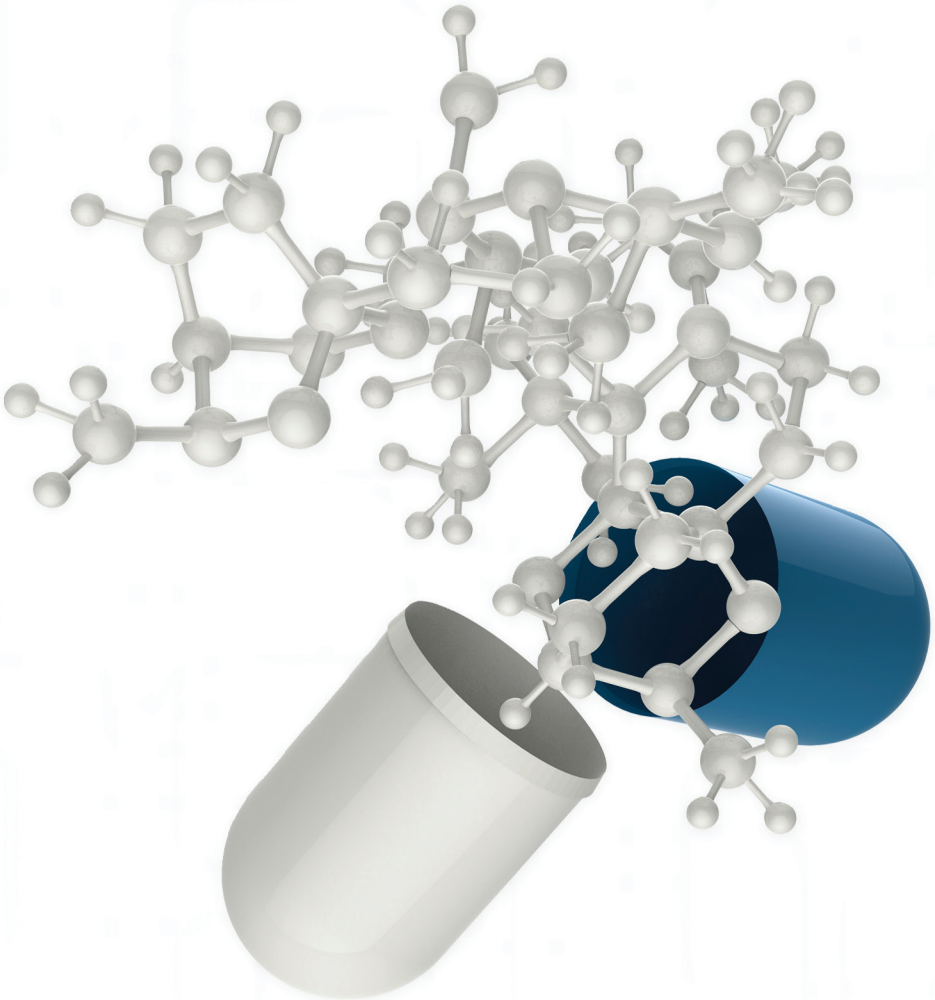
STATE AGENCY OF MEDICINES

ANNUAL REPORT

2012



ANNUAL REPORT OF STATE AGENCY OF MEDICINES

2012

PREFACE

It gives me great honour to present to you the annual report on the operation of the State Agency of Medicines in 2012 that demonstrates the professional, responsible and united work of SAM colleagues throughout the entirety of this year.

For SAM the year 2012 can be considered as a year of growth and quality. The operation of SAM undoubtedly shows that quality begins within our institution and it is the result of purposeful work, and is not merely a coincidence. This is demonstrated also by the annual survey of our clients showing that we have been recognised as a trustworthy partner in the system ensuring public health and as an integral component in the business processes of companies.

One of the fundamental principles of SAM operation is not only to evolve our operation and improve the quality of our services, but also to raise the professional knowledge of our employees. The level of education of SAM employees is high - 88% have a higher education degree, 5 civil servants out of those 88% have a doctorate degree and one is habilitation degree. In the year of review SAM ensured additional training in 57 courses and seminars organised by international organisations. SAM also continued collaboration with the leading scientists in Latvia in order to represent Latvia's position in the establishment and formation of an assessment regarding issues related to medicines and their regulation on an international level.

Naturally, there have been many complex tasks and difficult situations during this year, but there have also been challenges that have motivated us to change our way of thinking, seek new solutions and to be open towards change.

In addition to our main operational tasks we have also made a great investment in the development of a quality system. After evaluating the accomplishments this far we dared to be ambitious and we set upon ourselves another task - to complete the certification of the SAM integrated management according to the international standards ISO 9001:2008 and ISO/IEC 27001:2005.

It was a successful team effort where everyone was involved in the internal audits and in the visits of the Bureau Veritas Latvia.

In order to facilitate the work of healthcare specialists and pharmacists in choosing the medicines most appropriate for the patient, as well as in finding out or clarifying relevant information regarding safety of medicines, in 2012 for the first time SAM issued the Drug Register of the Republic of Latvia in a DVD format including summaries of product characteristics and patient information leaflets. The SAM prepared electronic format allows every user to find the necessary data regarding medicines by using a simple and convenient information search form.

In 2012 significant effort has been put into minimising the administrative burden of the marketing authorisation holders. Together with the previous amendments in the normative acts, the marketing authorisation holders now have the opportunity to combine several variations into a single group in the marketing authorisation documentation, thus, decreasing the number of applications and the costs of marketing authorisation services.

In the year of review SAM actively continued its participation in the work of international organisations and provided its input in accomplishing the objectives these organisations and SAM have in common. Special mention has to be made of the application evaluation carried out by SAM in the mutual recognition procedures where Latvia was the Reference Member State. Latvia has participated as a co-rapporteur in the repeated evaluation procedures of gene therapy carried out by the European Medicines Agency (EMA) Committee for Advanced Therapies (CAT) and in several EMA Paediatric Committee procedures, and SAM has also begun its work as a co-rapporteur in the EMA Committee for Medicinal Products for Human Use (CHMP).

In 2012 the Pharmaceutical Inspection Co-operation Scheme (PIC/S) conducted a repeated evaluation procedure of SAM with the objective of verifying that the normative acts of our country and the licensing system of medicines manufacturers, as well as procedures for conducting inspections comply with the unified standards of the organisation. During this evaluation an audit of SAM quality system was conducted with special attention paid to licensing and compliance evaluation processes, as well as the Medicines Examination Laboratory, and also an audit of the Health Inspectorate quality system was conducted to evaluate the procedures for investigation of quality defects and for the recall of medicines from the market. The evaluation also included inspections in several medicines manufacturing companies in Latvia where the work of SAM experts was evaluated by PIC/S observers from Estonia and the United Kingdom. As a result of the evaluation it was declared that the SAM quality system and procedures comply with the standards set by the organisation.

In order to promote cooperation between the medicines agencies of the Baltic States in November 2012 a meeting of the representatives from the medicines agencies of the Baltic States took place in SAM. During this meeting the directors of the medicines agencies of Latvia, Lithuania and Estonia signed a contract regarding collaboration in the fields of good manufacturing practice, good distribution practice, good pharmacovigilance practice and good clinical practice, as well as regarding the cooperation of laboratories in the Baltic States in the testing of medicines authorised in the national procedure. The signed contract involves not only the improvement of quality of work, for example, optimising the operation of the medicines examination laboratory and expanding its possibilities for testing, but also the training of agency employees in the aforementioned areas of cooperation.

Also a pleasant surprise was the international acknowledgment of our interactive map of pharmacies developed in 2011. In November 2012 we received an award in the international contest "Quality Innovation Award 2012" as the winner from the Republic of Latvia in the category of public sector. In its essence it is a creative information technology solution linking the SAM Information System (SAMIS) with an interactive map. The information regarding pharmacies is displayed in the map and various search options are available. It is in fact quite simple! It is interesting that due to this work we have received specifically the quality award. In my opinion, it gives evidence of a completely different added value of this solution - it is an easy and illustrative way of receiving necessary information, but in our everyday work - it is a belief in our ability to be a creative team.

I would like to thank all the employees of the SAM who have participated in the making of this publication and I hope that the prepared annual report will be useful not only to pharmaceutical professionals, but also to the residents of Latvia.

Director of SAM  Inguna Adoviča

ABBREVIATIONS

DCP	Decentralised procedure
EU	European Union
EMA	European Medicines Agency
CHMP	EMA Committee for Medicinal Products for Human Use
PRAC	EMA Pharmacovigilance Risk Assessment Committee
CPP	Certificate of Pharmaceutical Product
PIC/S	Pharmaceutical Inspections Co-operation Scheme
MD	Medical Device
LATMED	Electronic database of the Register of Medical Devices
CM	Cabinet of Ministers
NP	National Procedure
WHO	World Health Organization
MAH	Marketing authorisation holder
MRP	Mutual recognition procedure
CDPC	Center for Disease Prevention and Control
INCB	International Narcotics Control Board
VIC	Vaccine induced complications
MH	Ministry of Health
ADR	Adverse drug reaction
SAM	State Agency of Medicines
SAMIS	State Agency of Medicines information system

CONTENTS

1.GENERAL INFORMATION ON THE STATE AGENCY OF MEDICINES

1. Legal Status of the State Agency of Medicines

The SAM is state institution under the supervision of the Minister of Health. SAM operation is regulated by the State Administration Law, the Pharmaceutical Law, the Cabinet of Ministers Regulation No. 1006 "Statutes of the State Agency of Medicines" adopted on December 7th 2004 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 local and international pharmaceutical legislation in order to ensure that the products (medicines, medical devices, blood, cells, tissues and organs) used in health care, as well as the involved companies and their activities comply with certain requirements, and in addition provide objective and analytical information for the purposes of state administration, to the public, health care specialists, cooperation partners, as well as international and EU institutions.

SAM performs the following tasks:

- evaluate and authorise medicines, carry out expertise on quality of medicines, develop and update the Drug Register of Latvia;
- carry out pharmacovigilance;
- issue authorisation for conduct of clinical trials with medicinal products, evaluate the compliance of clinical trials with good clinical practice requirements, as well as evaluate the applications for non-interventional studies of medicines;
- issue authorisations for import, export, transit, distribution and purchase (to ensure 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 assemble and distribute information regarding consumption of medicines;
- issue authorisation cards for precursor operators and special permits (licences) for operation with precursors;
- authorise medical devices manufactured in Latvia, issue authorisations for placing specially supplied medical devices on the market, as well as carry out vigilance for medical devices;
- issue authorisations for conduct of clinical trials with medical devices;
- issue compliance certificates to procurement and storage (utilisation) organisations of human tissues, cells and organs, blood establishments, hospital blood banks and the State Blood Donor Center;

- issue special permits (licences) for pharmaceutical activity;
- issue good manufacturing practice compliance certificates;
- operate in the unified systems of the medicines and medical devices agencies in the European Economic Area member states, cooperate with European institutions and international organisations by participating in work-sharing and complying with the collective standards and procedures;
- collaborate with professional organisations of doctors and pharmacists, non-governmental organisations in the field, foreign and international institutions, as well as ensure mutual exchange of information in the SAM areas of operation;
- carry out the tasks of a competent authority in accordance to the requirements declared in the normative acts of the European Union;
- operate in the European medicines network by participating in work-sharing and complying with the collective standards and procedures, cooperate with other European and international organisations.

1.3. The Main Objectives of the Year of Review

In addition to the primary operation of SAM, in 2012 the following priority tasks were set for the year of review:

- continue discussions regarding the possible change of status of SAM (an institution non-financed from the state budget) that would ensure a possibility of rational management of procedures and finances;
- more actively participate in MRP/DCP procedures as the Reference Member State;
- participate in the centralised authorisation procedure assuming co-rapporteur responsibilities;
- promote and develop collaboration with academic and scientific institutions by ensuring the involvement of academic forces in complex expertise cases and by offering new skills to pharmacy and biomedical research centres to promote innovation;
- ensure the requirements of the new pharmacovigilance normative acts, as well as compliance inspections of pharmacovigilance systems after they are determined in normative acts;
- more actively participate in e-Health projects;
- improve the circulation of electronic marketing authorisation documentation (e-CTD);
- 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);
- continue to participate in EMA work, work-sharing programs within the European medicines network, WHO programs;
- ensure and coordinate the development of the list of active substances and excipients in Latvian, involving in the process academic forces and representatives of the State Language Center;
- continue to develop the quality system and prepare for ISO certification;
- review and update SAM internal procedures to improve work effectiveness;
- continue to improve the technical possibilities and content of the SAM website , especially the Drug Register, and expand the communication possibilities on the public website;
- promote a more active and broader two-way communication with SAM collaboration partners (doctors, pharmacists, clients, mass media representatives and other shareholders, as well as the public), thus, creating a positive understanding of SAM operation and pharmaceutics as a whole;
- continue to develop electronic communication with SAM collaboration partners;
- continue work on the establishment of a field data centre.

2. RESULTS OF OPERATION OF THE STATE AGENCY OF MEDICINES

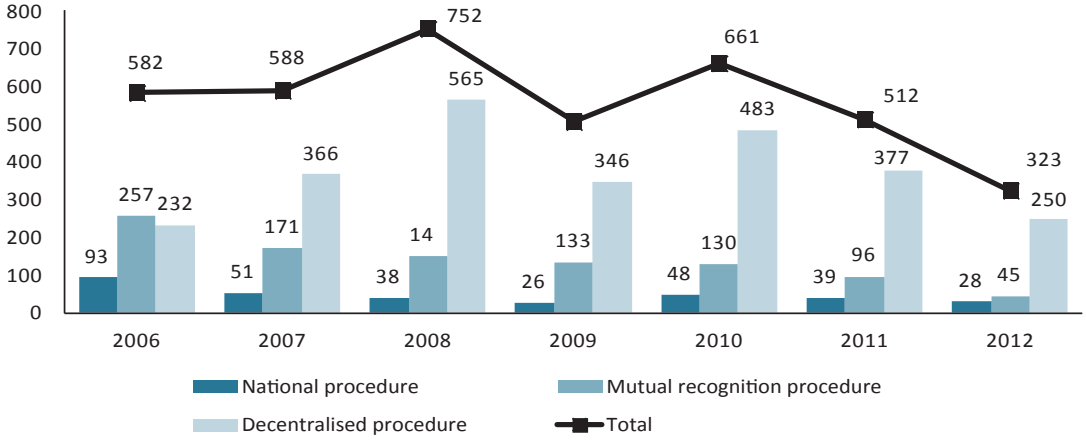
2.1. Authorisation of Medicines

In 2012 by evaluating documentation on quality, safety and effectiveness of medicines SAM has carried out expertise more than 2000 times on general, chemical and pharmaceutical, as well as preclinical and clinical sections of the documentation of medicines. Evaluation reports on 116 medicines have been prepared for the SAM Commission for Registration of Human Medicines for adoption of a decision regarding marketing authorisation and renewal of medicines in the national procedure. In 2012 Latvia as a Reference Member State has initiated 3 DCP procedures, has successfully lead 1 repeated MRP procedure and has initiated 2 MRP renewal procedures. During 2012 SAM has completed 323 marketing authorisation procedures and 262 renewal procedures.

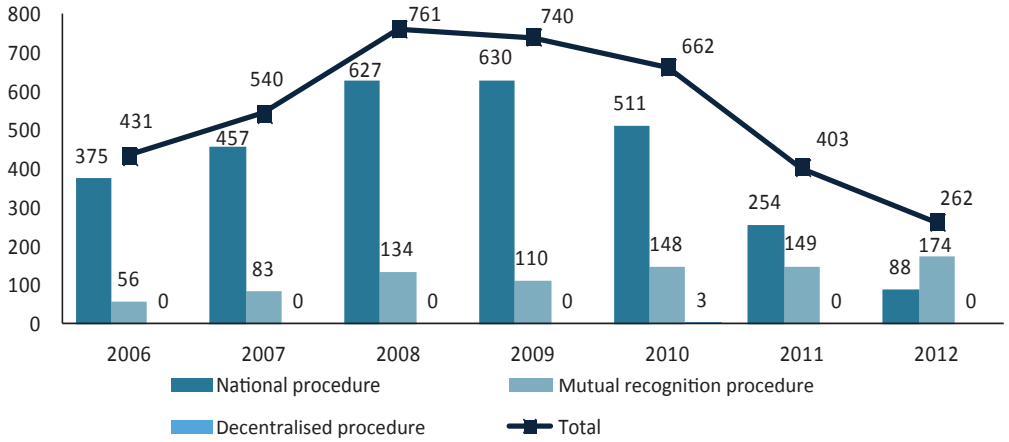
In the year of review SAM expert activity in international procedures has been higher than in the previous year of review. In 2012 Latvia as a co-rapporteur has participated in the repeated gene therapy evaluation procedure carried out by the EMA Committee for Advanced Therapies and also has begun to evaluate the indications of ceftriaxone containing medicines within the EMA Committee for Medicinal Products for Human Use (CHMP) in accordance to Article 30 of the Directive 2001/83/EC.

Latvia is now represented in the EMA Paediatric Committee and as a rapporteur has participated in 10 PIP (Paediatric Investigation Plan) procedures, as a co-rapporteur - in 3 procedures and as a rapporteur has participated in 4 PIP modification evaluations. The SAM nominated EMA Paediatric Committee expert has also participated as a paediatric expert in three SAWP (Scientific Advice Working Party) procedures and two COMP (Committee of Orphan Medicinal Products) procedures.

Marketing authorisation procedure

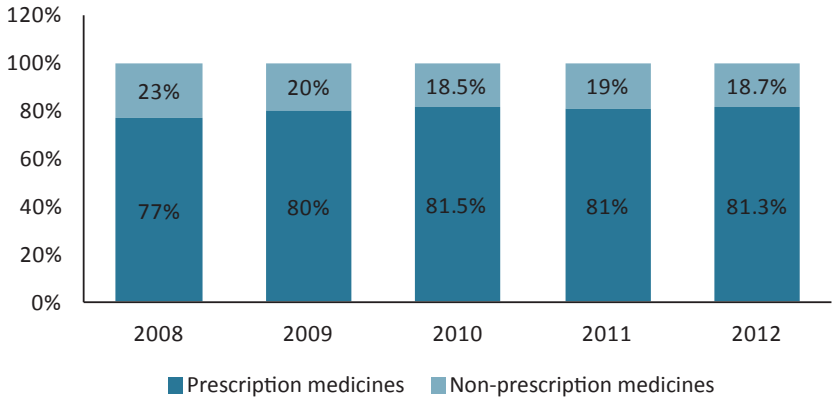


Renewal procedure



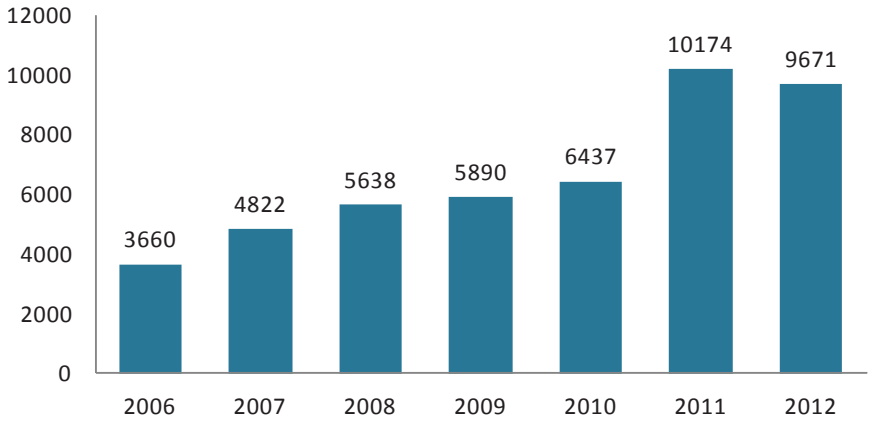
The ratio of prescription and non-prescription medicines in the Drug Register of the Republic of Latvia remains unchanged.

Ratio of prescription and non-prescription medicines in the Drug Register of the Republic of Latvia



9 671 variations to the marketing authorisation documentation of authorised medicines were submitted and evaluated in 2012.

Variations to the marketing authorisation documentation



In the year of review 31 applications were received for evaluation of product compliance/non-compliance with the definition of a medicinal product where SAM has given an opinion on the product status.

329 Periodic Safety Update Reports were evaluated in 2012. 77 letters containing evaluations and identified deficiencies were written regarding a total of 60 medicines.

In 2012 public assessment reports were written regarding 14 medicines authorised in the national procedure.

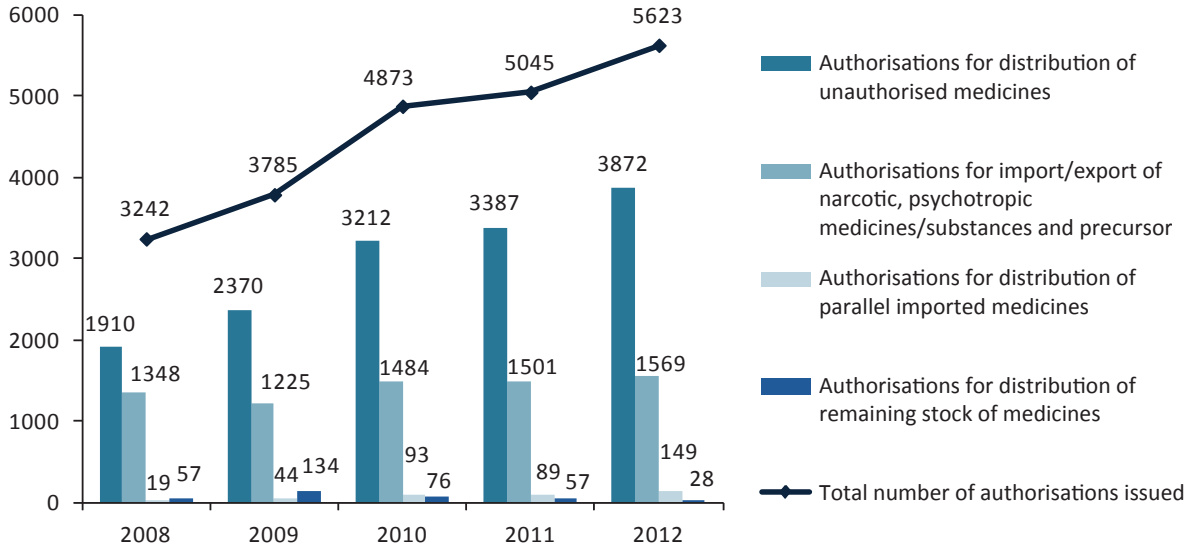
2.2. Issuing Authorisation for Distribution of Medicines

In 2012 within its competency SAM ensured 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 2012 SAM issued 5623 authorisations for import, export and distribution of medicines. This includes 3872 authorisations for distribution of unauthorised medicines, 149 authorisations for distribution of parallel imported medicines and 28 authorisations for distribution of remaining stock of medicines after the withdrawal of the medicines from the Drug Register of the Republic of Latvia.

Dynamics of the number of authorisations issued for import, export and distribution of medicines per each year



In addition to the aforementioned functions SAM carries out expertise on applications regarding:

- 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 15 authorisation cards were issued to precursor operators and 3 authorisations were issued for 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. Variations were made in the authorisations for 88 parallel imported medicines.

SAM ensures the recording 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 (hereinafter 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 Drug 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 compact disc format and is also published on SAM website.

It has to be noted 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 specialists and merchants, as well as provides routine consultations to clients.

2.3. Clinical Trials

In 2012 SAM received 86 applications for clinical trail projects for medicines. One clinical trial application was withdrawn due to the requirement for amendments to the trial protocol set forth during the expertise, but one clinical trial application was temporarily suspended by the sponsor due to strategic reasons.

In compliance with the current European guidelines regarding the voluntary harmonisation procedure for reviewing multinational clinical trials, during the year of review 7 applications for the international harmonisation procedure for clinical trials were submitted to SAM.

After the carrying out expertise on application documentation and after evaluating benefits and risks SAM employees decide on the approval of clinical trials. In 2012 SAM issued a total of 82 authorisations for initiation of clinical trials in Latvia, including 2 trials where conditional authorisations were issued. Applications of nine authorised clinical trials were evaluated in the international voluntary harmonisation procedure before they were submitted nationally.

12 clinical trials involving children and adolescents were authorised in 2012. Paediatric clinical trials were authorised in several medical specialities - pulmonology, cardiology, neurology and abdominal surgery.

Out of all the trial projects authorised in 2012, 22 clinical trials included biological medicinal products obtained with the help of recombinant DNA technology (for example, monoclonal antibodies, blood coagulation factors, hormones) and intended for the treatment of oncological, rheumatic, haematological, dermatological, cardiological and endocrinological diseases.

203 authorisations were issued for significant variations to clinical trial protocols or other documentation related to the clinical trial. 2 of the authorised variation applications were also evaluated 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 trials, as well as inspections of good clinical practice was regularly entered into the European clinical trial database Eudra CT. It is necessary to regularly ensure the aforementioned data for the maintenance and updating of the European Clinical Trials Register.

SAM ensured electronic data exchange in the EudraVigilance system by forwarding acknowledgements of receipt of safety reports relating to the 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. 51 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 developed by SAM. In total SAM received, reviewed and recorded 133 annual safety reports prepared by sponsors regarding clinical trials with medicinal products conducted in Latvia. 22 annual safety reports were analysed in depth and the assessment is reflected in an appropriate newly developed format.

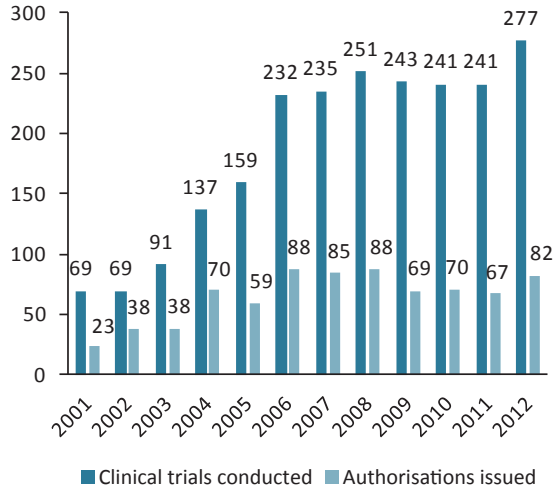
23 external experts were involved in the evaluation of documentation of authorised projects. Altogether expertise was carried out on 59 projects in 2012. 1 expert was involved for the first time.

Altogether 277 clinical trials were conducted in Latvia in 2012. 43 projects were completed.

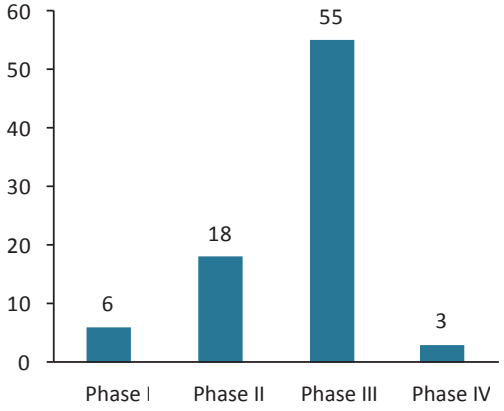
The authorised clinical trial projects were sponsored by a total of 43 foreign pharmaceutical companies. In accordance with the power of attorney from the sponsors, the following contract research organisations were involved in organising and ensuring the quality of conduct of clinical trials in Latvia:

- Quintiles (11 projects);
- ICON (9 projects);
- Parexel International (7 projects);
- Amber CRO (6 projects);
- Crown CRO (4 projects);
- Pharmaceutical Research Associates Sp.z o.o. (3 projects);
- Pharm – Olam International Ltd (3 projects);
- Covance CAPS Ltd (3 projects);
- and 13 other contract organisations (1-2 projects each).

Number of issued authorisations and conducted clinical trials with medicines



Distribution of clinical trials authorised in 2012 according to trial phase



Distribution of clinical trials authorised in 2012 according to medical speciality

Medical speciality	Number of clinical trials
Oncology	13
Pulmonology/Allergology	13
Endocrinology	10
Gastroenterology	9
Neurology/Psychiatry	8
Rheumatology	7
Cardiology	7
Urology/Nephrology	4
Surgery with an infection component	4
Dermatology	2
Haematology	2
Traumatology	1
Gynaecology	1
Infectology	1

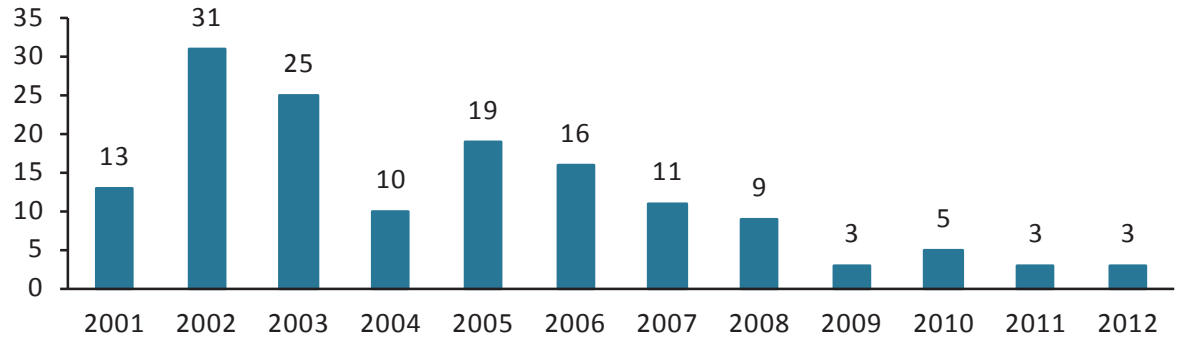
11 inspections of clinical trial compliance with good clinical practice were carried out in trail centres in 2012. 4 inspections were conducted in trial centres in Latvia, one of these inspections was initiated by the Committee for Medicinal Products for Human Use (CHMP). 7 inspections took place in foreign trial centres in Chile, Peru, Poland, Ukraine (all CHMP initiated inspections relating to 3 medicinal products to be authorised). Both major and other deficiencies were discovered during the inspections.

In the year of review SAM received and evaluated 3 applications for non-interventional studies. They are recorded in the list of SAM authorised non-interventional studies available on SAM website.

Clinical trial centres that started participating in authorised clinical trials in 2012

Clinical trial center	Number of clinical trials
P. Stradins Clinical University Hospital	51
Riga Eastern Clinical University Hospital:	41
• *Clinical hospital „Gailezers"*	*26*
• *Oncology Center of Latvia*	*9*
• *Clinic „Linezers"*	*4*
• *Clinic "Bikernieki", State Burn Centre*	*1*
• *Clinic "Tuberculosis and Lung Disease Centre"*	*1*
Daugavpils Regional Hospital	27
Vidzeme Hospital	13
Liepaja Regional Hospital	9
State LLC "Diagnostic and Treatment Centre for Allergic Diseases "	8
Health Center 4	7
Children Clinical University Hospital	7
Riga 1st Hospital	6
Northern Kurzeme Regional Hospital	5
VSV centre	5
Gastrointestinal Disease Centre „Gastro"	5
State LLC „Maritime Hospital"	5
V.Vēvere medical practice in Phthisiopneumology and Allergology	5
JSC "Health Centre Union", medical centre "OLVI"	5
Other clinical trial centers (79 in total)	1 - 4 at each centre

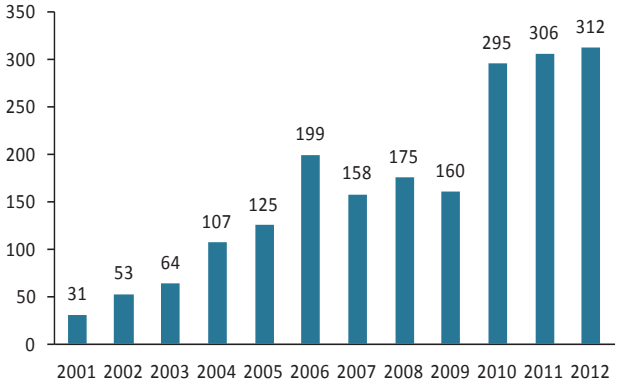
SAM authorised non-interventional studies



2.4. Adverse Drug Reaction Monitoring and Risk Minimisation

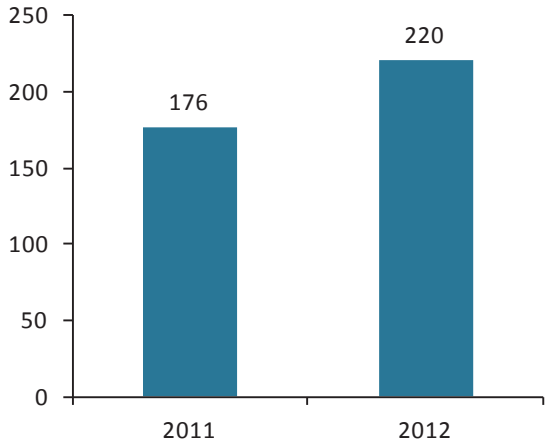
SAM has been maintaining the database for adverse drug reactions observed in Latvia since 2001 and since 2004 the reported information is being forwarded to the EU database EudraVigilance. Each year SAM analyses the information entered in the database and the reporting activity in Latvia. Similarly as in previous years, also in 2012 a tendency for the number of reports to increase was observed, though, slightly, but steadily. 312 reports regarding observed adverse drugs reactions (hereinafter - ADR) were received in SAM.

Adverse drug reaction reports



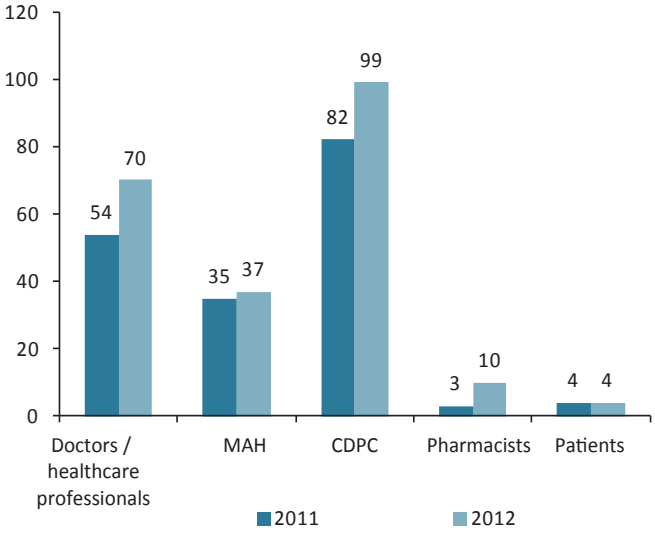
Several reports may be received regarding one and the same adverse event where the reporter has provided additional information. Therefore, an important criteria is also the number of clinical cases for which information was received during the year. This figure has also increased in comparison to 2011 - from 176 to 220.

Number of clinical cases of adverse drug reactions



The reporting activity among doctors is continuing to increase and this is very pleasing. The reporting activity among pharmacists has also increased, as is shown by the number of clinical cases for which information was received. Unwaveringly good is the data exchange with the Centre for Disease Prevention and Control regarding vaccine induced adverse reactions, and it has to be noted that the basis of this data are also reports from doctors in accordance with the CM Regulation No. 1040 "Procedure for Healthcare Professionals to Report Vaccine Induced Complications" adopted in December 27th 2005.

Adverse drug reaction cases in 2011 and in 2012 according to information provider



Among the most frequently reported medicines is the tuberculosis vaccine. It can be explained by the properties of the vaccine itself, the extensive coverage of infant vaccination in Latvia and the high quality monitoring of all vaccines, including the tuberculosis vaccine, ensured by SAM in collaboration with the Centre for Disease Prevention and Control.

A signal was detected in the adverse drug reaction database in Latvia: an increase in the number of reports on cases of suppurative post-BCG lymphadenitis. As the BCG Vaccine SSI (tuberculosis vaccine) is authorised and used not only in Latvia, in 2012 SAM informed the EMA Pharmacovigilance Risk Assessment Committee (PRAC) about the aforementioned signal in accordance to EU normative acts requiring collaboration and a

coordinated approach to issues relating to the safety of medicines authorised in the EU. A review of the SAM proposed issue was initiated within PRAC.

In order to ensure safe use of the BCG Vaccine SSI and decrease the risk of suppurative lymphadenitis, after a request from SAM in 2012 the manufacturer of the vaccine Statens Serum Institut has introduced additional risk minimisation measures for BCG Vaccine SSI in Latvia: has distributed a SAM approved (in collaboration with the Centre for Disease Prevention and Control) letter "A report on the increased number of cases of suppurative lymphadenitis, also serious cases, in relation to the use of BCG Vaccine SSI and the recommended risk minimisation measures" containing recommendations to healthcare professionals and also has distributed an educational brochure "Guidelines for intradermal administration of the BCG Vaccine SSI" . The aforementioned documents were also published in "Cito!" 2012/4 (51) issue and on SAM website.

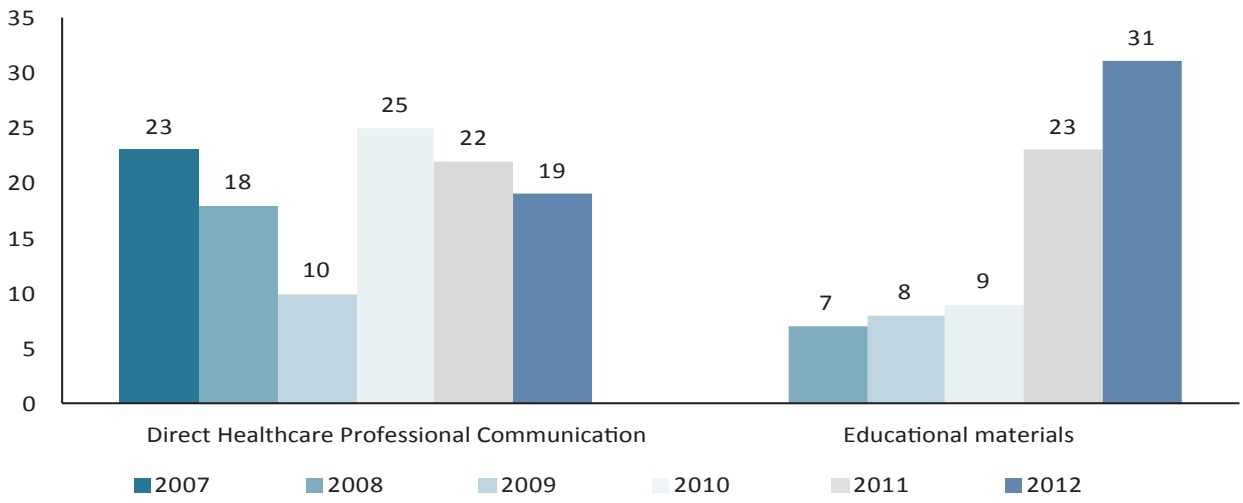
In the marketing authorisation process of medicinal products SAM carries out an evaluation of the description of the pharmacovigilance systems developed by marketing authorisation holders. In the period of review 375 descriptions of pharmacovigilance systems were evaluated. In accordance to the new EU pharmacovigilance normative acts coming into effect in 2012 the requirement for MAHs to submit the previous type of document is abolished, instead complying with a transitional period a new type of document shall be submitted - a summary of the pharmacovigilance system which is directly related to the introduction of the Pharmacovigilance System Master File. In 2012 such a document was submitted and reviewed in SAM regarding 208 medicinal products. The nature of this process is related to the pharmacovigilance inspections planned in the future.

In accordance to the EU work-sharing procedure which includes the assessment of Period Safety Update Reports (Periodic Safety Update Reports Worksharing), in 2012 SAM carried out an evaluation of 3 periodic safety update reports regarding original medicinal products for the necessities of the European Economic Area.

An ADR Monitoring Advisory Board operates within SAM and its activity is coordinated by SAM. 3 Board meetings were held during the period of review.

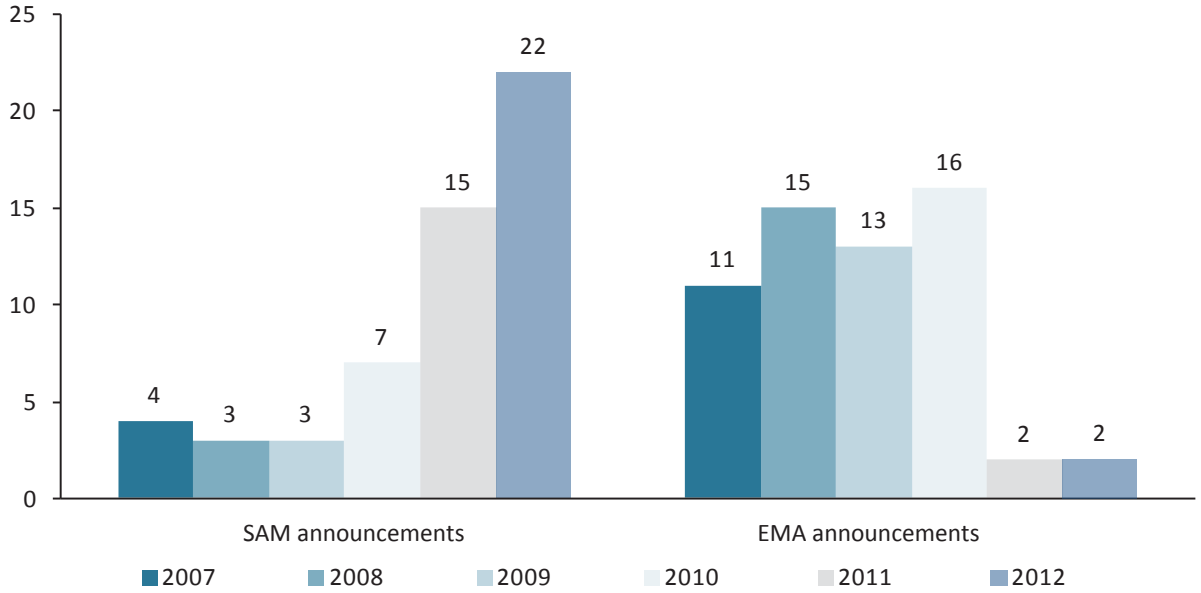
SAM operates in collaboration with the Qualified Persons Responsible for Pharmacovigilance for MAHs. Data exchange is carried out regarding ADRs observed in Latvia and implementation of MAH established risk minimisation measures in Latvia is ensured, including necessary communication with healthcare professionals, patients and the public regarding the safe use of medicines. In the period of review expertise was carried out on 31 educational materials for risk minimisation and 19 "Direct Healthcare Communication Letters" submitted by MAHs to SAM were approved.

Approval of informative risk minimisation measures



Information regarding safety of medicines intended for doctors, patients and the public, as well as marketing authorisation holders is continuously published on SAM website. 22 SAM and 2 EMA announcements regarding pharmacovigilance (medicines safety monitoring) were published on SAM website.

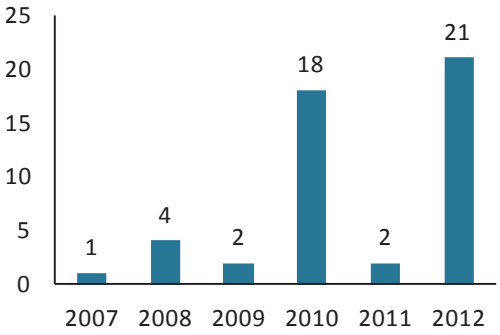
Informative Materials on SAM website regarding safety of medicines



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

In the period of review also published on SAM website were harmonised safety information standard texts required for MAHs to include in summaries of product characteristics and patient information leaflets of specific medicines and/or groups of medicines. The aforementioned standard texts are based on EMA PRAC recommendations on introduction of harmonised safety information in the product documentation of medicines authorised in European Economic Area countries.

Approval of safety information in marketing authorisation documentation (number of safety issues)

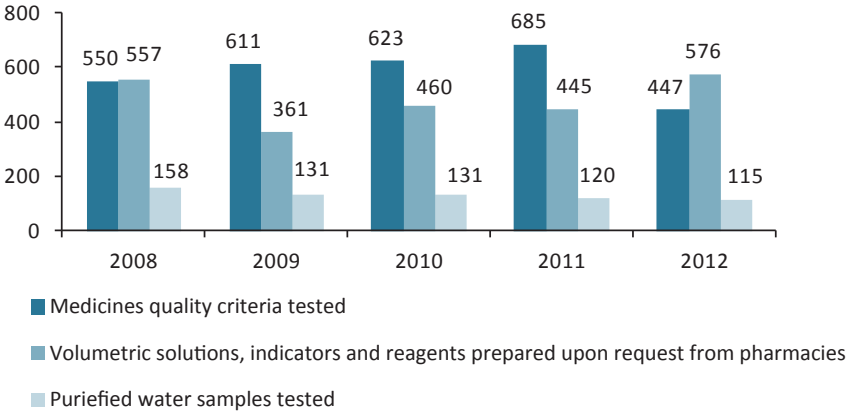


EU normative acts that shall regulate pharmacovigilance more precisely will be incorporated in the Cabinet of Ministers of the Republic of Latvia Regulations and will come into force in 2013. In the period of review SAM has actively worked on the development of a project for a new CM Regulation.

2.5. Quality Control of Medicines

In 2012 SAM laboratory carried out analysis of 68 samples of medicines. In the process of analysis 447 quality criteria were tested. 576 volumetric solutions, indicators and reagents were prepared upon request from pharmacies. 115 samples of purified water produced in pharmacies were selected and tested in 2012. Noncompliance with the requirements of the European Pharmacopoeia was discovered in 3 samples of purified water.

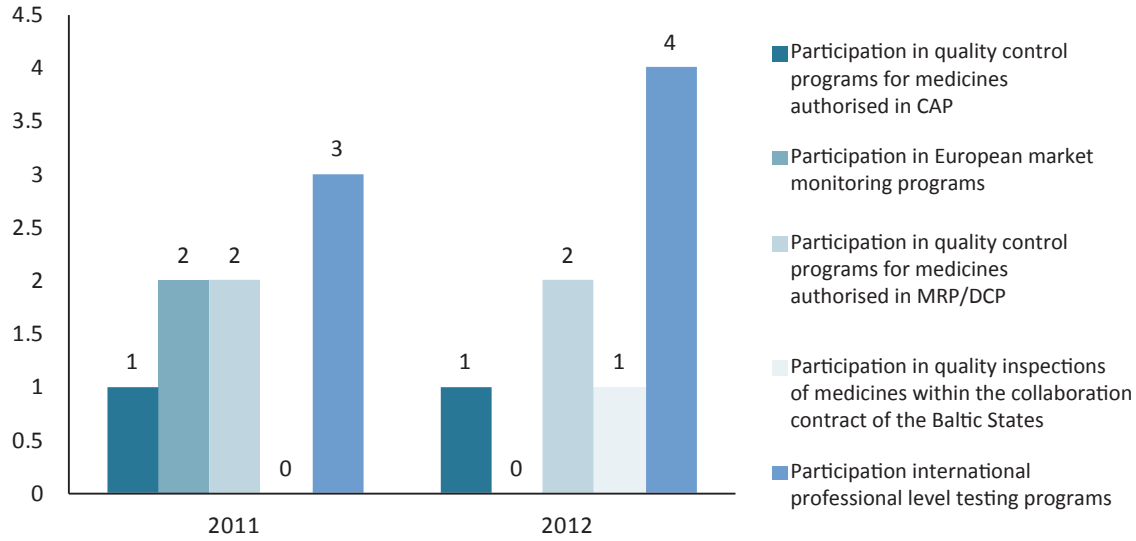
Results of operation of Medicines Examination Laboratory



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 medicinal products). Due to this amendment the number of non-sterile medicinal products to be tested in the SAM laboratory has increased.

SAM laboratory regularly participates in international programs for quality control of medicines and professional level testing programs. In 2012 SAM 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), as well as in a EDQM (European Directorate for the Quality of Medicines) organised study in the field of development of reference material.

Participation in international programs for quality control of medicines and professional level testing programs



The laboratory is accredited in accordance with the requirements of the LVS EN ISO/IEC 17025:2005 standard (further information in the section "Integrated Management System")

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

In 2012 three applications were submitted for authorisation of medical devices in Latvia and 298 notifications were added to the LATMED database regarding placement of medical devices on the market in the Republic of Latvia. 695 primary reports about accidents with medical devices were received within the vigilance system from competent institutions regarding medical devices in the EU member states, as well as from manufacturers, distributors and users of medical devices. In 176 of these cases it was found that the medical device involved in the accident is or possibly is available in Latvia and appropriate safety measures were taken.

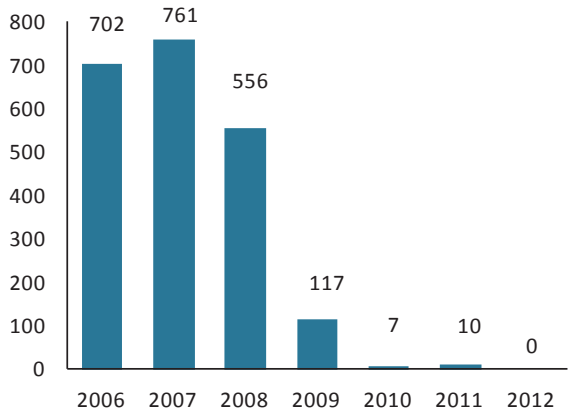
In the year of review expertise was carried out on documentation for grant of authorisation to 7 MD clinical trials (excluding expertise on application documentation for amendments to clinical trial protocols that have already received authorisation from SAM).

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 seminars and provide information regarding news in the field of medical devices. In the year of review SAM experts have begun to participate in the meetings of the European Council Working Group on Pharmaceutical Products and Medical Devices by engaging in the evaluation and development of proposals for regulation of medical devices.

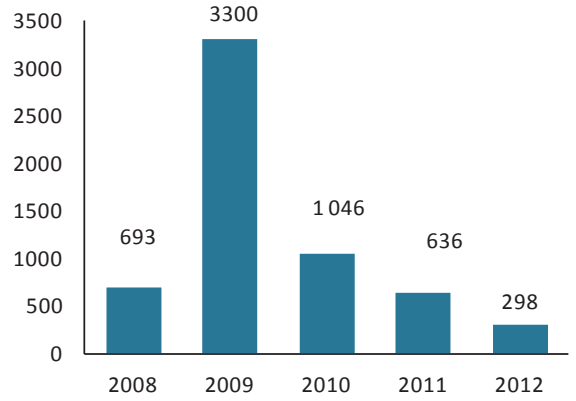
Compliance evaluation, authorisation, safety monitoring and clinical trials of medical devices

Criteria	Number
Expertise on authorisation documentation of MDs manufactured in the Republic of Latvia	3
Expertise on authorisation documentation of MDs without CE mark	0
Expertise on documentation for issue of authorisation to specially supplied MDs	3
Registration of information submitted within the notification procedure into the LATMED database	298
Registration of information provided by MD holders regarding purchase of safety group I and II MD into the LATMED database	3 089 (including www – 1 271)
Registration of information provided by MD holders regarding changes in use of safety group I and II MD into the LATMED database	4172
Acceptance of reports received within the Vigilance system, analysis and processing of information and registration of data into the LATMED database	695
Identification of non-compliant MDs in exploitation in Latvia and implementation of safety measures	176
Expertise of documentation submitted for authorisation of clinical trials with MDs	7
Expertise of documentation submitted for approval of amendments to a clinical trial with MDs	14
Applications for variations of previously issued MD authorisations	0

Authorisations issued for medical devices in the Republic of Latvia



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



2.7. Evaluation of Compliance of Pharmaceutical Activity

In 2012 there were 20 inspections conducted in manufacturing/importing companies and 1 inspection was conducted in a contract laboratory carrying out testing for a licensed active substance manufacturing company. In total this required 58 person-days. Three of the inspected manufacturing companies were located outside of the European Economic Area, but 3 inspections were carried out on the manufacturing of active substances upon request from the manufacturers themselves. In total the manufacturing of 4 active pharmaceutical ingredients was inspected. 5 product (medicines) samples were selected in the inspections of manufacturing companies. During the year of review 22 Good Manufacturing Practice compliance certificates were issued to manufacturing/importing companies.

One inspection of a manufacturing site in a country outside of the EEA was conducted in collaboration with WHO.

In 2012 SAM experts participated in two inspections of manufacturing companies (good manufacturing practice of active substances) located in other EU member states that were conducted together with inspectors from other PIC/S member agencies during experience exchange visits.

35 compliance evaluations of medicines wholesalers, as well as inspections of good distribution practice of medicines wholesalers were carried out in 2012 requiring a total of 37.5 person-days.

In 2012 one inspection of a Latvian medicines wholesaler (good distribution practice) was conducted together with Lithuanian experts during an experience exchange visit.

Upon request from medicines manufacturers and wholesalers in Latvia 53 product certificates and 31 free trade certificates were issued in 2012 to promote export of medicines manufactured in Latvia and their authorisation in countries outside the EU/ European Economic Area.

In 2012 compliance evaluation and monitoring procedures were carried out on 20 human blood and human blood component establishments and hospital blood banks and 7 supervision procedures were performed. 6 compliance evaluations of procurement and storage organisations of tissues/cells and 1 supervision procedure were conducted. 4 new tissue centres operating in the field of in vitro fertilisation were evaluated.

It has to be noted that SAM employees represent SAM in the EMA GMP Inspector Working Group, the Pharmaceutical Inspection Co-Operation Scheme activities (PIC/S), as well as in the working groups organised by the European Commission Directorate General for Health and Consumers (DG SANCO) regarding safety of human blood and blood components, tissues, cells and organs.

2.8. Licensing of Pharmaceutical Activity Companies

In accordance to the CM Regulation No. 610 "Criteria for Location of Pharmacies and Pharmacy Branches" adopted on August 2nd 2011 and CM Regulation No. 800 "Procedure for Licensing Pharmaceutical Activity" adopted on October 19th 2011 SAM reviews applications for opening or relocation of new general type pharmacies or pharmacy branches. In 2012 the number of applications and SAM adopted decisions regarding opening or relocation of new general type pharmacies or pharmacy branches increased: in 2011 - 11 decisions, but in 2012 - 95 decisions.

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 the local authority, SAM evaluated the availability of pharmaceutical care in a specific populated area where a general type 24 hour pharmacy was necessary.

In accordance to its competency SAM assembles and stores evaluation and licensing documentation of pharmaceutical activity companies, issues special permits (licences) for pharmaceutical and veterinary pharmaceutical activity, as well as regularly assembles and updates the data on SAM website regarding special permits (licenses) issued for pharmaceutical activity, general type pharmacy relocation cases and conditions for special activity.

In 2012 SAM received 1314 applications and additional documentation, provided 101 response letters, carried out compliance evaluation of documentation of 85 general and closed type pharmacies, conducted compliance evaluation of 35 medicines wholesalers, 5 medicines manufacturing or importing companies and their documentation, prepared 85 opinions regarding pharmacy compliance evaluations, 347 decisions regarding issuance, renewal, suspension, withdrawal of special permits (licences) for pharmaceutical activity and extension of case review term, renewed and issued 317 special permits (licences) for pharmaceutical activity to pharmaceutical activity companies.

At the end of 2012 the SAM developed interactive map of pharmacies received international recognition. Updated information regarding general type pharmacies in the territory of Latvia is regularly provided in the map of pharmacies. The SAM developed map of pharmacies is to be considered as the most precise search system of pharmacies, because the information is updated automatically following the adoption of a SAM decision regarding issuance/renewal of licence (see more information in the section "Integrated Management System").

Licences issued to pharmaceutical activity companies

Criteria	2007	2008	2009	2010	2011	2012
2008	2009	2010	2011	2012	759	287
Pharmacies	428	535	322	831	759	287
Wholesalers of medicinal and veterinary* medicinal products	34	25	29	44	24	14
Medicines manufacturing or importing companies	28	12	9	14	15	14
Medicines manufacturing companies that manufacture active pharmaceutical ingredients	0	0	0	2	3	2
Total	490	572	360	891	801	317

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

3. BUDGET AND EXPENSES OF THE STATE AGENCY OF MEDICINES

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

SAM income and expenses

No.	Financial Resources	Budget in 2011 (actual data)	Year of review (2012)	
			Statutory	Actual data
1.	Financial resources for covering expenses (total)	4 404 968	3 327 889	4 362 726
1.1.	Income from paid services and other independent income	4 404 968	3 327 889	4 348 529
2.	Expenses (total)	4 109 366	3 371 881	4 828 333
2.1.	Maintenance expenses (total)	3 860 909	3 090 881	4 608 599
2.1.1.	Regular expenses	2 093 851	3 090 881	2 300 364
2.2.	Expenses for capital investment	248 457	281 000	219734
-	Financial balance	-	-43992	-
-	Financing	-	43992	-
-	Financial Resources	-	43992	-
-	Increasing (-) or decreasing (+) change in surplus of financial resources from paid services and other independent income	-	43992	-

4. GENERAL ADMINISTRATION OF THE STATE AGENCY OF MEDICINES

4.1. Ensuring Public Procurement and Economic Activities

In 2012 SAM announced 14 procurement procedures. There were 38 candidates. Contracts for supply and services were signed for the conducted public procurement procedures. The most significant procurement procedures were:

- reconstruction of the SAM building heating system in the boiler building;
- improving the energy efficiency of the SAM administrative building - 2nd round of heat insulation of the facade;
- maintenance of the SAM territory and premises;
- ensuring high availability and technical support of the data network security devices;
- implementation of changes in the LATMED information system for medical devices and its maintenance;
- maintenance of the information technology service management software CA Service Desk Manager and requests for changes;
- implementation of changes and maintenance of the SAM information system.

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

In 2012 CM decided to maintain the SAM status as a public agency and in cooperation with the Ministry of Health new SAM statutes were developed - July 31st 2012 CM Regulation No. 537 "The Statutes of the State Agency of Medicines" that came into effect on January 1st 2013. Also a new SAM public paid service price list was developed - CM Regulation No. 75 "State Agency of Medicines Publicly Available Paid Service Price List" adopted on January 29th 2013.

To ensure the transposition of the Directive 2010/84/EU of the European Parliament and of the Council of December 15th 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use into the national normative acts SAM continued its work on the project for CM Regulation "Procedure for Pharmacovigilance" and on improving the annotation, as well as prepared proposals for amendments to the Pharmaceutical Law and SAM representatives participated in Saeima meetings for discussion of the draft law.

Relating to the transposition of the Directive 2010/84/EU SAM prepared proposals for amendments to several CM Regulations - CM Regulation No. 376 "Procedures for the Registration of Medicinal Products" adopted on May 9th 2006 and CM Regulation No. 57 "Regulations Regarding Procedures for Labelling of Medicinal Products and the Requirements to be set for Package Leaflets of Medicinal Products".

To improve the services SAM provides to its clients and decrease the administrative burden, several SAM proposals were submitted to the Ministry of Health for amendments to several CM Regulations, for example, CM Regulation No. 416 "Procedures Regarding Distribution and Quality Control of Medicinal Products" adopted on June 26th 2007, proposals for amendments to the Procedure for Licensing of Pharmaceutical

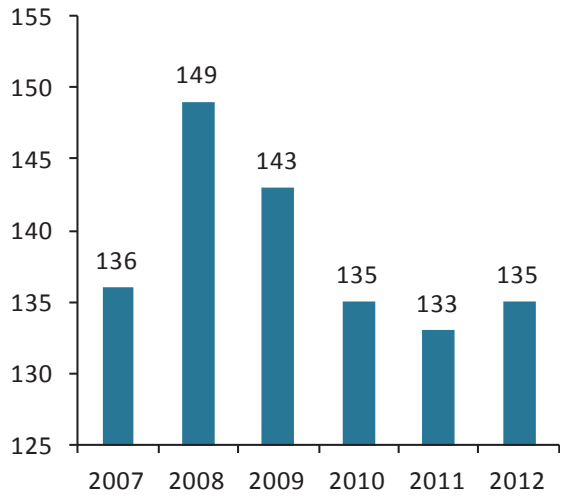
Activity, as well as proposals for amendments to the CM Regulation No. 891 "Procedure for the Clinical Trial of Medical Devices Intended for Human Use" adopted on September 21st 2010. In collaboration with the Ministry of Health SAM participated in the review and approval of more than 23 projects for normative acts, including the review of projects for the Law "On the Protection of the Body of Deceased Human Beings and the Use of Human Tissues and Organs in Medicine" and the CM Regulation "Regarding the Use of Human Organs in Medicines, as well as the Use of Human Organs and the Bodies of Deceased Human Beings in the Studies of Medicine".

In 2012 SAM representatives participated in regular meetings at the Ministry of Health to discuss the aforementioned projects for Laws and CM Regulations and for their amendments. Other institutions under the supervision of the Ministry of Health, pharmaceutical merchants and non-governmental organisations also participated.

4.3. Staff and Human Resources Management

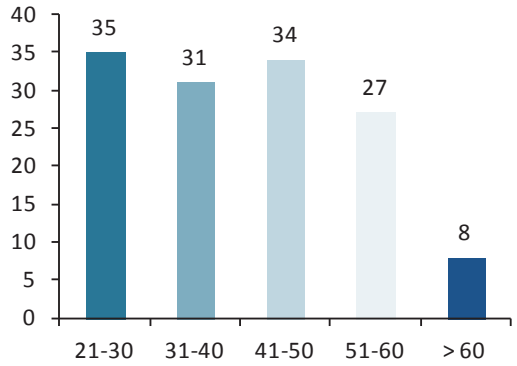
At the end of the 2012 there were 135 civil servants and employees actually working at SAM. In total there were 145 staff members in civil service or employment relationship with SAM in 2012: 70 civil servants and 75 employees.

Dynamics of the number of staff members according to year

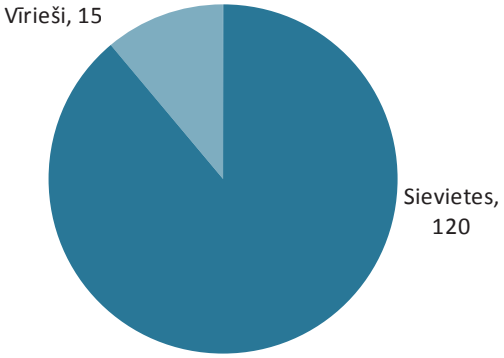


During 2012 four staff members and ten employees terminated their civil service or employment at SAM. A total of 18 staff members began to work in SAM in 2012. The staff turnover quotient in 2012 was 10% (staff turnover = number of released staff members in a definite time period/ average number of staff members in the same time period). The average age of staff members is 41.5 years.

Distribution of staff members according to age group

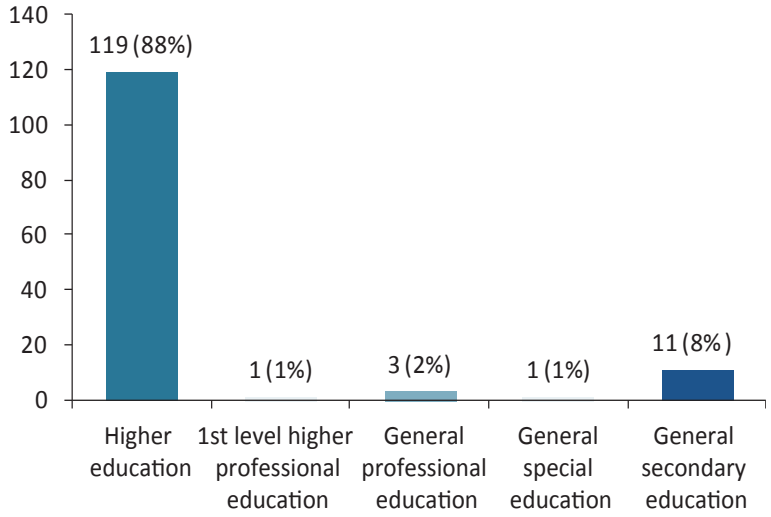


Distribution of staff members according to sex



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 5 civil servants have a doctorate degree and 1 civil servant has a habilitation degree.

Distribution of staff members according to level of education



One of the basic principles of SAM staff politics is to motivate staff members to raise their qualifications and level of education. In 2012 to raise their qualification SAM staff members have attended 57 training sessions and seminars organised by international organisations. To ensure the objective set by SAM - to complete the certification of the quality management system, 5 employees were trained in seminars for internal auditors regarding ISO 27001 quality standards. To ensure the unified preparation of SAM documents, as well as to promote employee understanding of the circulation of documents, including requirements for electronic documents, 43 employees participated in a seminar regarding management of records. With regard to work safety, 10 employees were trained in 1st level First Aid seminars.

Raising qualification of staff members

Category	2007	2008	2009	2010	2011	2012
Courses for raising qualification	123	125	269	107	162	181
Training, seminars, conferences coordinated by international organisations	51	62	52	64	52	57
Foreign language courses (2008 - 2011 English / 2012 French)	25	12	5	1	0	2

4.4. Integrated Management System

In collaboration with EMA, participating in the Benchmarking of European Medicines Agencies (BEMA) and in preparation for the pharmacovigilance system audit in accordance to the Directive 2010/84/EU of the European Parliament and of the Council of December 15th 2010, SAM acknowledged the necessity of introduction of an integrated management system.

Also in order to promote the recognition of SAM as an international competitor among local and international collaboration partners and clients, social partners and residents and to obtain an internationally recognised certification of the value of the achieved work, SAM made the decision to obtain the certificates in accordance to the requirements of the standards LVS EN ISO 9001:2009 "Quality management systems. Requirements (ISO 9001:2008)" and LVS ISO/IEC 27001:2005 "Information technology. Security techniques. Information security management systems. Requirements".

The certification audits were carried out at the end of 2012 by the Bureau Veritas Latvia and the SAM integrated management system was certified in accordance to the international standards ISO 9001:2008 and ISO/IEC 27001:2005. Certification area: "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."

The received Latvian National Accreditation Bureau (LATAK) and United Kingdom Accreditation Service (UKAS) accreditation certificates provide proof that SAM has worked consistently, purposefully and effectively in the implementation, maintenance and continuous development of its integrated management system.

In addition, since 15.07.2009 SAM Medicines Examination Laboratory has been accredited in accordance to the ISO/IEC 17025:2005 standard "General requirement for the competence of testing and calibration laboratories". On November 9th 2012 a LATAK supervision visit took place. The accreditation field: "Physical and physicochemical testing of medicinal products, veterinary medicinal products and active substances, physical testing of purified water."

The interactive map of pharmacies in Latvia developed by SAM in 2011 and publicly available on SAM website was nominated for the international contest "Quality Innovation Award 2012". This year the contest was organised in Finland, Estonia, Latvia and Sweden. In November 2012 SAM received the Quality Innovation Award 2012 as the winner from Latvia in the public sector category.

In accordance to the full transposition of the requirements of the Directive 2010/84/EU of the European Parliament and of the Council of December 15th 2010 and related amendments to normative acts SAM will have to regularly perform a pharmacovigilance system audit. To implement the requirement of the aforementioned Directive in accordance to conditions set forth in Section 5, Article 6 of the Internal Audit Law, a position for a supervisory auditor was established in SAM in 2012.

4.5. Development of Information Technologies

In 2012 work was continued to improve support processes for SAM information technologies (IT). The following State significance information systems and information systems under the supervision of SAM have been supplemented or partially reconstructed: SAMIS, MD Register LATMED, portal for receiving electronic documentation, system for management of records and personnel. The export of data regarding medicinal products and pharmacies to the e-Health platform has been ensured. The electronic format of the annual publication "Drug Register" has been improved - a convenient search form has been developed and summaries of product characteristics and patient information leaflets have also been added. SAMIS data export to EU central register of medicines EudraPharm was continued. Work was begun on the development of a patient form for reporting adverse drug reactions and on the improvement of the search form of the drug register on SAM website www.zva.gov.lv.

In the year of review work was done on the improvement of the SAM IS security by both updating technical devices and participating in the introduction of the SAM Information Security Management Policy within the ISO 27001:2005 standard.

In the context of long-term cost reduction SAM continued to work on combining the information technology resources available to SAM and to the Ministry of Health, thus, even further decreasing the number of physical and logical units employed in the field of health.

4.6. International Cooperation

SAM is a part of the European Medicines Regulatory Network 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 45 medicines regulatory institutions within the European Union and the European Economic Area (EEA). This network of cooperation gives EMA access to a great number 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 un scientific advisory groups, scientific committees, as well as other groups.

This puts a great responsibility upon SAM to ensure that our colleagues can fully participate in the collective work procedures. It should also be mentioned that the cooperation requires human and financial resources from SAM. SAM staff members are also involved in cooperation with 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).

In 2012 SAM Administration took a more active part in the Heads of Medicines Agencies (HMA) organisation by becoming a member of the HMA Management Group.

Since 2010 SAM has also been involved in the supervision of medical devices, blood and its components, tissue 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). The newly established 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 EMA and the State Agency of Medicines in Estonia and Lithuania. To promote cooperation between the medicines agencies of the Baltic States, a meeting of the representatives of the medicines agencies of the Baltic States took place in November 2012 in SAM. During the meeting the Heads of the medicines agencies of the Baltic States signed a contract on mutual cooperation and employee training.

On June 25th 2010 a memorandum of agreement was signed between the State Agency of Medicines of the Republic of Latvia and the Food and Drug Administration of the People's Republic of China regarding cooperation in normative regulation of medicines. The possibilities for future cooperation of both countries in the pharmaceutical field were discussed in 2012 by participating in the discussion between the Ministry of Health and the State Food and Drug Administration of China

5. COMMUNICATION WITH STAKEHOLDERS (PUBLIC, HEALTHCARE PROFESSIONALS, MERCHANTS)

In 2012 significant effort has been invested in the development and maintenance of external communication. 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.

It has to be noted that during the year of review significant work has been done in the preparation for implementation of EU normative act requirements on a national scale relating to the rights of the patient to submit reports about an observed adverse drug reaction. Not only did SAM begin working on updating the appropriate sections of SAM website regarding issues of monitoring safety of medicines and participate in the development of an electronic form for patients, but SAM also completed all preparations for the introduction of an informative campaign "Reveal the other side of medicines", thus, raising public discussions on the safe use of medicines.

In the year of review 26 press releases were prepared and forwarded to the mass media representatives, responses were provided to more than 142 journalist queries. Replies were prepared and provided to 138 questions from residents, as well as to more than 59 requests for information from subjects of the Ministry of Health, healthcare institutions and SAM clients. Information was updated on SAM website and in the Latvia State portal www.latvija.lv (information on SAM public services). In total SAM communication with the mass media includes more than 154 news articles in different types of mass media.

SAM publications according to topic

Topic of publication	Number of publications
Safety of medicines	24
The market, consumption and price of medicines	26
Price of medicines verification form	4
Digital map of pharmacies	9
SAM operations, collaboration and budget	3
Availability of medicines	18
Number of pharmacies, authorisation of pharmacies	2
Clinical trials	5
Normative acts	10
Other	53

In 2012 SAM prepared several informative publications in order to inform doctors, pharmacists and other healthcare professionals about 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 provides updated, objective, verified and concentrated 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 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 Drug 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 Drug 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 Drug Register was prepared in a DVD format containing summaries of product characteristics and patient information leaflets. A convenient information search form has been developed for this format. No internet connection is necessary to use this version in the daily work. The summary of product characteristics included in the electronic version of the Drug Register helps doctors and pharmacists to choose the most appropriate medicines for the patient, as well as 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 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 2005 until 2011 (according to DID - defined daily dose per 1000 inhabitants of Latvia per day).

In 2012 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 the World Medical Association with the newest amendments an information sources for healthcare professionals.

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 patient information leaflets in DVD format	500
SAM Annual Report (in Latvian and English)	100
Publication „Good Clinical Practice"	200

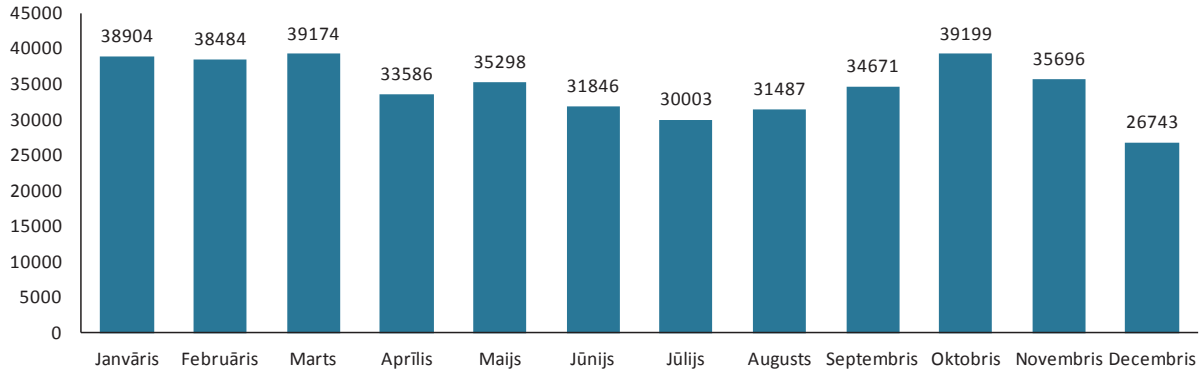
Along with the cooperation with mass media and informative publications, in February 2012 SAM participated in a "Job Shadow Day" project organised by Junior Achievement Latvia, thus, not only promoting pupil understanding of the daily work of the state administration, but also motivating them to choose further studies and employment options in the exact sciences. During the project 11 "shadows" visited SAM coming from not only Riga, but also from Aluksne, Preili and Liepaja. The pupils became acquainted with the daily work of employees in the Clinical Trials Department, Department of Information of Medicines Distribution, Pharmaceutical Activities Company Licensing Department, Adverse Drug Reaction Monitoring Department and Pharmaceutical Activities Adequacy Evaluation Department.

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 newest issues in the field of pharmaceutics. According to Google Analysis statistical data in 2012 SAM website has been visited 415 091 times and sections of the website have been browsed a total of 1 881 789 times. The results indicate that the average number of first time visitors of the SAM website per month is approximately 8 100.

Intensive work on the development of SAM website is planned for 2013 by transforming 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.

Website visitors in 2012



To enquire the opinion of the website visitors, 2 surveys were conducted in 2012 and replies from 406 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:

- Do you inform your doctor about adverse reactions to medicines?
- What information you pay most attention to in the patient information leaflet of medicines?

SAM external communication activities are not based solely on a one-way provision of information, but SAM also provides the opportunity for SAM cooperation partners to express their opinion about the quality of SAM client service and provided services. The received information is used for the improvement of SAM operations quality. In 2012 SAM organised 2 surveys:

- a survey for clients regarding SAM operations and provided services in order to improve the quality of client service and provided services according to the gathered data;
- a 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!

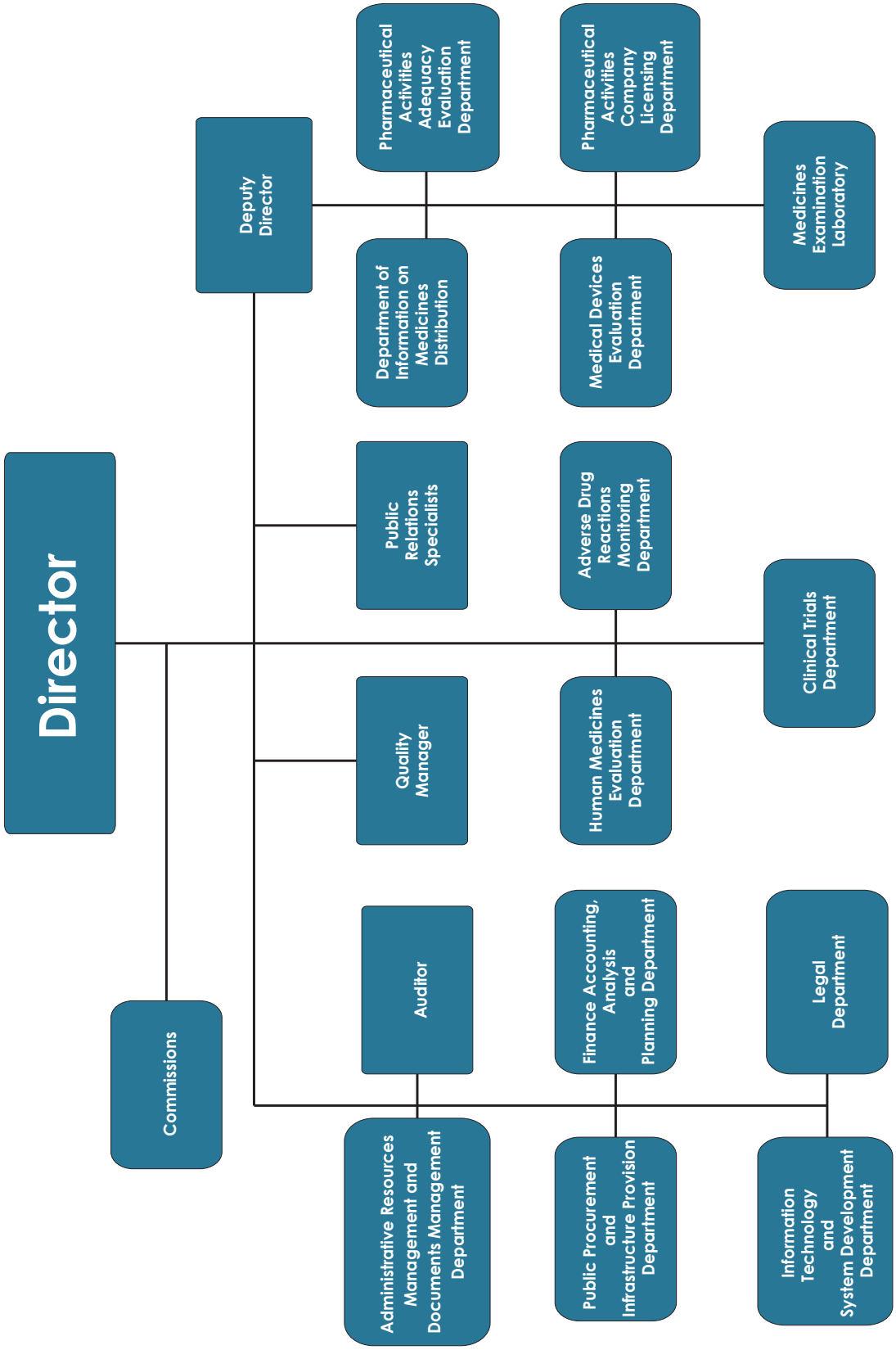
6. DEVELOPMENTAL PRIORITIES OF THE STATE AGENCY OF MEDICINES FOR 2013

The operational plan of the State Agency of Medicines for the year 2013 was approved on January 18th 2013. Taking into account the functions and tasks assigned to the State Agency of Medicines, the operational plan assigns specific tasks for each structural unit and the institution as a whole. In addition to the main operations of SAM the following objectives have been set as priorities for 2013:

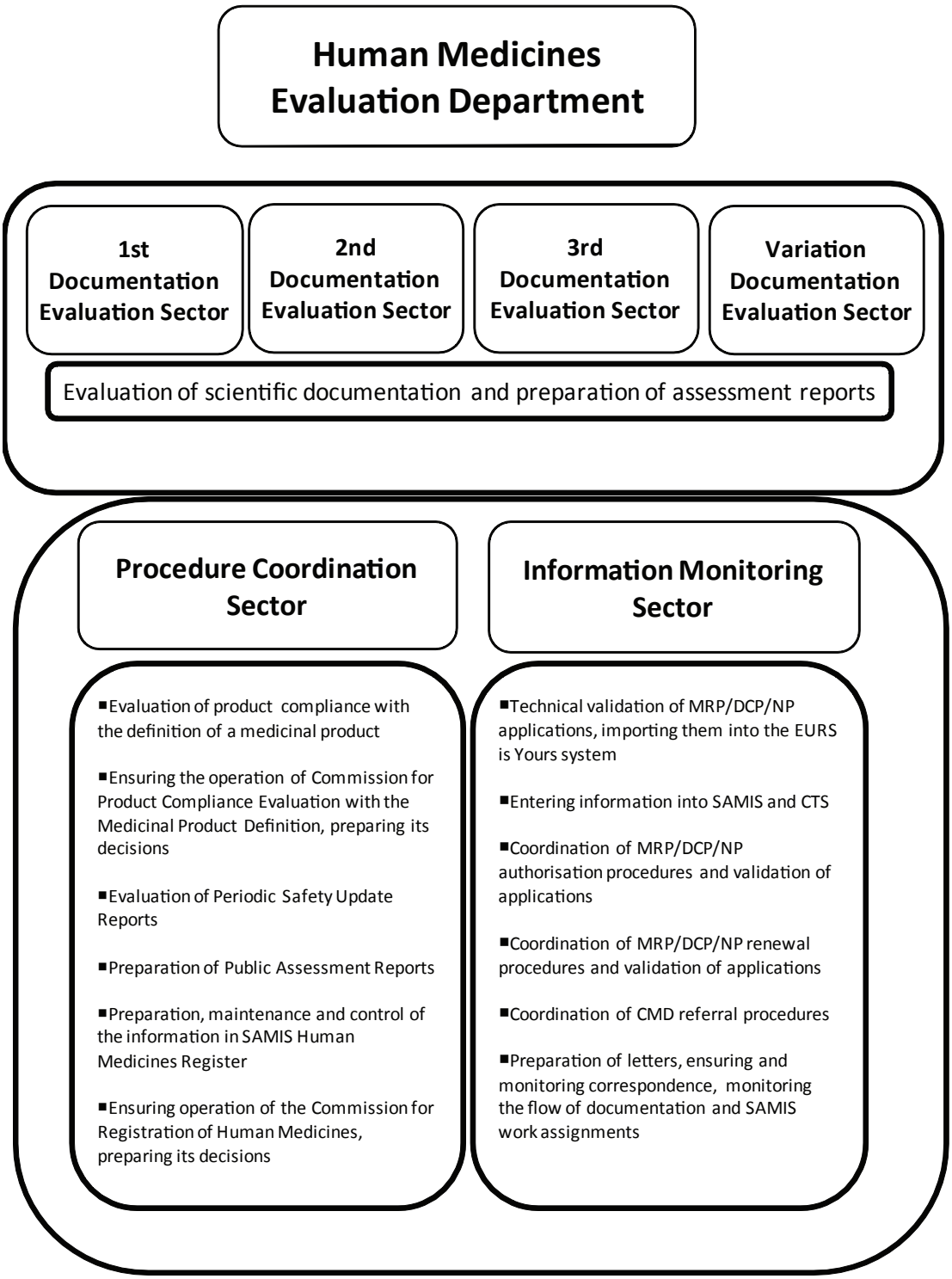
- begin operation as a public agency - an institution non-financed from the state budget;
- actively participate in MRP/DCP procedures by assuming the responsibilities of the Reference Member State;
- increase the involvement in CAP procedures by assuming co-rapporteur responsibilities;
- promote and develop cooperation with academic and scientific institutions;
- ensure the requirements of the new Pharmacovigilance normative acts, including pharmacovigilance system compliance inspections after they are defined in normative acts;
- actively participate in e-Health projects and ADAS;
- improve the circulation of electronic marketing authorisation documentation (e-CTD) and participate in the use of the Common European Submissions Platform (CESP);
- ensure 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);
- more actively participate in the EMA operation, in work-sharing programs within the Heads of Medicines Agencies network, in WHO programs;
- ensure and coordinate the development of the list of active substances and excipients in Latvian
- complete preparations for and ensure the BEMA III visit in he 1st quarter of 2014;
- update and review SAM internal procedures to increase work effectiveness;
- development of electronic communication with collaboration partners.

ANNEXES

Annex 1 - SAM Structure



Annex 2 - Structure of the Human Medicines Evaluation Department



Annex 3 - Functions of SAM structural units

HUMAN MEDICINES EVALUATION DEPARTMENT

- Performs marketing authorisation and renewal of medicines in the national, mutual recognition and decentralised procedures and accepts the submitted variations to documentation.
- Carries out expertise on chemical and pharmaceutical, pharmacological and toxicological documentation of medicines, on clinical trials, summaries of product characteristics, patient information 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 variation to parallel imported medicines in Latvia.
- Carries out expertise on applications and documentation and issues special permits (licences) for working 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 registration at 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. That includes approving the risk minimisation measures included in the risk management plan of the marketing authorisation holder and monitoring their results, as well as evaluating updates of risk management systems for medicines.
- Initiates compliance evaluation of the marketing authorisation holder with good pharmacovigilance 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 promote 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 foreign countries by determining the compliance of samples of medicines with the requirements of normative documentation submitted for authorisation.
- Carries out the selection and testing of purified water samples from pharmacies.
- Prepares volumetric solutions, indicators and reagents upon request from pharmacies.

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 trial procedure.
- 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 under such risks. Supervises corrective safety measures.

PHARMACEUTICAL ACTIVITIES COMPLIANCE EVALUATION DEPARTMENT

- Evaluates the compliance of the activity of pharmaceutical companies (human medicines manufacturing/importing companies, including foreign manufacturing companies, medicines wholesalers) 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 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 the property of SAM.

LEGAL DEPARTMENT

- Ensures the compliance of administrative acts devised 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 devises administrative documents regulating SAM operations.
- Legally solves legal issues and problems.
- Prepares and evaluates contracts, documentation projects, various opinions.
- Devises 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 personnel.
- Manages all issues regarding personal files and ensures the documentation of civil service and legal employment relationship in accordance to 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 the 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.

SUPERVISORY AUDITOR

- Develops 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.

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 SAM corporative identity.

Annex 4 - The State Agency of Medicines in dates

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
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)
1997	The publication of the annual issue "Drug Register of Latvia" is initiated
1998	The electronic record keeping program "Lotus Notes" is introduced
02.03.1998.	Clinical Trial Inspection Department is established
1999	The first Annual Report is published
1999	The first SAM website is developed
End of 2000	The second section of the agency building is commissioned
2000	International Harmonisation Conference guidelines regarding Good Clinical Practice are published (in Latvian and English)
2001	The preparation of an independent informative bulletin "CITO" for doctors and pharmacists is initiated
From 02.01.2001. until 31.12.2009.	The function of evaluating and approving advertisements of medicines is carried out.
02.01.2001.	Adverse Drug Reactions Monitoring Department is established
01.10.2002.	Internal audit is introduced and the development of a Quality Management System is initiated
17. - 18.03.2002.	The 5th European Union meeting of associated drug regulatory authorities takes place in Latvia - within the CADREAC cooperation agreement
2002	The Medicines Examination Laboratory is welcomed into the international network of Official Medicines Control Laboratories (OMCL)
2002	The SAM is welcomed into the WHO International Drug Monitoring Program as the 66th member state
2003	The first Benchmarking visit (BEMA) in the SAM
2003	The first edition of "Statistics on Medicines Consumption" is published
01.07.2003.	Legal Department is established
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
2004	Access to and unified operation in databases of EU member states is established via the EudraNET network
End of 2004	The Archive building is commissioned
2005	An educational publication "Introduction to Pharmacovigilance" is issued
25.04.2005.	Jānis Ozoliņš, the Director of SAM, tragically passes away
02.11.2005.	The Cabinet of Ministers of the Republic of Latvia appoints (Order No. 707) Inguna Adoviča as the Director of SAM
End of 2005	A new function is delegated to SAM - to develop and maintain a system for the monitoring of prices of medicines
2006	For the first time the evaluation of staff member operations and results is initiated and performed
2006	Participation within PIC/S is initiated
02.01.2006.	The Information Department is transformed and the Department of Information on Medicines Distribution and the Information Technology Department are established
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. – 31.12.2010.	The authorisation of veterinary medicines and monitoring their circulation is delegated to SAM
10.04.2006.	The pharmaceutical Activities Compliance Evaluation Department is established
06.-10.02.2006.	The European Union Benchmarking (BEMA I) takes place
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

10.11.2006.	A meeting of the State Agencies of Medicines of the Baltic states takes place in Riga
Dec-06	The technological updating and structural modification of the Drug Register is carried out and SAM Information System SAMIS is developed
01.02.2007.	Civil service is introduced at SAM
11.07.2007.	Memorandum of agreement with Estonia regarding cooperation in monitoring of medicines
09. – 12.2007.	The concept for the e-prescription information system is developed
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
2008	The first Mutual Recognition Procedure was carried out where Latvia was the Reference Member State
14.01.2008.	Memorandum of agreement with Lithuania regarding cooperation in monitoring of medicines
19.09.2008.	Recognition from the Riga City Council for original front lawn greenery
15.07.2009.	The Medicines Examination Laboratory is accredited in accordance to the ISO/IEC 17025:2005 standard
11.08.2009.	Contract between the Baltic State Agencies of Medicines regarding a united packaging of medicines in three languages
01.02.2010.	Establishment of a Client Service Centre
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
09.07.2010.	Memorandum of agreement with EMA regarding mutual exchange of information and documentation
06.-08.09.2010.	The EU Benchmarking (BEMA II) takes place
01.10.2010.	The function of compliance evaluation, authorisation and monitoring of safety of medical devices is adopted
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
02.02.2011.	Contract between the State Agencies of Medicines of the Baltic States regarding a unified procedure for labelling medicines
16.05.2011.	The first digital map of pharmacies with broad search options is developed on SAM website
19.07.2011.	The list of active substances is published on SAM website in three languages: Latvian / Latin / English
From 26.08.2011. until end of October	Participation as co-rapporteur in the EMA Committee for Advanced Therapies repeated review by authorising the newly introduced therapeutic 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"
13.10.2011.	The Baltic State Agencies of Medicines sign an agreement regarding cooperation in quality control of medicines
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"
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
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
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
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
19.12.2012.	The SAM integrated management system is certified in accordance to ISO/IEC 9001:2008 standard
21.12.2012.	The SAM integrated management system is certified in accordance to ISO/IEC 27001:2005 standard

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