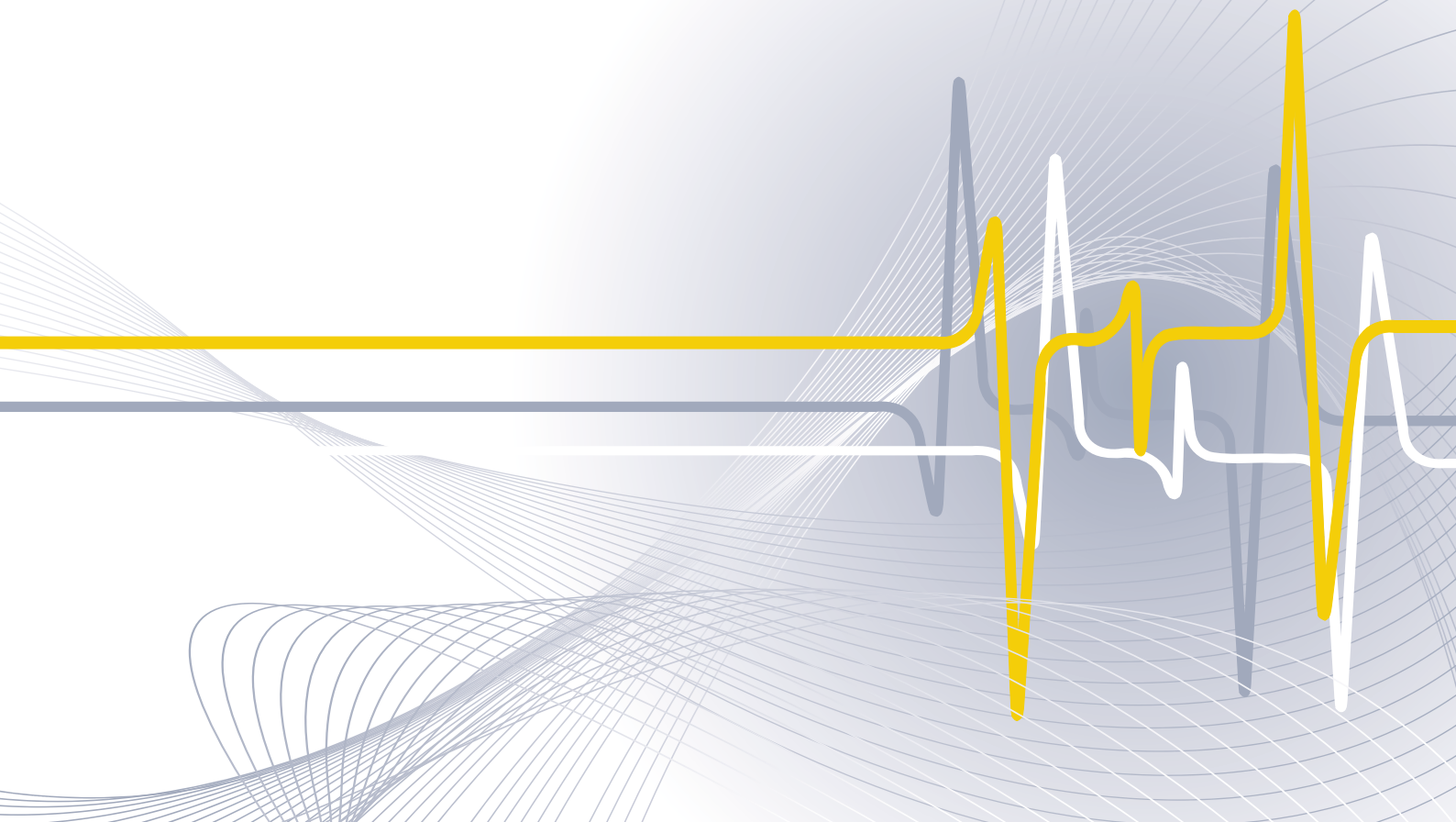
STATE AGENCY OF MEDICINES

ANNUAL REPORT 2013



STATE AGENCY OF MEDICINES

ANNUAL REPORT

2013

CONTENT

INTRODUCTION

Dear readers,

I have the great honour to present to you the annual report of the activities of the State Agency of Medicines in 2013, which reflects honourable operation throughout the year.

2013 was the first year that the State Agency of Medicines was operating as an institution not financed from the state budget in accordance with the July 31st, 2012, Cabinet of Ministers Regulation No. 537 "Statutes of the State Agency of Medicines" which laid down the change of status starting from January 1st, 2013.

In accordance with the "Law on Public Agencies" a strategy was developed in the Agency for the period of 2013-2015 and it was approved with the September 5th, 2013, Ministry of Health Order No. 158. After updating the strategy it now includes the time period 2014-2016. The budget of the State Agency of Medicines for 2013 was approved by the October 30th, 2012, Cabinet of Ministers Order No. 521 "Regarding the Approval of the Budget of the State Agency of Medicines for 2013". An important aspect was that this Order laid down that the remaining financial resources should be allocated for the financing of expenditures in 2013, thus, initiating a principle for the continuity of financial administration also through the turn of the year. Based on a similar concept the October 31st, 2013, Cabinet of Ministers Order No. 515 "On the Approval of the Budget of the State Agency of Medicines for 2014" approved the Agency's budget for 2014.

This year has also been characterised by significant changes in both European Union and national legislation and employees of the Agency have been active participants of this process. Special mention should be made on the amendments to the regulations on medical devices and clinical trials developing in the European Council. Also the establishment of a fee for carrying out pharmacovigilance activities in the European Medicines Agency is an issue that directly concerns the interests of national agencies. Therefore, participation in these processes has become even more important.

Introduction of new requirements in order to prevent

falsified medicines from entering the chain of legal supply of medicinal products with regard to requirements for manufacturers of active substances and intermediary transactions with medicines is only a part of the changes to be managed this year.

Even though there were reasonable concerns regarding possible significant disruptions in the supply of medicines relating to compliance issues of active substance manufactures in third countries, the risk was minimised as much as possible based on the cooperation methodology established by the European Medicines Agency and the national medicines agencies with the active participation of the European Commission.

The Heads of the Medicines Agencies in Europe have updated several collective initiatives in order to solve public health issues successfully, promote innovations in the development of medicinal products and increase the operational capacity of agencies. The most important

discussions are connected with the sustainable development of resources and the collaboration network. There are a lot of collective procedures already now - work sharing, unified databases, as well as teams of multi-national experts. These are the methods that are necessary in order to carry out the current work tasks in the time of globalisation. At the time when a strong trend of centralisation can be observed on a political level in Europe, the administrative procedures, formal aspects, abilities to allocate the available financial resources of the national agencies are not flexible enough and not enough coordinated to promote international cooperation and to ensure a sustainable collective growth. That is our next collective work task.

In the year of review the Agency continued active participation in international organisations and invested in the achievement of the collective goals of the organisations and of the Agency. Special mention should be made to the evaluation of applications in the mutual recognition procedures carried out by the Agency, when Latvia is the reference member state. Latvia has participated as a co-rapporteur in the procedures of the European Medicines Agency Committee for Advanced Therapies, in several procedures of the Paediatric Committee, as well as in the Committee for Medicinal Products for Human Use. Several experts regularly carry out expertise for the European Directorate for the Quality of Medicines. The Agency also involves the leading scientists in Latvia in the international expert work, this way representing the position of Latvia in both the preparation of the evaluation of medicines and in the issues regarding regulation of medicines on an international level.

The year of 2013 can be characterized as year of quality and growth. We have attempted to strengthen our operational capacity. At the end of 2013 a surveillance audit took place in accordance with the ISO 9001:2008 and ISO/IEC 27001:2005 international standards. We continuously improved the integrated management system. Certified areas: marketing authorisation of medicines, pharmacovigilance and vigilance and licensing of medical devices in accordance to authorisation etc. For the fourth time we participated in the comparison of European medicines agencies called Benchmarking (BEMA). In November 2013 we prepared a self-evaluation report, and the BEMA III visit took place in the State Agency of Medicines from February 24th until February 28th, 2014. In September 2013 we submitted a report to the European Commission on the audit of the pharmacovigilance system.

Amendments to the legislation this year also had influence on the patients. Now they themselves have the opportunity to report observed adverse drug reactions to the Agency. In addition, we have also ensured the submission of the reports electronically. In order to promote the new rights of the patients, we carried out an informative campaign and distributed a poster informing, "REVEAL THE OTHER SIDE OF MEDICINES, report adverse reactions!" to pharmacies, healthcare institutions and libraries, as well as performed other informative activities.

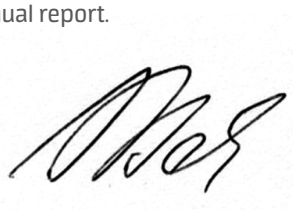
In order to facilitate the work of healthcare specialists and pharmacists in choosing the appropriate medicines for patients and in obtaining or clarifying significant information regarding safety of medicines, in 2013 for the first time State Agency of Medicines issued the Medicinal Product Register of the Republic of Latvia containing summaries of product characteristics and package leaflets also in an electronic data carrier - in a flash memory card. This electronic format prepared by State Agency of Medicines allows any user to find the necessary data regarding medicines with the help of a simple and convenient search form for electronic information.

This year within the cooperation of our medicines agencies in the Baltic States a publication "Baltic Statistics on Medicines 2010-2012" was prepared. In a way it is unique due to the fact that no other group of countries within the European Economic Area (EEA) has a similar publication and it is also historical because for the first time a publication has been prepared summarising reliable data regarding consumption of medicines in the Baltic States. The data on consumption of medicines in the Baltic States can be used in order to promote the rational use of medicines. This data also reflects the policy and the reality of practical life at the same time providing also information that would be useful in the argumentation of reasonable decisions.

In conclusion, I would like to mention the development of information technologies. Our specialists ensure not only integration in the unified European IT system made up by several unified databases and platforms, but they also serve the data centre services to the Ministry of Health and five institutions in the field: Pauls Stradins Museum of the History of Medicine, Centre for Disease Prevention and Control, State Blood Donor Centre, State Centre for Sports Medicine, State Centre of Forensic Medicine, a total of 500 unique users. The Agency personnel also ensure system changes, improvements and maintenance.

I would like to thank all of the employees of the Agency that have ensured the accomplishment of the delegated tasks with their fair and hard work. We have performed our tasks professionally and with the feeling of responsibility.

I invite you to read our annual report.



Director of the State Agency of Medicines,
Inguna Adoviča

ABBREVIATIONS USED IN THIS REPORT

ADR	Adverse Drug Reaction
BEMA	Benchmarking of European Medicines Agencies
CDPC	Centre for Disease Prevention and Control
CHMP	EMA Committee for Medicinal Products for Human Use
CM	Cabinet of Ministers
CPP	Certificate of Pharmaceutical Product
CRP	Centralised Registration Procedure
DCP	Decentralised Procedure
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GPP	Good Pharmacovigilance Practice
IMS	Integrated Management System
INCB	International Narcotics Control Board
ISO	International Organization of Standardization
LATMED	Electronic Database of the Register of Medical Devices
MAH	Marketing Authorisation Holder
MD	Medical Device
MH	Ministry of Health
MRP	Mutual Recognition Procedure
NP	National Procedure
PIC/S	Pharmaceutical Inspections Co-operation Scheme
PRAC	EMA Pharmacovigilance Risk Assessment Committee
SAM	State Agency of Medicines
SAMIS	State Agency of Medicines Information System
VIC	Vaccine Induced Complications
WHO	World Health Organization

1. ABOUT THE STATE AGENCY OF MEDICINES

1.1. Legal Status of the State Agency of Medicines

The State Agency of Medicines (hereinafter also - SAM) is a state institution under the supervision of the Minister of Health. SAM operation is regulated by the State Administration Law, the Law on Public Agencies, the Pharmaceutical Law, the Cabinet of Ministers Regulation No. 537 "Statutes of the State Agency of Medicines" adopted on July 31st, 2012, and other normative acts.

SAM was established on October 9th, 1996, based on the Cabinet of Ministers of the Republic of Latvia (hereinafter - CM) Order No. 403 "Regarding the Non-profit Organisation State Joint Stock Company "State Medicines Agency"". Jānis Ozoliņš was appointed as its first Director. Since November 2nd, 2005, the Director of SAM has been Inguna Adoviča.

1.2. Functions of the State Agency of Medicines

The operational objective of SAM is to implement qualitative and reasonable services in the evaluation of medicinal products used in healthcare, production and storage (utilisation) organisations of human blood, tissues, cells and organs, as well as pharmaceutical activity companies in accordance with the interests of the State and of the public in the field of healthcare.

SAM performs the following tasks:

- evaluates and authorises medicines, carries out expertise on quality of medicines, develops and updates the Medicinal Product Register of Latvia;
- carries out pharmacovigilance;
- issues authorisations for conduct of clinical trials with medicinal products, evaluates the compliance of clinical trials with good clinical practice requirements, as well as evaluates the applications for non-interventional studies of medicines;
- issues authorisations for import, export, transit, distribution and purchase (to ensure self operation) of medicines, as well as authorisations for use of plants, substances and medicines included in the lists of narcotic, psychotropic substances and precursors controlled in Latvia for medical and veterinary medical scientific research or training, as well as determining their physical and chemical properties;
- regularly collects, summarizes and distributes information regarding consumption of medicines;
- issues authorisation cards for precursor operators and special permits (licences) for operation with precursors;
- authorises medical devices manufactured in Latvia, issues authorisations for placing specially supplied medical devices on the market, as well as carries out vigilance for medical devices;
- issues authorisations for conduct of clinical trials with medical devices;
- issues compliance certificates to production and storage (utilisation) organisations of human tissues, cells and organs, blood establishments, hospital blood banks and the State Blood Donor Centre;
- issues special permits (licences) for pharmaceutical activity;
- issues good manufacturing practice compliance certificates;
- participates in the unified system of the medicines and medical devices agencies in the member states of the European Economic Area, cooperates

with European institutions and international organisations by participating in work-sharing and complying with the collective standards and procedures;

- collaborates with professional organisations of doctors and pharmacists, non-governmental organisations in the field, foreign and international institutions, as well as ensures mutual exchange of information in the areas of operation of SAM;
- carries out the tasks of the competent authority in accordance to the requirements laid down in the normative acts of the European Union;
- operates in the European medicines network by participating in work-sharing and complying with the collective standards and procedures, cooperates with other European and international organisations.

1.3. Main Objectives of the Year of Review

Agency's Work Plan for 2013 was approved on January 18th, 2013. The Work Plan lays down specific tasks for each structural unit and for the institution as a whole taking into account the functions and tasks delegated to SAM. In addition to the primary operation of SAM, in 2013 the following priority tasks were set for the year of review:

- begin operation as a public agency - an institution non-financed from the state budget;
- actively participate in MRP/DCP procedures as the Reference Member State;
- participate in the centralised authorisation procedures (CRP) assuming co-rapporteur responsibilities;
- promote and develop collaboration with academic and scientific institutions;
- ensure the requirements of the new pharmacovigilance normative acts, as well as compliance inspections of pharmacovigilance systems after they are laid down in normative acts;
- actively participate in e-Health projects and automated document processing systems (ADPS);
- improve the circulation of electronic marketing authorisation documentation (e-CTD) and take part
- in the use of the Common European Submission Platform (CESP);
- ensure data exchange with European databases for data regarding 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*);
- more actively participate in the work of EMA, in work-sharing programs within the European network of Heads of Medicines Agencies and WHO programs;
- ensure and coordinate the development of a list of active substances and adjuvant in Latvian;
- prepare for and ensure the BEMA III visit in the first quarter of 2014;
- review and update SAM internal procedures with the aim to increase work effectiveness; development of electronic communication with collaboration partners.

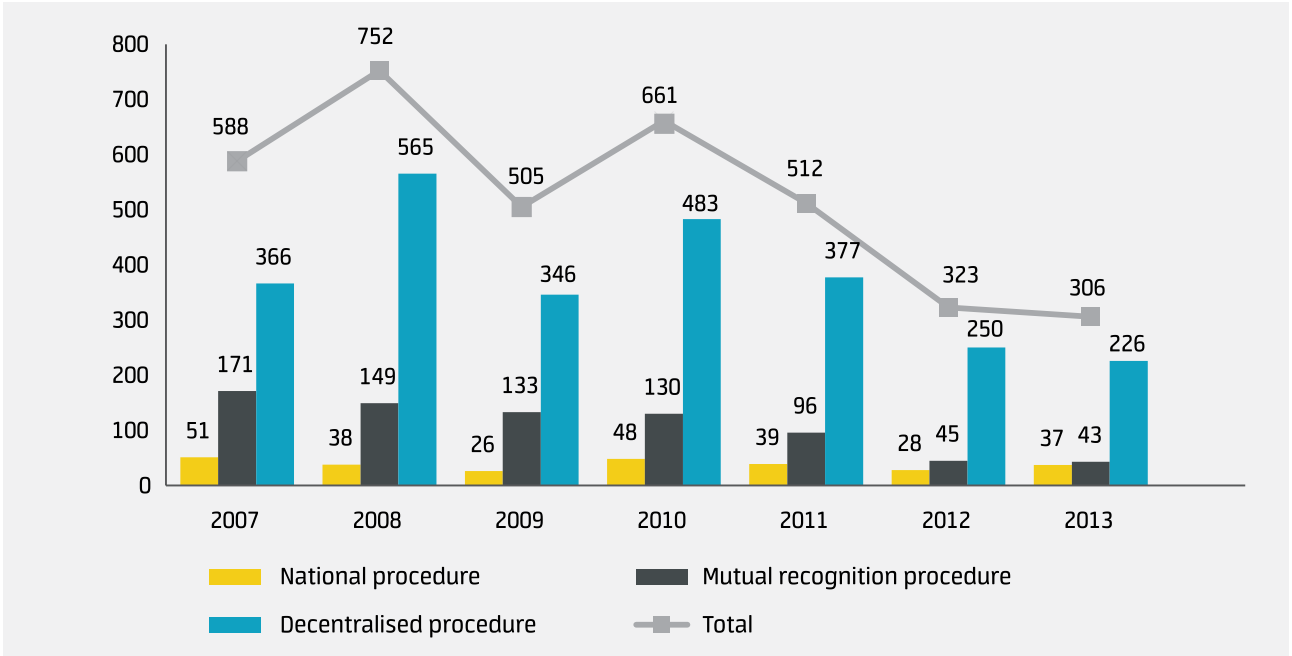
2. RESULTS OF OPERATION OF THE STATE AGENCY OF MEDICINES

2.1. Marketing Authorisation of Medicines

In 2013 by evaluating documentation on quality, safety and effectiveness of medicines SAM has carried out expertise more than 9000 times on general, chemical and pharmaceutical, as well as preclinical and clinical sections of the documentation of medicines. Evaluation reports on 61 medicines have been prepared for the SAM Commission on Marketing Authorisation of Human Medicines for adoption of a decision regarding marketing authorisation and renewal of medicines in the national procedure. In 2013 Latvia has led 3 mutual recognition procedures (MRP) and 4 decentralised procedures (DCP) as a Reference Member State. Also in 2013 Latvia has taken over 4 DCP procedures and 1 MRP procedure from other member states, thus, becoming the Reference Member State for these procedures. Latvia has also evaluated one Periodic Update Safety Report (PSUR) as a Reference Member State in a work-sharing procedure and has started another procedure which is still on-going. 269 DCP and MRP authorisation procedures and 187 MRP renewal procedures have been carried out in 2013 with Latvia actively participating as a Concerned Member State.

In the year of review SAM experts' activity in international procedures has been higher than in the previous year. In 2013 Latvia as a co-rapporteur has participated in EMA Committee for Medicinal Products for Human Use (CHMP) evaluating the indications of *ceftriaxone* containing medicines in accordance with Article 30 of the Directive 2001/83/EC. A team from the State Agency of Medicines has also successfully evaluated product documentation as the responsible rapporteur in a centralised authorisation

MARKETING AUTHORISATION OF MEDICINES



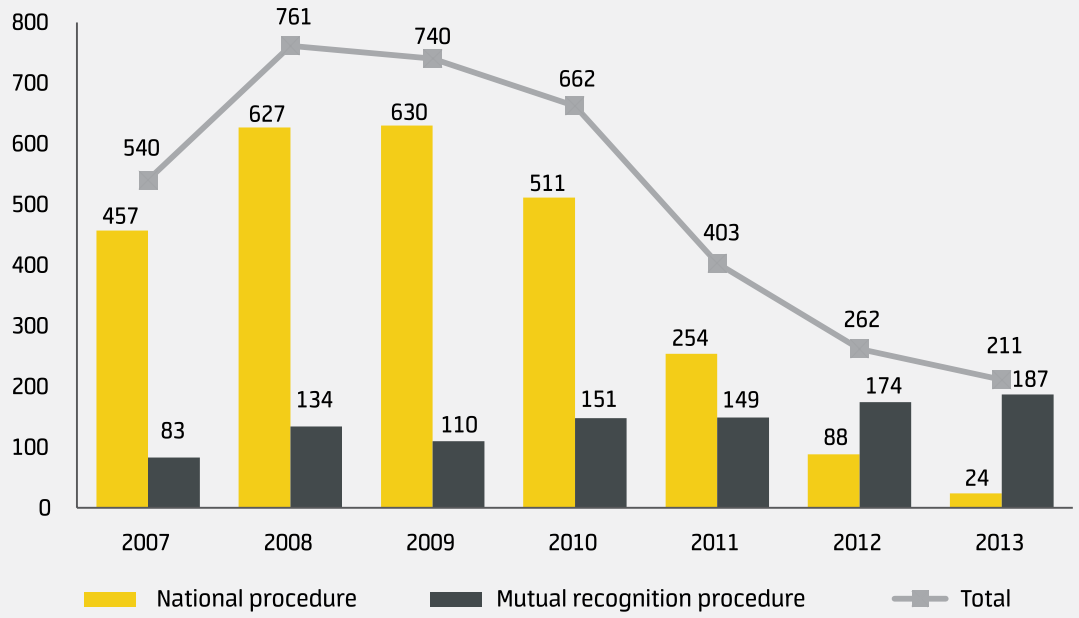
procedure. In another case SAM experts together with external experts have participated as co-rapporteurs.

Latvia is represented in the EMA Paediatric Committee and as a rapporteur participated in 10 PIP (Paediatric Investigation Plan) procedures, as a co-rapporteur - in 3 procedures and as a rapporteur participated in 4 PIP modification evaluations.

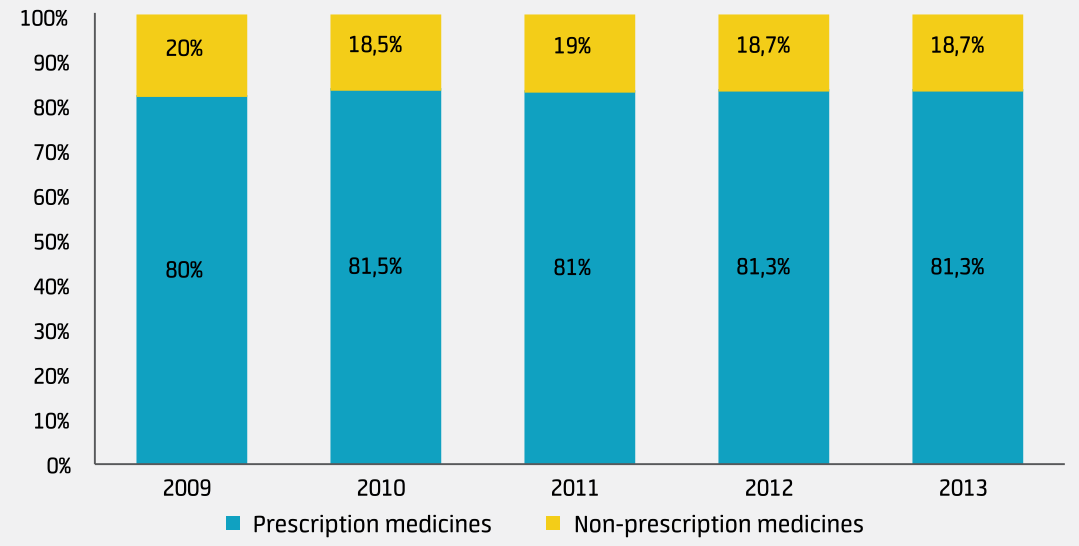
SAM internal and external experts have successfully led a paediatric work-sharing procedure of the MRP and DCP coordination work group for the active substance *Phytomenadion* by evaluating documentation in accordance with Article 45 of the Paediatric regulation and have also led an evaluation procedure for the *varicella* vaccine documentation in accordance with Article 46 of the Paediatric regulation.

Experts from the Human Medicines Evaluation Department together with external experts have actively participated in the work of the Committee on Herbal Medicinal Products. In 2013 work was continued on the development of a new Union monograph on *Ononis spinosa L., radix* and a 5-year review procedure was initiated for the current Union monograph on *Eleutherococcus senticosus*

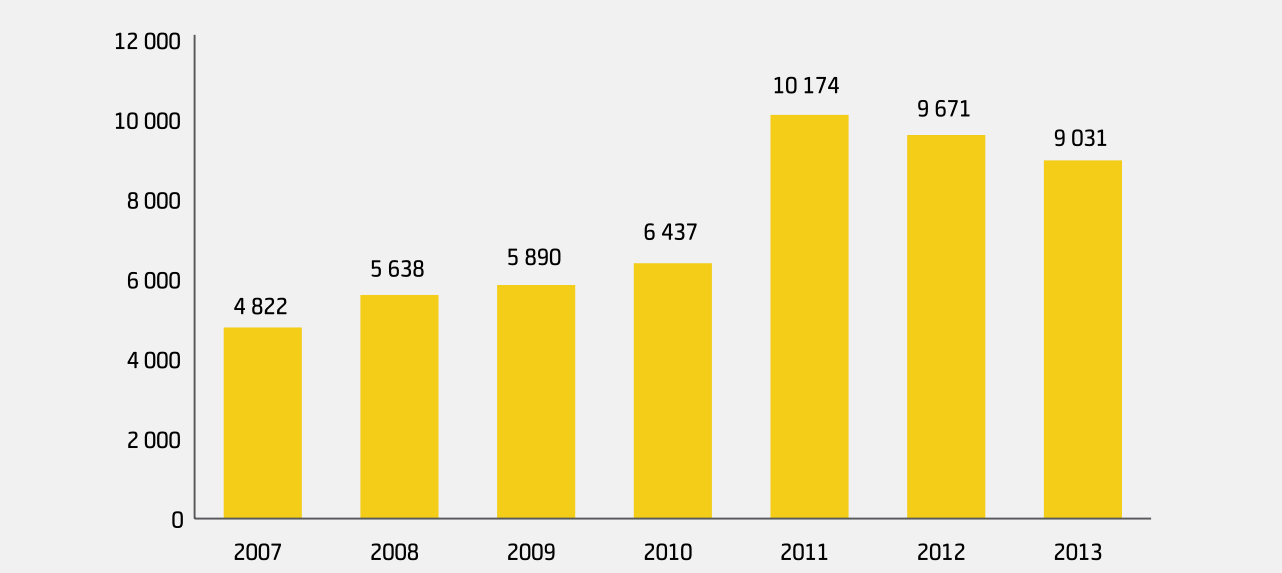
RENEWAL PROCEDURE OF MEDICINES



PROPORTION OF PRESCRIPTION AND NON-PRESCRIPTION MEDICINES



VARIATIONS TO THE MARKETING AUTHORISATION DOCUMENTATION



(Rupr. et Maxim.) Maxim., radix.

In 2013 experts from the Human Medicines Evaluation Department have regularly carried out compliance evaluations on master files of active substances in EDQM.

Even though the total number of medicines has slightly decreased, the proportion of prescription and non-prescription medicines in the Medicinal Product Register of the Republic of Latvia has remained the same.

9031 variations to the documentation of authorised medicines were submitted and evaluated in 2013.

In the year of review 11 applications were received for the evaluation of compliance with the definition of medicinal products laid down in the Pharmaceutical Law and SAM issued its opinion regarding these applications.

342 periodic update safety reports were evaluated in 2013. 7 public assessment reports for nationally authorised medicines were written, coordinated with marketing authorisation holders and published in 2013.

2.2. Issuance of Authorisations for Distribution of Medicines

In 2013 within its competency SAM provided monitoring of distribution of medicines in Latvia, provided consultations to clients and collaboration partners regarding distribution of medicines and carried out expertise on applications and documentation regarding:

- import and export of psychotropic, narcotic medicines/substances and precursors;
- distribution of unauthorised medicines;
- import of samples of medicines;
- distribution of remaining stock of medicines;
- distribution of parallel imported medicines in Latvia and their variations.

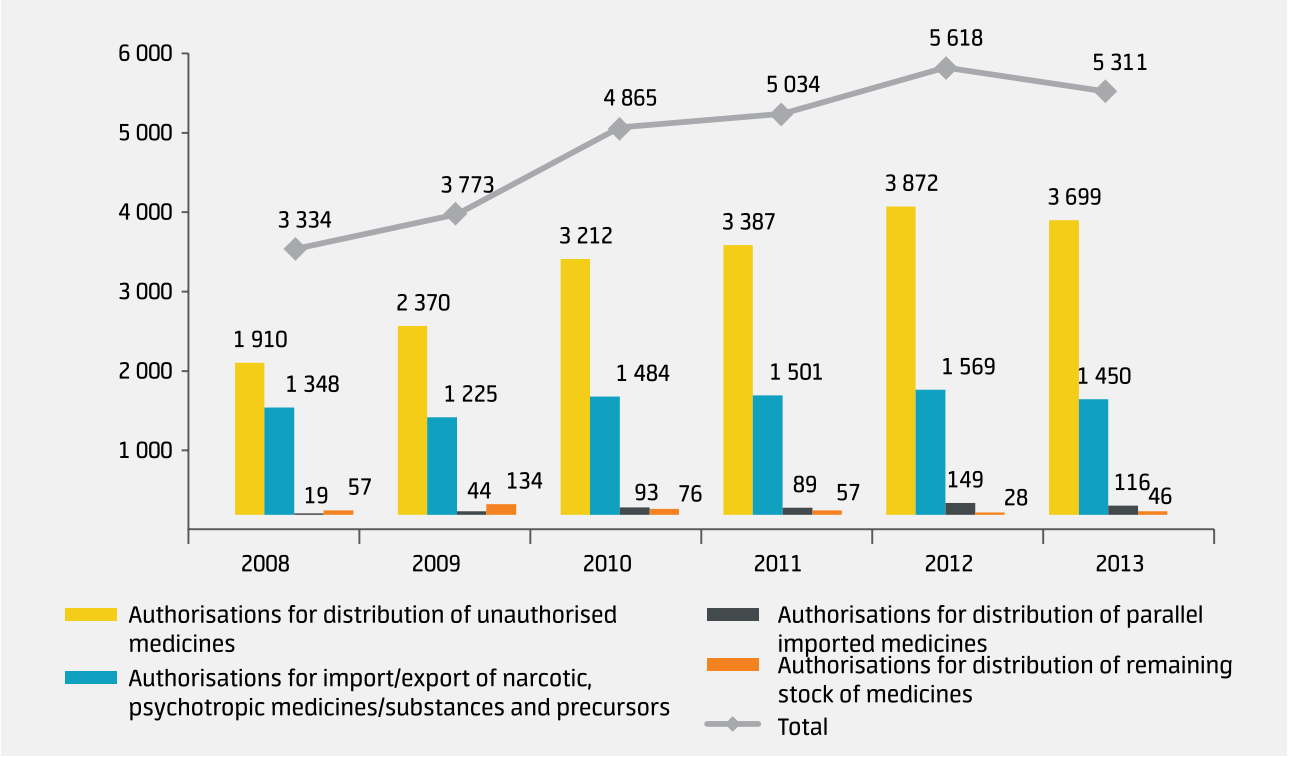
In 2013 SAM issued 5322 authorisations for import, export and distribution of medicines. This includes 3699 authorisations for distribution of unauthorised medicines, 116 authorisations for distribution of parallel imported medicines and 46 authorisations for distribution of remaining stock of medicines after the withdrawal of the medicines from the Medicinal Product Register of the Republic of Latvia.

In addition to the aforementioned functions SAM has carried out expertise on applications for:

- issuance of special permits (licences) for operation with precursors and issuance of precursor operator cards;
- use of plants, substances and medicines included in the I, II and III list of narcotic, psychotropic substances and precursors controlled in Latvia for medical and veterinary medical scientific research or training, as well as determining their physical and chemical properties;
- purchase of medicines (to ensure operation).

In the year of review 14 authorisation cards were issued to precursor operators and 5 authorisations were issued for use of plants, substances and medicines included in the I, II and III list of narcotic, psychotropic substances and

DYNAMICS OF THE NUMBER OF AUTHORISATIONS ISSUED PER YEAR



precursors for medical and veterinary medical scientific research or training, as well as determining their physical and chemical properties. Variations were made to marketing authorisations for 165 parallel imported medicines.

SAM provides the registration and control of legal circulation of narcotic substances, psychotropic substances and precursors controlled in Latvia. SAM prepares a quarterly report on the import and export of narcotic substances and an annual report on the consumption of narcotic and psychotropic substances within the state and forwards them to the International Narcotics Control Board (INCB). SAM also prepares a quarterly report on the circulation of illegal precursors and an annual report on the circulation of legal precursors and forwards them to the European Commission.

SAM regularly processes and updates the information in the Medicinal Product Register regarding availability and prices of medicines, gathers and processes data regarding the turnover of pharmacies, wholesalers and manufacturing companies. Every month SAM compiles statistical information regarding consumption of medicines submitted by wholesalers and once a year prepares a publication "Statistics on Medicines Consumption" that is available in a electronically applicable format and is also published on SAM website. In 2013 by collaborating with colleagues in Estonia and Lithuania a publication "Baltic Statistics on Medicines 2010-2012" was prepared and it is also available on SAM website.

It has to be pointed out that SAM continuously prepares and provides recommendations to the Ministry of Health and via its mediation also to the European Commission for amendments to normative regulations regarding distribution of medicines. Following amendments to legislation SAM prepares explanatory materials and educational seminars to healthcare professionals and merchants, as well as provides routine consultations to clients.

2.3. Clinical Trials with Medicines

In 2013 SAM received 63 applications for clinical trial projects for medicines. During the expertise of documentation two clinical trial applications were withdrawn by the sponsor for strategic reasons.

During the year of review 13 applications for the international harmonisation procedure for clinical trials were submitted to SAM (in accordance with the European guidelines regarding the voluntary harmonisation procedure for evaluation of multinational clinical trials).

After the carrying out expertise on application documentation and after evaluating benefits and risks SAM employees from the Clinical Trials Department adopted decisions regarding the approval of clinical trials in 29 department meetings. In 2013 SAM issued a total of 59 authorisations for initiation of clinical trials in Latvia,

including 2 trials where conditional authorisations were issued. Applications of ten authorised clinical trials were evaluated in the international voluntary harmonisation procedure before they were submitted nationally.

Two clinical trials (in the field of neurology and pulmonology) involving children and juveniles were authorised in 2013.

Out of all the clinical trials authorised in 2013, 2 clinical trial projects planned to investigate newly introduced somatic cell therapy medicinal products for treatment of oncological and rheumatological diseases, but 12 clinical trials planned to investigate medicinal products obtained with recombinant DNA technology (for example, monoclonal antibodies, hormones) and intended for the treatment of oncological, rheumatological, heart, eye and lung diseases.

245 authorisations were issued for significant amendments to clinical trial protocols or other documentation related to the clinical trial. 20 variation applications were received in the international voluntary harmonisation procedure.

Information regarding applications for clinical trials with medicinal products, the time of their authorisation, the dates of approval of applications for significant amendments, opinions of ethical committees, completion of clinical trials, as well as inspections of good clinical practice was regularly entered into the European clinical trial database *EudraCT*. It is necessary to regularly ensure the aforementioned data for the maintenance and updating of the European Clinical Trials Register.

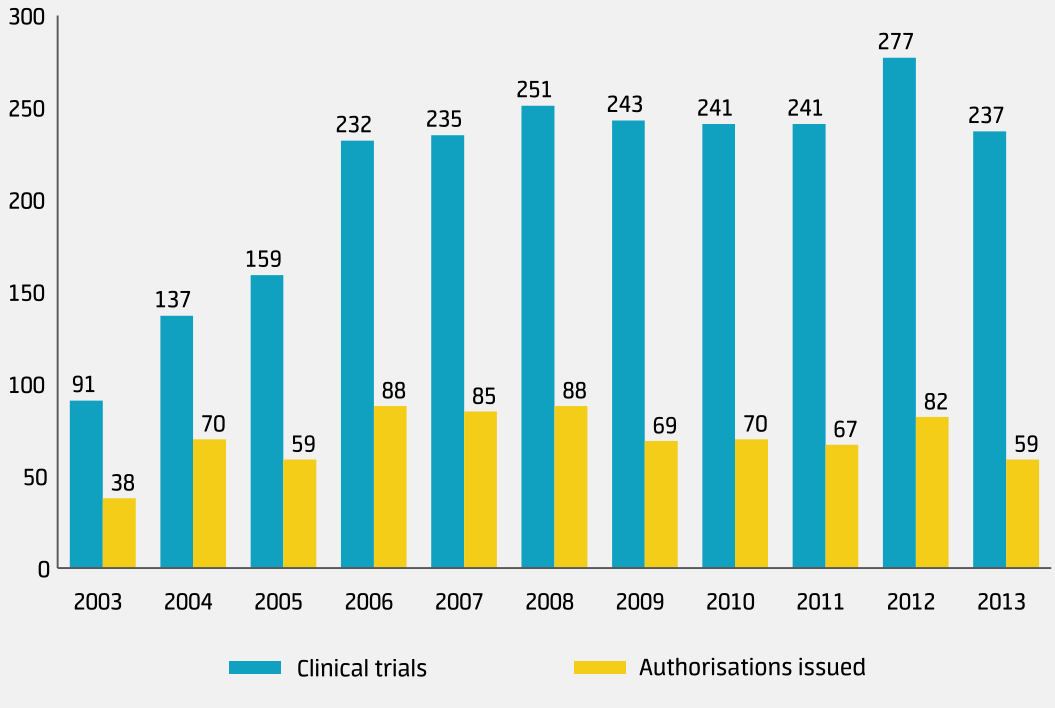
Department employees ensured electronic data exchange in the *EudraVigilance* system by forwarding acknowledgements of receipt of safety reports concerning clinical trials in Latvia to clinical trial sponsors that had submitted safety reports in the Clinical Trial Module of the *EudraVigilance* database according to European and local normative requirements. 44 reports were received in the year of review regarding serious adverse drug reactions observed at clinical trial centres in Latvia. These reports were analysed and included in a register established by SAM. In total SAM received, reviewed and recorded 144 annual safety reports prepared by sponsors regarding clinical trials with medicinal products conducted in Latvia. Separate annual safety reports were analysed in depth and the assessment is reported in an appropriate format.

15 external experts were involved in the evaluation of documentation of authorised projects. Altogether expertise was carried out on 31 projects in 2013 and 3 experts were involved for the first time.

A total of 237 clinical trials were conducted in Latvia in 2013. 50 projects were completed.

In accordance with the power of sponsors' authorization, the following contract research organisations

NUMBER OF ISSUED AUTHORISATIONS AND TOTAL NUMBER OF CLINICAL TRIALS WITH MEDICINES (2003-2013)

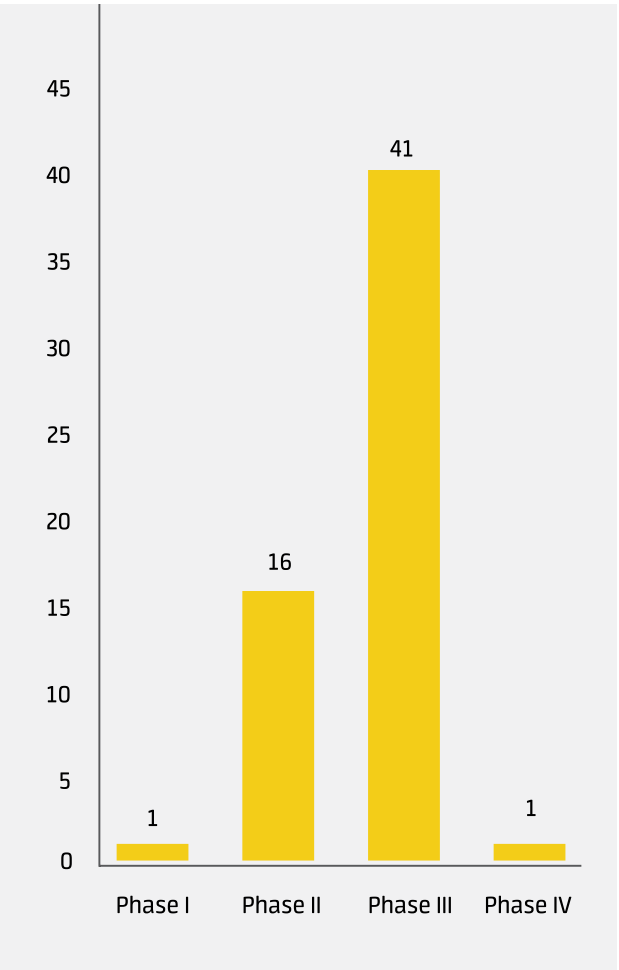


were involved in organising and providing the quality of conduct of clinical trials in Latvia:

- *Quintiles* (6 projects);
- *ICON Clinical Research* (5 projects);
- *Parexel International* (4 projects);
- *Amber CRO* (4 projects);
- *PSI Company Limited* (4 projects);
- *Crown CRO* (3 projects);
- 9 other contract organisations (1-2 projects each).

7 inspections of clinical trial compliance with good clinical practice were carried out in trial centres in 2013 (one inspection was related to a patient complaint submitted to SAM). Five inspections were conducted in trial centres in Latvia, but two inspections - in foreign trial centres in Turkey and Canada which were initiated by the CHMP in relation to marketing authorisation procedures. Both major and other discrepancies were disclosed during the inspections.

NUMBER OF CLINICAL TRIALS AUTHORISED IN 2013 ACCORDING TO PHASE



In the year of review employees of the SAM Clinical Trials Department participated in the development of the regulation of the European Parliament and the Council on clinical trials with medicinal products.

NUMBER OF CLINICAL TRIALS AUTHORISED IN 2013 ACCORDING TO MEDICAL SPECIALITY

Medical speciality	Number of clinical trials
Rheumatology	8
Pulmonology/Allergology	6
Endocrinology	6
Oncology	5
Cardiology	5
Surgery	5
Urology/Nephrology	4
Psychiatry	4
Neurology	3
Ophthalmology	3
Gastroenterology	2
Dermatology	2
Traumatology	2
Infectology	2
Gynaecology	1
Otorhinolaryngology	1

CLINICAL TRIAL CENTRES OF THE CLINICAL TRIALS AUTHORISED IN 2013 (82 TRIAL CENTRES IN TOTAL)

Clinical trial centre	Number of clinical trials
P. Stradins Clinical University Hospital	37
Riga Eastern Clinical University Hospital	31
• Clinical hospital "Gailezers"	24
• Latvian Oncology Center	5
• Clinic "Bikernieki", State Burn Centre	1
• Clinic "Tuberculosis and Lung Disease Centre"	1
Daugavpils Regional Hospital	18
Liepaja Regional Hospital	15
Vidzeme Hospital	10
LLC "Clinical Practice of Dr. D. Saulīte-Kandevica in Cardiology and Rheumatology"	8
"Health Center 4"	7
Clinic "ORTO"	6
Northern Kurzeme Regional Hospital	6
JSC "Health Centre Union", medical centre "OLVI"	6
Latvian Maritime Medicine Centre	5
Other clinical trial centers (68 in total)	1 - 4 at each centre

2.4. Monitoring of Adverse Drug Reactions and Risk Minimisation

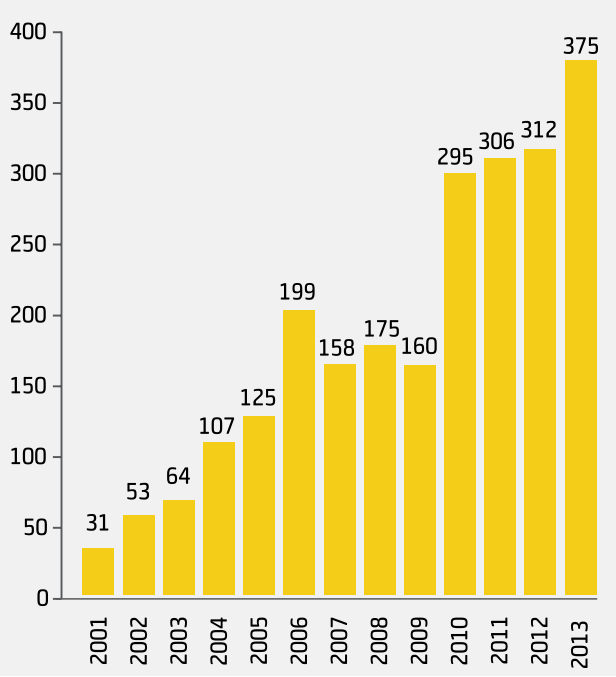
In February 2013 a new Cabinet of Ministers of Latvia Regulation "Procedure for Pharmacovigilance" (January 22nd, 2013, CM Regulation No. 47) came into force. The new regulation clarified the responsibilities of stakeholders (marketing authorisation holders, the SAM) not only in the process of adverse drug reaction monitoring, but also determined aspects such as risk management for medicines and procedures to ensure risk minimisation regarding medicines.

By the regulations coming into force the responsibilities of healthcare professionals, pharmacists, healthcare institutions, medical and pharmaceutical professional organisations, patient organisations and competent institutions of the State healthcare system were also specified regarding monitoring of adverse reactions, exchange of information on adverse reactions and their risk minimisation.

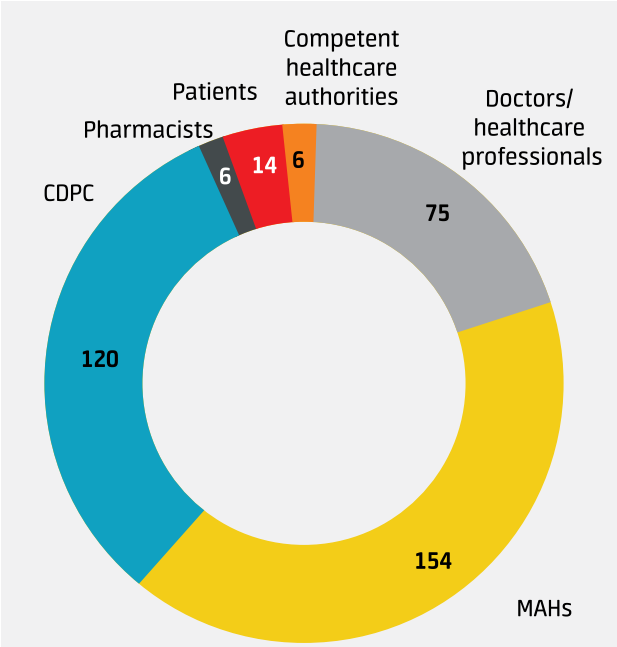
For the first time patient rights to report observed adverse drug reactions to SAM have been laid down on a normative act level in Latvia.

SAM has been maintaining the database for adverse drug reactions observed in Latvia since 2001 and since 2004 the reported information is being forwarded to the European Union database *EudraVigilance* for identification of new risks of medicines. Each year SAM analyses the information entered in the database in Latvia and the reporting activity

TOTAL NUMBER OF ADVERSE DRUG REACTION REPORTS 2001-2013



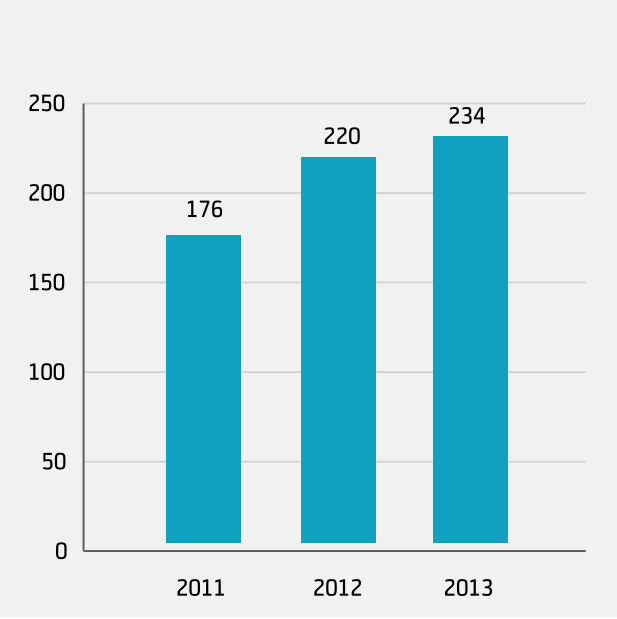
NUMBER OF ADVERSE DRUG REACTION REPORTS ACCORDING TO PROVIDER OF INFORMATION



in Latvia. Similarly as in previous years, also in 2013 there was a stable increase in the number of reports. 375 reports regarding observed adverse drugs reactions (hereinafter - ADR) were received in SAM.

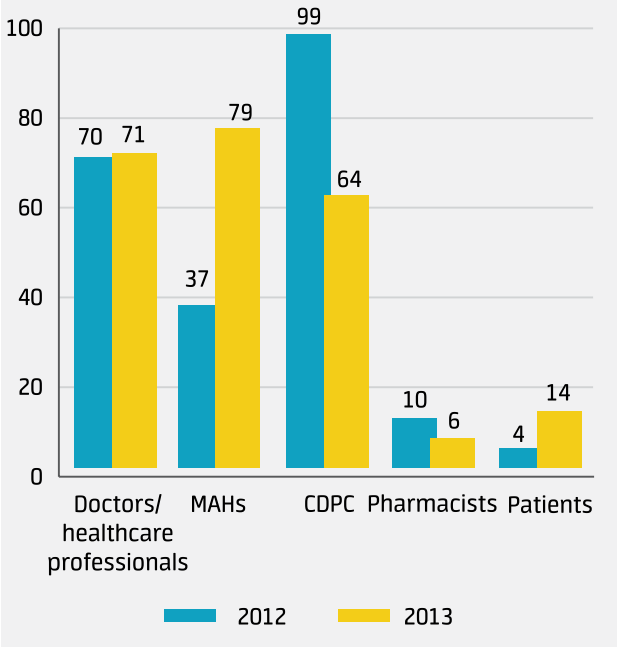
Several reports may be received regarding one and the same adverse event where the reporter has provided additional information. Therefore, an important criterion is also the number of clinical cases for which information was received during the year. This figure also slightly increased in comparison to 2012 - from 220 to 234.

NUMBER OF CLINICAL CASES OF ADVERSE EVENTS WITH MEDICINES



The reporting activity among doctors has remained equally stable, while the activity among marketing authorisation holders (MAH) has increased significantly, which indicates a more serious collaboration of MAHs and doctors to ensure identification and reporting of adverse reactions. Statistical data also indicates that the work of MAHs in further investigating ADR cases has improved as the number of additional reports submitted by MAHs has increased.

NUMBER OF CASES OF ADVERSE EVENTS ACCORDING TO PROVIDER OF INFORMATION IN 2012 AND IN 2013



In the marketing authorisation process of medicinal products SAM approves amendments in the pharmacovigilance documentation of MAHs - in descriptions of pharmacovigilance systems and summaries of pharmacovigilance systems. In the period of review 947 amendments were made. In addition in 2013 SAM also reviewed 28 Risk Management Plans (RMP) in relation to both new marketing authorisation applications and variations to RMPs of previously authorised medicines.

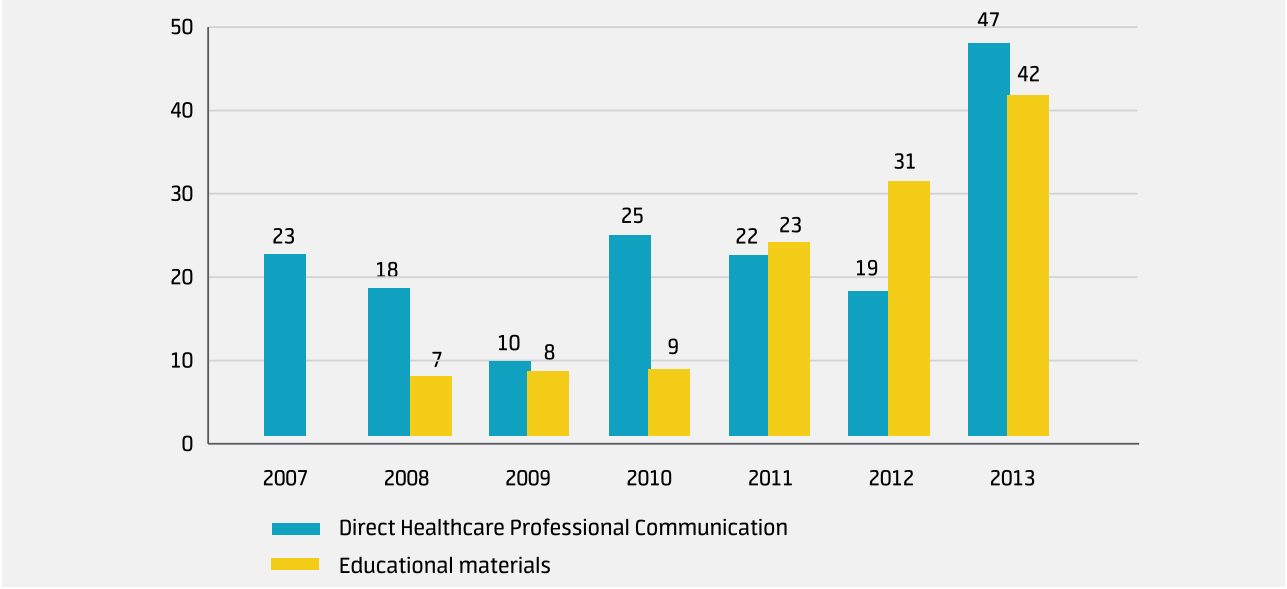
SAM began to evaluate the compliance of MAHs with good pharmacovigilance practice and carried out two such inspections in MAH companies in 2013.

In 2013 the Adverse Drug Reactions Monitoring Department carried out evaluation of 3 periodic safety update reports regarding original medicinal products in accordance with the EU work-sharing procedure (Periodic Safety Update Reports Worksharing), which includes the assessment of periodic safety update reports for the necessities of the whole European Union.

A Pharmacovigilance Council operates within the Agency and the agenda of its meetings is coordinated by the SAM Adverse Drug Reactions Monitoring Department. Four Council meetings took place during the period of review. In these meetings SAM employees, representatives of professional associations and medical universities were informed in presence about the evaluation of medicines in EMA and pharmacovigilance activities in the national agency.

SAM operates in collaboration with the Qualified Persons Responsible for Pharmacovigilance for MAHs. Data exchange is carried out regarding ADRs observed in Latvia and the implementation of MAH established risk minimisation measures is ensured in Latvia, including necessary communication with healthcare professionals, patients and the public regarding the safe use of medicines. In the period of review expertise was carried out on 42 educational

APPROVAL OF INFORMATIVE RISK MINIMISATION MEASURES



materials for risk minimisation, and 47 "Direct Healthcare Communication Letters" submitted by MAHs to SAM were approved.

Information regarding safety of medicines intended for doctors, patients and the public, as well as for marketing authorisation holders was published on SAM website in collaboration with Public Relations specialists. Employees of the Adverse Drug Reactions Monitoring Department initiated and prepared for publication on SAM website one SAM announcement, four EMA announcements, seven informative announcements for MAHs and 39 SAM approved "Direct Healthcare Communication Letters".

Information about current issues regarding safety of medicines and recommendations regarding necessary risk minimisation measures are regularly provided in the SAM informative bulletin "*Cito!*".

2.5. Quality Control of Medicines

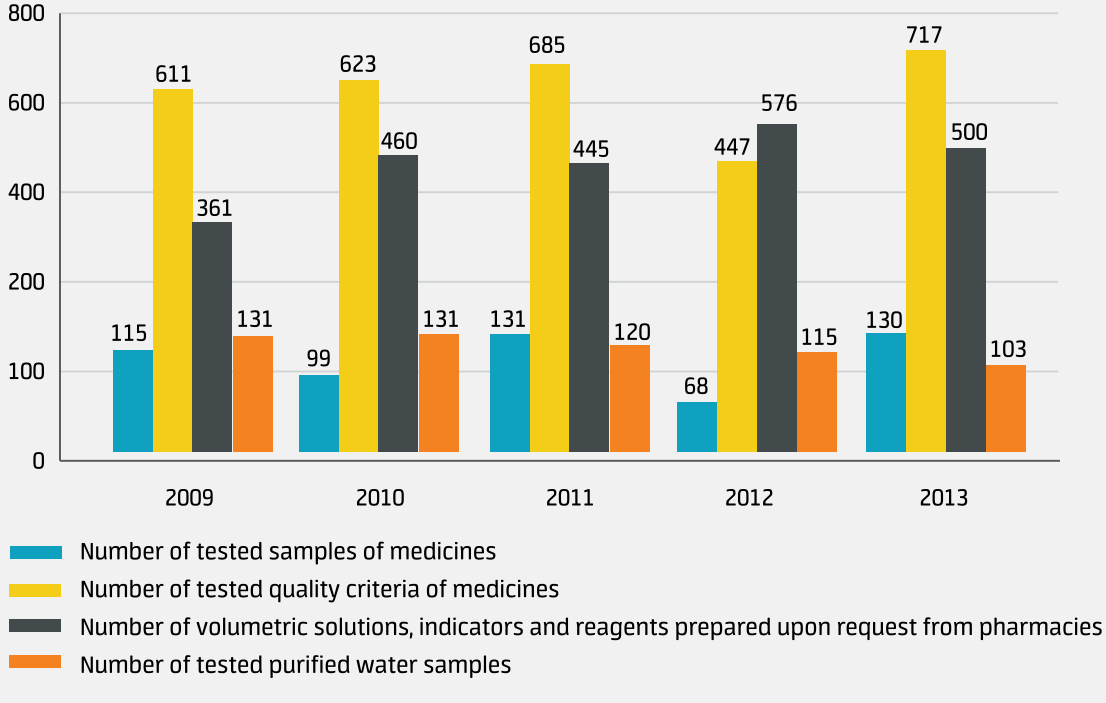
In 2013 SAM Laboratory carried out analysis of 130 samples of medicines. In the process of analysis 717 quality criteria were tested. As a result of testing one sample of medicines was found to be non-compliant with the requirements of the European Pharmacopoeia with regard to the criterion of "Mechanical additives" and a labelling non-compliance with the labelling approved by the SAM was discovered for one sample of parallel imported medicines. Approximately 500 volumetric solutions, indicators and reagents were prepared upon request from pharmacies. 103 samples of purified water produced in pharmacies were selected and tested in 2013. Non-compliance with the requirements of the European Pharmacopoeia was discovered in 8 samples of purified water.

Amendments to the June 26th, 2007, CM Regulation Nr. 416 "Procedures Regarding the Distribution and Quality Control of Medicinal Products" came into force on October 1st, 2012, (determining regular quality control of non-sterile pharmaceutical forms of medicinal products). Because of this amendment the quality control of non-sterile pharmaceutical forms of medicinal products was priority of our Laboratory last year.

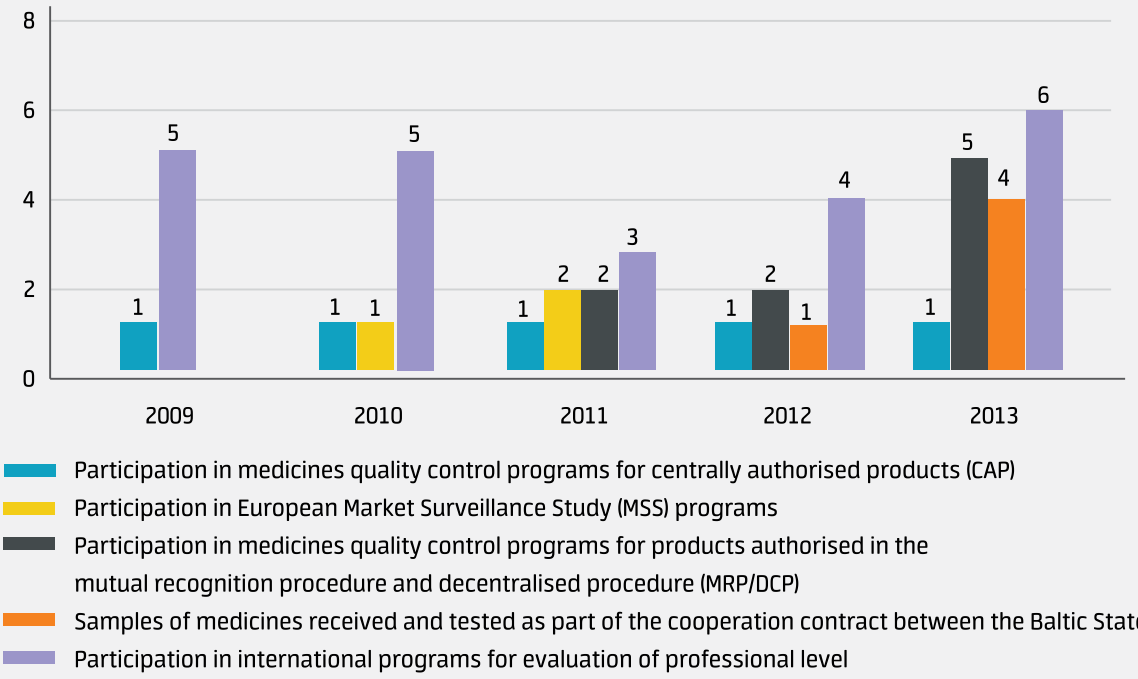
SAM Laboratory regularly participates in international programs for quality control of medicines and professional level examination programs. In 2013 SAM Laboratory specialists participated in quality control programs for medicines authorised in the centralised authorisation procedure (CAP), mutual recognition procedure and decentralised procedure (MRP/DCP) and national procedure (in accordance with the collaboration agreement between the Baltic States).

A re-accreditation visit by the Latvian National Accreditation Bureau took place on May 28th and 29th, 2013. The Laboratory once again received accreditation regarding compliance with the requirements of the LVS EN ISO/IEC 17025:2005 standard: physical and physical-chemical testing of medicines, pharmaceutical active substance and adjuvant, physical testing of purified water. The fixed field of accreditation was expanded into a flexible one. The expiration date of the accreditation of the Laboratory is June 16th, 2018.

RESULTS OF OPERATION OF THE MEDICINES EXAMINATION LABORATORY



PARTICIPATION IN INTERNATIONAL PROGRAMS FOR QUALITY CONTROL OF MEDICINES AND PROFESSIONAL LEVEL EVALUATION PROGRAMS



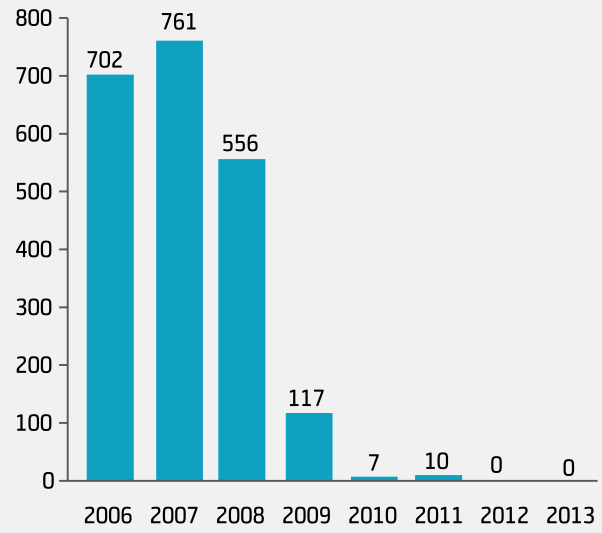
2.6. Compliance Evaluation and Authorisation of Medical Devices, Safety and Clinical Trials Monitoring

In 2013 seven applications were submitted for authorisation of medical devices in Latvia and 353 notifications were added to the LATMED database regarding placement of medical devices on the market in the Republic of Latvia. 927 primary reports about accidents with medical devices were received within the vigilance system from competent institutions on medical devices in the EU member states, as well as from manufacturers, distributors and users of medical devices. In 204 of these cases it was found that the medical device involved in the accident is or possibly is available in Latvia and appropriate safety

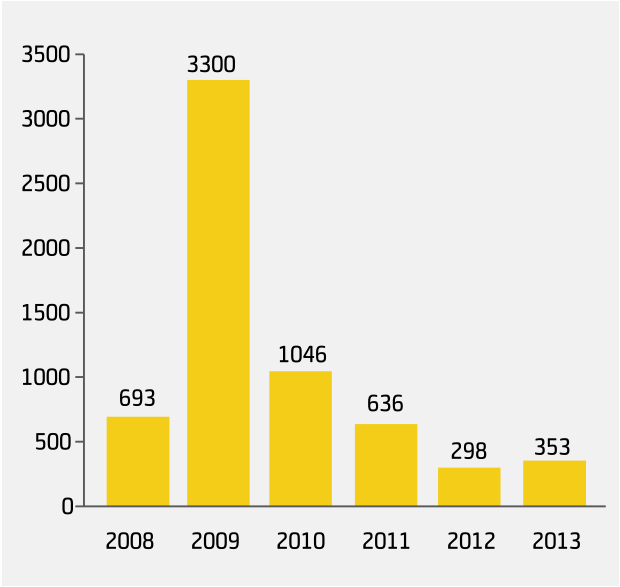
AUTHORISATION, CLINICAL TRIALS AND SAFETY MONITORING OF MEDICAL DEVICES

Criteria	Number
Expertise on authorisation documentation of MDs manufactured in the Republic of Latvia	7
Expertise on authorisation documentation of MDs without CE mark	0
Expertise on documentation for issue of authorisation to specially supplied MDs	2
Registration of information submitted within the notification procedure in the LATMED database	353
Registration of information provided by MD holders regarding purchase of safety group I and II MDs in the LATMED database	3667
Registration of information provided by MD holders regarding changes in use of safety group I and II MDs in the LATMED database	1721
Acceptance of reports received within the Vigilance system, analysis and processing of information and registration of data in the LATMED database	927
Identification of non-compliant MDs utilised in Latvia and implementation of safety measures	204
Expertise of documentation submitted for authorisation of clinical trials with MDs	12
Expertise of documentation submitted for approval of amendments to a clinical trial with MDs	7
Applications for variations to previously issued MD authorisations	0

NUMBER OF AUTHORISATIONS ISSUED FOR MEDICAL DEVICES IN THE REPUBLIC OF LATVIA



ANNOUNCEMENTS OF MEDICAL DEVICES ENTERING CIRCULATION IN THE REPUBLIC OF LATVIA (INCLUDING MEDICAL DEVICES FOR IN VITRO DIAGNOSTICS)



measures were taken.

In the year of review expertise was carried out on documentation for grant of authorisation to 12 clinical trials with medical devices (excluding expertise on application documentation for amendments to clinical trial protocols that have already received authorisation from SAM).

Consultations have been regularly provided to clients regarding procedures for authorisation, announcement of MDs, as well as regarding preparation of documentation and normative acts regulating this field. SAM specialists participate in European Commission working groups in fields related to SAM functions, organise seminars and perform other activities to provide information regarding news in the field of medical devices. In the year of review SAM experts continued to participate in the meetings of the European Council Working Group on Pharmaceutical Products and Medical Devices by taking part in the evaluation of proposals for regulation of medical devices prepared by the European Commission.

2.7. Compliance Evaluation of Pharmaceutical Activity

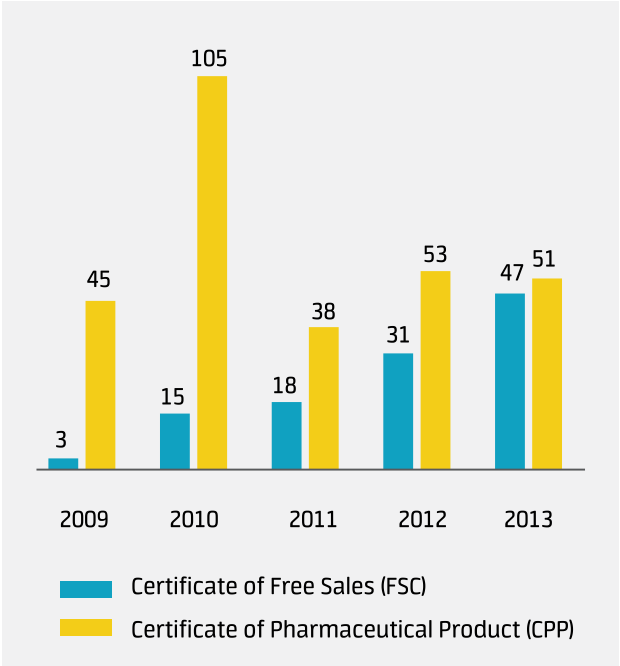
In 2013 the Pharmaceutical Activities Compliance Evaluation Department conducted 19 inspections in manufacturing/importing companies in Latvia, 2 inspections in Ukraine and 2 contract evaluations (related to licence renewal). 13 of the 19 inspections performed in Latvia were conducted for the purposes of surveillance, 1 inspection was related to licence renewal, 1 inspection was conducted in a contract laboratory and 4 inspections were related to manufacturing of active substances. 2 contract evaluations were related to licence renewal. 2 "third country" inspections were conducted in Ukraine (both were part of surveillance) - at manufacturing sites. All the manufacturing sites were found to be compliant after correction of deficiencies and received good manufacturing practice (GMP) certificates (in total 22) which were entered in the *EudraGMP* database.

4 inspections were carried out on the manufacturing of active substances upon request from the manufacturers themselves and GMP certificates were issued. 2 inspections related to active substances were conducted together with PIC/S inspectors during experience exchange visits. The competency of agency inspectors and the interpretation of GMP requirements were evaluated as compliant with European practice.

In 2013 two inspections of manufacturers were conducted in a "third country" - Ukraine. The planned inspections in India were not conducted because the applicant withdrew the applications for the marketing authorisation of these medicines. During one inspection in Ukraine the scope of the inspection was expanded because an application for a new pharmaceutical form was received.

In 2013 experts participated in experience exchange with colleagues from Estonia and Lithuania - the cooperation with inspectors from the Baltic States was continued. In 2013 GMP inspectors from Lithuania and Estonia observed

DYNAMICS OF THE NUMBER OF CERTIFICATES ISSUED TO NATIONAL MANUFACTURERS



3 inspections (manufacturing of non-sterile pharmaceutical forms, manufacturing of active substances and (wholesale) manufacturing of medicinal oxygen). Inspectors from Latvia participated as observers in one inspection in Estonia and in one inspection in Lithuania.

Agency's GMP experts also participated in one inspection of Good Distribution Practice (GDP), conducted one inspection relating to authorisation of a distributor of active substances. GMP experts actively participated in the authorisation of manufacturers, distributors and importers of active substances (clarification of information and entering information into the *EudraGMP* database). Department specialists actively participated in MH and EMA coordinated processes related to the implementation of the requirements of the so called Falsified Medicines Directive (Directive 2011/62/EU of the European Parliament and of the Council) and to provision of information.

37.5 person-days were required to carry out all the Good Distribution Practice (GDP) inspections in 2013. SAM inspectors participated in training regarding the requirements of the new GDP guidelines and the role of the "Responsible Person" in medicines wholesale companies and also participated in regional training regarding fighting against falsified medicines.

Most of the challenges in 2013 were created by the field of human tissues, cells and organs - the normative regulation was completely changed (new requirements regarding organs, their use in higher education institutions and also regarding tissues and cells at the end of 2013). In 2013 there was also a high number of surveys and studies (5 in total) initiated by the European Commission in all of the fields.

In 2013 nine compliance evaluations of human blood establishments (5) and blood banks (4) were performed and surveillance procedures were carried out in 23 hospital blood banks and in 1 hospital blood establishment. 6 compliance evaluations of tissue production and storage organisations were conducted.

Department experts established standard operating procedures (SOP) for biovigilance of tissues, cells, organs and one survey of a tissue centre and one survey of a healthcare institution (hospital) was conducted. No reports regarding observed serious adverse reactions or adverse events were received from tissue centres certified in Latvia.

In the year of review 51 certificates of pharmaceutical products (CPP) and 47 certificates of free sale (FSC) were issued to medicines manufacturing companies and medicines wholesalers authorised in Latvia.

2.8. Licensing of Pharmaceutical Activity Companies

The main task of the Pharmaceutical Activities Company Licensing Department is to deal with pharmaceutical activity company licensing issues in order to ensure the issuance of special permits (licences) to pharmaceutical activity companies in accordance with the current normative acts. The procedure for licensing of pharmaceutical activity and for review of documentation and adoption of decisions in the SAM regarding issuance, renewal, suspension and annulment of special permits (licences) is determined by the October 19th, 2011, CM Regulation No. 800 "Procedure for Licensing of Pharmaceutical Activity" (hereinafter - Regulation No. 800).

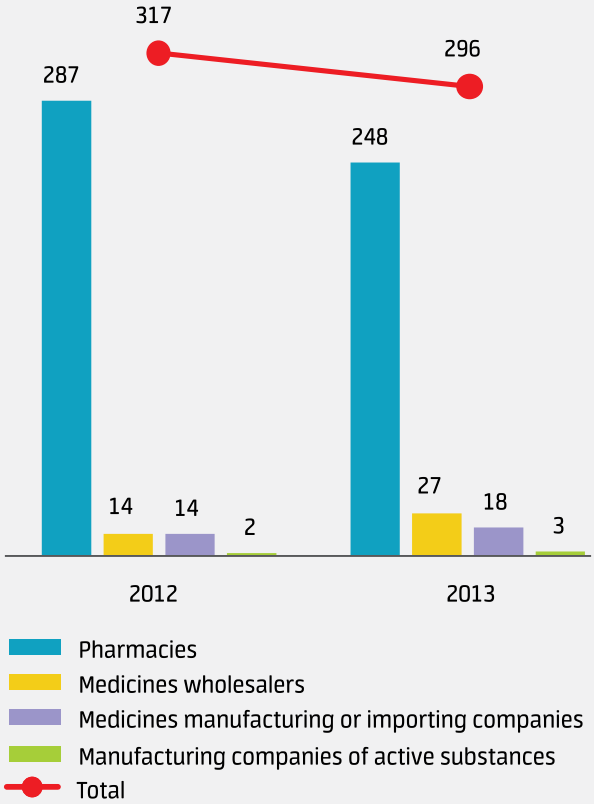
The competency of the Department is to perform evaluation of the documentation submitted by pharmaceutical activity companies (medicines wholesalers, medicines manufacturing or import companies, manufacturing companies of active pharmaceutical ingredients, general or closed type pharmacies) to receive special permits (licences) in the Agency. In 2013 the Department carried out evaluation on plans of premises of general and closed type pharmacies in accordance with the requirements of normative acts, prepared conclusions on pharmacy compliance evaluations and decision projects on issuance, renewal, suspension or annulment of special permits (licences).

Most significant tasks of the Department in 2013:

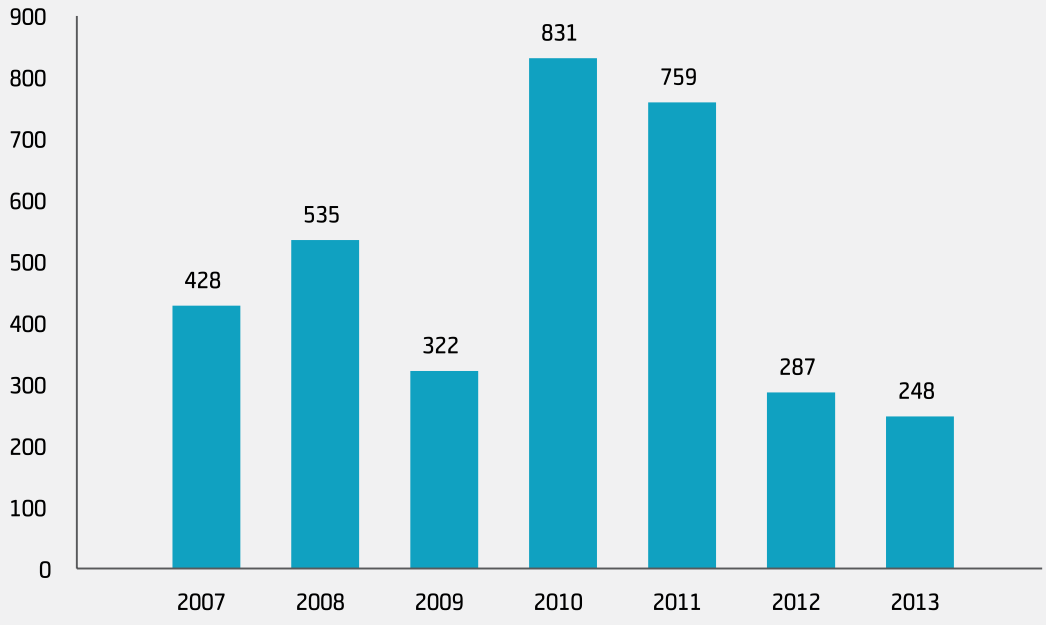
- Assembly of the documentation related to compliance evaluation and licencing of pharmaceutical activity companies;
- Storage of information submitted by licenced pharmacies, medicines wholesalers, medicines manufacturing or import companies, manufacturing companies of active pharmaceutical ingredients;
- Preparation of special permits (licences) for pharmaceutical activity;
- Regular updating of data on special permits (licences) issued for pharmaceutical activity after adoption of decision in the Agency regarding cases of relocation of general type pharmacies, special activity cases (initiation of preparation medicines) by placing this information on the Agency's website www.zva.gov.lv
- Organisational preparations and protocolling of meetings of the Commission on Licensing of Pharmaceutical Activity (hereinafter - Commission). 15 Commission meetings were held in 2013.

Before the Agency adopted a decision on issuance, renewal, suspension or annulment of special permits (licences) the Commission reviewed the issues related to licencing. Commission decisions have the nature of a recommendation. The Commission operates in accordance

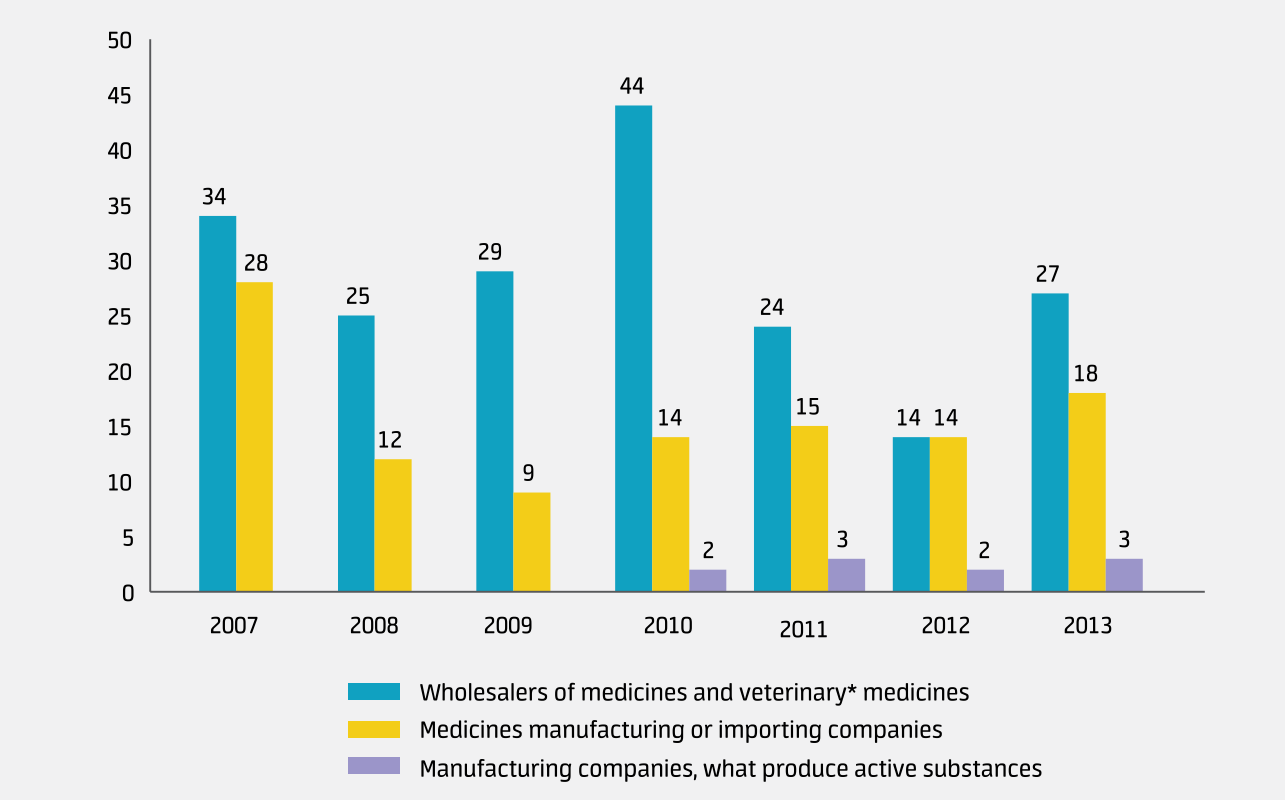
COMPARISON OF NUMBER OF ISSUED AND RENEWED LICENCES FOR PHARMACEUTICAL ACTIVITY



NUMBER OF LICENCES FOR PHARMACEUTICAL ACTIVITY COMPANIES - PHARMACIES



NUMBER OF LICENCES FOR PHARMACEUTICAL ACTIVITY COMPANIES



*Data regarding licences issued in the field of veterinary medicines until December 31st, 2010.

with the regulations approved by the Agency Director.

Review of applications for opening of new general type pharmacies or pharmacy branches or relocation of pharmacies was carried out in accordance with the requirements of the CM Regulation No. 610 "Criteria for Location of Pharmacies and Pharmacy Branches" adopted on August 2nd, 2011, (hereinafter - Regulation No. 610) and Regulation No. 800.

In 2013 the number of applications and SAM adopted decisions regarding opening of new general type pharmacies or pharmacy branches or relocation of pharmacies increased in comparison with previous years (for example, in 2011 - 11 decisions, in 2012 - 95 decisions, in 2013 - 103 decisions). The Agency continued cooperation with the State Agency "Latvian Geospatial Information Agency" in order to precisely measure the distance between general type pharmacies and also requested regional building authorities to provide information regarding the planned initiation of exploitation of the premises of general type pharmacies. Regulation No. 610 stated that, upon carrying out evaluation of the availability of pharmaceutical care, the local authority can submit an application to SAM regarding the necessity of a general type pharmacy or a 24 hour pharmacy in a populated area where there are enough general type pharmacies, but there is no functional 24 hour pharmacy or other pharmacies are located further than 3 kilometres away. Following a request from City Council of Jelgava, SAM evaluated the availability of pharmaceutical care in that specific populated area where a general type 24 hour pharmacy was necessary.

The June 25th, 2013, Cabinet of Ministers Regulation No. 344 "Procedure for Import and Distribution of Active Substances" (hereinafter - Regulation No. 344) came into force on July 2nd, 2013, laying down a new authorisation procedure for manufacturers, importers and distributers of active substances. This regulation delegated new tasks to the Agency related to issuance of authorisations and entering data into the EudraGMP database. The Department cooperates with experts from the Pharmaceutical Activities Compliance Evaluation Department to evaluate these issues. Since the Regulation No. 344 came into force and until the end of 2013 the Agency adopted 3 decisions regarding authorisation of manufacturers, importers and distributers of active substances, issued authorisations and entered the data into the EudraGMP database.

With the December 3rd, 2013, amendments to the June 26th, 2007, Cabinet of Ministers Regulation No. 416 "Procedures Regarding the Distribution and Quality

Control Medicinal Products", which came into force on December 12th, 2013, the agency's responsibilities now include authorisation of persons performing international transactions with medicines. The Department cooperates with experts from the Pharmaceutical Activities Compliance Evaluation Department to evaluate this issue and expertise was carried out on documentation submitted by 2 merchants.

In 2013 the performance of the following functions laid down in the Article 12, 12^1, 12^2, 12^3, 16 of the Pharmaceutical Law and in the Article 4.10. of the July 31st, 2012, CM Regulation No. 537 "Statutes of the State Agency of Medicines" was ensured in cooperation with the Pharmaceutical Activities Compliance Evaluation Department:

- Compliance evaluation of pharmaceutical activity companies;
- Inspections of medicines manufacturing or import companies and manufacturing companies of active pharmaceutical ingredients;
- Evaluation of compliance of qualification and experience of the responsible person of a medicines wholesaler with the requirements of normative acts regarding manufacturing and distribution of medicines;
- Review of documents and preparation of decisions regarding authorisation of manufacturers, importers and distributors of active substances and person performing international transactions with medicines, as well as issuance of authorisations.

In 2013 SAM received 1232 applications and additional documentation, provided 128 response letters, carried out compliance evaluation of documentation of 74 general and closed type pharmacies, in cooperation with the Pharmaceutical Activities Compliance Evaluation Department conducted compliance evaluation of 14 medicines wholesalers, 4 medicines manufacturing or importing companies and their documentation, prepared 74 opinions regarding pharmacy compliance evaluations, 392 decisions regarding issuance, renewal, suspension, annulment of special permits (licences) and extension of case review term.

During the year of review 296 special permits (licences) for pharmaceutical activity were renewed and issued to pharmaceutical activity companies (248 pharmacies, 27 medicines wholesalers, 18 medicines manufacturing or importing companies, 3 manufacturing companies of active pharmaceutical ingredients).

Agency's interactive map of pharmacies available on the website ww.zva.gov.lv regularly ensures provision of updated information regarding general type pharmacies in the territory of Latvia.

3. BUDGET AND EXPENSES OF THE STATE AGENCY OF MEDICINES

3.1. Budget and expenses of the State Agency of Medicines

No.	Financial Resources	Budget in 2011 (actual data)	Budget in 2012 (actual data)	Year of review (2013)	
				Statutory	Actual data
1.	Financial resources for covering expenses (total)	4 404 968	4 362 726	3 239 728	3 809 607
1.1.	Income from paid services and other independent income	4 404 968	4 348 529	3 239 728	3 808 793
2.	Expenses (total)	4 109 366	4 828 333	4 325 803	4 055 270
2.1.	Maintenance expenses (total)	3 860 909	4 608 599	4 044 803	3 842 823
2.1.1.	Regular expenses	2 093 851	2 300 364	3 228 705	3 026 725
2.2	Transfers of maintenance expenses			816 098	816 098
2.3	Expenses for capital investment	248 457	219 734	281 000	212 447
	Financial balance			-1 086 075	
	Financing			1 086 075	
	Financial Resources			1 086 075	
	Increasing (-) or decreasing (+) change in surplus of financial resources from paid services and other independent income			1 086 075	

3.2. The Opinion of a Certified Auditor

A Report from an Independent Auditor to the State Agency of Medicines.

A report on the financial report.

We have conducted an audit of the financial report included in the 2013 annual account of the State Agency of Medicines and it is reflected in page 1-95. The audited financial report includes the balance on December 31st, 2013, calculations of profit or loss for 2013, review of changes in own capital and review of financial flow, as well as a summary of significant accounting record principles and other explanatory information in the annex.

Responsibility of the State Agency of Medicines Management regarding the preparation of the financial report

The State Agency of Medicines Management is responsible for the preparation of this financial report and the truthful reflection of the information provided in this report in accordance with the Annual Accounts Law of the Republic of Latvia. This responsibility includes the establishment, introduction and maintenance of internal control system that ensures the preparation and truthful reflection of a financial report, that does not include major discrepancies due to fraud or errors, as well as choosing and implementing appropriate accounting policy and preparation of accounting estimations in accordance with the circumstances.

Responsibility of the Auditor

We are responsible for the opinion that we provide regarding this financial report basing on the audit we have carried out. We conduct the audit in accordance with the International Standards on Auditing. These standards determine that we have to comply with ethical requirements and we have to plan and conduct the audit so that we obtain sufficient proof that the financial report does not contain major discrepancies.

The audit includes procedures that are conducted to obtain audit evidence regarding the amounts indicated in the financial report and information disclosed in the report. The procedures are selected basing on the professional evaluation of the auditor, including an assessment of the risk of major discrepancies due to fraud or errors in the financial report. Upon conducting this assessment the auditor takes into account internal control, that is established to ensure preparation of the financial report and the truthful reflection of information in that report, in order to determine the appropriate audit procedures for the circumstances, but not to form an opinion regarding the effectiveness of the control. The audit also includes a general evaluation on the suitability of the utilised accounting principles and of the significant conjectures made by the Administration, as well as on the information provided in the financial report.

We consider that the evidence obtained in our audit is sufficient and appropriate for making the conclusion of our audit.

Conclusion

In our opinion the aforementioned financial report provides a truthful and clear impression of the financial condition of the State Agency of Medicines on December 31st, 2013, as well as of the financial results of its operation and of the financial flow in 2013 in accordance with the Annual Account Law of the Republic of Latvia.

Report on the compliance of the report by the Administration

We have also viewed the report of the Administration for the year of 2013 that is contained on 11 pages and we have not discovered any major discrepancies between the financial information included in this report by the Administration and in the 2013 financial report.

Emphasis on circumstances:

Not providing conclusions on these conditions:

– we point out that it is impossible to compare the included data over the periods, because in 2012 the total active and passive amount of the balance has been increased by 1 101 778 LVL and no savings have been made for suspicious debtors.

– from the amount indicated in the expenses of the following periods 176 000 LVL will not be written off in 2014, but in the following periods.

Member of the Board of LLC "REVUSS", certified auditor

Māra Zabrauska

ID code 010163-10738 (Cert. No. 23.)

Commercial merchant licence No. 49.

Riga, 26.02.2014.

4. GENERAL ADMINISTRATION OF THE STATE AGENCY OF MEDICINES

The "Operational Strategy of the State Agency of Medicines for 2014-2016" was prepared in 2013 and it was approved by the September 5th, 2013, Ministry of Health Order No. 158. This strategy is an operational planning document that was prepared, is maintained and published in accordance with the requirements of the Law on Public Agencies and January 4th, 2011, Cabinet of Ministers Instruction No. 1 "Procedure for Preparation and Updating of the Operational Strategy of An Institution and for Evaluation of its Implementation". The strategy indicates agency's:

- operational autorisation;
- objective;
- implemented operational directions and the related services;
- priorities;
- and other characteristics.

In this strategy the SAM has set three priorities that are important for the public health, as well as for the development of the Agency and the improvement of services in the planning period of the strategy:

- promote sustainable development of the national market of medicines;
- ensure the prerequisites for the safe and rational use of medicines, medical devices, tissues, cells, organs, blood and its components;
- improve the effectiveness of the Agency's operation.

4.1. Ensuring Public Procurement and Economic Activities

In 2013 the SAM announced 13 procurement procedures in accordance with the Public Procurement Law. There were 27 candidates. Contracts for supply and services were signed for the conducted public procurement procedures. The most significant contracts were signed for:

- technical support of the *Lotus Notes* software for 36 months;
- daily maintenance of SAM territory and premises, planting and maintenance of greenery by the windows of the building facade and in the territory for 24 months;
- modernisation of the system for storage of backup data;
- equipement of offices in the SAM administrative building with LED light elements, electrical installations and renovation of commutation elements.

In 2013 the Public Procurement and Infrastructure Provision Department of the SAM ensured organisation of public procurements and management of material assets, organised work safety measures, as well as managed the building complex and territory in the property of SAM.

4.2. Legal Provisions and the Development of Normative Acts

In 2013 the SAM within its competency has actively participated in the preparation of proposals for necessary amendments to normative acts in order to introduce requirements regarding the system for safety of medicines, the so called pharmacovigilance packet, as well as in the preparation of proposals for amendments to the Pharmaceutical Law and other normative acts. Altogether proposals were prepared for amendments to more than 12 normative acts. Some of these proposals were approved in 2013. In return the amendments to the normative acts require corresponding changes in the internal procedures of the Agency and in its work with clients.

In cooperation with the Ministry of Health the Agency

participated in the development of several projects for normative acts in order to introduce the norms mentioned in the Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products (hereinafter - Directive 2011/62/EU), including requirements regarding surveillance of manufacturing of active substances and excipients used in medicinal products for human use.

In cooperation with the Ministry of Health a new June 25th, 2013, Cabinet of Ministers Regulation No. 344 "Procedure for Import and Distribution of Active Substances" was prepared and issued and amendments were made to the Pharmaceutical Law and October 19th, 2011, Cabinet of Ministers Regulation No. 800 "Procedure for Licencing of Pharmaceutical Activity.

In order to fully introduce the norms of the Directive 2011/62/EU the Agency participated in the preparation of amendments to the following normative acts:

Project for Cabinet of Ministers Regulation "Amendments to the June 26th, 2007, Cabinet of Ministers Regulation No. 436 "Procedure for Import and Export of Medicinal Products"" in order to increase surveillance of medicines;

Project for Cabinet of Ministers Regulation "Amendments to the May 9th, 2006, Cabinet of Ministers Regulation No. 376 "Procedures for the Registration of Medicinal Products"" in order to supplement the documentation to be submitted for marketing authorisation of medicines by determining stricter requirements for inspections of manufacturers of active substances and to clarify procedures for adoption of decisions in the SAM;

Project for Cabinet of Ministers Regulation "Amendments to June 26th, 2007, Cabinet of Ministers Regulation No. 416 "Procedures Regarding Distribution and Quality Control of Medicinal Products"" in order to increase the reliability of the chain of supply of medicines and to determine the procedure in the Agency for authorisation of international transactions with medicines in accordance with Article 25^3 of the Pharmaceutical Law and also in order to determine the requirements for intermediary transactions with medicines, clarify norms regarding purchase of medicines from third countries and for export of medicines from the European Union, increase control and surveillance of medicines (also in the distribution of medicines within the network) and introduce a form for the certificate of Good Distribution Practice in accordance with the European Union format.

Taking into account the December 28th, 2012, Prime Minister Resolution No. 2012-REZ-111-1/127-2481 regarding the fulfilment of the tasks mentioned in the Chapter IV of the Declaration of the Government and in the Article 101, 103, 104 and 105 of the Action Plan of the Government that attempt to decrease the administrative burden and to ensure effective operation of the state administration, as well as taking into account the new evaluation system of employees of the state administration and the priority tasks in fighting against bureaucracy, the Agency n cooperation with the Ministry of Health evaluated the provided services in order to introduce the "Silence Means Agreement" principle in the processes under the responsibility of the Agency.

In 2013 the SAM participated and ensured representation of the interests of Latvia in the meetings of the European Union Council Working Group on Pharmaceutical Products and Medical Devices where the new European Commission proposals were reviewed for regulations of the European Parliament and Council regarding medical devices and medical devices for *in vitro* diagnostics. The Agency will be represented in the meetings of the Pharmaceutical Group of the European Union where the proposal will be reviewed for the regulation of the European Parliament and of the Council regarding clinical trials with medicines for human use and for the revocation of the Directive 2001/20/EC. As the Agency was involved in the preparation of the national position, proposals will be submitted for the regulation of the European Parliament and of the Council regarding the fee to be paid to the EMA for carrying out pharmacovigilance activities for medicines for human use.

4.3. Staff and Human Resources Management

The function of human resources management is carried out by the Administrative Resources Management and Documents Management Department which resolves issues of human resources management, ensures the work processes for enlistment, selection, assessment and development of personnel, as well as processes the documentation related to personnel issues.

At the end of the 2013 there were 136 civil servants and employees actually working at SAM. In total there were 152 staff members in civil service or employment relationship with SAM in 2013.

During 2013 four civil servants and 19 employees terminated their civil service or employment at SAM, but 18 staff members began their work in SAM. The staff turnover quotient in 2013 was 16% (*staff turnover = number of released staff members in a definite time period/ average*

number of staff members in the same time period).

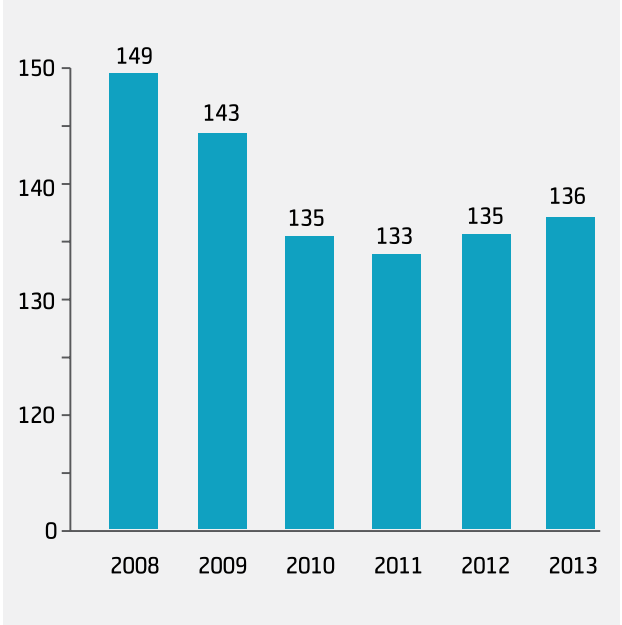
Well-educated, competent and highly qualified specialists are necessary to successfully ensure the functions assigned to SAM. The education level of SAM staff members is high - 88 % of SAM staff members have a higher education, of these 3 civil servants have a doctorate degree and 1 civil servant has a Doctor of Science degree.

One of the basic principles of SAM staff policy is to motivate staff members to raise their qualification. During 2013 in order to raise their qualification SAM civil servants and employees attended 51 training sessions and seminars organised by international organisations. In addition, 36 staff members expanded their knowledge by participating in international Webinar training.

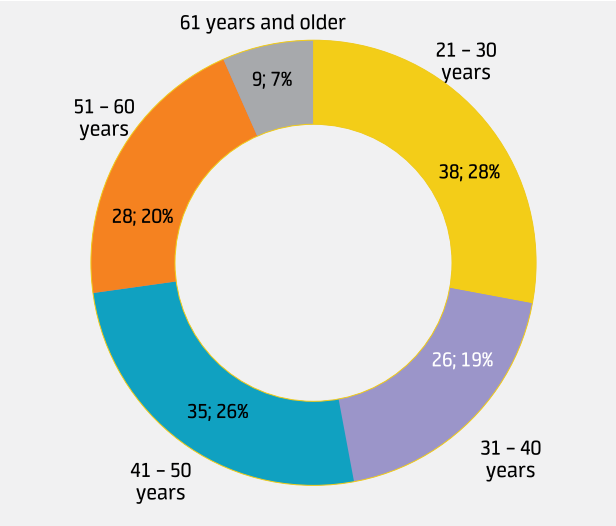
To obtain insight in the context of the preparations for the Latvian Presidency of the European Union, 21 SAM employees were introduced with the processes for development of EU legislation and for preparation and representation of the opinion of Latvia by listening to the seminar of the Ministry of Health Department of European Affairs and International Cooperation. Leading members of staff that will be directly involved in the processes of the Latvian Presidency regularly participate in the training sessions organised by the Secretariat of the Presidency and the School of Public Administration. In addition, 29 staff members improved their knowledge of the English language.

In order to ensure the ISO 27001 requirements in the management of safety of information 129 Agency staff members have received training on IT security issues.

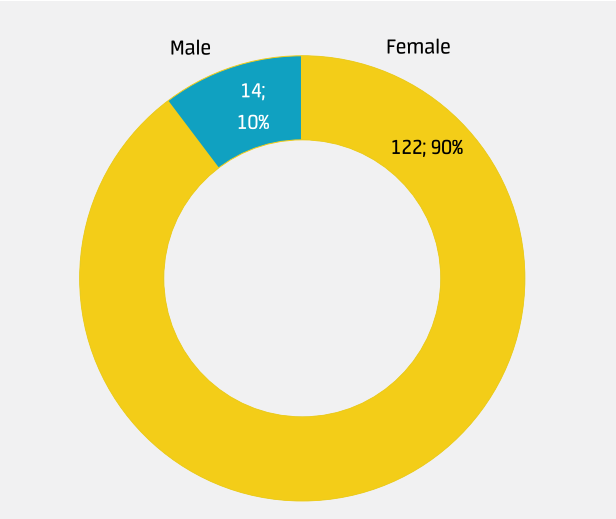
NUMBER OF AGENCY STAFF MEMBERS 2008-2013



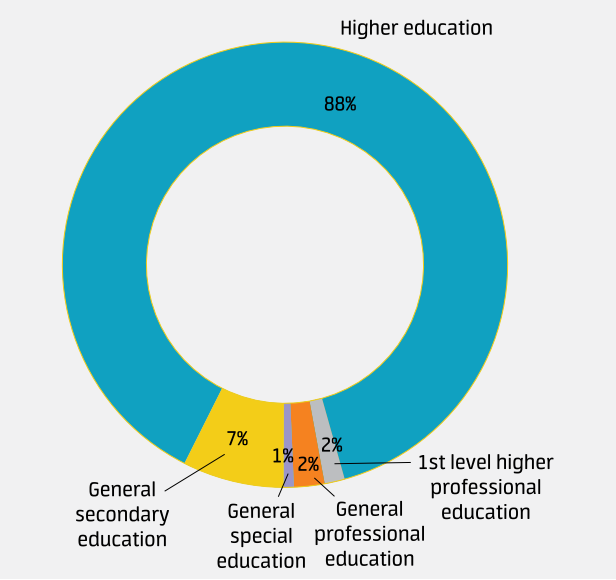
STAFF MEMBERS ACCORDING TO AGE GROUP



STAFF MEMBERS ACCORDING TO GENDER



STAFF MEMBERS ACCORDING TO LEVEL OF EDUCATION



RAISING QUALIFICATION OF STAFF MEMBERS

	2009	2010	2011	2012	2013
Courses for raising qualification	269	107	162	181	325
Training, seminars, conferences organised by international organisations	52	64	52	57	51
Foreign language courses (English in 2009-2013, French in 2012)	5	1	0	2	29

During 2013 special attention was paid to SAM internal seminars that allow senior experts, with respect to experience and professionalism, to train new colleagues or allow colleagues, who have participated in external seminars, to present and explain new issues in the field to other colleagues. 109 staff members have participated internal seminars like these in 2013.

4.4. Integrated Management System

In 2013 in collaboration with the EMA and during participation in the BEMA III cycle, a self-evaluation was carried out and it was submitted to the BEMA Secretariat. The visit of BEMA auditors in SAM was set for the first quarter of 2014.

In accordance with the requirements of the Directive 2010/84/EU of the European Parliament and of the Council of December 15th 2010, a report on the audit of the pharmacovigilance system of the SAM was forwarded to the European Commission on September 19th, 2013.

The certification accredited by the Latvian National Accreditation Bureau (LATAK) and United Kingdom Accreditation Service (UKAS) was maintained in accordance with the requirements of the international standards ISO 9001 and ISO 27001. The certifications included the following areas: expertise on marketing authorisation and post-authorisation documentation of medicinal products and medical devices, expertise on quality of medicinal products, pharmacovigilance and vigilance of medical devices; issuance of special permits (licences), authorisations and marketing authorisations according to authorisation; expertise on related documentation; compilation and publishing of information according to authorisation."

In 2013 SAM Medicines Examination Laboratory expanded its accreditation in accordance with the requirements of the international standard ISO 17025. More information is available in Chapter 2.5.

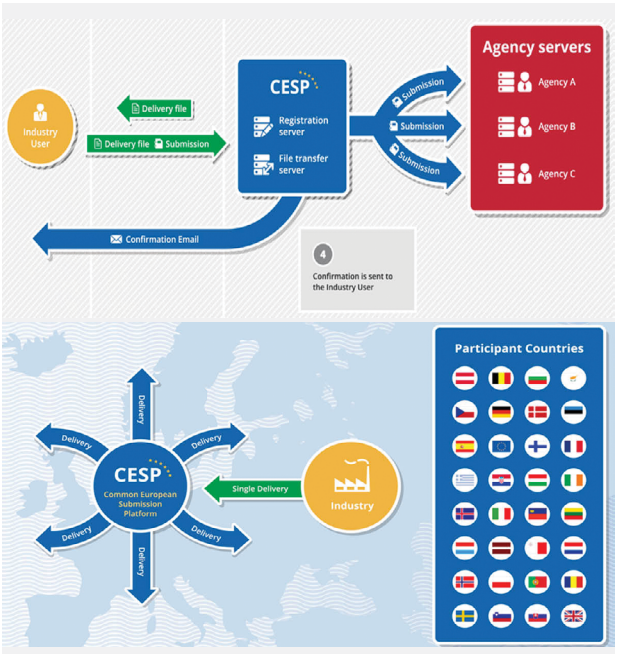
4.5. Development of Information Technologies

In 2013 work was continued to improve the information systems of the SAM and to improve the availability, utilisation and support processes of information technology solutions. Staff member training regarding IT security issues was conducted. Improvements were made in the information systems used by SAM, as well as in the state information systems SAMIS and LATMED. The Information Technologies and System Development Department made changes in the information systems (IS) by ensuring support for the use of Euro currency. In 2013 improvements were made to information processing forms and possibilities, as well as in the mechanism for authorisation and connection of external users in the LATMED database. Also updates were made to the system's documentation. Information filtering and processing algorithms, print-out forms were refined in SAMIS and improvements were made by introducing new functionality and user roles. Faster communication with clients was ensured by improving the data display in the public module.

In 2013 a solution was developed in the SAM for electronic submission of patient adverse drug reaction reports on SAM website by integrating it with the unified user authentication e-service of the portal www.latvija.lv.

In addition, work was continued on the introduction of the automatic document circulation system for health related fields and on the unification and more effective utilisation of field resources. In 2013 a contract was signed

COMMON EUROPEAN SUBMISSION PORTAL



to ensure the possibility for electronic receipt of marketing authorisation applications from merchants with the help of the Common European Submissions Platform (CESP).

4.6. International Cooperation

SAM is a part of the network of national medicines agencies in Europe and the successful realisation of the institutional functions and tasks is closely related to the participation in the unified European Medicines Regulatory network - it entails cooperation between the EMA, European Commission and more than 47 medicines regulatory institutions within the European Union and the European Economic Area (EEA). This network of cooperation gives EMA access to a wide range of experts allowing EMA to provide the best possible scientific expertise for regulation of medicines in the EU. Experts participate in the work of EMA as members of working groups and scientific advisory groups, scientific committees, as well as other groups.

In order for SAM colleagues to fully participate in the collective work procedures, SAM human and financial resources are required. In 2013 SAM staff members have been involved in cooperation with the European Commission and Council working groups, European Commission Directorate General for Health and Consumers (DG SANCO), the World Health Organisation, The Uppsala monitoring centre (UMC), European Pharmacopoeia Commission, PIC/S, European Directorate for the Quality of Medicines & Healthcare (EDQM), as well as in compliance inspections of clinical trials on behalf of the EMA. In order for the Agency to provide appropriate services to its clients and provide consultations on different issues, cooperation with other institutions, training and exchange of experience are mandatory prerequisites. This year we have actively participated in work-sharing procedures, for example, in the expertise on paediatric data, in the evaluation of periodic update safety reports, in the voluntary harmonisation procedure for clinical trials. To ensure appropriate quality of expertise we invited additional experts from universities in Latvia who have scientific degrees.

In 2013 SAM Administration took a more active part in the Heads of Medicines Agencies (HMA) organisation by fully participating in the work of the HMA Management Group. Working in this group has allowed active participation in the solutions of different issues during preparation for discussions with European or international institutions. Significant is also the fact that the work experience in the Management Group will be useful in planning and implementing measures during the Latvian Presidency.

Since 2010 SAM has also been involved in the surveillance of medical devices, blood and its components, tissues and cells. SAM is also the competent institution with regards to authorisation of medical devices, issuance of authorisation for clinical trials with medical devices and monitoring the safety of medical devices. The responsible SAM specialists regularly participate in the meetings of the representatives from national competent authorities for medical devices in Europe. Participation is also ensured in Competent Authorities for Medical Devices (CAMD) meetings, Central Management Committee (CMC) meetings and European Commission Directorate General for Health and Consumers (DG SANCO) meetings.

To represent the opinion of the Republic of Latvia on issues regarding monitoring of the safety of medicines, in 2012 SAM Administration became a member of the newly established EMA Pharmacovigilance Risk Assessment Committee (PRAC). This committee deals with issues regarding risk management of medicinal products distributed in EU, this includes supervising risk management plans and systems for both nationally and centrally authorised medicinal products and evaluating Periodic Safety Update Reports, as well as acting as an advisor on various pharmacovigilance issues.

There are effective cooperation contracts between SAM and the medicines agencies in Estonia and Lithuania in order to promote cooperation between the medicines agencies of the Baltic States. In 2013 as part of this cooperation a statistical data publication "Baltic Statistics on Medicines 2010-2012" was issued. It contains data regarding consumption of medicines and trends in the three Baltic States summarised by using the same methodology.

To characterise directions of international cooperation it has to be mentioned that the memorandum of agreement signed between the SAM and the Food and Drug Administration of the People's Republic of China regarding cooperation in normative regulation of medicines is still in effect.

To support national manufacturers 51 (53 in 2012, 20 in 2011) certificates of pharmaceutical products (CPP) and 47 (31 in 2012, 20 in 2011) certificates of free sales (FSC) were issued. This increases the competitive capacity of national manufacturers in many third countries.

5. PROVIDING INFORMATION TO THE PUBLIC AND COMMUNICATION WITH DIFFERENT AUDIENCES

One of the directions of the main operation of our institution laid down in the "Operational Strategy of the State Agency of Medicines for 2014-2016" approved in September 2013 was the information direction - provide objective, thorough and updated information regarding products and companies, as well as SAM operation to the public and to professionals, as well as cooperation partners in Latvia and in other countries in order to promote public health, carry out disease prevention and to prevent threats to human health. In 2013 in accordance with the strategy of the institution the agency defined objectives of communication and target audiences, values and basic principles of communication, communication activities and tools for assessing the effectiveness of communication.

In 2013 significant effort has been invested in the development and maintenance of external communication. For the first time the public relations campaign "REVEAL THE OTHER SIDE OF MEDICINES, report adverse reactions!" was implemented and it included a press conference, visual information (printed posters and stickers), several press releases regarding the significance of reporting adverse drug reactions, as well as detailed information regarding reporting in the informative bulletin "Cito!" and other activities promoting public discussion regarding safe use of medicines. The objectives of the campaign were:

- to inform and educate the public regarding the surveillance system for safety of medicines;
- to inform residents of Latvia about possibilities to report observed adverse drug reactions;
- to promote recognition of SAM website as a place, where to submit reports of adverse drug reactions and seek official and objective information regarding medicines and their safe use.

In 2013 the communication with SAM cooperation partners has been purposefully increased by providing independent and objective information regarding issues within SAM competency to professionals, as well as the general public.

In the year of review 44 press releases were prepared and forwarded to the mass media representatives, responses were provided to more than 100 journalist queries. Replies were prepared and provided to questions from residents of Latvia, as well as to requests for information from institutions under the supervision of the Ministry of Health, from healthcare institutions and SAM clients. Information was updated on SAM website and in the state portal www.latvija.lv (information on SAM public services). In total SAM communication with the mass media included more than 150 news articles in different types of mass media.

INFORMATIVE MATERIALS OF THE CAMPAIGN

Various topics of publications prepared within SAM communication activities

Topic of publication	Example of publication
Safety of medicines	*TV3, Nekā personīga:* While the global market of falsified medicines is expanding, no falsified medicines have been discovered in Latvia, 17.03.2013. *Diena.lv:* Invitation to report adverse drug reactions, 04.04.2013.
The market, consumption and price of medicines	*Delfi.lv:* Latvian manufacturers of medicines have increased their turnover and export last year, 21.02.2013.
Price of medicines verification form	*Latvijas Avīze:* One medicinal product, different prices? 28.06.2013.
SAM operation, collaboration and budget	*Materia Medica:* Management of the State Agency of Medicines - quality and reliability, 29.01.2013 *Materia Medica:* Inguna Adoviča and Jaks Kopels become honorary members of the Pharmacists' Society of Latvia, 03.12.2013.
Availability of medicines	*apollo.lv:* Consumption of antibacterial medicines increased by 14% last year, 19.11.2013.
Number of pharmacies, authorisation of pharmacies	*Latvijas Radio 1, Business News: SAM:* The number of pharmacies in Latvia is too large, but the distribution of pharmacies in uneven, 25.01.2013.
Clinical trials	*Tvnet.lv:* To be the first one to swallow a pill that no longer kills rats, 10.02.2013.
Normative acts	*LR-1 "Europe Today":* Plans for simplification of clinical trial requirements in the EU, 07.05.2013.
Other	*Radio SWH, "News":* Today the State Agency of Medicines begins communication on Twitter, 12.07.2013.

In 2013 SAM prepared several informative publications in order to inform doctors, pharmacists and other healthcare professionals about the newest issues in pharmaceutics and in SAM operations, as well as about the safety of medicines. Although doctors, pharmacists and other healthcare professionals can obtain information from various sources like seminars and conferences and professional publications from other countries, SAM printed publications provide updated, objective, verified and focused information for those who wish to follow the most important events in the field of pharmaceutics and its development.

The SAM informative bulletin "Cito!" has already become an integral part of daily operations by providing thorough and updated information regarding safety of medicines. In the pages of "Cito!" field specialists - SAM experts - share their experience, publish articles regarding new medical issues, as well as exchange their opinions. Changes in the Medicinal Product Register of the Republic of Latvia are published in each issue of "Cito!".

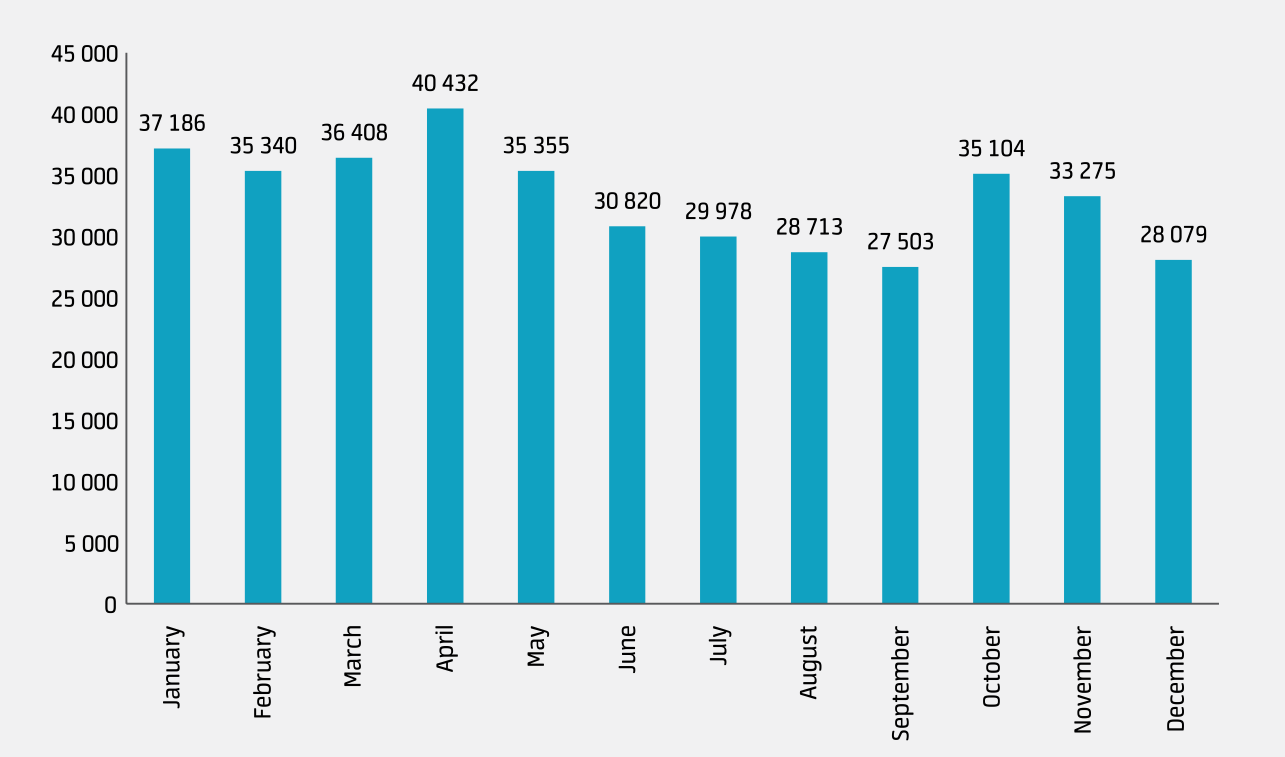
An official and independent source of information for doctors and pharmacists is the LR Medicinal Product Register containing information regarding medicines authorised in the national, mutual recognition, decentralised and centralised procedures, as well as parallel imported medicines. In addition to the book, for the first time an electronic edition of the Medicinal Product Register was prepared in a USB data carrier format containing summaries of product characteristics and package leaflets. A convenient information search form has been developed for this format. No Internet connection is necessary to use this format in the daily work. The summary of product characteristics included in the electronic version of the Medicinal Product Register helps doctors and pharmacists to choose the most appropriate medicines for the patient, as well as to find out or clarify relevant information regarding the correct use of medicines, possible adverse reactions, etc., thus, promoting safe use of medicines.

To provide information regarding trends in medicines consumption according to consumer groups, SAM prepared an informative publication "Statistics on Medicines Consumption" publicly available on SAM website. The data

PUBLICATIONS PREPARED BY SAM

Publications	Number of copies
Informative bulletin "Cito!"	1200
Drug Register of the Republic of Latvia	380
Electronic edition of the Drug Register of the Republic of Latvia containing summaries of products characteristics and package leaflets in DVD format	500
SAM Annual Report (in Latvian and English)	100
Publication „Good Clinical Practice"	200

NUMBER OF VISITORS OF SAM WEBSITE WWW.ZVA.GOV.LV IN 2013



resource is the data provided by medicines wholesalers and manufacturers and it has been categorised according to various criteria (sales amount to hospitals, pharmacies, other healthcare institutions and medicines wholesalers). Every year the distribution of medicines consumption according to the dispensing status of medicines is published. The electronic edition also contains a comparison of consumption of medicines sold from 2008 until 2012 (according to DID - defined daily dose per 1000 inhabitants of Latvia per day).

In 2013 SAM repeatedly issued the informative publication "Good Clinical Practice" intended for those conducting clinical trials with medicinal products and other specialists connected to the clinical research of medicines. Good Clinical Practice is an internationally acknowledged standard of ethics and quality that is complied with in planning and conduct of clinical research involving humans. The re-issued edition also contains the Declaration of Helsinki devised by the World Medical Association with the latest amendments and information sources for healthcare professionals.

In addition to the aforementioned activities regular updates of the information on SAM website (www.zva.gov.lv) are also ensured. In the age of technology the maintenance of the website is not only one of the most cost-effective channels for communication, but it also allows to provide information directly to the target audience using Internet.

Maintaining the website is an effective way of ensuring the provision of official and operative information to every member of the public (also to SAM clients) regarding SAM operations and latest issues in the field of pharmaceutics. According to Google Analysis statistical data in 2013 SAM website was visited 398 193 times.

Development of SAM website is planned in 2014 and it will include improving the arrangement of information and the design, thus, ensuring that the information is clear and easily perceptible not only to healthcare professionals, but also to any inhabitant of Latvia.

To enquire the opinion of the website visitors, 6 surveys were conducted in 2013 and replies from 1498 respondents were received (the results of these surveys are available on SAM website, in the section "Homepage. Survey archive"). Website visitors answered the following questions:

- Which information do you pay most attention to in the package leaflet of medicines?
- Do you use social networks (Draugiem.lv, Youtube, Facebook, Twitter, LinkedIn, Skype etc.) for private

and/or work related necessities?

- Have you noticed informative materials of the SAM initiated campaign "Reveal the other side of medicines!"?
- How do you evaluate the improved SAM search form of the Medicinal Product Register?
- Do you believe that it is possible to purchase falsified medicines and medical devices?
- How often do you check the expiration date of the medicines in the medicines cabinet in your home?

SAM communication activities are not based solely on a one-way provision of information, but SAM also provides the opportunity for SAM cooperation partners and staff members to express their opinion about the quality of SAM client service and provided services. The received information is used for the improvement of quality of SAM operations. In 2013 SAM organised 2 surveys:

1) survey for clients regarding SAM operations and provided services in order to improve the quality of client service and provided services basing on the collected data;
2) survey for SAM staff members with the purpose of discovering the opinion of staff members regarding important and relevant work aspects, that would allow to determine priorities in working with personnel and make rational and deliberate decisions with respect to staff members in the future.

USEFUL INFORMATION FOR PHARMACEUTICAL PROFESSIONALS!

6. DEVELOPMENT PRIORITIES OF THE STATE AGENCY OF MEDICINES IN 2014

SAM has set three priorities that are significant for public health in the strategic planning period, as well as for the development of SAM and for the improvement of services:

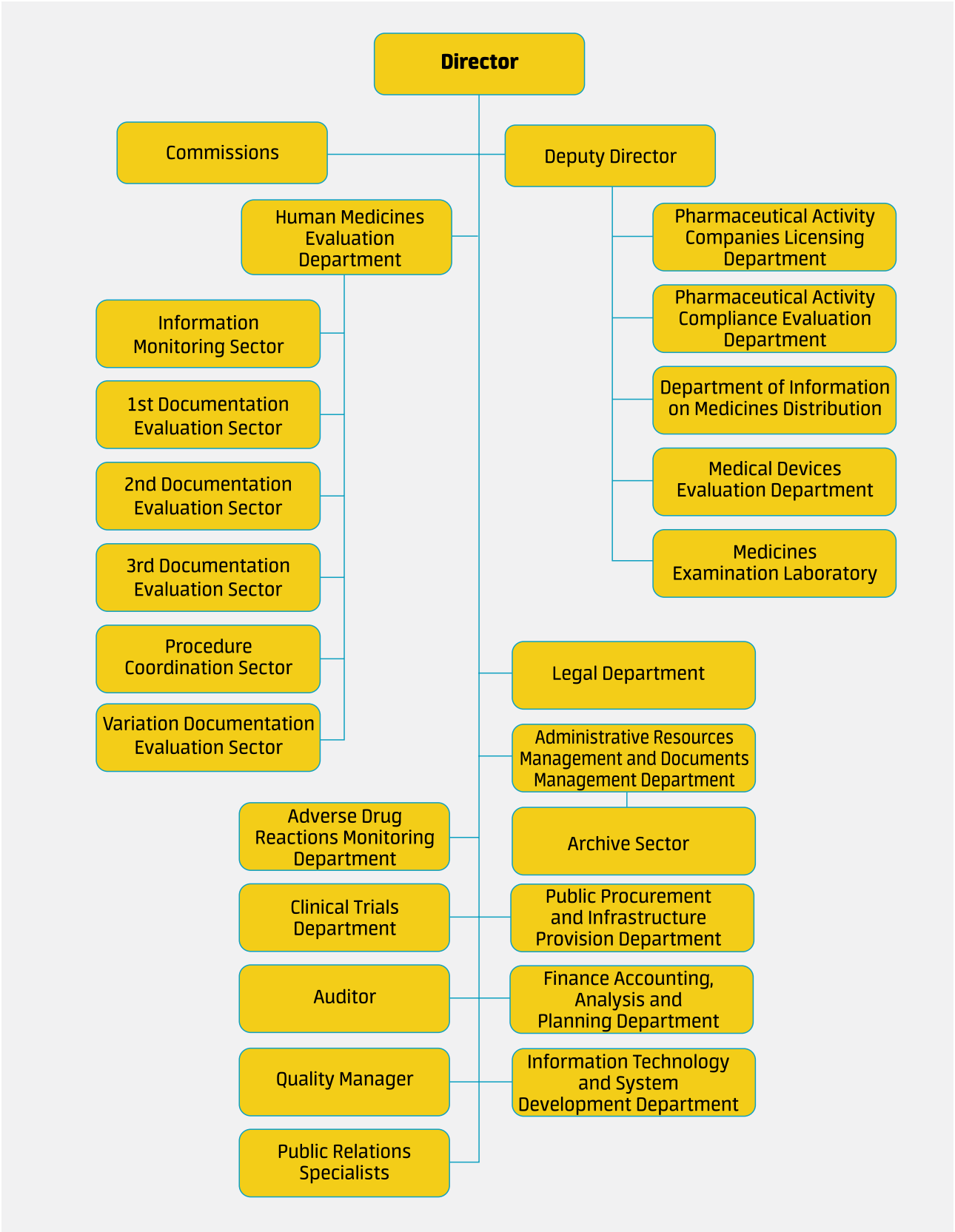
- promote the sustainable development of the national market of medicines;
- ensure the prerequisites for the safe and rational use of medicines, medical devices, tissues, cells, organs, blood and its components;
- improve the effectiveness of the Agency's operation, also by using the BEMA III experience.

Taking into account the functions and tasks assigned to the SAM, the operational plan assigns specific tasks for each structural unit and the institution as a whole. In addition to the primary operations of SAM the following objectives have been set as priorities for 2014:

- full operation as a public agency - an institution non-financed from the state budget;
- active participation in MRP/DCP/CRP procedures by assuming the responsibilities of the Reference Member State and the co-rapporteur;
- promotion and development of cooperation with academic and scientific institutions, by ensuring involvement of academic forces in complex expertise cases and by offering new skills to pharmaceutical and biomedical research centres to promote innovations;
- increasing expert professionalism and within the range of possibilities - active participation in EMA scientific committees and working groups, work-sharing programs within the network of European medicines agencies, WHO programs;
- ensuring the requirements of the new pharmacovigilance demands, including development of pharmacovigilance system compliance inspections;
- expansion and development of the capacity of the Medicines Examination Laboratory;
- improvement of the receipt and processing of the electronic marketing authorisation documentation (e-CTD, CESP), as well as sending of electronic documentation to clients and circulation of electronic documentation within the Agency;
- ensuring data exchange with European databases with respect to data regarding medicines, medical devices, clinical trials, manufacturers, distributors 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*);
- participation in e-Health projects and in projects for IT development in the health field;
- ensure and coordinate the development of the list of active substances and adjuvant in Latvian by involving academic forces and the State Language Centre;
- development of the integrated management system and participation in the BEMA III audit;
- update and review of SAM internal procedures to increase work effectiveness;
- increase the participation of the public.

7. ANNEXES

7.1. Annex. SAM Structure



7.2. Annex. Structure of the Human Medicines Evaluation Department

7.3. Annex. Functions of the Structural Units of SAM

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 chemical and pharmaceutical, pharmacological and toxicological documentation of medicines, on clinical trials, summaries of product characteristics, package leaflets, labelling and on other documents

Department of Information on Medicines Distribution

- Carries out expertise on applications and documentation and issues authorisation for:
  - import and export of psychotropic, narcotic medicines/substances and precursors;
  - use of 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;
  - distribution of unauthorised medicines;
  - import of samples of medicines;
  - distribution of remaining stock of medicines;
  - distribution of and variations to parallel imported medicines in Latvia.
- Carries out expertise on applications and documentation and issues special permits (licences) for operation with precursors, issues precursor operator cards.
- Carries out expertise on applications and issues authorisations for purchase of medicines (to ensure operation).
- Assembles and provides information regarding consumption, prices and availability of medicines, turnover of pharmacies, medicines wholesalers and manufacturing companies.
- Records and controls the legal circulation of narcotic substances, psychotropic substances and precursors controlled in Latvia.

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.
- In relation to applications for marketing authorisation of medicines, carries out good clinical practice inspections at clinical trial centres within the European Economic Area (EEA), as well as in countries outside of EEA.
- Evaluates the applications for non-interventional studies and ensures their authorisation in SAM.

Adverse Drug Reactions Monitoring Department

- Collects, updates, evaluates and carries out expertise on data regarding adverse drug reactions observed in Latvia and in foreign countries.
- Carries out data exchange regarding adverse drug reactions and safety of medicines with marketing authorisation holders and institutions in the European Union and in the world, as well as with the EU *EudraVigilance* database for adverse drug reactions.
- Monitors data within the *EudraVigilance* database to determine whether there are new risks, the risks have changed or whether these risks have an impact on the benefit-risk balance.
- Cooperates with marketing authorisation holders regarding pharmacovigilance issues, approves the risk minimisation measures included in the risk management plan of the marketing authorisation holder and monitors their results, as well as evaluates updates of risk management systems for medicines.
- Evaluates the compliance of marketing authorisation holders with good pharmaco-vigilance practice.

- Prepares information regarding safety of medicines for communication with doctors, pharmacists and the public, participates in the preparation of the SAM bulletin *"Cito!"*. Cooperates with EMA, especially in order to develop pharmacovigilance procedures. Informs competent authorities of other EEA countries, the EMA, as well as the marketing authorisation holder, if new risks have been detected, the current risks have changed or changes in benefits and risks have been detected.

Medicines Examination Laboratory

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

Medical Devices Evaluation Department

- Performs compliance evaluation and authorisation of medical devices.
- Develops, maintains and updates the LATMED medical devices database that contains information regarding medical devices, their manufacturers, distributors, clinical trials, as well as vigilance system reports.
- Evaluates the compliance of clinical trial documentation with the requirements of normative acts before the initiation of the clinical trial, adopts decisions regarding issuance of authorisations for conduct of clinical trials and monitors the conduct of the trials.
- Performs vigilance for medical devices, ensuring a timely circulation of information regarding risks or danger of using medical devices to people receiving healthcare services and users of medical devices that could be exposed to such risks. Supervises corrective safety measures.
- Pharmaceutical Activities Adequacy Evaluation Department
- Evaluates the compliance of the activity of pharmaceutical companies (human medicines manufacturing/importing companies, including foreign manufacturing companies, medicines wholesalers) in accordance with the legislation and normative acts of the Republic of Latvia, and the requirements of the European Commission.
- Monitors and evaluates the compliance of procurement and storage centres of tissue, cells and organs, blood establishments, hospital blood banks and the State Blood Donor Centre.

Pharmaceutical Activities Company Licensing Department

- Ensures licensing of pharmaceutical activity companies to issue special permits (licences) to companies for pharmaceutical activity.
- Develops and maintains the informative base of licensed pharmaceutical activity companies.

Finance Accounting, Analysis and Planning Department

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

Public Procurement and Infrastructure Provision Department

- Organises public procurements.
- Ensures management of material assets and organises activities for work safety.
- Manages the building complex and territory that is in the property of SAM.

Legal Department

- Ensures the compliance of administrative acts prepared by SAM with the requirements of current legislation, including requirements of the

European Union legislative acts and rulings of the Court of Justice of the European Union, and also prepares administrative documents regulating SAM operations.

- Lawfully solves legal issues and problems.
- Prepares and evaluates contracts, documentation projects, various opinions.
- Prepares projects for normative acts.
- Represents the interests of SAM in Court institutions.

Administrative Resources Management and Documents Management Department

- Devises, implements, controls and develops work processes for planning, selection, involvement, maintenance, evaluation and development of human resources.
- Manages all issues regarding personal files and ensures the documentation of civil service and legal employment relationship in accordance with legislative acts.
- 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 procedure for receiving 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.
- Manages SAM Archive.

Information Technology and System Development Department

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

Quality Manager

- Organises and carries out the activities necessary for the maintenance of the integrated management system.
- Carries out monitoring and analysis of processes.
- Coordinates SAM participation in BEMA.

Auditor

- Prepares internal audit plans.
- Organises and performs pharmacovigilance system audits, internal audits.
- Together with the quality manager organises and carries out the activities necessary for the maintenance of the integrated management system.
- Coordinates the assessment of SAM risks.

Public Relations Specialists

- Inform the public about field politics in the competency of SAM by creating a clear and accurate impression of SAM operations and new developments in the field.
- Represent a SAM administration approved opinion in the mass media.
- Coordinate information updates on the internal and external SAM website.
- Develop the corporative identity of SAM.

7.4. Annex. SAM History

Date	Event
17.06.2013.	SAM Medicines Examination Laboratory is re-accredited as compliant with the requirements of the ISO 17025 standard, the fixed area of accreditation is expanded into a flexible one.
01.01.2013.	In accordance with the Law on Public Agencies SAM begins operation as apublic agency non-finfnaced from the state budget.
21.12.2012.	The SAM integrated management system is certified in accordance with the ISO/IEC 27001:2005 standard
19.12.2012.	The SAM integrated management system is certified in accordance with the ISO/IEC 9001:2008 standard
22.11.2012.	A meeting of the Baltic State Agencies of Medicines takes place in Riga. The Heads of the Agencies sign a contract on cooperation regarding areas of good manufacturing practice, good distribution practice, good pharmacovigilance practice and good clinical practice, as well as on cooperation of the laboratories of the Baltic States regarding testing of medicines authorised in the national procedure. The signed contract entails training of employees of the Agencies in the aforementioned areas of cooperation
08.11.2012.	SAM receives the Quality Innovation Award 2012 for its interactive map of pharmacies in Latvia developed in 2011 and publicly available on SAM website. Organisers of the contest - Finnish Quality Association and Estonian Association for Quality
31.07.2012.	The CM Regulation No. 537 "The Statutes of the State Agency of Medicines" is approved and will come into effect on January 1st 2013 determining that starting from January 1st 2013 SAM will operate in accordance with the Public Agency Law and Law on Budget and Financial Management as an institution non-financed from the budget
23.07.2012.	SAM participates in the opening meeting of the newly established EMA Pharmacovigilance Risk Assessment Committee, Latvia is represented in the Committee by Andis Lācis, the Head of the Residency Section of the Faculty of Continuing Education within the Riga Stradins University, and Inguna Adoviča, the Director of SAM
26.06.2012.	SAM releases a new electronic publication for doctors and pharmacists "Drug Register of the Republic of Latvia including summaries of product characteristics and patient information leaflets in DVD format"
13.10.2011.	The Baltic State Agencies of Medicines sign an agreement regarding cooperation in quality control of medicines
09.10.2011.	15 years since the establishment of SAM. To celebrate the 15th anniversary SAM personnel plants a white fir in the Garden of Destiny with an inscription "Pledge to Motherland"
From 26.08.2011. until end of October	Participation as co-rapporteur inthe EMA Committee for Advanced Therapies repeated review by authorising the newly introduced therapeutic medicines
19.07.2011.	The list of active substances is published on SAM website in three languages: Latvian / Latin / English
16.05.2011.	The first digital map of pharmacies with broad search options is developed on SAM website
02.02.2011.	Contract between the State Agencies of Medicines of the Baltic States regarding a unified procedure for labelling medicines
01.10.2010.	The compliance evaluation and monitoring of procurement and storage organisations of human tissues, cells and organs, blood establishment, hospital blood banks and the State Blood Donor Centre is initiated
01.10.2010.	The function of compliance evaluation, authorisation and monitoring of safety of medical devices is adopted
06.-08.09.2010.	The European Union Benchmarking (BEMA II) takes place
09.07.2010.	Memorandum of agreement with EMA regarding mutual exchange of information and documentation
25.06.2010.	Memorandum of agreement with the Food and Drug Administration of the People's Republic of China about cooperation regarding normative regulation of medicines
01.02.2010.	Establishment of a Client Service Centre
11.08.2009.	Contract between the Baltic State Agencies of Medicines regarding a united packaging of medicines in three languages
15.07.2009.	The Medicines Examination Laboratory is accredited in accordance to the ISO/IEC 17025:2005 standard
19.09.2008.	Recognition from the Riga City Council for original front lawn greenery
14.01.2008.	Memorandum of agreement with Lithuania regarding cooperation in monitoring of medicines
2008	The first Mutual Recognition Procedure was carried out where Latvia was the Reference Member State
27.12.2007.	Memorandum of agreement between national medicines agencies of the EEA member states and the European Medicines Agency about the exchange of information and documents regarding pharmacovigilance
09. – 12.2007.	The concept for the e-prescription information system is developed

11.07.2007.	Memorandum of agreement with Estonia regarding cooperation in monitoring of medicines
01.02.2007.	Civil service is introduced at SAM
December 2006	The technological updating and structural modification of the Drug Register is carried out and the State Agency of Medicines Information System SAMIS is developed
10.11.2006.	A meeting of the State Agencies of Medicines of the Baltic states takes place in Riga
01.07.2006.	Due to the introduction of new principles in the quality control of medicines prepared in pharmacies, the Medicines Quality Control Laboratory and its branches in Riga, Daugavpils, Cesis and Liepaja cease their operation
10.04.2006.	The pharmaceutical Activities Compliance Evaluation Department is established
06.-10.02.2006.	The European Union Benchmarking (BEMA I) takes place
02.01.2006. – 31.12.2010.	The authorisation of veterinary medicines and monitoring their circulation is delegated to SAM
02.01.2006.	The Pharmaceutical Activities Company Licensing Department is established by reorganising the Legal Department and adopting from it the function of licensing pharmaceutical activity companies
02.01.2006.	The Information Department is transformed and the Department of Information on Medicines Distribution and the Information Technology Department are established
2006	Participation within PIC/S is initiated
2006	For the first time the evaluation of staff member operations and results is initiated and performed
End of 2005	A new function is delegated to SAM - to develop and maintain a system for the monitoring of prices of medicines
02.11.2005.	The Cabinet of Ministers of the Republic of Latvia appoints (Order No. 707) Inguna Adoviča as the Director of SAM
25.04.2005.	Jānis Ozoliņš, the Director of SAM, tragically passes away.
2005	An educational publication "Introduction to Pharmacovigilance" is issued
End of 2004	The Archive building is commissioned
2004	Access to and unified operation in databases of EU member states is established via the EudraNET network.
01.11.2004.	The non-profit organisation, state JSC "State Medicines Agency" is reorganised as the public agency "State Agency of Medicines" and Jānis Ozoliņš is reappointed as the Director
01.07.2003.	Legal Department is established
2003	The first edition of "Statistics on Medicines Consumption" is published
2003	The first Benchmarking visit (BEMA) in the Agency
2002	The Agency is welcomed into the WHO International Drug Monitoring Program as the 66th member state
2002	The Medicines Examination Laboratory is welcomed into the international network of Official Medicines Control Laboratories (OMCL)
17. - 18.03.2002.	The 5th European Union meeting of associated drug regulatory authorities takes place in Latvia - within the CADREAC cooperation agreement
01.10.2002.	Internal audit is introduced and the development of a Quality Management System is initiated
02.01.2001.	Adverse Drug Reactions Monitoring Department is established
From 02.01.2001. until 31.12.2009.	The function of evaluating and approving advertisements of medicines is carried out.
2001	The preparation of an independent informative bulletin "CITO" for doctors and pharmacists is initiated
2000	International Harmonisation Conference guidelines regarding Good Clinical Practice are published (in Latvian and English)
End of 2000	The second section of the agency building is commissioned
1999	The first SAM website is developed
1999	The first Annual Report is published
02.03.1998.	Clinical Trial Inspection Department is established
1998	The electronic record keeping program "Lotus Notes" is introduced
1997	The publication of the annual issue "Drug Register of Latvia" is initiated
05.03.1997.	The first marketing authorisation No. 97-0001 is issued for the medicine "PNU-Imune 23" (Marketing authorisation holder - Cyanamid-Lederle Arzneimittel GMbH)
09.10.1996.	A non-profit organisation - state joint stock company "State Medicines Agency" is established. Jānis Ozoliņš is appointed as the General Director and Chairman of the Board

Address: Jersikas street 15, Riga, LV-1003
Phone No.: +371 67078424
Fax No.: +371 67078428
E-mail: info@zva.gov.lv
Website: www.zva.gov.lv