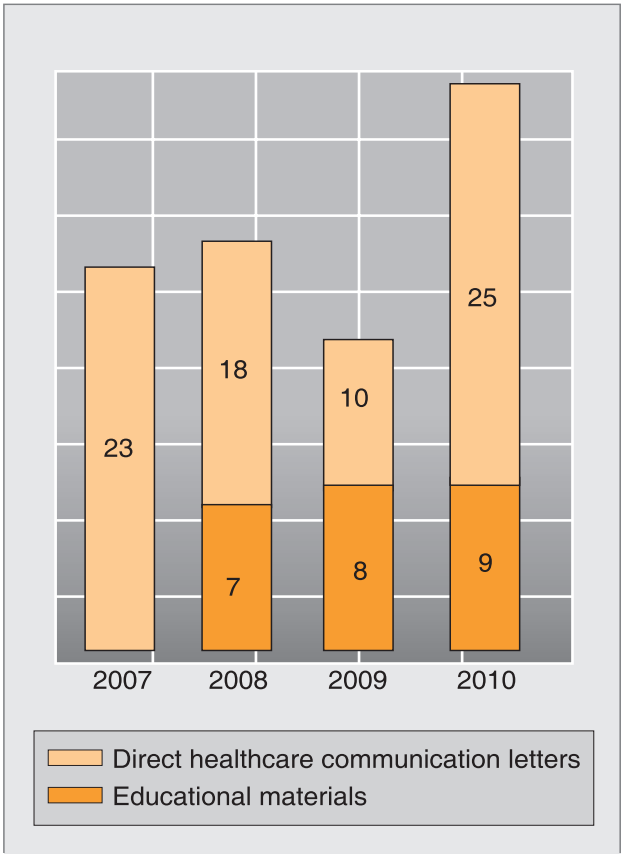
Number of ADR reports



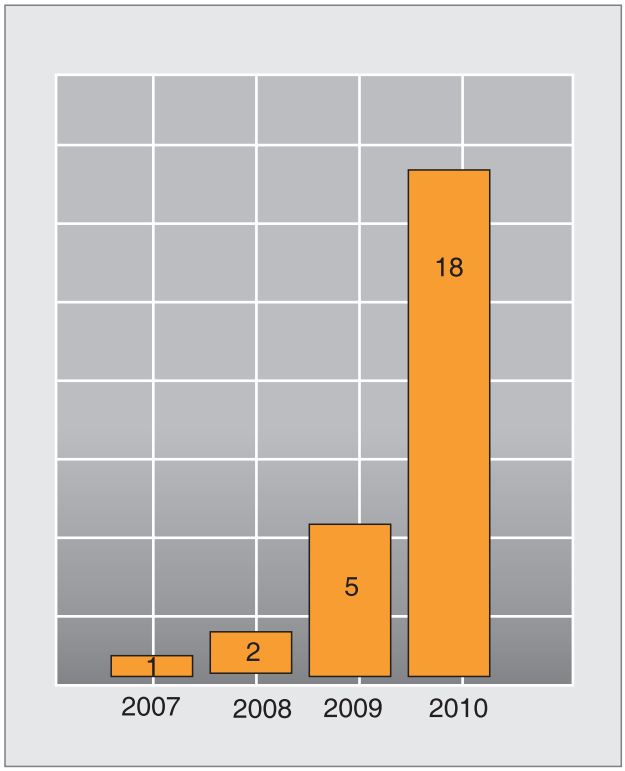
Number of communication materials published on SAM website regarding safety of medicines



Approval of informative risk minimisation measures



Harmonisation of safety information in the authorisation documentation



process is also related to the future pharmacovigilance inspections.

As a part of the EU Periodic Safety Update Reports Work-sharing in 2010 two PSUR evaluations were carried out for the European Comunity.

The procedures for harmonisation of medicines safety information in the authorisation documentation of medicines were developed at the end of 2007 and the beginning of 2008 and were improved in 2009. The procedure is based on EU suggestions and in 2010 marketing authorisation holders for 18 groups of medicinal products were asked to change their documentation due to 18 specific risk problems.

The ADR Monitoring Advisory Board operates within SAM and it is coordinated by the ADR Monitoring Department. 6 Board meetings were conducted during the period of review

SAM cooperates with qualified persons for pharmacovigilance for MAH regarding issues of ADR reports, as well as regarding communication with health care specialists, patients and the public and regarding other issues of pharmacovigilance. In the period of review expertise was carried out on 9

risk minimisation educational materials submitted by MAH at SAM.

In the year of review 25 "Direct Healthcare Communication Letters" were approved. Information intended for physicians, patients and the public regarding safety of medicines is constantly published in the SAM website. 16 announcements from the European Medicines Agency and 7 announcements from the SAM were prepared for publishing. Issues of safety of medicines and risk minimisation are updated in the SAM informative bulletin *"Cito!".*

2.5. Quality Control of Medicines

In 2010 the SAM laboratory carried out analyses of 99 samples of medicines. In the process of analysis 623 quality indicators were examined. 460 volumetric solutions were prepared upon the request from pharmacies.

According to the Cabinet of Ministers Regulation No. 304 "Regulations Regarding the Procedures for the Manufacture and Control of Medicinal Products, the Requirements for the Qualification and Professional Experience of a Qualified Person and the Procedures for the Issuance of the Certificate of Good Manufacturing Practice to a Medicinal Products Manufacturing Undertaking" a new function has been assigned to the laboratory: analysis and quality control of samples of purified water obtained in pharmacies according to the requirements of the European Pharmacopoeia. 131 samples of purified water were collected and tested in 2010.

On July 15th 2009 the Latvian National Accreditation Bureau accredited the State Agency of Medicines according to the requirements of the LVS EN ISO/IEC 17025:2005 standard in the following field: physical and physicochemical testing of medicines, veterinary medicines and active substances, physical testing of purified water. The accreditation has been issued until July 14th 2013. On April 15th 2010 an inspection of conformity visit by the Latvian National Accreditation Bureau took place. The laboratory maintained its accreditation for the requirements of the LVS EN ISO/IEC 17025:2005 standard in the current field of accreditation.

Results of the operations of Medicines Examination Laboratory

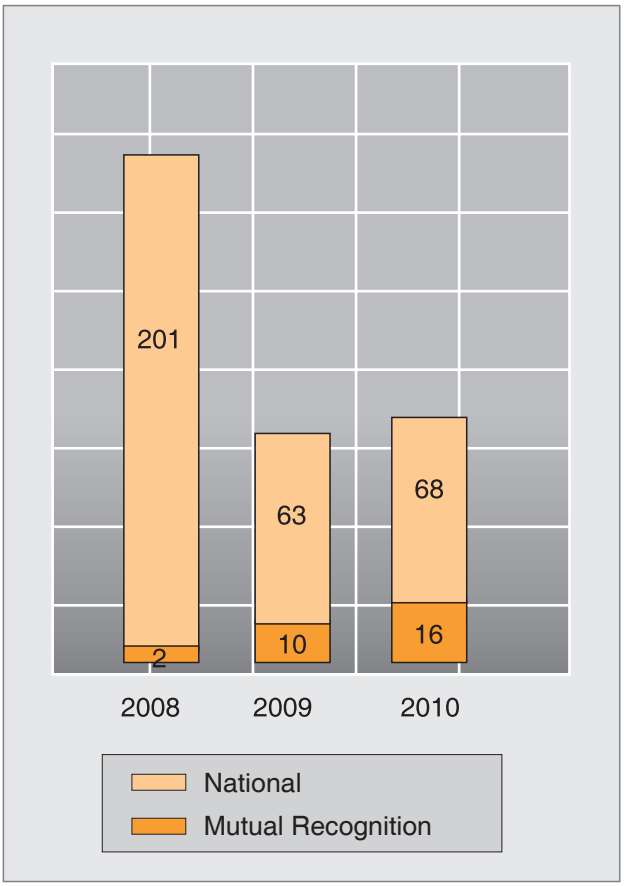
Year	Number of staff members	Number of analysed medicines samples	Number of examined medicines quality indicators	Number of volumetric solutions, indicators and reagents prepared upon the request from pharmacies	Number of examined purified water samples	Participation in quality control programs for centrally authorised medicines (CAP)	Participation in European Market Surveillance Studies (MSS)	Participation in international professional level inspection programs
2006	9	436	2984	–	–	1	1	4
2007	9	222	905	1004	–	1	–	5
2008	8,5	111	550	557	158	1	2	5
2009	8 (until 30.06.09.) 7 (from 01.07.09.)	115	611	361	131	1	–	5
2010	6	99	623	460	131	1	1	5

2.6. Evaluation and Safety Surveillance of Veterinary Medicines

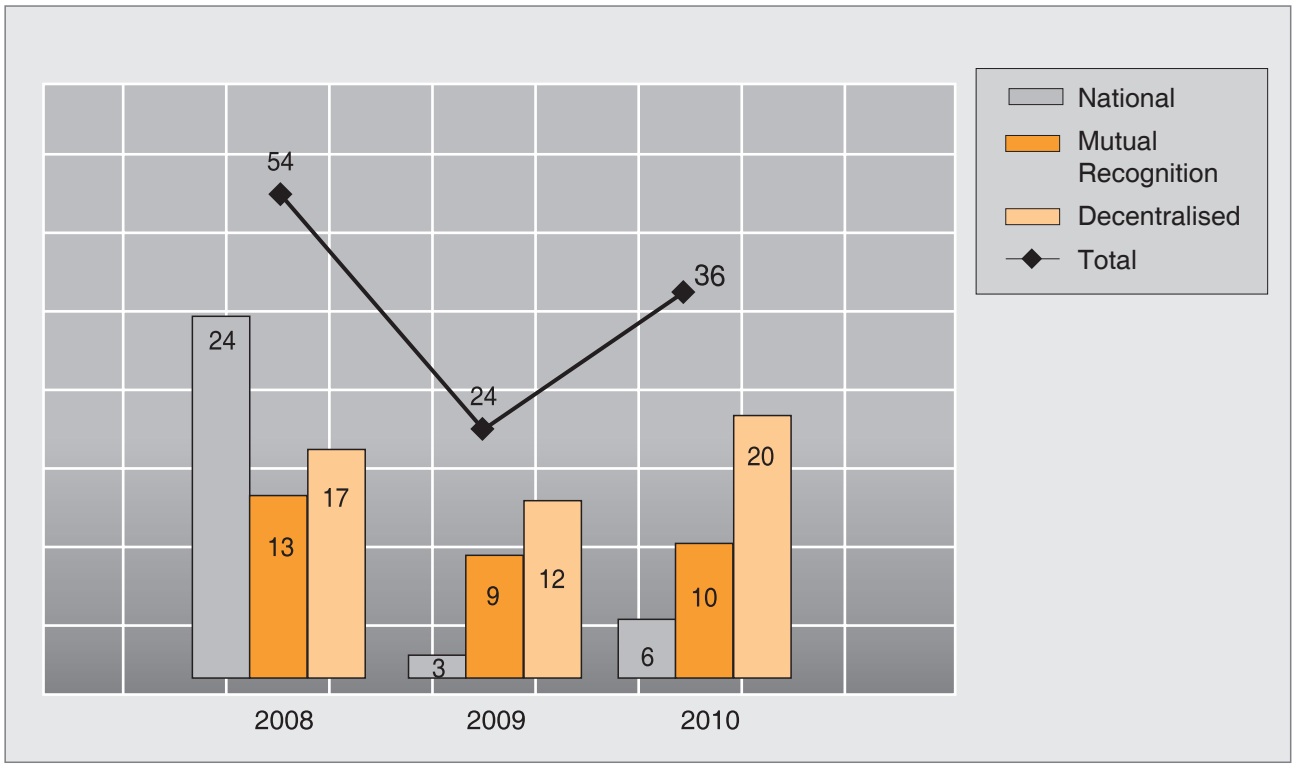
In 2010 by evaluating the submitted documentation, the following marketing authorisation procedures have been carried out:

- 6 marketing authorisations of veterinary medicines through national authorisation procedure, 10 marketing authorisations of veterinary medicines through mutual recognition procedure and 20 marketing authorisations of veterinary medicines through decentralised procedure;
- 68 renewals of veterinary medicines through national authorisation procedure and 16 renewals of veterinary medicines through mutual recognition procedure;
- 285 variations to marketing authorisations of veterinary medicines for all procedures.

Renewal procedures for veterinary medicines



Marketing authorisation procedures of veterinary medicines



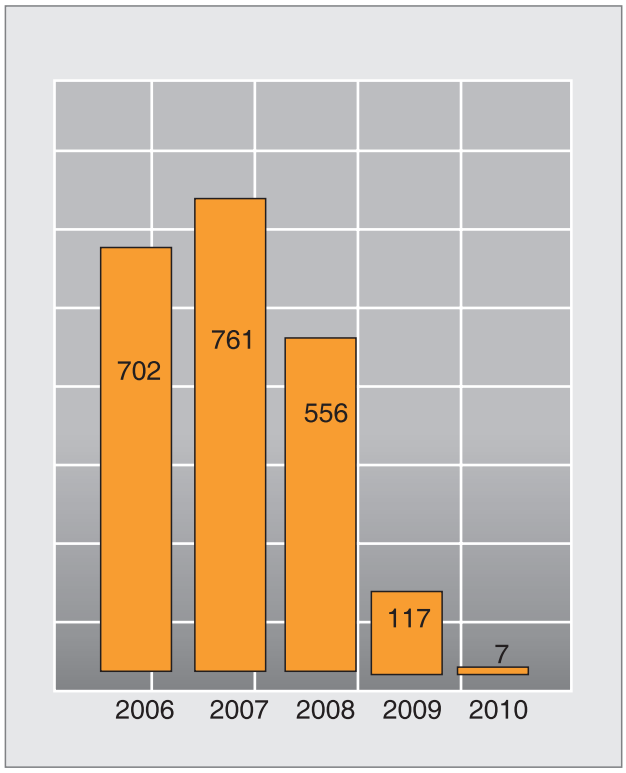
2.7. Assessment and Registration of Medical Devices, Surveillance of the Safety and Clinical Trials of Medical Devices

In 2010 seven medical devices were registered in Latvia and 1046 notifications were added to the LATMED database regarding placement of medical devices on the market of the Republic of Latvia. 539 reports of accidents with medical devices were received in the vigilance system from institutions responsible for medical devices in EU

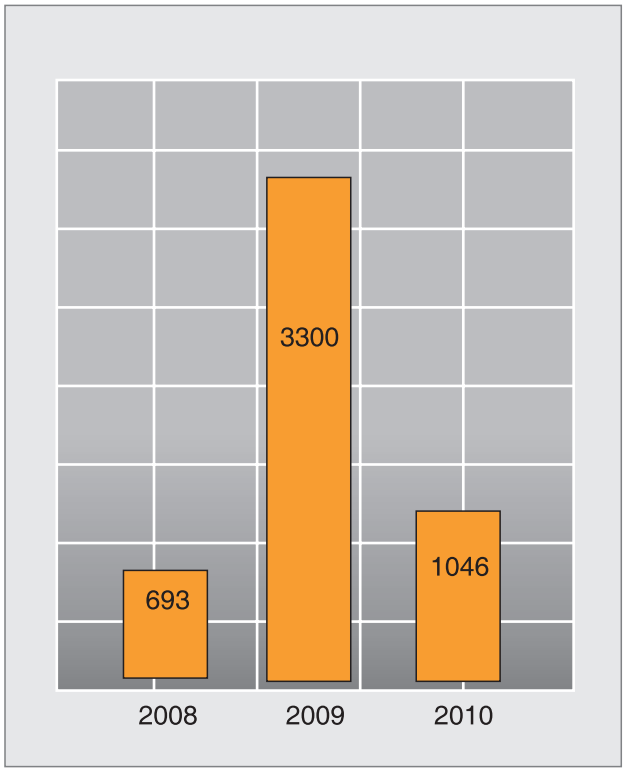
Evaluation of compliance, registration, surveillance of safety and clinical trials of medical devices (MD) in 2010

Expertise on registration documentation of medical devices manufactured in the Republic of Latvia	10
Expertise on registration documentation of medical devices without CE marking	2
Expertise on documentation for issue of authorisation to specially supplied medical devices	1
Registration of information submitted within the notification procedure into the LATMED database	1046
Registration of information provided by MD holders regarding purchase of safety group I and II MD into the LATMED database	2108
Registration of information provided by MD holders regarding changes in use of safety group I and II MD into the LATMED database	449
Acceptance of reports received within the Vigilance system, registration, analyzing and processing of information and registration of data into the LATMED database	539
Identification of non-compliant medical devices in exploitation within Latvia and implementation of safety measures	156
Expertise of documentation submitted for authorisation of clinical trials of medical devices	9
Applications for variations to previously issued MD authorisations	5

Number of registration certificates issued for medical devices in the Republic of Latvia



Number of notifications regarding placement of medical devices on the market of the Republic of Latvia (including medical devices for *in vitro* diagnostics)



Member States, as well as from manufacturers and distributors. In 156 cases safety measures were applied. In the year of review was issued 9 approvals for realization of clinical trials of medical devices (excluding expertise on application documentation for protocol amendments of clinical trials that have already been granted authorisation by SAM).

Consultations have been provided to clients regularly regarding procedures for the registration, notifications of medical devices, as well as preparation of documentation and normative acts regulating this field. Also a seminar regarding new information on regulations for medical devices was prepared and organised.

After the adoption of functions from the Health Statistics and Medical Technologies State Agency on October 1st 2009, department specialists began research and development of regulations defining the procedure for clinical trials with medical devices for human use. With the support of the SAM administration and in cooperation with the Ministry of Health, regulations were developed that determine the procedure for clinical trials with medical devices and on September 21st 2010 the Cabinet of Ministers issued Regulation No. 891 "Procedure for Clinical Trials with Medical Devices for Human Use" that came to effect on October 1st 2010.

2.8. Evaluation of Compliance of Pharmaceutical Activity

In 2010 there were 20 inspections carried out on manufacturing/importing companies and 1 contract re-evaluation conducted (related to renewal of marketing authorisation). In total this required 38 person-days. 2 of the inspections were of manufacturing companies outside of the European Economic Area, but 2 inspections were carried out on the manufacturing of active substances upon the request from the manufacturers themselves. In 2010 one inspection was conducted together with PIC/S inspectors during an exchange of experience visit.

14 product samples were selected in the inspections of manufacturing companies. During the year of review 14 Good Manufacturing Practice certificates were issued to manufacturing/importing companies.

In 2010 there were 36 evaluations carried out on compliance of wholesalers of medicines and veterinary medicines, as well as inspections of good distribution practice of wholesalers. Altogether this required 30 person-days.

6 evaluations of compliance of blood offices in medical care institutions were carried out and 2 monitoring procedures were conducted in 2010. Evaluations were carried out on 2 tissue harvesting and storage centres, also 2 evaluations of compliance were carried out on stem cell harvesting and storage centres.

2.9. Licensing of Pharmaceutical and Veterinary Pharmaceutical Activity Companies

In 2010 SAM received 1617 applications and supplementary documentation, forwarded 102 letters of response, evaluated the compliance of 235 pharmaceutical and veterinary pharmaceutical activity companies, prepared 209 opinions regarding the evaluation of compliance of pharmacies and 652 decisions were made (from April 1st 2010) regarding issue, renewal, suspension and withdrawal of special authorisations (licences) to pharmaceutical and veterinary pharmaceutical activity companies. 891 special authorisations (licences) for pharmaceutical and veterinary pharmaceutical activity were issued to pharmaceutical activity companies (831 – to pharmacies, 44 – to wholesalers of medicines and veterinary medicines, 14 – to manufacturing or importing companies of medicines and veterinary medicines, 2 – to medicines manufacturing companies that manufacture active pharmaceutical substances (from July 1st 2010).

Basing on Section 12 of August 24th 2010 Cabinet of Ministers Order No. 500 "Regarding Procedure for "Adoption of Functions from the Ministry of Health in the Field of Veterinary Medicines"", the department has prepared licensing documentation received from 27 wholesalers of veterinary medicines, 2 veterinary medicines manufacturing companies,

Number of licences issued to pharmaceutical activity companies

	2007	2008	2009	2010
Pharmacies	428	535	322	831
Wholesalers of medicines and veterinary medicines	34	25	29	44
Manufacturing or importing companies of medicines	28	12	9	14
Manufacturing companies that manufacture active pharmaceutical substances	0	0	0	2
Total	490	572	360	891

Number of evaluations of compliance of pharmaceutical companies

	2007	2008	2009	2010
Pharmacies	233	176	131	209
Wholesalers of medicines and veterinary medicines	2	8	19	19
Manufacturing or importing companies of medicines	10	14	4	7
Total	245	198	154	235

10 eliminated companies and the documentation received from Food and Veterinary Service since 2006 for consignment to the Food and Veterinary Service until December 30th 2010.

Since January 1st 2010 it is in the competence of SAM to carry out evaluations of pharmacy documentation and interior planning according to requirements of normative acts. The department prepares opinions on evaluations of pharmacy compliance. New requirements for specific activity have been introduced regarding the distribution of psychotropic substances, narcotic substances and the equivalent psychotropic substances, operating 24 hours a day. It is no longer required to indicate in the pharmacy licence the wholesale distribution of medicines to medical and social care institutions (ensuring the requirements of good distribution practice of medicines) and packaging of medicines according to a physician's prescription to an individual patient. The direct responsibilities of the department include gathering documentation relating to evaluations of compliance and licensing of pharmaceutical and veterinary pharmaceutical activity companies, storage of information submitted by licensed pharmacies, wholesalers and manufacturing companies of medicines and veterinary medicines, production and issue of special authorisations (licences) for pharmaceutical and veterinary pharmaceutical activity, regular updating of data regarding issued special authorisations (licences) for pharmaceutical and veterinary pharmaceutical activity after routine commission meetings, organisational preparation of Pharmaceutical Activity Licensing Commission meetings.

3. BUDGET AND EXPENSES OF THE STATE AGENCY OF MEDICINES

SAM obtains 100% of the financial resources necessary for carrying out the delegated functions and ensuring operations from provision of paid services.

No.	Financial Resources	Budget in 2009 (actual data)	2010	
			Statutory	Actual data
1.	Financial resources for covering expenses	5 455 975	4 971 573	4 293 025
1.1.	Income from paid services and other independent income	5 455 975	4 971 573	4 293 025
2.	Expenses (total)	2 397 115	3 969 477	5 698 794
2.1.	Maintenance expenses (total)	2 244 482	3 638 477	5 472 215
2.1.1.	Regular expenses	2 244 482	3 638 477	5 472 215
2.2.	Expenses for capital investment	152 633	331 000	224 579

4. GENERAL ADMINISTRATION OF THE STATE AGENCY OF MEDICINES

4.1. Ensuring Public Procurement and Economic Activities

In 2010 SAM Commission for Procurements announced 14 procurement procedures. A relatively large number of contestants participated. For all the announced and performed procurement procedures contracts for supply and services were signed. The most significant procurement procedures were:

- Maintenance of record-keeping and human-resources management information system;
- Supplementing the existing servers and their virtualisation system;
- Ensuring 24 hour security for property of SAM - on Jersikas street 25 and Daugavpils street 62/66;
- Purchase of office equipment, auxiliary materials and spare parts;
- Implementation and maintenance of changes in the *Horizon* record-keeping software.

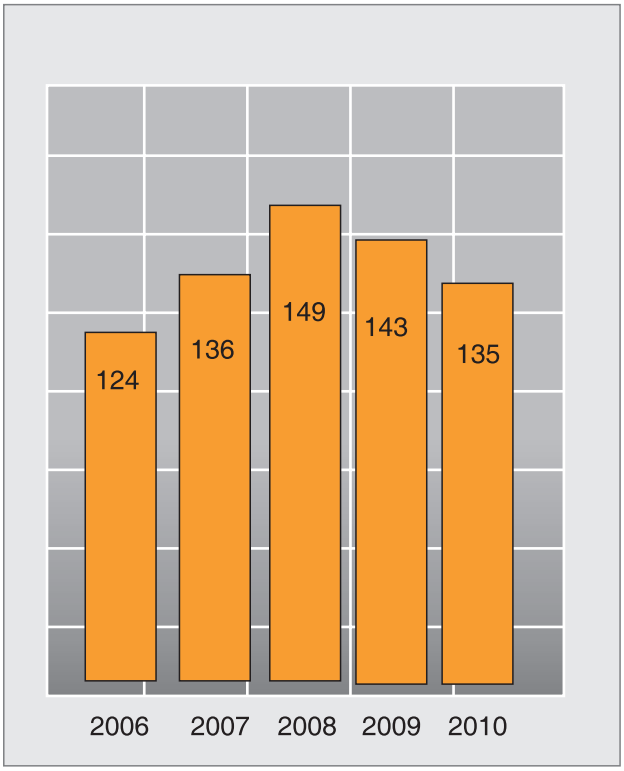
4.2. Cooperation with State Administration Institutions in the Development of Normative Acts

The year 2010 was highlighted by the review and analysis of several proposals for normative acts significant to SAM and preparation of recommendations for amendments to these acts. SAM submitted several recommendations to the Ministry of Health regarding amendments to several Cabinet of Ministers Regulations (amendments to July 18th 2006 Regulation No. 600 "Procedure for Registration of Veterinary Medicines", December 7th 2004 Regulation No. 1006 "Statutes of the State Agency of Medicines", March 8th 2005 Regulation No. 175 "Regulations for Manufacture and Storage of Prescription Forms, as well as Writing out and Storage of Prescriptions", May 9th 2006 Regulation No. 376 "Procedure for Registration of Medicines", January 17th 2006 Regulation No. 61 "Regulation on State Agency of Medicine's publicly available paid service pricelist"), as well as amendments to laws, for example, the Pharmaceutical Law. SAM also participated in the review and analysis of new normative acts, for example July 27th 2010 Cabinet of Ministers Regulation No. 684 "Procedure for Composing Prescriptions for Veterinary Medicines", August 10th 2010 Cabinet of Ministers regulation No. 757 "Procedure for Writing out and Storage of Special Prescriptions for Veterinary Medicines", May 25th 2010 Cabinet of Ministers Regulation No. 469 "Procedure for Development, Evaluation, Registration and Implementation of Clinical Guidelines". In 2010 a representative from the Legal Department participated in regular meetings at the Ministry of Health for discussion of the aforementioned amendments.

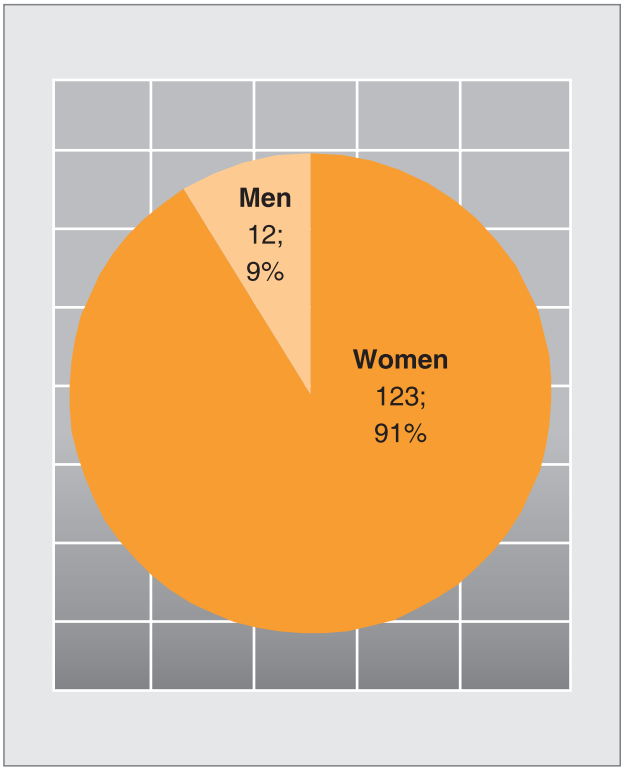
4.3. Staff and Human Resources Management

In 2010 SAM had an average of 135 staff members of which 69 were civil servants and 66 were employees. There were 20 staff members that

Number of staff members



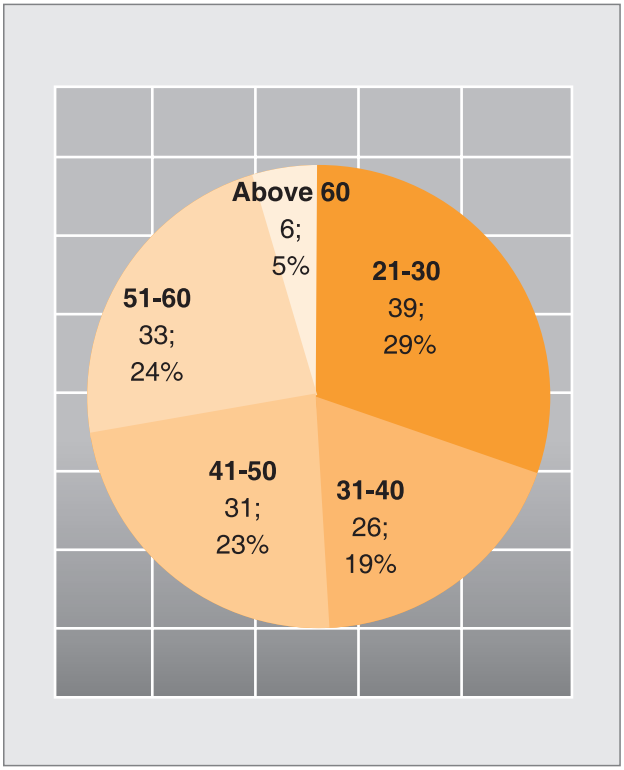
Distribution of SAM staff members according to sex



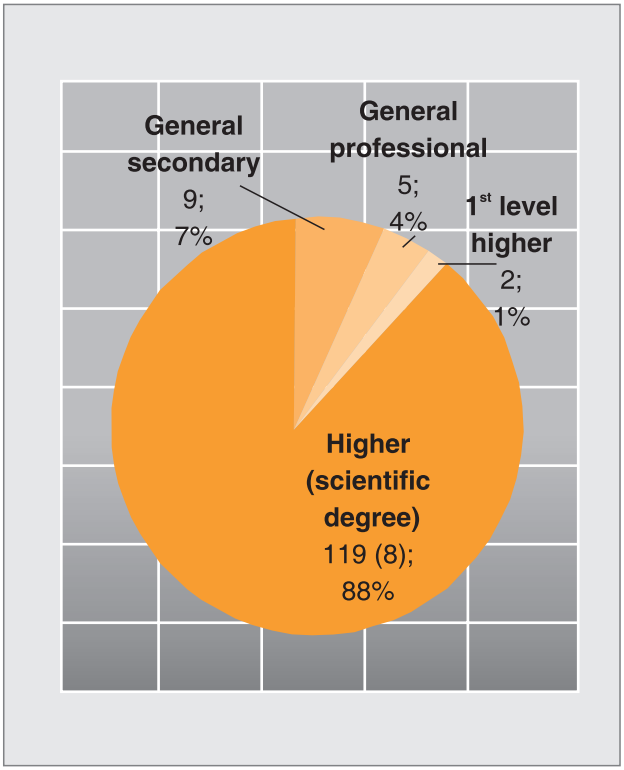
terminated and 23 staff members that began their civil service or employment regal relationship with SAM in 2010. In addition external experts were recruited for scientific expertise of specific documentation.

In 2010 the staff turnover quotient was 14% (staff turnover = number of released staff members in a

Distribution of SAM staff members according to age groups



Distribution of SAM staff members according to education



Raising qualification of staff members

	2007	2008	2009	2010
Training, seminars, conferences coordinated by international organisations	51	62	52	64
Courses for raising qualification	123	125	269	107
English language courses	25	12	5	1

definite time period/ average number of staff members in the same time period), but it has to be taken into account that 7 members of staff were released/ transferred basing on the October 28th 2010 Saeima approved amendments to the Pharmaceutical Law stating that monitoring, control and responsibility of the field of veterinary medicines is pertaining to the Ministry of Agriculture. Therefore, it would not be accurate to take into account the release of these 7 staff members when calculating the turnover quotient. Accordingly it can be concluded that the actual staff turnover quotient for 2010 is 9%. On the other hand, the staff renewal quotient was 16% (staff renewal = number of hired staff members / average number of staff members).

Well-educated, competent and highly qualified specialists are necessary to successfully ensure the functions assigned to SAM. 89.6% of SAM staff members have higher education, 7 civil servants have a doctorate degree and 1 civil servant has a habilitation degree.

One of the basic principles of SAM staff politics is to motivate staff members to raise their qualifications and level of education. Due to the economic crisis in 2010 the possibilities of staff motivation, as well as raising of qualifications were decreased. Nonetheless, to raise their qualification SAM staff members have attended 107 events, as well as 64 training sessions, seminars and forums organised by international organisations. Also several internal SAM seminars have been successfully planned and organised: experts have attended SAM organised seminars on authorisation of medicines, 44 staff members have increased their knowledge on SAM requirements for record-keeping by attending the seminar “Procedure for SAM record-keeping”.

4.4. Quality Management

SAM continuously improves the introduced Quality Management System taking into account both amendments to normative acts and significant structural changes within the organisation. In the year of review the Quality Management System was updated accordingly to the existing situation.

The year of 2010 was dedicated to qualitative preparations for benchmarking (comparative evaluation). In the benchmarking process the following areas were evaluated and compared with each other in 69 criteria: organisation and administration, Quality Management System, the process of marketing authorisation of medicines, pharmacovigilance and performing control of compliance, cooperation with clients, other institutions and the society, safety of information and work.

The purpose of the aforementioned audit is to ensure a united medicines regulatory system in Europe, as well as introduce examples of the best practice.

In the year of review 47 standard operating procedures (SOP) were designed/updated, 6 action descriptions were updated and the development of 6 other plans of action was initiated. The results of the audit were good, even better than the previously prepared self-evaluation.

4.5. Information Technologies

In 2010 SAM information technologies support processes were significantly improved by partial reconstruction or introduction of new information systems: SAMIS, improvement of the Medical Device Register LATMED and other information systems; a pilot project of an information system has been

developed for accepting electronic documentation online; data export from SAMIS to the EU central drug register *EudraPharm* has been performed with a regular frequency of data updates.

To continue to improve the high performance of SAM information systems, as well as their availability to SAM clients, a series of improvements have been made to the virtualisation of technical platforms. By optimising the available technical resources the number of physical units has been decreased and that has provided a significant reduction in costs for maintenance of electrical energy and technical resources.

4.6. Cooperation with International Organisations

SAM is a part of the European Medicines Regulatory Network. The European medicines network is the key to the success of SAM - it entails cooperation with European Medicines Agency, European Commission and more than 40 medicines regulatory institutions within the European Union and the European Economic Area (EEA). This network of cooperation gives European Medicines Agency access to a great number of experts allowing EMA to provide the best possible scientific expertise for regulation of medicines in the European Union. Experts participate in the work of the European Medicines Agency as members of work groups un scientific advisory groups, scientific committees, as well as other groups.

It puts a great responsibility upon SAM, so that our colleagues could fully participate in the collective work procedures. It should also be mentioned that the cooperation requires human and financial resources from SAM. SAM staff members are also involved in cooperation with European Commission and its work groups, as well as the World Health Organisation, *The Uppsala monitoring centre* (UMC), European Pharmacopoeia Commission, *Pharmaceutical Inspection Cooperation Scheme* (PICs), *European Directorate for the Quality of Medicines &Healthcare* (EDQM). Since 2010 SAM has also been involved in monitoring of medical devices, blood and its components, tissue and cells.

There are effective cooperation contracts between SAM and EMA and the State Agency of Medicines in Estonia and Lithuania. On June 25th 2010 a memorandum of agreement was signed between the State Agency of Medicines of the Republic of Latvia and the Food and Drug Administration of the People's Republic of China regarding cooperation in normative regulation of medicines.

5. COMMUNICATION WITH STAKEHOLDERS

(SOCIETY, HEALTH CARE SPECIALISTS, CLIENTS)

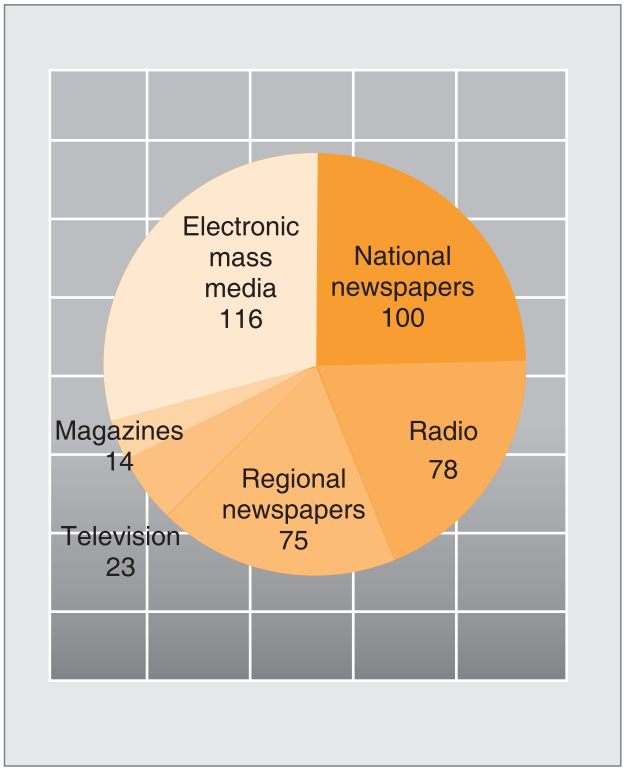
In 2010 SAM has implemented a precise, systematic, purposeful and target audience oriented communication program that has allowed SAM to receive positive publicity.

In the year of review 24 press releases were prepared and forwarded to the mass media representatives and replies were prepared to 81 question from journalists. Proactive communication includes 406 news in different types of mass media. Mostly the publications have been in national newspapers, as well as radio and regional newspapers.

The most significant SAM announcements distributed to mass media representatives in 2010 were regarding safety of nimesulide preparations, conduct of clinical trial with the medicine "*Avandia*" in Latvia, safe use of ketoprofen containing medicines, statistics of quarterly consumption of medicines, purchase of medicines in unlicensed pharmacies. SAM also provided estimate calculations of the increase in expenses for citizens, if the reduced Value Added Tax (VAT) rate for medicines would be increased.

In the year of review 27 interviews of SAM administration and staff members were coordinated

Number of SAM publications in different types of media



Distribution of SAM publications according to topic

Safety of medicines	103
Number of pharmacies, authorisation of pharmacies	37
SAM budget	19
Clinical trials	33
Consignment of the function of veterinary medicines authorisation to FVS	17
The market, consumption and price of medicines	120
Availability of medicines	20
Marketing authorisation of medicines	8
Normative acts	23
Medical devices	2
Society	12
Other	12

with the mass media (8 interviews for press, 10 - for radio, 11 - for television). SAM representatives gave interviews to such representatives of mass media as the magazine "Ir", newspaper "Telegraf", LTV1 program "Panorāma", TV5 news, Latvian Radio 1 news and the program "Kā labāk dzīvot?", Latvian Radio 2 news and Latvian Radio 4 news, TV3 news and the program "Bez tabu", LNT news and the program "Tautas balss" and the program "Vides fakti".

The results of content analysis show that in 2010 from the issues in the competency of SAM the greatest resonance in the public media was caused by issues regarding prices of medicines and the market of medicines. SAM received wide publicity by providing the media with estimations on the increase in citizen expenses, if the reduced VAT rate for medicines would be increased. The information provided by SAM regarding various safety issues of medicines was also widely reflected in the media.

3 surveys were carried out in 2010: a client survey (to determine client satisfaction with the services provided by SAM), health care specialists survey (to determine the quality and perceptibility of the safety information provided by SAM, as well as determine what form and size of information they favour), as well as a staff member survey.

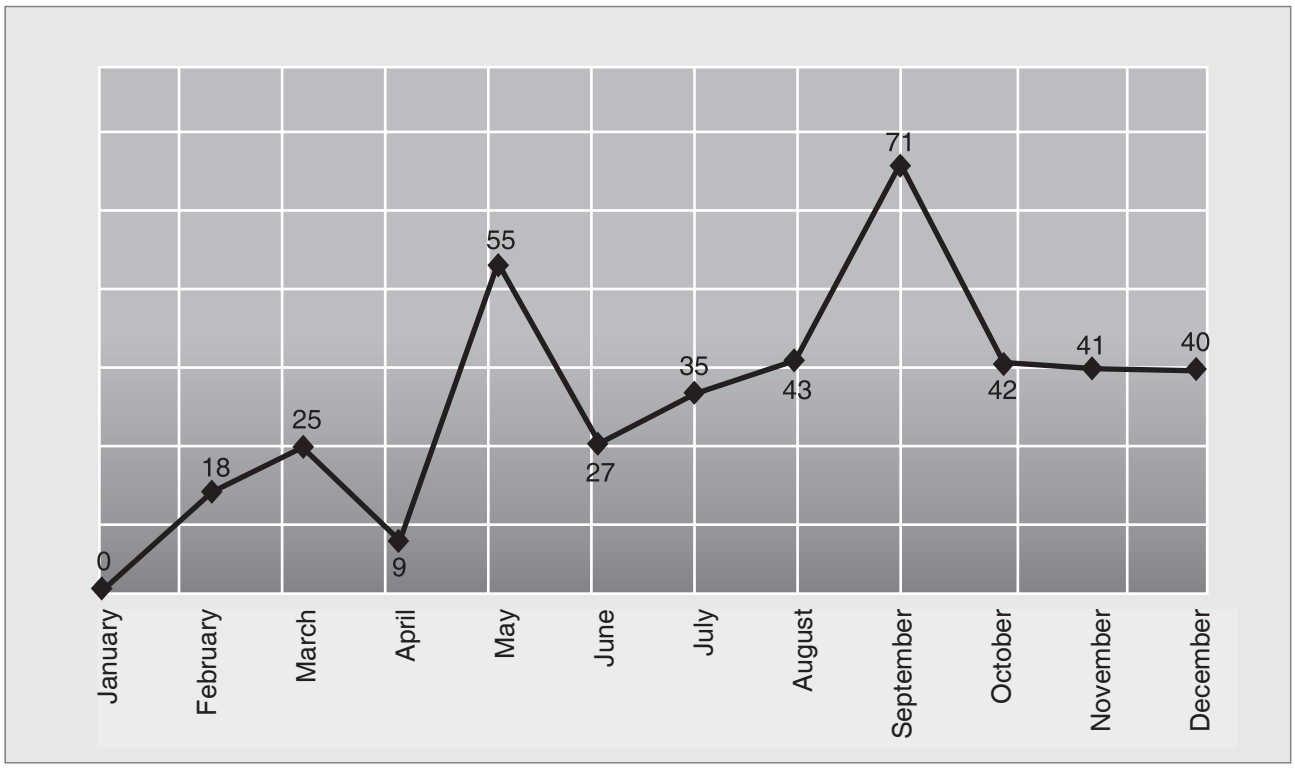
In 2010 the following publications were prepared

4 issues of the informative bulletin *"Cito!"*	4x3000 copies
Drug Register of the Republic of Latvia	400 copies
Register of Veterinary Medicines of the Republic of Latvia	200 copies
Statistics of Medicines Consumption	60 copies
Annual Review	100 copies

There were also 4 surveys posted on SAM website enquiring the opinion of the website visitors (2000 responses were received):

- Is the information you require easily and quickly found on the SAM website?
- How do you evaluate the client service point created by SAM?
- Should a list of excipients (in Latvian) used in medicines be put on the SAM website?
- To which medicines in your opinion should the 21% VAT rate be applied?

Number of SAM publications during the year



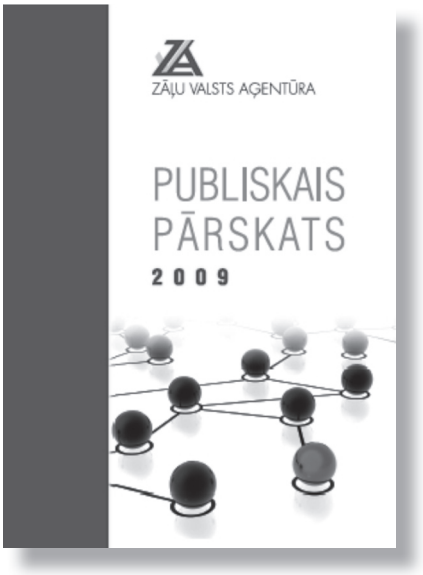
In 2010 SAM has released 4 issues of the informative bulletin *"Cito!"* for physicians, pharmacists and other health care specialists. Upon request, starting from this year the bulletin is also distributed electronically.

To inform clients about amendments to normative acts and other news, 3 seminars were organised for SAM clients:

- about news on issues regarding medical devices;
- regarding amendments to Cabinet of Ministers Regulation No. 416 "Distribution and Quality Control of Medicines";
- regarding amendments to Cabinet of Ministers Regulation No. 376 "Procedure for Registration of Medicines".

To support the initiative of young adults to obtain their first working experience, as well as to try increasing the knowledge and understanding of procedures for registration of medicines and monitoring of the market, SAM offered 4 vacant internship positions to students. After the end of the internship and following positive reviews, one intern continued his work as a member of staff.

In 2010 the European medicines agencies (also SAM) carried out an audit of their websites. The results show that the average number of visitors to the SAM website www.zva.gov.lv per month is 11 000.



6. DEVELOPMENTAL PRIORITIES OF THE STATE AGENCY OF MEDICINES FOR 2011

The operational plan for the SAM for year 2011 was approved on February 11th 2011.

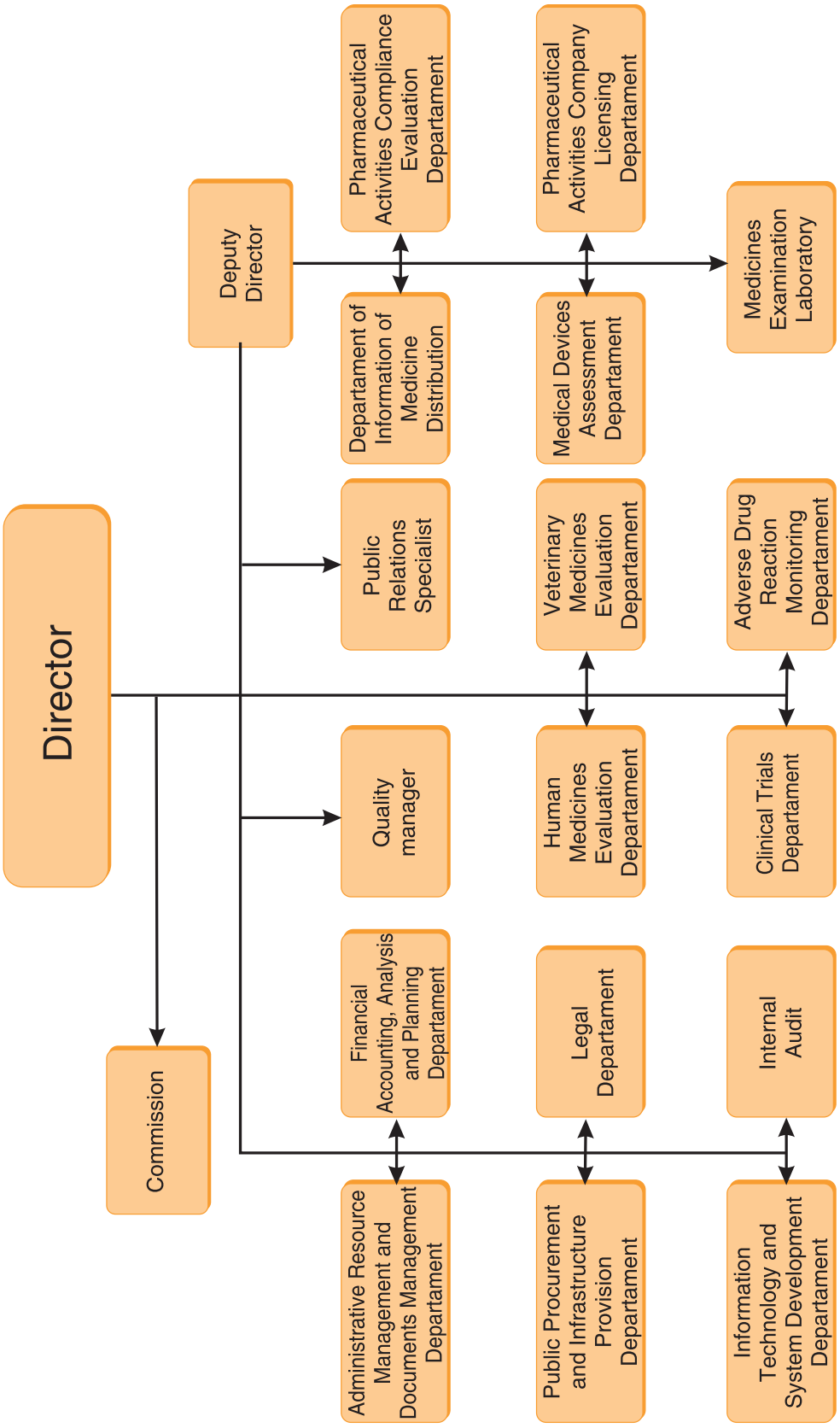
Taking into account the functions assigned to the SAM and the main directions of its operation, the operational plan assigns specific tasks for each structural unit and agency as a whole.

In addition to the main operations of SAM the following objectives have been set as priorities for 2011:

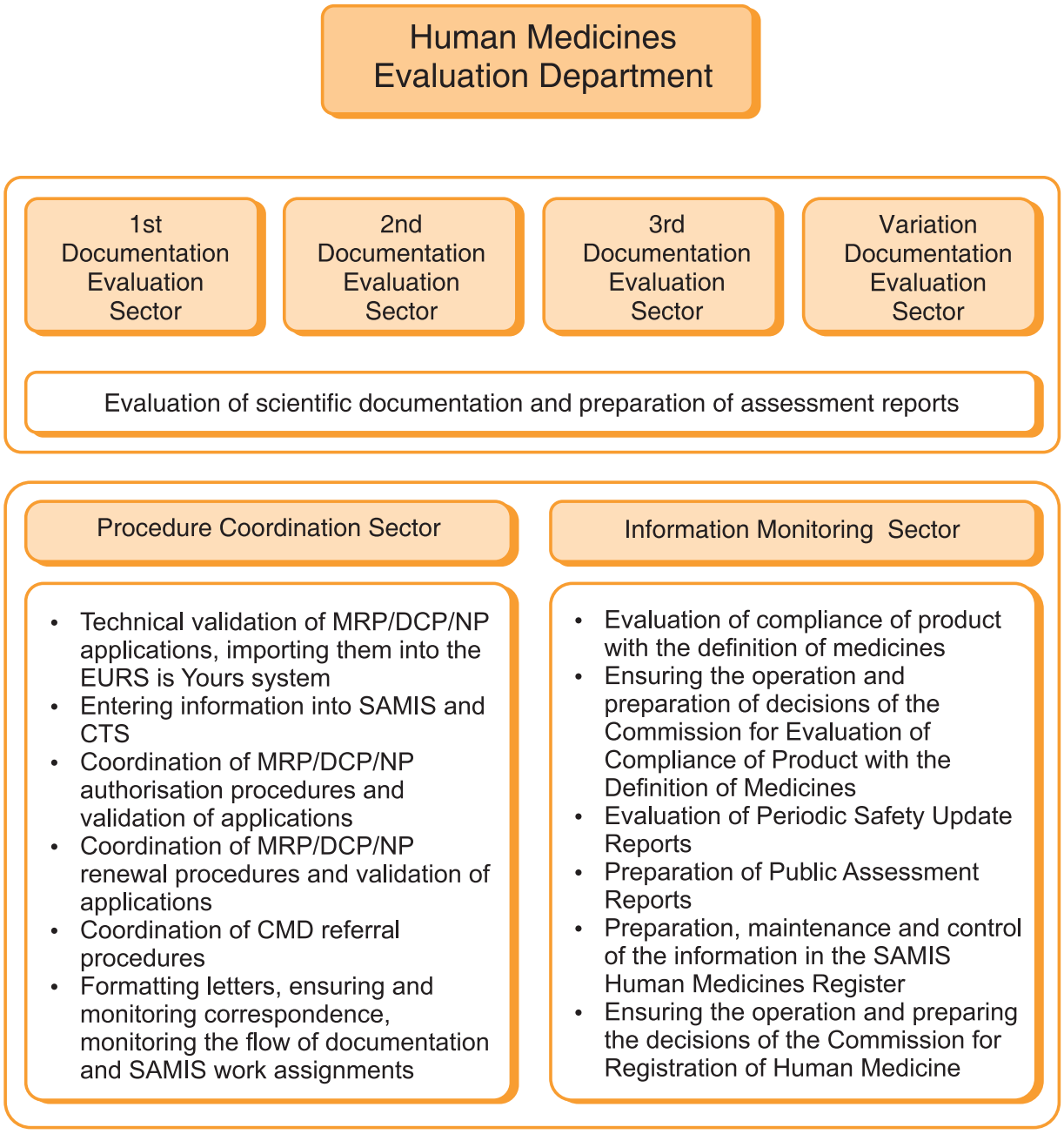
- Develop a long-term strategy for the period 2011-2015;
- Increase the number of MRP/DCP procedures where Latvia is the responsible Member State;
- Participate in the centralised authorisation procedure;
- Improve the acceptance and processing of electronic authorisation documentation (e-CTD);
- Ensure data exchange with European databases with respect to data regarding medicines, medical devices, clinical trials, manufacturers, distributers and tissue, cell and organ centres (undertake the commitments defined by the *Memorandum of Understanding on the Exchange of information in the context of EU Telematics*);
- Actively participate in e-health projects;
- Ensure inspections of compliance of pharmacovigilance systems after they are defined by the law;
- Actively participate in the work of EMA and work-sharing programs within the European Medicines Regulatory Network and also WHO programs;
- Ensure and coordinate the development of the list of active substances and excipients in Latvian, involving academic forces and the State Language Center in the process;
- Update and review SAM internal procedures to increase work effectiveness;
- Ensure annual SAM publications in paper and electronic format to SAM clients;
- Continue to develop electronic communication with clients;
- Implement the intended measures to ensure the certification of SAM Quality Management System according to the international standard ISO 9001:2009 “Quality Management System. Requirements.”

APPENDICES

APPENDIX No. 1. The Structure of the State Agency of Medicines



APPENDIX No. 2. The structure of the Human Medicines Evaluation Department



Distribution of functions among structural units

Human Medicines Evaluation Department

- Performs marketing authorisation and renewal of medicines in the national, mutual recognition and decentralised procedures and accepts the submitted variations to documentation.
- Carries out expertise on pharmaceutical, pharmacological and toxicological documentation, clinical trials, Summary of Product Characteristics, Package Leaflet, labelling and other documents.

Department of Information on Medicines Distribution

- Carries out expertise and issues authorisations for importing, exporting and distribution of human and veterinary medicines, including narcotic, psychotropic medicines/substances and precursors, parallel imported and unauthorised medicines.
- Prepares, corrects and updates information on the availability and price of medicines.
- Assembles and analyses statistical data on consumption of medicines.
- Assembles data on sales figures of pharmacies, wholesalers and manufacturing companies.
- Records and controls the legal circulation of narcotic, psychotropic substances and precursors.

Clinical Trials Department

- Evaluates the applications and the related documentation of clinical trials received from local and foreign sponsors, as well as issues authorisations for the initiation of clinical trials in Latvia.
- Supervises and controls the clinical trials carried out in Latvia, as well as evaluates the compliance of clinical trials with the requirements of good clinical practice.
- Evaluates the applications for non-intervention studies and ensures their registration.

Adverse Drug Reactions Monitoring Department

- Collects, updates, evaluates and carries out expertise of data on adverse drug reactions observed in Latvia and in foreign states.
- Exchanges data on safety of medicines with marketing authorisation holders and institutions in the European Union and in the world.
- Assesses the detailed descriptions of pharmacovigilance systems of the marketing authorisation holders within the national authorisation procedure.
- Approves the educational materials submitted by marketing authorisation holders as an additional risk minimisation activity.
- Prepares medicines safety information for communication with physicians, pharmacists and the society.
- Participates in the preparation of the SAM bulletin *"Cito!"*.

Medicines Examination Laboratory

- Carries out testing of samples of medicines and veterinary medicines manufactured in Latvia and foreign states by determining the compliance of samples of the medicines with the requirements of normative documentation submitted for authorisation.
- Carries out the selection and testing of purified water samples from pharmacies.
- Prepares volumetric solutions, indicators and reagents upon request from pharmacies.

Veterinary Medicines Evaluation Department

- Performs marketing authorisation and renewal of veterinary medicines in the national, mutual recognition and decentralised procedures, as well as evaluates and accepts submitted variations to documentation.
- Carries out expertise on the quality, safety and residue substances, pre-clinical and clinical documentation, as well as other documentation of veterinary medicines.
- Evaluates the compliance of Summary of Product Characteristics, Package Leaflet

and labelling of veterinary medicines with the requirements of normative acts.
- Ensures maintenance and updating of information in the Veterinary Medicines Register database of the Republic of Latvia.
- Regularly updates the system for monitoring of adverse drug reactions (ADR) to veterinary medicines, evaluates and forwards ADR reports to the European Medicines Agency and competent institutions of other states where the veterinary medicines have been authorised.

Medical Devices Assessment Department

- Performs evaluation of compliance and registration of medical devices.
- Develops, maintains and updates the LATMED medical devices database that contains information on the medical devices, manufacturers, distributors, clinical trials, as well as vigilance system reports.
- Evaluates the conformity of clinical trials documentation with the requirements of legislation before the initiation of the clinical trial, decides on the issuing of authorisation for conduct of clinical trials with medical devices and supervises the trial procedure.
- Performs safety surveillance of medical devices, ensures the well timed flow of information regarding risk or danger of using medical devices to healthcare services receivers and users of medical devices that could be under such risk. In certain cases ensures and supervises the performance of corrective safety actions.

Pharmaceutical Activities Compliance Evaluation Department

- Evaluates the compliance of the activity of pharmaceutical companies (medicines (both human and veterinary) manufacturing/importing companies, including foreign manufacturing companies) with the legislation and normative acts of the Republic of Latvia, and the requirements of the European Commission.
- Monitors and evaluates the compliance of tissue, cell and organ harvesting and storage centres, blood offices in medical care institutions, blood preparation departments and the State Blood Donor Centre.

Pharmaceutical Activities Company Licensing Department

- Ensures licensing of pharmaceutical and veterinary pharmaceutical activity companies, so that the companies are issued a special authorisation (licence)for pharmaceutical and veterinary pharmaceutical activity.
- Devises and maintains informative base of licensed pharmaceutical and veterinary pharmaceutical activity companies.

Financial Accounting, Analysis and Planning Department

- Conducts account of finances.
- Assembles information about economic activities of SAM.
- Prepares and submits reports and declarations.
- Ensures the internal control of accounting processes over the application of material, human and financial resources.
- Ensures strategic and short-term financial planning.

Public Procurement and Infrastructure Provision Department

- Organises public procurements.
- Ensures management of material assets and organises measures for work protection.

Legal Department

- Ensures the compliance of administrative acts devised by SAM with the requirements of effective legislation, including European Community regulations and the requirements of effective Court of Justice of the European Community judgments, as well as devises administrative documents regulating SAM operations.
- Legally solves juridical issues and problems.

- Prepares and evaluates contracts, documentation projects, prepares various conclusions and statements.
- Devises projects for normative acts.
- Represents the interests of the SAM in the Case of justice.

Administrative Resources Management and Documents Management Department

- Carries out planning, selection and account of the personnel.
- Organises the establishment of work regal relationship with employees and appointment of civil servants, termination of employment regal relationship with SAM and release of civil servants from their duty, transferring employees and civil servants to other staff positions.
- Devises and stores the personal files of SAM employees and civil servants.
- Organises and supervises the record keeping process and the system for management of documentation in the institution.
- Ensures SAM client service by providing information about processes ensuring the functions of the agency and the appropriate order of acceptance and issuing of documents.
- Carries out certain functions delegated to it by the SAM administration in accordance with the requirements of the State Administration Structure Law.
- Ensures the operation of the SAM library.
- Carries out the management of the SAM Archives.

Quality Manager

- Organises the introduction, maintenance and improvement of the Quality Management System.
- Carries out monitoring and analysis of processes.

Information technology and System Development Department

- Ensures the maintenance of a united, standardised environment for local network, servers, software and work stations, provides consultations to staff members and practical help in dealing with IT issues.
- Ensures the connection to the data transmission network for all staff members and SAM clients.
- Ensures the creation of data reserve copies, logical protection of the computer network and data, electronic communication and internet information service and prevention of damage to the facilities.

Public Relations Specialist

- Ensures communication with the public.
- Directly and with the help of mass media provides information about the politics of the field in the competency of the SAM and about the work of the SAM.

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