State Agency
of Medicines
Republic of Latvia

STATE AGENCY OF MEDICINES

ANNUAL REPORT

2016

CONTENT

FOREWORD

Svens Henkuzens,
Director of the State Agency of Medicines

Dear readers,

As every year, the State Agency of medicines has prepared an overview of the accomplishments in the field of medicinal products, human blood, tissues, cells and organs, as well as pharmaceutical activity.

In addition to the performance of principal functions, the following priorities were set for 2016: firstly, the issue regarding minimising the impact of risks created by disruptions in the supply of medicines, secondly, resources were allocated for strengthening communication with the pharmaceutical field and the public, thirdly, attention was brought to the improvement of information technologies and their effective utilisation.

In order to minimise the impact of disruptions in supply of medicines on the supply chains and provision of medical treatment, a convenient catalogue of disruptions in supply of medicines was established last year. Every month approximately 300 Agency website visitors use the option to receive updated information on a medicinal product affected by disruptions in supply and the estimated date for renewal of supply, as well as to search for alternative medicines, report online a potential disruption in supply of medicines to the Agency and other functionalities.

Last year, supervision was initiated over various remaining stocks of medicines at wholesalers and pharmacies (for example, stocks of seasonal influenza vaccines), in order to promptly coordinate communication with parties involved in the supply chain and minimise potential risks to the public health.

In 2016, we have strengthened communication with the public regarding rational use of medicines. Taking into account how important the issue of cost of medicines is to patients, we have made the extra effort to inform the public on treatment options without overpaying.

Special attention will be paid to the issues of affordability and accessibility of medicines also in 2017. Similarly, we have promoted collaboration with clients and a client-oriented approach, as well as improved the quality of services, and we are proud of the positive client assessment. According to the data from the client survey in 2016, more than 90% of Agency clients gave a positive assessment of the quality of services provided, employee competency and responsiveness.

With regard to the improvement of information technologies, we have introduced a variety of changes in the internal processes to increase circulation of electronic documents and use the opportunities to increase process efficiency. In comparison to 2015, last year the proportion of electronic documents at the Agency increased by 51%, and we aim towards an even greater circulation of electronic documents in 2017. This allows not only optimisation of tasks and resources, but also promotion of process transparency.

During the period or review continuous development of the quality management was continued, and at the end of 2016 it was assessed as compliant with the new 2015 ISO 9001 standard and the ISO/IEC 27001:13 information security standard.

Regular invitations for Latvia to assume the position of a reference member state in European marketing authorisation procedures and take the lead in evaluation procedures is an acknowledgement of the high level of competence and esteem of Agency experts among field professionals. In 2016, Agency experts were trusted with four centralised authorisation procedures in the European Union where the Agency took the role of the main rapporteur in the evaluation of medicines, and in one case Agency was the co-rapporteur. We have also taken the leading role – rapporteur and co-rapporteur respectively – in two procedures at the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA). In 2016, for the first time Agency's clinical trial experts took the leading role in the assessment of an international clinical trial within the Voluntary Harmonisation Procedure.

It has to be noted that last year was the 20th anniversary of the foundation of SAM. In 2016, we also organised the annual meeting of the Baltic medicines agencies, giving us the opportunity to discuss important regulatory issues in the pharmaceutical field within the region, as well as to agree on collective tasks in all of the Baltic states. This was the first time that non-governmental organisations (NGOs) in the field participated in the meeting; the NGOs represented medicines manufacturers and wholesalers - Association of International Research-based Pharmaceutical Manufacturers (SIFFA) from Latvia, Association of Pharmaceutical Manufacturers (APME) from Estonia, Innovative Pharmaceutical Industry Association (IFPA) from Lithuania. They discussed the issues that will have a direct impact both on the field and on patients in the near future – the implementation of the Directive of the European Parliament and of the Council regarding prevention of the entry into the legal supply chain of falsified medicinal products. The meeting included also the presentation of the publication *Baltic Statistics on Medicines 2013-2015* prepared by Agency experts regarding statistics of consumption of medicines in Latvia, Lithuania and Estonia during the previous three years.

I invite you to see in more detail the important information published in this report regarding the achievements of the Agency in 2016!

ABBREVIATIONS USED IN THIS REPORT

BEMA	Benchmarking of European Medicines Agencies
CHMP	EMA Committee for Medicinal Products for Human Use
CPP	Certificate of Pharmaceutical Product
CRP	Centralised authorisation procedure
DCP	Decentralised authorisation procedure
EC	European Commission
EMA	European Medicines Agency
EU	European Union
ISO	International Organization for Standardization
LATMED	Electronic database of the Register of Medical Devices
MD	Medical device
MH	Ministry of Health
MRP	Mutual recognition procedure
NP	National procedure
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PRAC	EMA Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SAM	State Agency of Medicines
SAMIS	State Agency of Medicines information system
WHO	World Health Organization

1. ABOUT THE STATE AGENCY OF MEDICINES

1.1. Legal Status of the State Agency of Medicines

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

SAM was established on 9th October 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"".

The objective of SAM

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

1.2. Functions of the State Agency of Medicines

SAM performs the following tasks:

- Evaluation and authorisation of medicines, expertise on quality of medicines, development and updating of the Medicinal Product Register of the Republic of Latvia;
- Pharmacovigilance;
- Issuance of authorisations for conduct of clinical trials with medicinal products, compliance evaluation of clinical trials with good clinical practice requirements, as well as evaluation of applications for non-interventional studies of medicines;

- Issuance of authorisations for import, export, transit, distribution and purchase (to ensure own 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;
- Regular assembly and distribution of information regarding consumption of medicines;
- Issuance of authorisation cards for precursor operators and special permits (licences) for operation with precursors;
- Authorisation of medical devices manufactured in Latvia, issuance of authorisations for placing specially supplied medical devices on the market, as well as vigilance for medical devices;
- Issuance of authorisations for conduct of clinical trials with medical devices;
- Issuance of compliance certificates to procurement and storage (utilisation) organisations of human tissues, cells and organs, blood establishments, hospital blood banks and the State Blood Donor Centre;
- Issuance of special permits (licences) for pharmaceutical activity;
- Issuance of good manufacturing practice compliance certificates;
- Evaluation and inspection of compliance of active substance manufacturers and importers with the requirements of good manufacturing practice and issuance of good manufacturing practice certificates;
- Evaluation and inspection of compliance of active substance distributors with the requirements of good distribution practice and issuance of good distribution practice certificates;
- Registration of manufacturers, importers and distributors of active substances;
- Registration of persons conducting international business transactions (brokers) with medicines for human use;
- Participation in the unified systems of medicines and medical devices agencies in the member states of the European Economic Area, cooperation with European institutions and international organisations by participating in work-sharing and complying with the collective standards and procedures;
- Collaboration with professional organisations of doctors and pharmacists, non-governmental organisations in the field, foreign and international institutions, as well as ensuring mutual exchange of information in the areas of operation of SAM;
- Fulfilment of the tasks of the competent authority in accordance with the requirements laid down in the normative acts of the European Union.
- Operation in the European medicines agencies' network by participating in work-sharing and complying with the collective standards and procedures, cooperation with other European and international organisations.

1.3. Main Tasks in the Year of Review

In 2016, the State Agency of Medicines operated in accordance with the previously determined priorities that were important for the implementation of the institutional strategy with regard to the public health, as well as development of the Agency and improvement of the quality of services, including provision of the prerequisites for the safe and rational use of medicines, medical devices, tissues, cells, organs, blood and blood components and improving the operational efficiency of the Agency.

In 2016, special attention was paid to:

- Availability of safe, qualitative and effective medicinal/healthcare products
- Ensuring objective information, communication and cooperation
- Efficacy of the operation of the State Agency of Medicines

By operating within the framework of normative acts, as well as by submitting proposals for their improvement within the range of possibility, SAM promoted availability of new medicinal products, at the same time contributing to the safety of medicinal products and healthcare products.

In 2016, according to its authorisation, the State Agency of Medicines ensured easily available and qualitative information to cooperation partners, professionals in the field and the public, drawing more attention to the rational use of medicinal products and news in the field. SAM promoted reporting of adverse events related to any kind of medicinal product.

In addition, the State Agency of Medicines directed special attention to the development of human resources and technologies. The basis of any organisation is the professionals working within it, and it is necessary to continuously promote their growth, develop their cooperation with field experts and educational institutions. By ensuring this, the State Agency of Medicines also ensured competitive pay, quality of work environment, decreasing of the administrative burden, rationality and transparency of processes.

In the Benchmarking of the European Medicines Agencies (BEMA) national agencies are assessed and compared with each other in accordance with pre-defined unified criteria. The BEMA IV visit in Latvia is set to take place at the end of 2017.

2. RESULTS OF OPERATION OF THE STATE AGENCY OF MEDICINES

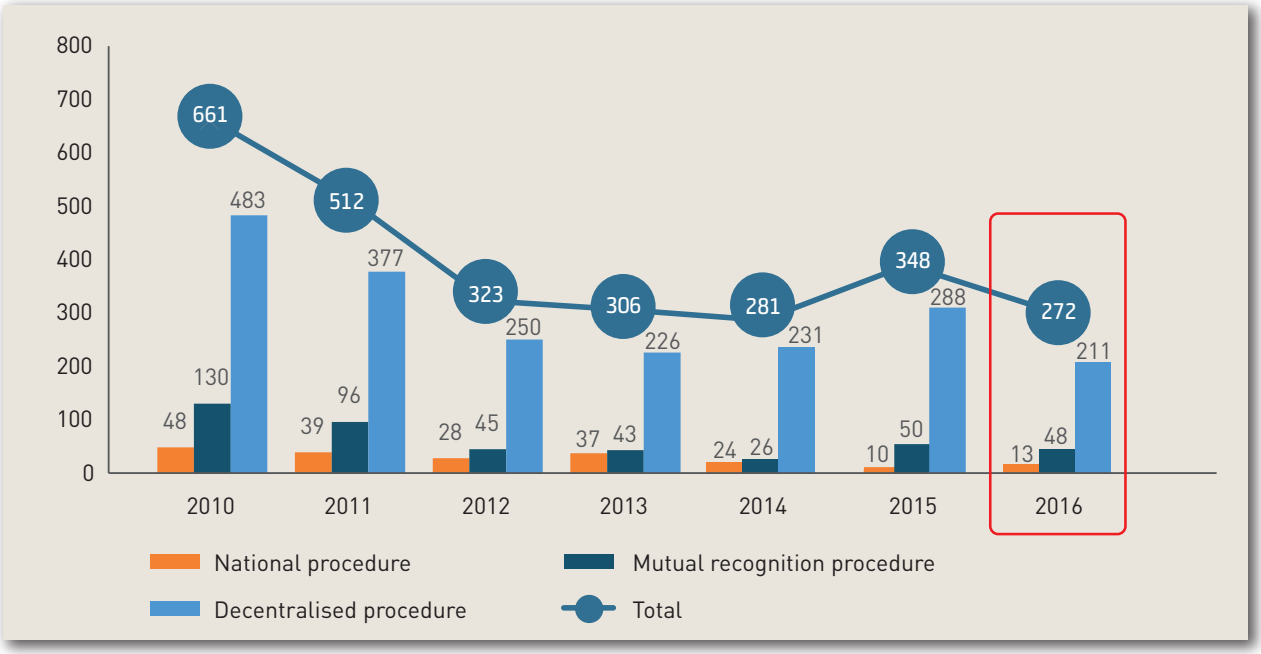
2.1. MEDICINES

2.1.1. Marketing Authorisation of Medicines

In accordance with the Cabinet of Ministers Regulation No. 376 of 23 June 2006 "Procedure for Registration of Medicinal Products" and other legal acts, in 2016, by evaluating medicinal product documentation with regard to quality, safety and efficacy the State Agency of Medicines conducted expertise on more than 8000 applications for marketing authorisation, renewal and variations to medicinal product marketing authorisation documentation. General, chemical and pharmaceutical, as well as pre-clinical and clinical sections of the documentation were evaluated.

In 2016, assessment reports regarding 35 medicinal products were prepared for the SAM Commission on Marketing Authorisation of Human Medicines for the adoption of decision regarding marketing authorisation and renewal of medicines in the national procedure. In 2016, Latvia successfully led three mutual recognition procedures (MRP) and five decentralised procedures (DCP), as well as two MRP renewal procedures as a Reference Member State. Also in 2016, Latvia

Marketing authorisation of medicines

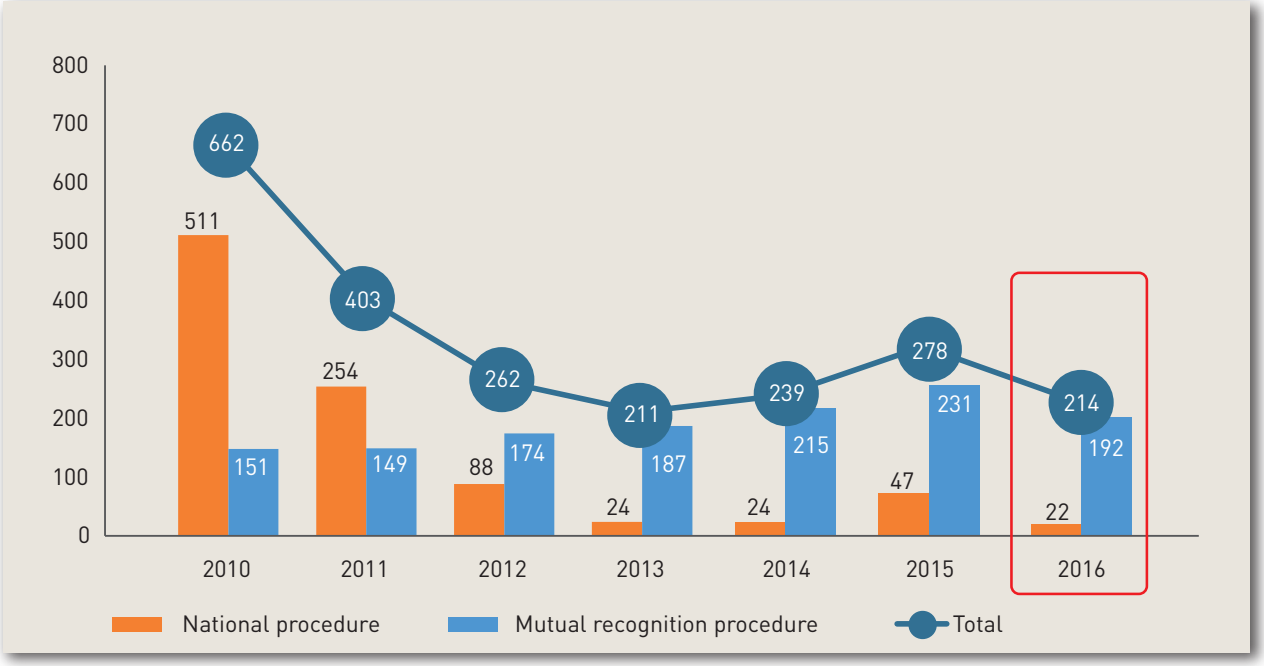


took over four DCP procedures from other member states, thus, becoming the Reference Member State for these procedures. In 2016, Latvia initiated and continued four DCP procedures and one MRP procedure as a reference member state.

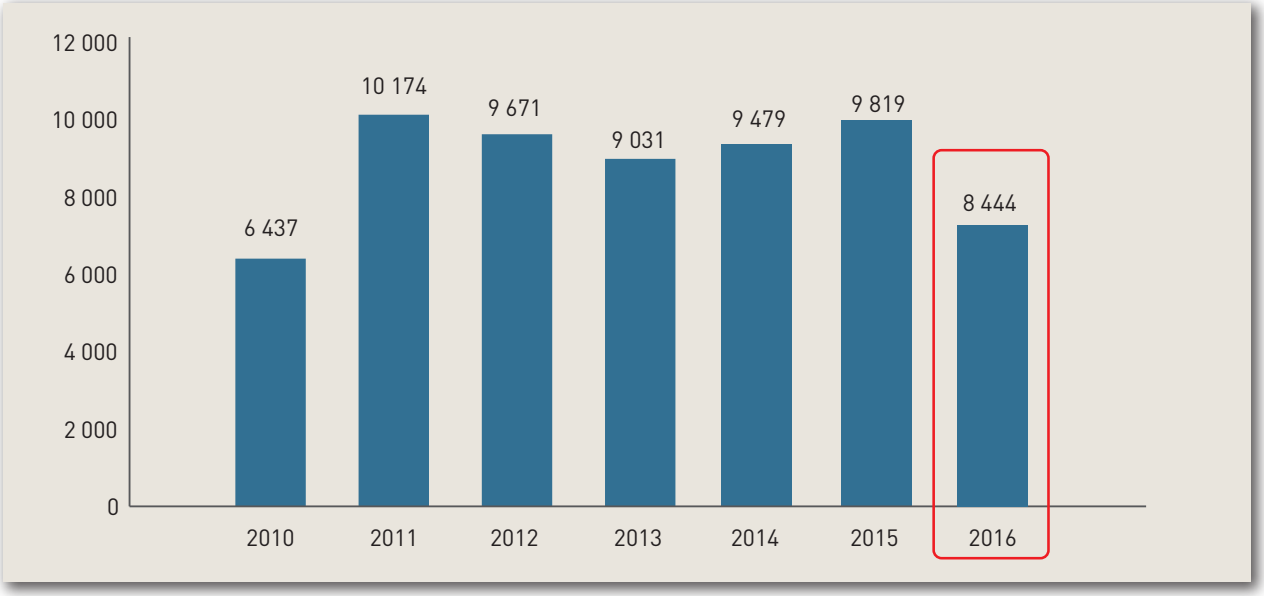
In 2016, the State Agency of Medicines carried out a total of 259 MRP/DCP authorisation procedures and 192 renewal procedures, as well as approved 8444 variations to marketing authorisation documentation.

In the year of review, SAM expert activity in international procedures was relatively higher than in the previous year. In 2016, Latvia participated in the EMA Committee for Medicinal Products for Human Use (CHMP) by evaluating six centralised marketing authorisation procedures. In two of these centralised marketing authorisation procedures SAM fulfilled the peer review

Renewal procedure of medicines



Variations to the marketing authorization procedure



function, in three of the procedures SAM was the responsible rapporteur, and in one procedure - co-rapporteur. Latvia was the responsible rapporteur for two type II variation procedures for centrally authorised medicinal products and participated in a review procedure of a centrally authorised medicinal product as the responsible rapporteur of the Pharmacovigilance Risk Assessment Committee (PRAC).

Latvia was the leading member state in the single assessment procedures of periodic safety update reports (PSUR) regarding two active substances. Latvia is represented within the EMA Paediatric Committee and participated in 8 primary Paediatric Investigation Plan (PIP) assessment procedures, 5 PIP modification assessment procedures and in 4 EMA Scientific advice preparation procedures.

In 2016, as part of an international team, an expert from the SAM Medicines Marketing Authorisation Department participated in compliance inspections of the analytical section of bioequivalence studies in foreign countries for two medicinal products intended for centralised marketing authorisation.

Experts from the Medicines Marketing Authorisation Department together with external experts have actively participated in the work of the Committee on Herbal Medicinal Products. In 2016, evaluation of the Union monograph on *Ribes nigri folium* was carried out.

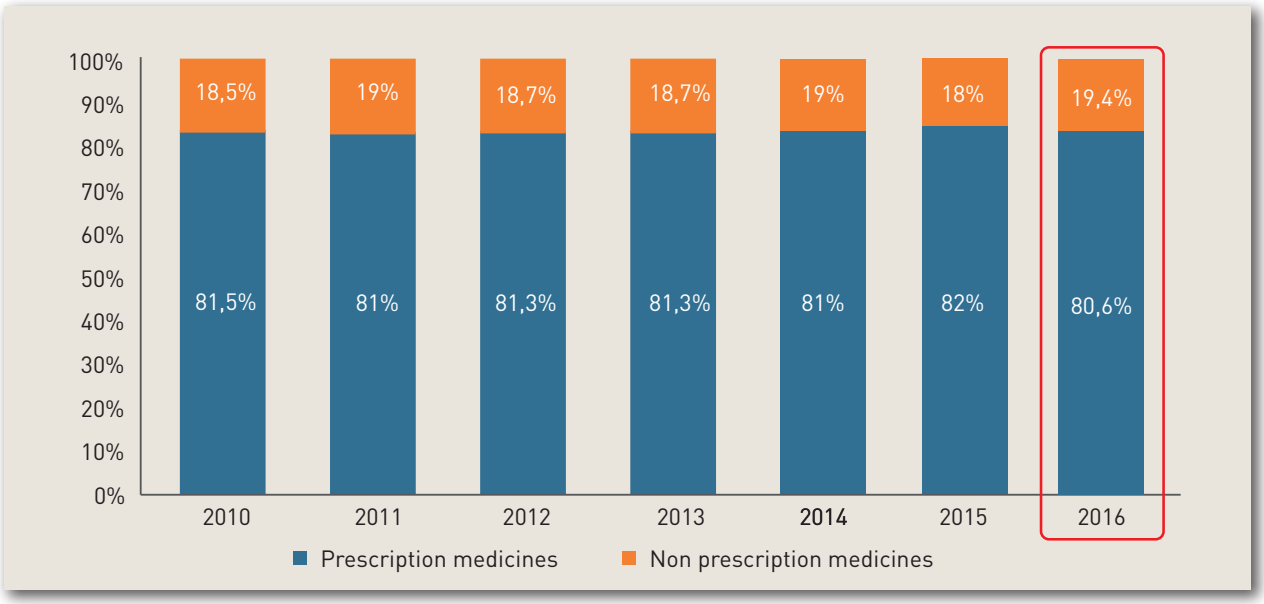
Last year, in collaboration with professor Maris Baltins, Director of the State Language Centre, SAM experts created the translation of the first three levels of the Anatomical Therapeutic Chemical (ATC) classification, thus, creating an accurate and precise Latvian equivalent of the English terminology. The ATC code classification is available on SAM website www.zva.gov.lv, in the section "Register" > "Classifier of ATC".

In the year of review, 18 applications were received for the evaluation of product compliance with the definition of a medicinal product and SAM issued its opinion regarding the status of these products.

Twenty-two public assessment reports for nationally authorised medicines were prepared, coordinated with marketing authorisation holders and published in 2016.

The proportion of prescription and non-prescription medicines included in the Medicinal Product Register of Latvia has

The proportion of prescription and non-prescription medicines



remained unchanged from year to year – with approximately 80% prescription medicines and 20% nonprescription medicines. In 2016, the precise proportion was 80.6% and 19.4%.

2.1.2. Issuance of Authorisations for Distribution of Medicines

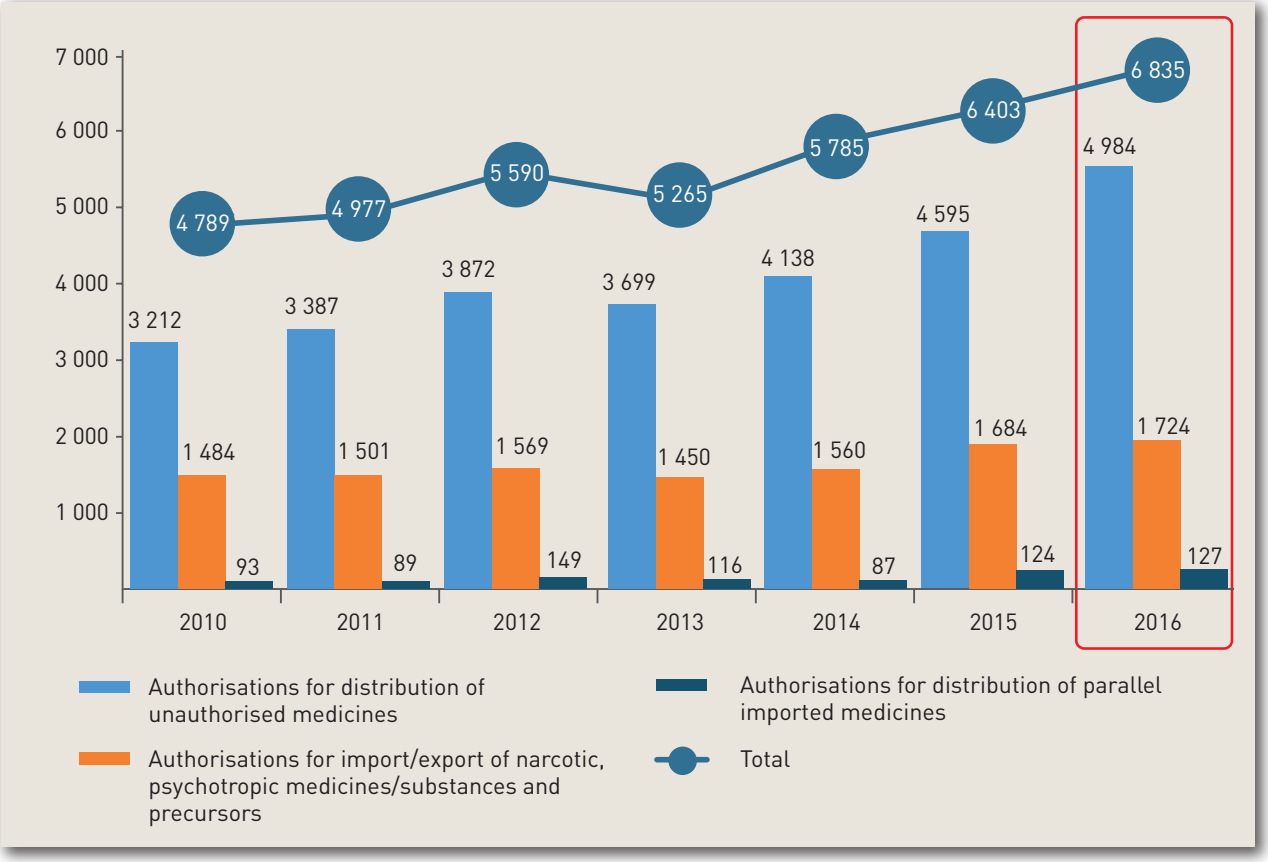
In 2016, SAM ensured expertise on applications and documentation in the field of distribution of medicines:

- Import and export of psychotropic, narcotic medicines/substances and precursors
- Distribution of unauthorised medicines
- Import of samples of medicines
- Distribution of parallel imported medicines in Latvia and their variations

In 2016, upon request SAM issued 6854 authorisations for import, export, transit and distribution of medicines. In addition, SAM carried out expertise on applications and documentation, as well as issued 8 licences and authorisation cards to precursor operators and seven authorisations 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. Last year, variations were made to distribution authorisations of 287 parallel imported medicines.

Information regarding consumption and price of medicinal products was assembled monthly

Number of authorisations for import, export and distribution of medicines from 2010 until 2016



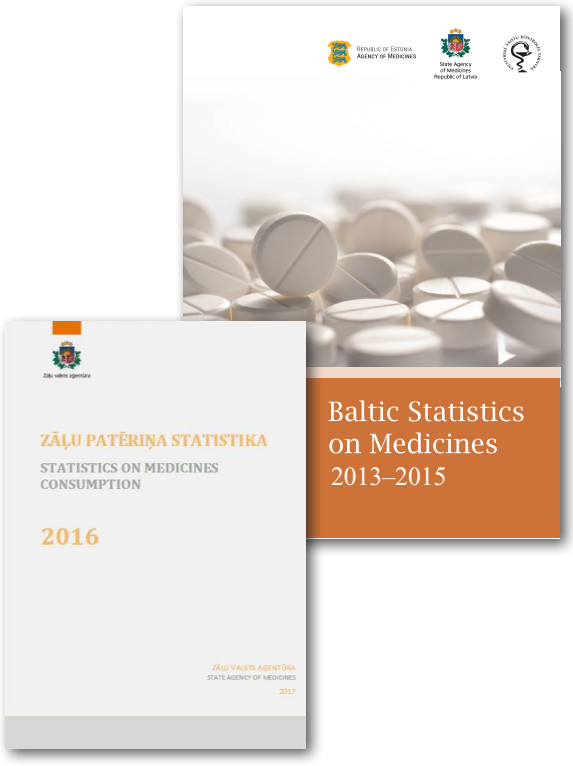
and published on SAM website www.zva.gov.lv. List of disruptions in the supply of medicines was established last year, and it is publicly available in the "Register" section of SAM website. Public involvement was ensured in the provision of information regarding disruptions in the supply of medicines via a report form available on SAM website.

In 2016, SAM ensured also the accountancy and control of legal circulation of narcotic substances, psychotropic substances and precursors controlled in Latvia. 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 was prepared and forwarded to the International Narcotics Control Board (INCB). A quarterly report on the circulation of illegal precursors and an annual report on the circulation of legal precursors was prepared and forwarded to the European Commission.

The data on consumption of medicines published in the book were analysed using the ATC classification system, the international unit for consumption of medicines was DDD (defined daily dose used for the main indication in an adult patient), and the data on consumption of medicines were expressed in DID units.

The annual publication "Statistics on Medicines Consumption" was prepared, based on the statistical information regarding sales of medicines submitted by wholesalers. The report includes information regarding total turnover of medicines in euros, number of packages sold, distribution of the turnover according to different consumer groups, dispensing status, turnover of medicines expressed in defined daily doses (DDD) per 1000 inhabitants of Latvia per day (DID). Information was also provided regarding the highest selling medicines in Latvia and further information was provided about the market of medicines manufactured in Latvia. The publication is available on the website of SAM, in the section "Publications" > "Statistics of Medicines Consumption".

As a result of cooperation between the medicines agencies of the Baltic States, a new publication "Baltic Statistics on Medicines 2013-2015" was released. It includes data regarding consumption of medicines in Latvia, Estonia and Lithuania during the previous three years, as well as information regarding the market of medicines, regulatory requirements and reimbursement systems in these countries. We invite you to see the electronic version of "Baltic Statistics on Medicines 2013-2015" on SAM website www.zva.gov.lv, in the section "Publications" > "Baltic Statistics on Medicines". The first publication "Baltic Statistics on Medicines 2010-2012" summarising the data regarding consumption of medicines in the Baltic States was issued in 2013, and is also available on SAM website.



2.1.3. Clinical Trials with Medicines

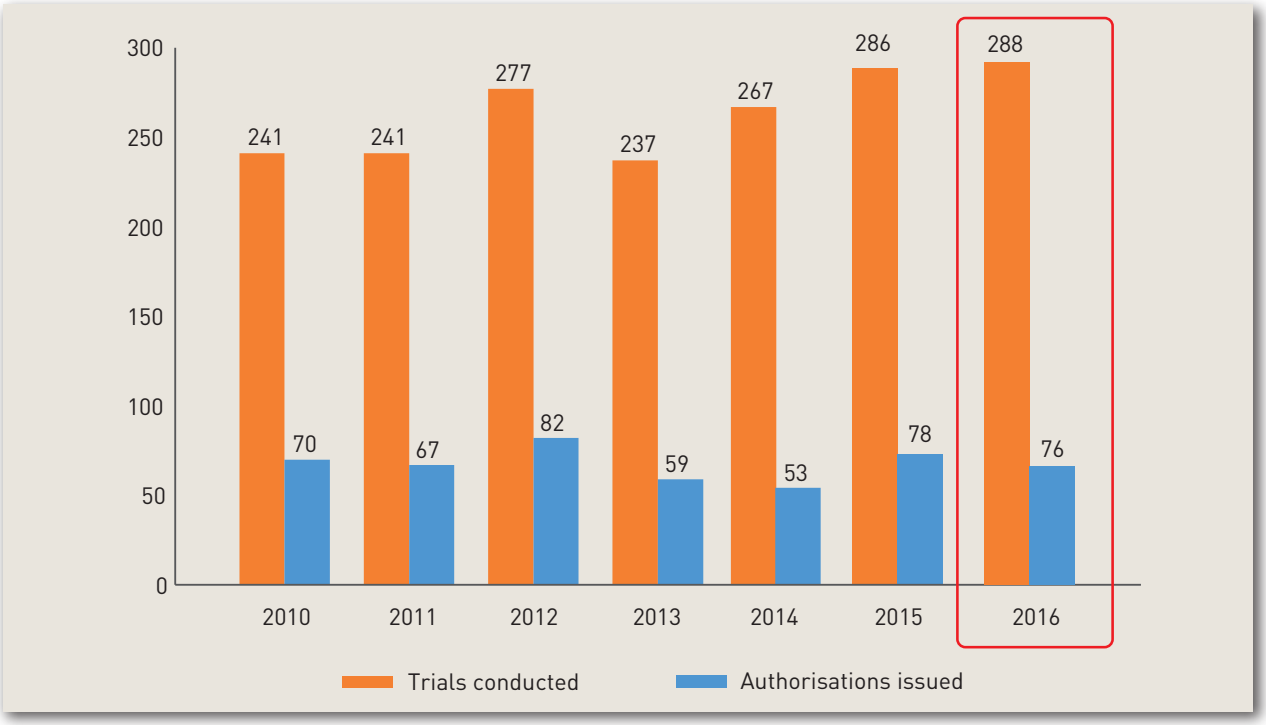
In accordance with the Cabinet of Ministers Regulation No. 289 of 23 March 2010 "Regulations Regarding the Procedures for Conduct of Clinical Trials and Non-interventional Trials of Medicinal Products, Labelling of Investigational Medicinal Products and the Procedures for Assessment of Conformity of Clinical Trial of Medicinal Products with the Requirements of Good Clinical Practice" and legal acts of the European Union, in 2016 the State Agency of Medicines received 72 clinical trial projects for review, 17 of which were submitted for evaluation as part of the International Harmonisation Procedure. Latvia was the reference member state for one of the clinical trial projects submitted in 2016 within the International Harmonisation Procedure.

In 2016, the State Agency of Medicines issued authorisations for the conduct of 76 clinical trials with medicines, including 20 clinical trials within the International Harmonisation Procedure. One of the authorised clinical trials was approved with limiting conditions. In 2016, the State Agency of Medicines granted 247 authorisations for amendments to clinical trials and two authorisations for non-interventional studies. During the year of review good clinical practice compliance inspections were conducted at seven trial sites both in Latvia and foreign countries.

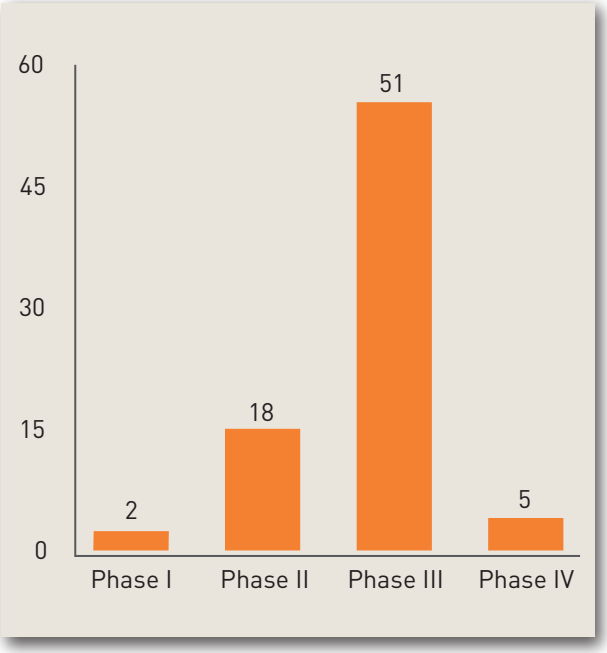
Information regarding applications for clinical trials with medicinal products, the time of their authorisation, the dates of approval of applications for significant amendments, opinions of ethical committees, completion of clinical trials, as well as inspections of good clinical practice was regularly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

Department employees ensured electronic data exchange within the EudraVigilance system by forwarding acknowledgements of receipt of safety reports concerning clinical trials in Latvia to clinical trial sponsors that had submitted safety reports in the Clinical

Number of authorisations issued and clinical trials conducted (2010–2016)



Number of clinical trials authorised in 2016 according to trial phase



Number of clinical trials authorised in 2016 according to medical speciality

Speciality	Number of trials
Psychiatry/Neurology	12
Gastroenterology	10
Infectology	9
Oncology	8
Pulmonology/Allergology	8
Endocrinology	8
Rheumatology	6
Cardiology	5
Urology/Nephrology	4
Dermatology	2
Ophthalmology	2
Haematology	1
Traumatology	1

Trial Module of the EudraVigilance database in accordance with the local and European normative requirements. During the year of review, 44 reports were received regarding serious adverse drug reactions observed at clinical trial centres in Latvia. These reports were analysed and included in a register established by SAM. In total, SAM received,

Trial sites of clinical trials with medicinal products authorised in 2016

Trial site (total)	Number of trials
State LLC Pauls Stradins Clinical University Hospital	50
Riga Eastern Clinical University Hospital • Clinic "Gailezers" • Latvian Oncology Center • Clinic "Tuberculosis and Lung Disease Centre" • Clinic "Bikernieki"	37 27 6 3 1
LLC Daugavpils Regional Hospital	21
LLC Liepaja Regional Hospital	15
LLC "Vidzeme Hospital"	9
LLC Health Centre 4	9
"Digestive Diseases Centre "GASTRO"", Riga	8
State LLC "Children's Clinical University Hospital", Riga	7
LLC "Rezekne Hospital", Rezekne	5
JSC "Latvian Maritime Medicine Centre", Riga	5
Other clinical trial sites (56 in total))	1-4 trials at each site

reviewed and registered 167 annual safety reports prepared by sponsors regarding clinical trials conducted in Latvia. Certain annual safety reports were analysed in depth and the assessment is reflected in an appropriately established format.

Six external experts were involved in the evaluation of documentation of authorised clinical trial projects, conducting expertise in 8 cases.

A total of 288 clinical trials were conducted in Latvia in 2016 and 68 projects were completed during the year, one of the projects was withdrawn.

The authorised clinical trial projects were sponsored by 95 foreign pharmaceutical companies. In accordance with the power of attorney from the sponsors, 60 contract research organisations were involved in organising and ensuring the quality of conduct of clinical trials in Latvia in 2016.

A total of 7 inspections of clinical trial compliance with good clinical practice were carried out in 2016, six of these were conducted at trial sites in Latvia, but one of them – in a foreign country. This includes also inspections upon request from EMA that were conducted at two trial sites of a single clinical trial. Both major and minor deficiencies were discovered during the inspections.

In the year of review, employees of SAM Clinical Trials Department participated in the preparation of Regulation regarding clinical trials with medicinal products of the European Parliament and Council, as well as the European Commission and the related normative acts and portal.

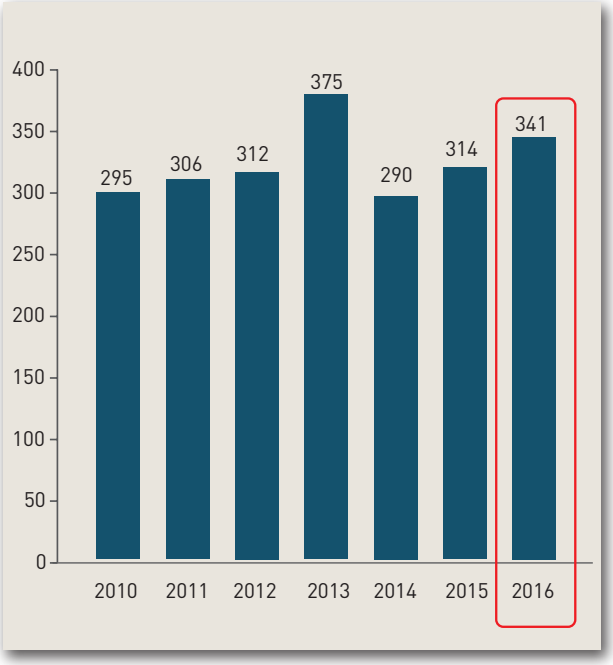
2.1.4. Monitoring of Adverse Drug Reactions and Risk Minimisation

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 European Union database *EudraVigilance* for identification of new risks with medicines. Every year SAM analyses the information entered into the database in Latvia and the reporting activity in Latvia.

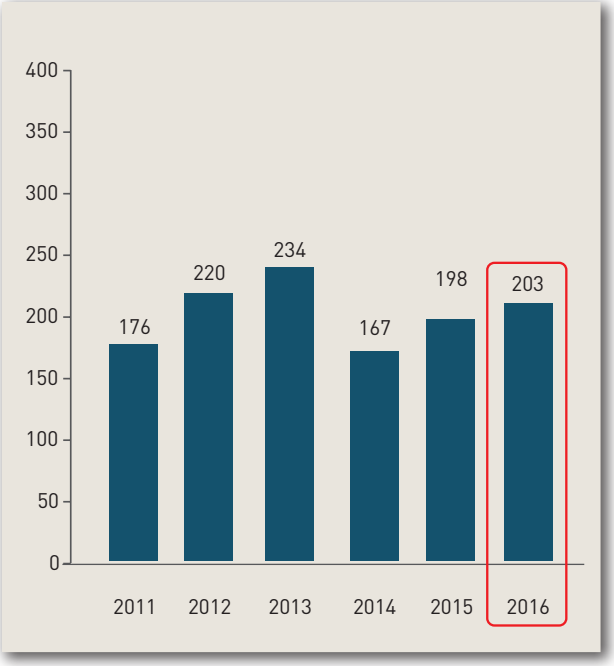
In 2016, the adverse drug reaction reporting activity in Latvia increased slightly. During the year of review the total number of adverse drug reaction cases reported to the State Agency of Medicines was 341. Doctors and pharmacists submitted 56 reports. The Centre for Disease Prevention and Control (CDPC) submitted 63 reports regarding adverse reactions to vaccines. The reporting activity among marketing authorisation holders (MAHs) remained stable in comparison with the previous year. The number of clinical events reported to SAM in 2016 increased, reaching 203 events.

The quality of the data provided by SAM pharmacovigilance specialists to the international adverse reaction database received recognition in the *VigiGradeTM – Completeness score Latvia* prepared by the WHO Uppsala Monitoring Centre. The analytical report assessed the quality of the data provided in the adverse drug reaction reports submitted to medicines agencies by doctors, pharmacists, patients, MAHs, including the aforementioned reporters in Latvia (the following quality criteria were assessed in the adverse drug reaction reports: precision of the administered medicinal product dosage, indications, indication of the precise time of start and end of treatment and others). Obtaining, processing and analysis of complete, thorough and qualitative information regarding adverse drug reactions, as well as SAM cooperation with reporters is

Adverse drug reactions reports 2010-2016



Clinical cases of adverse events with medicines 2011-2016



essential for assessing the severity of the risk and the required risk minimisation measures (for example, supplement the summary of product characteristics and package leaflet, urgently inform doctors via Direct Healthcare Professional Communication (DHPC), prepare educational materials regarding risk minimisation measures or introduce specific risk prevention programs) to minimise or prevent any potential harm to public health.

In 2016, SAM carried out 4 good pharmacovigilance practice inspections of marketing authorisation holders.

Operating within the EU single assessment procedure, SAM pharmacovigilance experts evaluated periodic safety update reports (PSUR) regarding medicines for the purposes of the whole European community. In 2016, Latvia was a reference member state in the single assessment procedures of periodic safety update reports for 4 active substances. During the year, PSURs were evaluated for 22 nationally authorised medicinal products, that are not included in the EU single assessment procedure, and their assessments with recommendations regarding the necessary actions were forwarded to the marketing authorisation holders.

Since 2016, SAM has taken up the responsibility of signal monitoring for 20 active substances as part of the EMA work-sharing procedure. Pharmacovigilance experts carried out regular surveillance of the safety information regarding these products.

In comparison with the previous year, the number of risk management plans (RMPs) submitted for evaluation remained unchanged. RMP related documentation was evaluated for a total of 59 MAH applications.

During the period of review, SAM collaborated with the MAH Qualified Persons Responsible for Pharmacovigilance. This ensured that the MAH established risk minimisation measures were implemented in Latvia, including the necessary communication with healthcare professionals, patients and the public regarding the safe use of medicines. SAM approves the MAH submitted DHPC projects and the educational materials (EM) intended for patients with the purpose of risk minimisation. During the year

of review, expertise was ensured for 72 MAH submitted EMs and 13 DHPCs.

SAM regularly ensures the preparation of medicines safety information intended for doctors, patients, the public and MAHs, and its publication on SAM website, as well as prepares announcements regarding safety issues brought up by EMA. Information regarding the latest medicinal product safety issues intended for healthcare professionals and recommendations regarding the required risk minimisation measures are provided in the informative bulletin "Cito!" for healthcare professionals and pharmacists.

2.1.5. Quality Control of Medicines

In 2016, SAM Laboratory carried out analysis of 107 samples of medicines. In the process of analysis 830 quality criteria were tested. 431 volumetric solutions, indicators and reagents were prepared upon request from pharmacies. 96 samples of purified water produced in pharmacies were selected and tested in 2016. Non-compliance with the requirements of the European Pharmacopoeia was discovered in two samples of purified water. Upon request from the SAM Medicines Marketing Authorisation Department, expertise was carried out on 22 names of medicinal products by evaluating the methods for analysis of the active substance and/or the final product and their validation. In comparison to 2015, last year there was an increased the number of quality criteria tested, but the number of volumetric solutions, indicators and reagents prepared remained the same. The number of tested purified water samples (96) has decreased slightly in comparison to 2015, and this number has a tendency to go down due to the decreasing number of pharmacies obtaining purified water. In 2016, expertise was carried out on an increased number of documentation submitted for authorisation.

The criteria of the SAM Laboratory for selecting medicinal product samples for testing were based on the potential risks to the public health, that is:

- A great quantity of the medicinal product on the market
- Medicinal products for which samples have not been tested in the last 5 years
- Medicines originating from third countries
- Information from the EU or the Health Inspectorate regarding withdrawal of the medicinal product
- GMP inspection results
- End-product manufacturer is not well-known in the national market
- Medicinal products intended for special patient groups (children)
- Parallel imported medicinal products
- Recently authorised medicinal products
- New end-product manufacturer
- Medicinal products with a low active substance content

SAM Laboratory regularly participates in international programs for quality control of medicines and professional level assessment programs. In 2016, specialists from the Laboratory participated in quality control programs for medicines authorised in the centralised authorisation procedure (CAP), MRP, DCP and the national procedure (in accordance with the collaboration agreement between the Baltic States), as well as in the European Market Surveillance Study (MSS) program.

A routine monitoring visit by the Latvian

National Accreditation Bureau took place on 18 May 2016. The Laboratory maintained the accreditation regarding compliance with the requirements of the LVS EN ISO/IEC 17025:2005 standard in the following areas:

- Physical and physical-chemical testing of medicines, pharmaceutical active ingredients and excipients (fixed and flexible field)
- Physical testing of purified water (fixed field)

The expiration date of the accreditation of the Laboratory is 16 June 2018.

In 2016, technical specifications were established and new testing devices were purchased: water purification system *Elix® Essential 3, Agilent* gas chromatography system, titration device *915 KF Ti-Touch*, titration device *848 Titrino plus*.

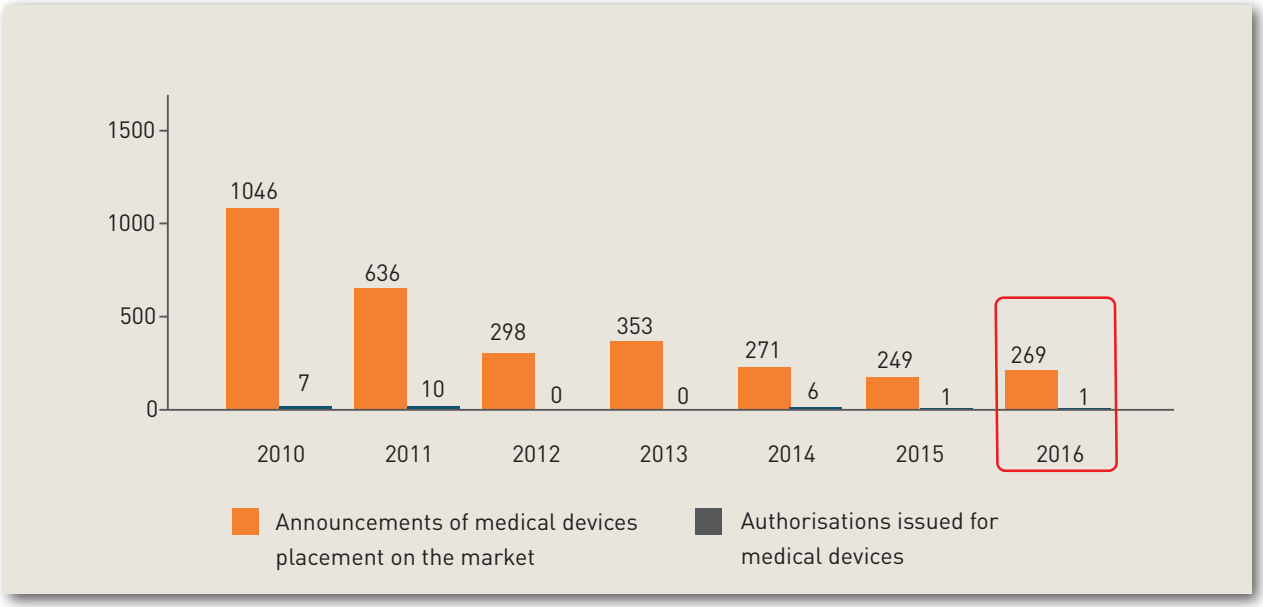
2.2. MEDICAL DEVICES

REGISTRATION, CLINICAL TRIALS AND SAFETY MONITORING

In 2016, in accordance with the Cabinet of Ministers Regulation No. 581 "Procedures for Registration, Conformity Assessment, Distribution, Operation and Technical Supervision of Medical Devices", SAM carried out expertise on documentation of 6 products as part of the registration procedure for medical devices manufactured in the Republic of Latvia. Last year, SAM also carried out expertise on registration documentation of 3 specially supplied medical devices not labelled with the CE compliance marking.

In 2016, 269 notifications were submitted within the notification procedure and were added to the LATMED medical device database of Latvia. Furthermore, information regarding purchase of safety group I and II medical devices was also entered in LATMED – 4253 reports, regarding variations to utilisation of the aforementioned medical devices – 2621

Number of authorisations issued to medical devices manufactured in the Republic of Latvia and Number of notifications received by SAM regarding placement of medical devices on the market in the Republic of Latvia



reports. SAM received 1063 primary reports about accidents with medical devices within the vigilance system. In 172 cases identification and implementation of safety measures was ensured with regard to non-compliant medical devices in operation in the Republic of Latvia. In the year of review, SAM issued authorisation for 13 clinical trials with medical devices and 9 approvals for amendments to clinical trials that were already being conducted in Latvia in accordance with the Cabinet of Ministers Regulation No. 891 of 21 September 2010 "Procedures for the Clinical Trial with Medical Devices Intended for Human Use".

To provide informative support to manufacturers of medical devices, in 2016, SAM prepared a clear explanatory material regarding the procedure that manufacturers in Latvia are required to comply with to receive CE marking for Class I medical devices and to place them on the market in accordance with the Guidance notes for manufacturers of Class I medical devices prepared by the European Commission Market Surveillance Operations Group for medical devices and approved on 1 December 2009. The information is published on SAM website, section "Services" > "Medical Devices" > "Registration and notification".

Registration, clinical trials and safety monitoring of medical devices in 2016

Position	Number
Number of primary applications for registration of medical devices manufactured in the Republic of Latvia	6
Number of primary applications for registration of medical devices without CE marking	0
Number of primary applications for expertise on documentation of specially supplied medical devices	3
Registration of information submitted within the notification procedure in the LATMED database	269
Registration of information provided by MD holders regarding purchase of safety group I and II MDs in the LATMED database (number of documents received)	4253
Registration of information provided by MD holders regarding changes in use of safety group I and II MDs in the LATMED database (number of documents received)	2621
Acceptance of reports and related documentation received within the Vigilance system, analysis and processing of information and registration of data in the LATMED database: - Total number of received reports - Number of primary reports	 2476 1063
Number of implemented safety measures: - Following receipt of initial report on the necessity of corrective actions in relation to medical devices in operation in Latvia - Following receipt of initial report regarding accident with medical devices in Latvia	 172 61
Primary applications for authorisation of clinical trials with medical devices	13
Primary applications for authorisation of amendments to clinical trials with medical devices	9
Applications for variations to previously issued MD authorisations	0

2.3. PHARMACEUTICAL ACTIVITIES COMPANIES

2.3.1. Licensing

The main task of the Pharmaceutical Activities Company Licensing Department is to address pharmaceutical activity company licensing issues in order to ensure the issuance of special permits (licences) to pharmaceutical activity companies in accordance with the normative acts currently in force in Latvia.

The procedure for licensing of pharmaceutical activity and for review of documentation and adoption of decisions in SAM regarding issuance, renewal, suspension and annulment of special permits (licences) is laid down in the CM Regulation No. 800 of 19 October 2011 "Procedure for Licensing of Pharmaceutical Activity" (hereinafter – Regulation No. 800).

Prior to the SAM decision regarding issuance, renewal, suspension or annulment of a special permit (licence), issues related to the licencing process are reviewed by the Commission on Licencing Pharmaceutical Activities Company (hereinafter – Commission). Commission decisions have the nature of a recommendation and the Commission operates in accordance with the regulations approved by the Director of the Agency. Organisational preparations and recording of the minutes of Commission meetings are in the competency of the department and 17 Commission meetings were held in 2016.

The department performs evaluation of the documentation submitted by pharmaceutical activity companies – medicines wholesalers, medicines manufacturing or import companies, manufacturing companies of active pharmaceutical ingredients, general or closed type pharmacies. In 2016, the department assessed the compliance of projects for facilities of general and closed type pharmacies with the requirements of normative acts, prepared opinions on compliance evaluation of pharmacies (167), prepared draft decisions (473) for issuance, renewal, suspension or annulment of special permits (licences).

To ensure the functions of issuing special permits (licences) for pharmaceutical activity to medicines wholesalers, medicines manufacturing or import companies, general type pharmacies and closed type pharmacies delegated to the State Agency of Medicines in accordance with Section 10, Clause 12 and Clause 16 of the Pharmaceutical Law, in 2016, SAM carried out expertise on documents submitted by 1380 licence holders. Last year a trend could be observed among general type pharmacy licence holders to expand the range of services provided with new types of special activity, for example, preparation of medicines at the pharmacy, distribution of psychotropic substances, extension the terminated general type pharmacy activity to a new five-year term or an indefinite time period.

In 2016, SAM renewed (issued) special permits (licences) for pharmaceutical activity to 385 pharmaceutical activity companies (310 pharmacies, 52 medicines wholesales (in accordance with the issuance (renewal) of special permit (licence) for pharmaceutical activity, good distribution practice compliance evaluation was conducted at 23 medicines wholesalers), 19 medicines manufacturing or import companies, 4 companies manufacturing active pharmaceutical ingredients). The majority of licencing documents submitted for renewal of special permits (licences) were related to replacement of pharmacy managers, responsible officers, change of legal address, relocation of pharmaceutical activity, initiation of new special activity conditions, change of address of pharmaceutical activity location in accordance with the decision of the Construction Board.

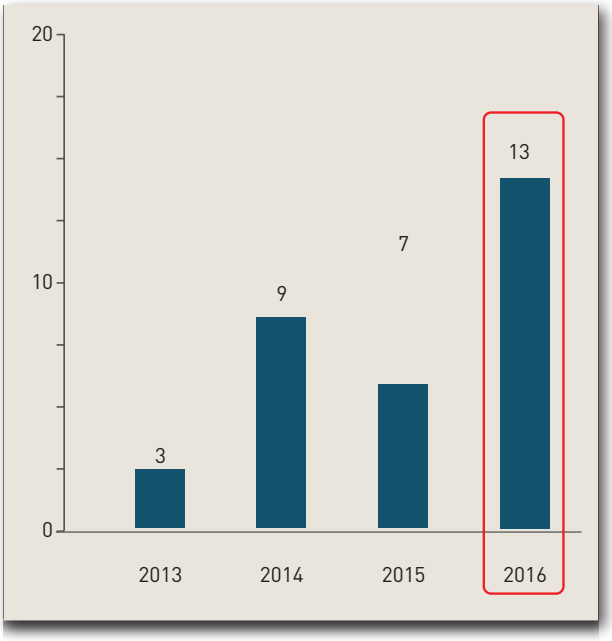
In accordance with the CM Regulation No. 344 of 25 June 2013 "Procedure for Import and Distribution of Active Substances" (hereinafter - Regulation No. 344) laying down the authorisation procedure for manufacturers, importers and distributors of active

substances, in 2016, SAM adopted decisions regarding authorisation or authorisation of variations to 13 manufacturers, importers and distributors of active substances (4 of these to new manufacturers, importers and distributors of active substances) by issuing authorisation certificates, uploading this information to the website www.zva.gov.lv and entering the data into the EU EudraGMDP database in collaboration with SAM Pharmaceutical Activities Compliance Evaluation Department.

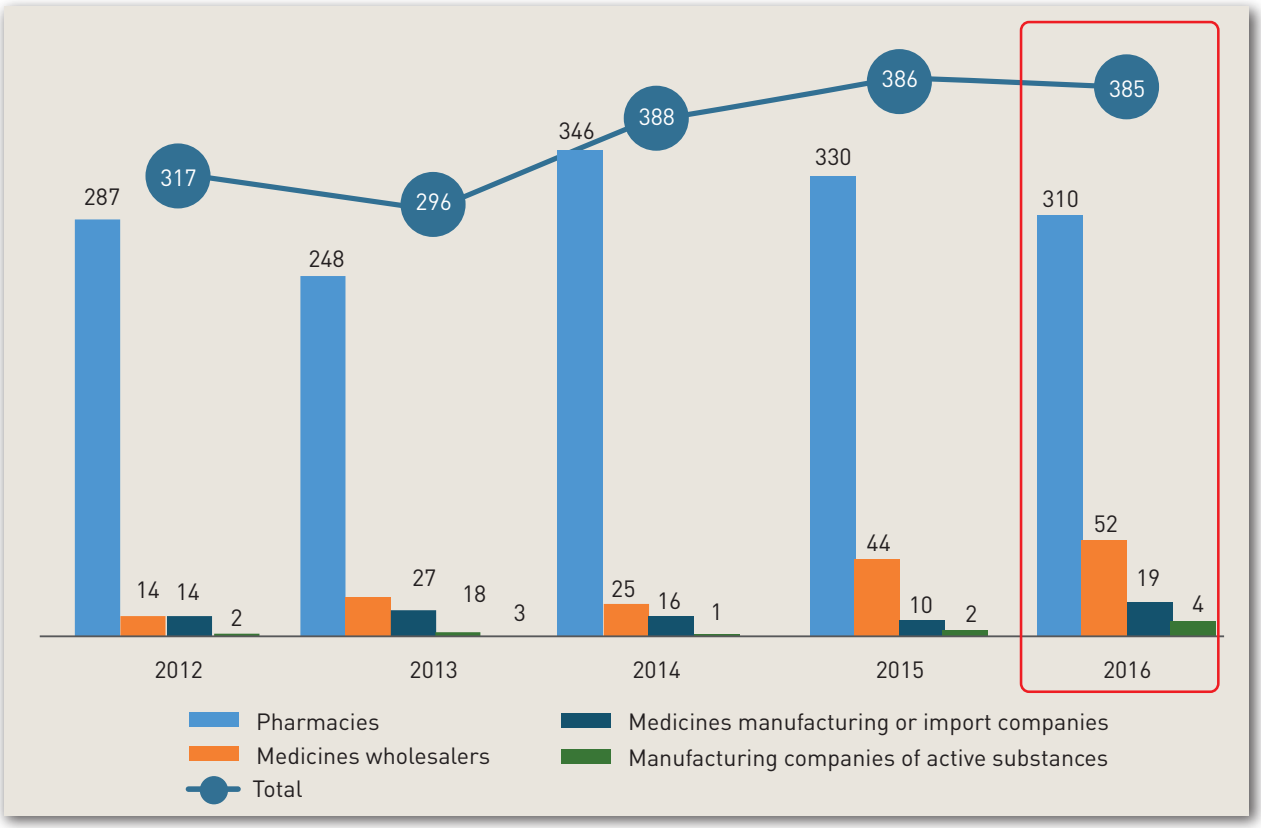
In comparison to the previous year, in 2016, there was an increased number of requests from wholesale companies of medicines for issuance or renewal of special permits (licences) for wholesale distribution of medicines for human use (52 cases of licence renewal/issuance to medicines wholesalers).

In 2016, SAM adopted the decision to issue special permits (licences) for pharmaceutical acitvity to 7 new medicines wholesalers, 1 new closed type pharmacy, 3 new general type pharmacies. One of these general type pharmacies was opened where before that there were no general type pharmacies or pharmacy branches, and 2 pharmacies were opened in places where a general type pharmacy owned by a different merchant terminated its pharmaceutical activity.

Registration of active substance manufacturers, importers and distributors (including primary registrations and renewals)



Licences for pharmaceutical activity companies



2.3.2. Compliance Evaluation

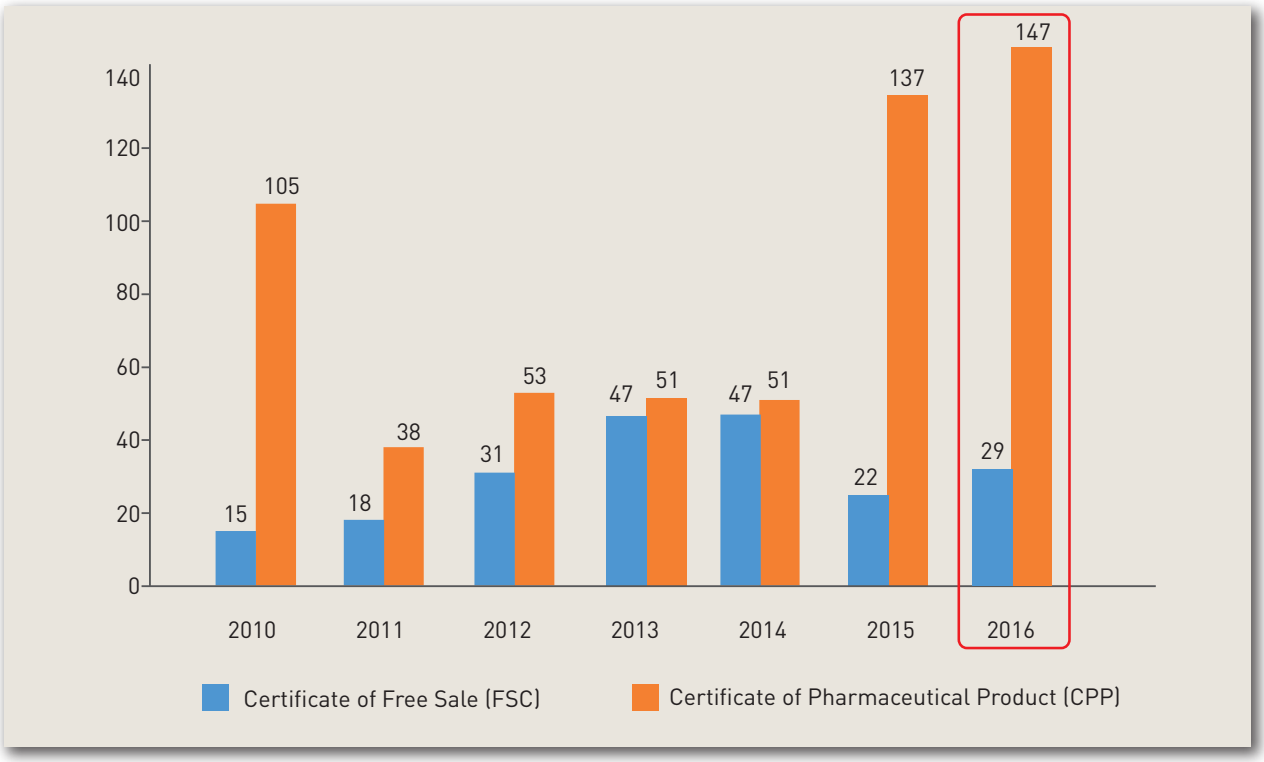
In 2016, SAM conducted 18 inspections of medicines manufacturing/import companies and it required 76 person-days in total. One of the inspected medicinal product manufacturing companies was located in country outside of the European Economic Area (EEA), but three inspections were related to the inspection of manufacturing of active substances. Overall, inspections were conducted regarding manufacturing of 10 chemically synthetized active pharmaceutical ingredients. SAM Pharmaceutical Activities Compliance Evaluation Department employees in cooperation with the Pharmaceutical Activities Company Licensing Department authorised 4 new active substance manufacturers, importers and distributors, and ensured variations to 5 previously registered merchants. Nine herbal (medicinal) product samples and 12 label samples were selected for compliance evaluation during inspections of manufacturing companies.

In the year of review 12 good manufacturing practice certificates were issued to medicinal product manufacturing/import companies. Upon request from medicines manufacturers and wholesalers in Latvia, 147 certificates of pharmaceutical products and 29 certificates of free sale were issued in 2016 in order to promote export of medicines manufactured in Latvia and their marketing authorisation in countries outside of the EU or EEA.

In 2016, Department experts participated in two inspections (good manufacturing practice) of manufacturing companies in other EU member states, and they were conducted as part of inspector experience exchange.

35 compliance evaluations of medicines wholesalers, as well as good distribution practice inspections of medicines wholesalers were carried out in 2016, requiring a total of 40.5 person-days. One inspection was carried out in relation to distribution of active

Dynamics of the number of certificates issued to national manufacturers



substances. In the year of review, 34 good distribution practice certificates were issued to medicines wholesalers.

28 compliance evaluations and surveillance procedures for human blood and blood component establishments and hospital blood banks were performed in 2016. Twelve compliance evaluations were conducted at tissue/cell procurement establishments and tissue centres. Three surveillance procedures were conducted at tissue centres, including the implementation of procedures for haemovigilance and biovigilance surveillance.

Department specialists prepared annual reports to the European Commission regarding serious adverse reactions and serious adverse events in the field of blood, tissues and cells, and prepared information for the surveys included in the joint action projects ARTHIQ and VISATRT, surveys received from the European Commission Directorate General for Health and Food Safety (DG-SANTE) and EMA regarding the current practice in Latvia in relation to the surveillance of producers of blood preparations, DG-SANTE survey regarding the final assessment of EC report "Action Plan on Organ Donation and Transplantation (2009-2015)". Department experts actively evaluated and commented on the draft amendment prepared by the Ministry of Health for the transposition of the new directive in the field of tissues and cells.

In addition, information was provided in response to the query from EC regarding the progress in transposition of the new directive in the field of tissues and cells, implementation of the requirements was coordinated with EC, and data entries and changes in the codes of tissue centres were ensured in the EC maintained database (EUTC) by simply linking the tissue centre codes in Latvia with the number of authorisation for utilisation of tissues and cells.

Department employees ensured representation of SAM in the EMA Good Manufacturing and Distribution Practice Inspectors Working Group, in the activities of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), in training (ARTHIQ) and working group meetings (VISATRT) organised within the Joint action projects, as well as in the working groups organised by the European Commission Directorate General for Health and Food Safety (DG-SANTE) regarding human blood and blood components, tissues, cells and organs.

3. INTERNATIONAL COOPERATION

3.1. State Agency of Medicines – part of a united European network

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

In order to fully participate in the European collective work procedures, that bring additional responsibilities and tasks for the Latvian Agency, qualified human resources, as well as financial resources are necessary. In 2016, SAM employees were involved in the cooperation with the European Commission and Council working groups, European Commission Directorate General for Health and Food Safety (DG SANTE), WHO, PIC/S, European Directorate for the Quality of Medicines & Healthcare (EDQM), as well as in compliance inspections of clinical trials on behalf of the EMA and in cooperation with other organisations.

In order for the Agency to provide appropriate services to its clients and provide consultations on different regulatory issues, cooperation with institutions in other countries, training and exchange of experience are mandatory prerequisites. In 2016, SAM actively participated in work-sharing procedures, for example, in the field of paediatrics, in the evaluation of periodic safety update reports, in the voluntary harmonisation procedure for clinical trials. To ensure high quality of expertise, SAM invited additional experts also from the academic field – from the University of Latvia.

In 2016, SAM administration actively participated in the organisation of the Heads of Medicines Agencies' cooperation network by providing the opportunity to proactively participate and solve issues related to regulatory issues of medicinal products on a European level. SAM administration also participated in the EMA Management Board meetings where the agenda included the evaluation of EMA participation in international projects such as the Innovative Medicines Initiative. The objective of this project is to speed up the development of better and safer

medicines for patients, new developments in creating the common EU portal and database for clinical trials, data assembly within the system for safety surveillance of medicines and other relevant issues.

Since 2010, SAM has been involved in the cooperation for surveillance of medical devices, blood and its components, tissues and cells. SAM is a competent authority with regard 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 representatives from national competent authorities for medical devices in Europe. Participation is ensured in Competent Authorities for Medical Devices (CAMD) meetings, Central Management Committee (CMC) meetings and European Commission Directorate General for Health and Food Safety (DG SANTE) meetings.

To represent the opinion of the Republic of Latvia on issues regarding monitoring of the safety of medicines, since 2012, SAM is participating in the EMA Pharmacovigilance Risk Assessment Committee (PRAC). This committee deals with issues related to the risk management of medicinal products distributed in the EU, including supervision of risk management plans and systems for both nationally and centrally authorised medicinal products, evaluation of Periodic Safety Update Reports, as well as acting as an advisor on various pharmacovigilance issues. Additional information regarding international cooperation of SAM is detailed also in Section 2 "Results of Operation of the State Agency of Medicines" of this report and its subsections.

3.2. Cooperation between the medicines agencies of the Baltic States in the regulatory field of medicinal products

There are effective cooperation contracts between SAM and the medicines agencies in Estonia and Lithuania in order to promote closer cooperation between the medicines agencies of the Baltic States. A meeting of experts from the medicines agencies of the Baltic States takes place every year in one of the Baltic countries in relation to normative regulation of the pharmaceutical field and news in the industry. The cooperation of the Baltic

Work session of the medicines agencies of the Baltic States in 2016

States is significant not only from a perspective of unity of the countries in the region, but also because in the market situation of small countries it is important to create stable market conditions for all participants. This far, the common Baltic packaging is the most successful example of cooperation between the three countries. It was initiated with the objective of decreasing administrative burden and consumption of merchant resources, as well as promote availability of medicines in the market and to create a simpler, faster and more transparent procedure for approval of the medicinal product packaging. Since 2010, marketing authorisation holders no longer have to contact each of the medicines agencies separately.

In 2016, SAM organised the meeting of experts from the medicines agencies of the Baltic States in Riga. The meeting agenda included a review of the trends in consumption of medicinal products in the Baltics, medicinal product safety issues and additional safety elements on medicinal product packaging, solutions to medicinal product supply disruption problems in all three Baltic States, as well as aspects of future collaboration. During the meeting in Riga, discussions were held regarding the introduction of a common Baltic packaging also for veterinary medicines. For

the first time in the history of the cooperation between the medicines agencies, institutions representing each of the countries held a work session together with industry representatives (merchants) to discuss the implementation of the Directive of the European Parliament and of the Council with regard to prevention of falsified medicines from entering the legal supply chain.

At the meeting, Latvia was represented by the State Agency of Medicines, Estonia – by the Estonian Agency of Medicines, Lithuania – by the State Medicines Control Agency under the Ministry of Health of Lithuania. Regulators of the field of veterinary medicinal products were represented by the Latvian Food and Veterinary Service and National Food and Veterinary Risk Assessment Institute of Lithuania. The following non-governmental organisations representing medicinal product manufacturers and wholesalers participated in the work session of the 2016 meeting - Association of International Research-based Pharmaceutical Manufacturers (SIFFA) from Latvia, Association of Pharmaceutical Manufacturers (APME) from Estonia, Innovative Pharmaceutical Industry Association (IFPA) from Lithuania.

4. GENERAL GOVERNANCE OF THE STATE AGENCY OF MEDICINES

The Operational Strategy of the State Agency of Medicines for 2014–2016 is a document for operational planning and it is established, maintained and published in accordance with the requirements of the Law on Public Agencies and Cabinet of Ministers Instruction No. 3 of 28 April 2015 "Procedure for Preparation and Updating of the Operational Strategy of an Institution and for Evaluation of its Implementation". The strategy is approved by the Ministry of Health Order No. 158 of 5 September 2013 and every year it is updated in accordance with the law on the state budget for that year.

The strategy defines the Agency's:

- Operational authorisation;
- Objective;
- Implemented operational directions and the related services;
- Priorities.

In accordance with the Strategy the objective of the operation of the Agency is to ensure qualitative and reasonable services in the assessment of the medicinal products used in healthcare, procurement and utilisation sites of human blood, tissues, cells and organs, as well as pharmaceutical activity companies in accordance with the interests of the State and the public interests in healthcare.

The Agency has set three priorities that are important for the public health in the period of planning and for implementation of the Strategy, as well as for the development of the Agency and the improvement of its services:

- Promotion of sustainable development of the national market of medicines;
- Ensuring the prerequisites for the safe and rational use of medicines, medical devices, tissues, cells, organs, blood and blood components;
- Improving the efficiency of the operation of the Agency.

4.1. Legal Provisions and the Preparation of Normative Acts

The objective of the operation of the Legal Department of the State Agency of Medicines is to improve and promote compliance with the administrative process and its implementation in the Agency so that the decisions adopted by the State Agency of Medicines would be justified, legal and compliant with the requirements of normative acts, as well as to ensure the defence of the Agency's interests in courts, thereby, reiterating the legality of the decisions adopted by SAM within the administrative process, if necessary.

In 2016, the State Agency of Medicines in cooperation with the Ministry of Health pre-

pared several proposals for amendments to normative acts that were also approved by the Cabinet of Ministers in 2016. For example:

- In order to improve surveillance of distribution of medicines (including also import and export requirements for medicines), labelling and manufacturing requirements, the State Agency of Medicines submitted proposals regarding Cabinet of Ministers Regulation No. 57 of 17 January 2006 "Regulations Regarding Procedures for the Labelling of Medicinal Products and the Requirements to Be Set for Package Leaflets of Medicinal Products", Cabinet of Ministers Regulation No. 416 of 26 June 2007 "Procedures Regarding Distribution and Quality Control of Medicinal Products", Cabinet of Ministers Regulation No. 436 of 26 June 2007 "Procedure for Import and Export of Medicinal Products".
- The State Agency of Medicines in cooperation with the Ministry of Health prepared amendments to Cabinet of Ministers Regulation No. 175 of 8 March 2005 "Regulations for Manufacture and Storage of Prescription Forms, as well as Writing out and Storage of Prescriptions", supplementing Annex 5 of this regulation with Clause 17 including ephedrine hydrochloride, setting a maximum amount that a doctor may prescribe on a single prescription, taking into account that ephedrine-containing medicines are abused with the intent of intoxication, as well as the fact that ephedrine hydrochloride is used in the illegal manufacturing of amphetamine.
- Amendments were prepared to Cabinet of Ministers Regulation No. 610 of 2 August 2011 "Criteria for the Location of Pharmacies and Pharmacy Branches", allowing relocation of general-type pharmacies within the confines of a single building registered in the national real estate cadastre information system (including cases where the building is registered at several addresses), or relocation within a 50 m distance from an address indicated on a special permit (licence) for pharmaceutical activity, and laying down that the restriction stating that relocation of a general type pharmacy is permitted, based on the existing special permit (licence), within the borders of one populated area where there is no functioning general type pharmacy within a radius of 500 metres, where medicinal products are prepared or which operates 24 hours a day, shall not be applicable in these cases.
- A new condition was introduced in the Cabinet of Ministers Regulation No. 1037 of 27 December 2005 "Regulation Regarding Quality and Safety Standards for Procurement, Testing, Processing, Storage and Distribution of Human Blood and Blood Components and Compensation of Expenses for Restoration of the Volume of Blood Lost", stipulating that human blood and blood components shall not be exported out of the country, except cases where the blood and blood components are prepared for manufacturing of blood preparations using state budget financial resources, ensuring blood preparations for healthcare institutions in Latvia. This amendment laid down more stringent requirements for quality and safety control of blood and blood components, as well as clarified requirements with regard to the competency of the State Agency of Medicines in the haemovigilance

surveillance, as well as compliance evaluation of blood cabinets at health-care institutions.

- Requirements of the Cabinet of Ministers Regulation No. 344 of 25 June 2013 "Procedure for Import and Export of Active Substances" were clarified with regard to good manufacturing practice and good distribution practice of active substances, and the list of third countries was supplemented, including Brazil and Israel, stipulating that import of active substances from these countries shall not require written confirmation of compliance with good manufacturing practice from the competent authority of the appropriate country, and requirements were laid down for pharmacies with regard to purchase, registration, storage and supervision of active substances, because no such regulation existed previously.

Out of the 10 317 decisions adopted by the State Agency of Medicines in 2016, only 3 decisions were abolished, that is 0.029% of all decisions.

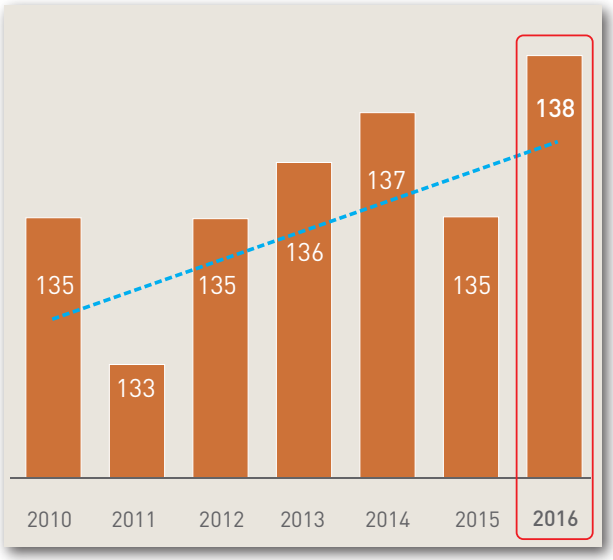
4.2. Staff and Human Resources Management

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

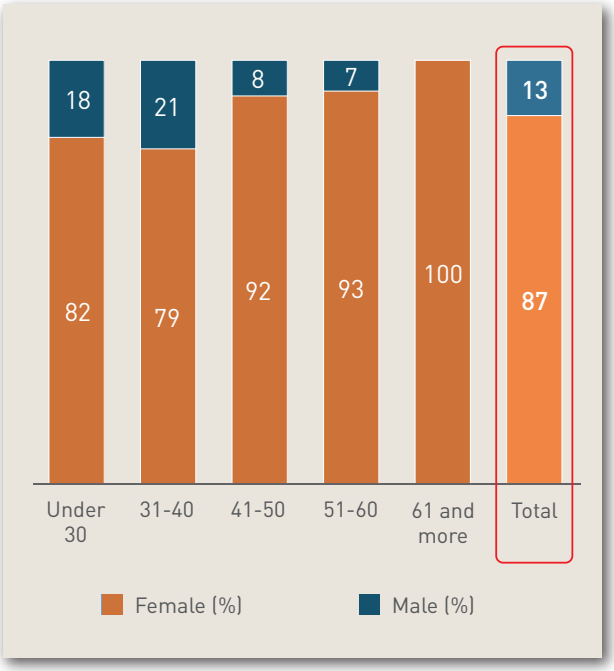
At the end of the 2016, there were 138 civil servants and employees actually working at SAM. In total 150 persons were in a civil service or an employment relationship with SAM in 2016.

In 2016, 20 new employees (7 civil servants and 13 employees) began their employment at the Agency and 13 persons terminated their civil service or employment. The average staff turnover quotient was 10% (*staff turnover = number of staff members who have terminated employment in a definite time period/ average*

Changes in the number of actual employees from 2010 until 2016



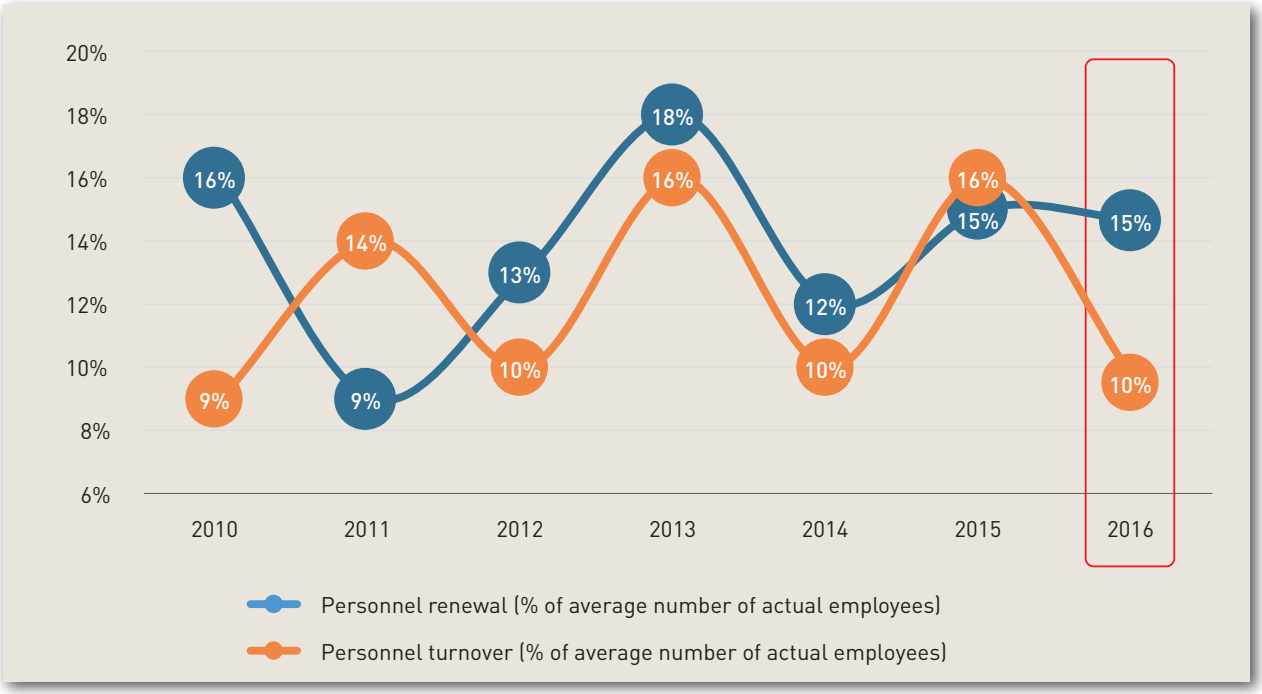
Employees according to age and gender



Reasons for termination of civil service or employment

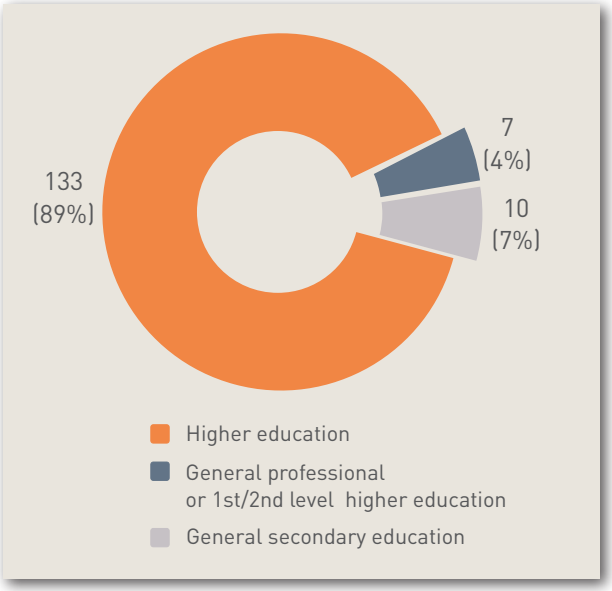
Reasons for termination of civil service or employment	Legal basis	Number
Notice of termination by an employee	Section 100 of the Labour Law	5
Agreement between employee and employer	Section 114 of the Labour Law	2
Notice of termination by an employer due to reduction in the number of employees	Section 101, Paragraph 1, Clause 9 Of the Labour Law	1
Employee does not perform work due to temporary incapacity for more than six months	Section 101, Paragraph 1, Clause 11 Of the Labour Law	1
Termination of an employment contract entered into for a specified period	Section 113 of the Labour Law	1
Based on his or her own will	Section 41, Paragraph 1, Clause a of the State Civil Service Law	1
Based on mutual agreement	Section 41, Paragraph 3 of the State Civil Service Law	1
State determined age of retirement	Section 41, Paragraph 1, Clause f of the State Civil Service Law	1

Dynamics of personnel turnover and renewal from 2010 until 2016



number of staff members in the same time period). The turnover quotient decreased by 6% in comparison to the previous year, but remains relatively high from the perspective of theory of personnel management and this means that it is still necessary to pay special attention to processes related to incorporation of new employees within the staff, training for new work tasks, development and training of professional and personal competencies.

Employees according to the level of education

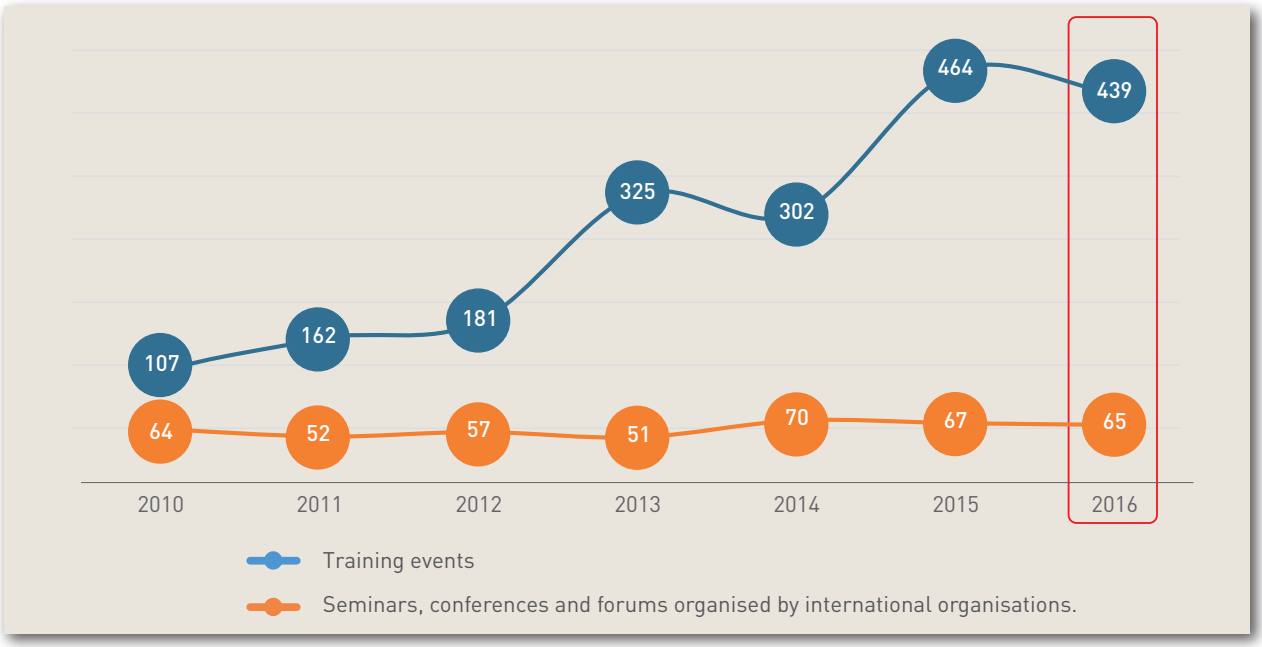


Well-educated, competent and highly qualified specialists are necessary to ensure the functions assigned to SAM. The overall level of education of SAM staff members is high - 133 (89%) of SAM employees have a higher education, four of these staff members have a doctoral degree.

One of the basic principles of SAM personnel policy is to motivate staff members to raise their qualification. In order to ensure this, based on the training requirements identified in the annual personnel assessment, in 2016 SAM civil servants and employees (hereinafter – employees) attended 439 training events, including 65 seminars, conferences and forums organised by international organisations. Statistical information regarding events for personnel development is shown in the image.

For the management process automatization of centrally organised training process, EMA Training Centre established and implemented the Training Management System (EU NTC LMS). In the second half of 2016, SAM participated in the pilot phase of the EU NTC

Raising personnel qualification from 2010 until 2016



LMS implementation. With the introduction of EU NTC LMS as a collective training platform, it is foreseeable that the proportion and availability of extramural training (webinars) will increase, thus, decreasing long-term administrative and business trip expenses of medicines agencies in EU member states related to organisation and provision of training.

Taking into account the knowledge and qualification of Agency experts, based on the collaboration contracts signed between the Agency and European institutions, in 2016, 27 experts and 4 employees with a supportive function participated in the performance of tasks delegated by European institutions.

4.3. Integrated Management System

At the end of 2016, SAM received a certification issued by *Bureau Veritas Latvia* regarding the compliance of the quality management system with the requirements of the new *ISO 9001:2015* standard, which is a considerable acknowledgement, and compliance of the information security management system with the requirements of the *ISO/IEC 27001:2013* standard.

Certified areas of operation:

- 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 of the institution, expertise on related documentation
- Assembly and publishing of information according to authorisation

After the supervisory visit by the *Latvian National Accreditation Bureau*, SAM Medicines Examination Laboratory maintained accreditation for compliance with the requirements of the *LVS EN ISO/IEC 17025:2005* standard with regard to physical and chemical testing of medicines, pharmaceutical active

ISO certificates at the SAM client service centre

substances, excipients, as well as purified water prepared at pharmacies.

The awarded certificates verify the professionality of SAM employees and unwaveringly high quality of the provided services. As Agency experts are participating in complex procedures related to marketing authorisation of medicinal products also in EMA scientific committees and international working groups, compliance with the requirements of international standards is important also to ensure that SAM may continue to be an equal partner within the network of European medicines agencies.

In 2016, several external audits were conducted at SAM at the request of SAM and the Ministry of Health, and internal audits of principal processes were ensured, including compliance of the pharmacovigilance management quality system with the good practice guidelines.

The Agency continuously developed and improved the integrated management system by introducing the latest changes in accordance with the requirements of ISO standards and involving a considerable number of SAM employees.

In 2017, SAM will face several external assessments. The periodic Pharmaceutical Inspection Co-operation Scheme audit is expected to take place during the first half of 2017 and it will assess the harmonised implementation of good manufacturing practice standards in Latvia and in the field of compliance evaluation of SAM quality systems.

At the end of 2017, for the fourth time SAM will participate in the mutual benchmarking of the good practice and results achieved by the operation of medicines agencies in the EU member states. This benchmarking will be conducted by independent observers and auditors from medicines agencies in other EU member states and it will provide additional information and vision for the improvements of processes and administrative capacity in the institution.

4.4. Development of Information Technologies

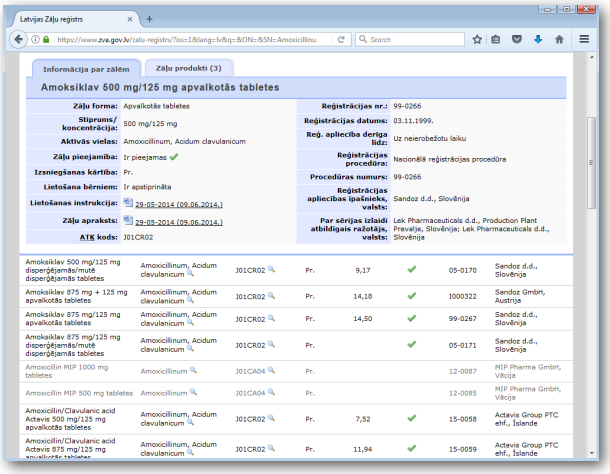
In 2016, SAM continued to develop and improve solutions for SAM information systems and information and communications technology (ICT), as well as to improve their availability and management, and the IT infrastructure was expanded by integrating new technical devices. As part of improving the ICT security, all Agency employees were supplied with a two-factor authentication solution, the IS security management system was improved ensuring compliance with Cabinet of Ministers Regulation No. 442 of 28 July 2016 "Procedure for Ensuring Compliance of Information and Communications Technology Systems with Minimal Security Requirements".

The algorithms for selection and processing of information in the ZVAIS and LATMED

information systems were refined, and significant improvements were made to the LATMED section publicly available to clients.

In 2016, the integration solution for the electronic document management system for SAMIS was completed, thus, automating electronic signing of documents, improving document processing, linking to medicines, option to determine the stages of completion of different procedures by following the whole life-cycle of authorisation of medicines. The implementation of this solution significantly improves circulation of information between the Agency and MAHs.

The improvements made on Agency's website provide new important options to search for information and its availability and comprehensibility. Agency's website dynamically reflects updated information from the Medicinal Product Register of Latvia regarding active substances, ATC codes, as well as MAHs and their representatives. Now Agency clients are also able to obtain information from the Medicinal Product Register of Latvia regarding exporting country, parallel importer of a medicinal product, date of withdrawal from the Register, expiry date for distribution of stocks of medicinal products. Clients may also see assessment files of medicinal products and easily peruse information on availability of medicines in Latvia, as well as their maximal price range. An improved solution for disruptions in the supply of medicines and a report form for disruptions in the supply of medicines is also available.



As part of the ICT centralisation in the field, the purchase and implementation of ICT solutions required by the Ministry of Health was ensured.

An audit of IS security was carried out and measures were taken to minimise the identified risks, staff training was conducted regarding IT security issues, including training conducted by a guest lecturer from CERT.LV. Collaboration in the exchange of information was continued with different European institutions, competent authorities in other countries by using the collective IT and data exchange solutions, for example, the European clinical trial database EudraCT, the secure e-mail and data exchange system Eudralink, the pharmacovigilance system EudraVigilance, terminology database for telematics EUTCT, the European database for medical devices EUDAMED, the Communication and Tracking System (CTS) solution for mutual recognition procedures, the Common European Submission Platform (CESP) for marketing authorisation documentation and others.

4.5. Ensuring Public Procurement and Economic Activities

Public procurement and the economic activity of the State Agency of Medicines are ensured by the Public Procurement and Infrastructure Provision Department. The operational objective of this department is to ensure the prerequisites and conditions for the successful operation of all of the structural units of the Agency.

The most important functions of the SAM Public Procurement and Infrastructure Provision Department are as follows:

- Organisation of public procurements
- Management of material assets and organisation of work safety measures
- Maintenance of the building complex and the territory on Jersikas street 15 owned by the Agency and maintenance of other rented properties
- Maintenance of the stock of automobiles owned by the Agency and provision of related services
- Ensuring continuous operation of the infrastructure of the Agency (electricity, water supply, sewage and heating system, communication network, ventilation system, security and fire safety alarm)

In 2016, SAM announced 20 procurement procedures. There were 55 candidates. Contracts for supply and services were signed for the conducted public procurement procedures. The most important contracts were signed to ensure infrastructure and primary functions, for example:

- Ensuring the stock of automobiles
- Construction of a grounding contour and lightening-conductor for the building
- Ensuring quality control and testing of medicines (purchase of gas chromatography systems and automated titration devices)
- Modernisation of IBM RISC infrastructure to newer servers, at the same time increasing the technical resources available within IS
- Preparation of a project for the website content structure and design

5. PROVIDING INFORMATION TO THE PUBLIC AND COMMUNICATION

In 2016, SAM ensured communication with SAM cooperation partners by providing independent and objective information regarding issues in the competency of SAM to professionals and the general public. Last year, communication was strengthened with professional associations and other non-governmental organisations, patient organisations and State institutions in the field.

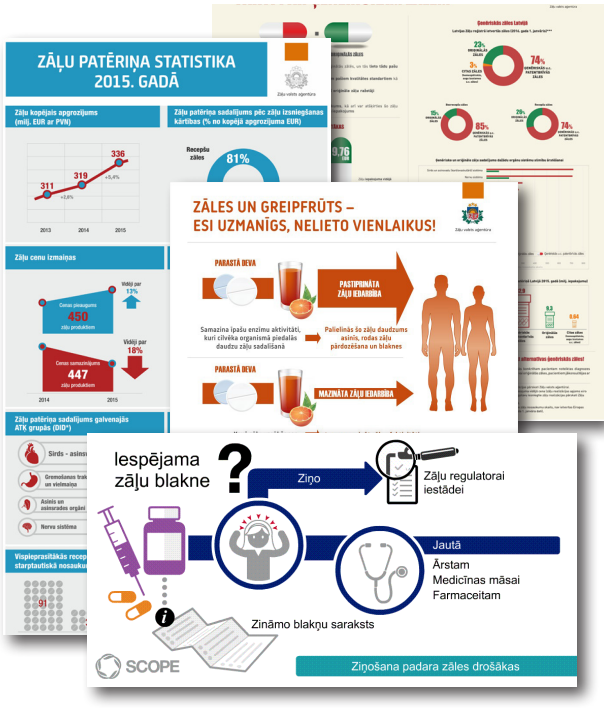
In 2016, the State Agency of Medicines provided information to the public and carried out communication activities in accordance with the "Communication Strategy of the State Agency of Medicines 2014-2016" and the "Operational Strategy of the State Agency of Medicines 2014-2016". Three operational directions are to be followed in order to achieve the objectives laid down in the SAM Strategy. One of the directions is the information direction: ensure provision of objective, thorough and updated information to the public and to professionals, as well as cooperation partners in Latvia and foreign countries.

Media publicity

In the year of review, 39 different press releases were prepared and forwarded to mass media representatives, and more than 150 responses were provided to media queries. Replies were prepared and provided to questions from residents of Latvia, as well as to requests for information from the Ministry of Health and institutions under its governance and supervision, and cooperation with SAM clients – merchants in the pharmaceutical field, was promoted.

To provide information in a more easily perceptible way, seven infographics were prepared and distributed in 2016:

- "Medicines and grapefruit – be careful, don't use together!"



Topic	Examples of publications
Availability of medicines	• *LNT News*: Reimbursable flu vaccines have been used-up. 03.01.2016.
Adverse drug reactions and safety of medicines	• *Medicine.lv*: SAM participated in European campaign on adverse drug reactions. 02.12.2016.
Consumption of medicines	• *Db.lv:* Last year Latvian manufacturers sold medicines and other goods worth 132 million euros. 01.03.2016. • *LETA:* Total turnover of medicines wholesalers increased by 9% in September. 31.10.2016
Generic and original medicines	• *36,6 °C Veselīgāk. Saskanīgāk. Gudrāk.:* Original or generic medicines. 04.10.2016.

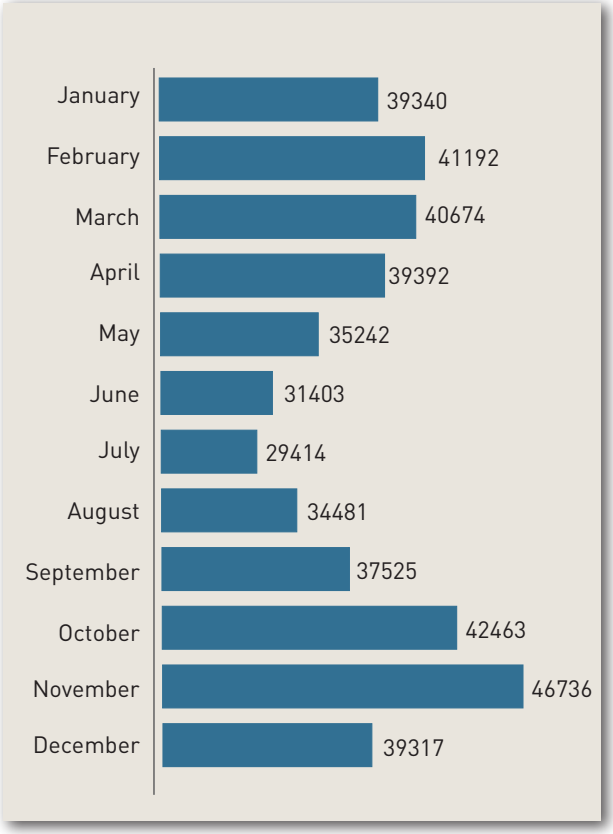
- "Statistics on consumption of medicines in 2015"
- "Facts regarding generic medicines"
- "20 years of SAM"
- Three interactive infographics "Reporting adverse drug reactions contributes to the future of public health"

The infographics were distributed to the media and via the SAM informative bulletin "Cito!", published on www.zva.gov.lv and forwarded individually to other interested parties. By following the normative regulation of the field of medicinal products in Europe and Latvia, and by evaluating the information regarding safety of medicines, regular updates were made on SAM profiles on the social networks *Facebook, Twitter, LinkedIn* and *Youtube*. As a result of SAM communication activities, in 2016, the news agency "LETA" prepared 65 articles mentioning the key-word "State Agency of Medicines" and there were several hundreds of publications on different media (the main media with the highest number of publications, news stories: "Neatkarīgā Rīta Avīze Latvijai" "Materia Medica", "Dienas bizness", "Latvijas Radio" and other portals).

In addition to the aforementioned, in 2016, information was regularly updated on SAM website www.zva.gov.lv. In the era of technology, maintenance of the website is not only one of the most cost-effective communication channels, but also allows to provide information directly to the target audience using the Internet.

According to Google Analytics statistical data, in 2016, SAM website was visited 457 179 times. Maintaining the website is an effective way of ensuring the provision of official and operative information to every member of the public regarding SAM operations and latest issues in the field of pharmaceutics.

WWW.ZVA.GOV.LV WEBSITE VISITORS IN 2016



In 2016, a project was developed for transformation of the arrangement of sections, functionality and design of SAM website to ensure provision of user-oriented information in separate sections for different SAM target audiences – healthcare professionals, marketing authorisation holders and patients.

SAM publications

In order to inform doctors, pharmacists and other healthcare professionals regarding the latest issues in pharmaceutics and SAM operation, as well as regarding safety of medicines, several informative publications were prepared in 2016. Even though doctors, pharmacists and other healthcare professionals can obtain information from different sources such as seminars and conferences, as well as professional publications from various countries, the publications printed by SAM provide updated, objective, verified and focused information to the interested parties who wish to follow the most important developments in pharmaceutics.

The SAM informative bulletin "Cito!" for doctors, pharmacists and other healthcare professionals has already become an integral part of daily operation by providing thorough and updated information regarding the safety of medicines. In the pages of "Cito!" field specialists, including SAM experts, share their experience, publish articles regarding current medical issues, as well as exchange their opinions. Changes in the Medicinal Product Register of the Republic of Latvia are published in each issue of "Cito!", and each issue is also accompanied by an adverse drug reaction report form for healthcare professionals and pharmacists to promote reporting of adverse drug reactions. Four issues of "Cito!" were released in 2016.

The Medicinal Product Register of the Republic of Latvia is an official and independent source of information for doctors and pharmacists,

PUBLICATIONS - COPIES

- Bulletin "Cito!" – 5600
- Medicinal Product Register of the Republic of Latvia – 100
- Electronic version of the Medicinal Product Register of the Republic of Latvia in USB format including summaries of product characteristics and package leaflets*
- SAM Annual Report 2015 (Latvian and English version) – 200
- "Baltic Statistics on Medicines 2013–2015" – 300

* Provided by SAM upon request

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, an electronic edition of the Medicinal Product Register is prepared in a USB data carrier format containing summaries of product characteristics and package leaflets. A convenient information search form has been developed for this format. No Internet connection is necessary to use this format in the daily work. The summaries of product characteristics included in the electronic version of the Medicinal Product Register help doctors and pharmacists to choose the most appropriate medicines for the patients, as well as to find out or clarify relevant information regarding the correct use of medicines, possible adverse reactions and other information, thus, promoting safe use of medicines. In addition, in 2016, an option was introduced on SAM website to download updated information from the Medicinal Product Register in a structured manner in XML format.

To provide information regarding trends in the consumption of medicines, in 2016, the annual statistical report on the consumption of medicines in Latvia "Statistics on Medicines Consumption 2016" was published, including consumption data regarding the period 2012-2016. By cooperating with the medicines agencies in the Baltic states, the new publication "Baltic Statistics on Medicines 2013-2015" was also prepared and published in 2016, providing a summary and analysis of data on consumption of medicines in Latvia, Lithuania and Estonia during the three-year period. "SAM Annual Report 2015" was also published in 2016, providing summarised information regarding the operation of the Agency in 2015. We invite you to see SAM publications on the Agency's website under the section "Publications".

Cooperation with the non-governmental sector of the pharmaceutical industry

In 2016, SAM promoted discussions with the industry and continued the previously initiated dialogue with non-governmental organisations representing medicines manufacturers, wholesalers and pharmacies, as well as manufacturers and distributors of medical devices. Regular meetings between the associations in the field and SAM representatives were organised at the Agency in order to discuss the implementation of the requirements of the new normative acts.

In relation to the European Commission delegated Regulation regarding safety symbols on packaging of medicinal products for human use that was adopted at the beginning of 2016 and will be implemented from February 2019, repeated discussions were organised regarding the introduction of new safety elements - unique identifier and two-dimensional bar-code - on every packaging of medicinal products. These new safety elements will ensure authenticity of medicinal products and strengthen the safety of the supply chain of medicines from manufacturers to distributors

- pharmacies and hospitals, thus, protecting the public from the risk created by falsified medicines. In 2016, for the first time non-governmental organisations representing medicines manufacturers and wholesalers participated also in the work meeting of experts from the medicines agencies of the Baltic States organised by SAM regarding latest news and normative regulations in the field, including the introduction of new safety elements on medicinal product packaging. The participating non-governmental organisations included the Association of International Research-based Pharmaceutical Manufacturers (SIFFA) from Latvia, Association of Pharmaceutical Manufacturers (APME) from Estonia, Innovative Pharmaceutical Industry Association (IFPA) from Lithuania. During the year of review, discussions with non-governmental organisations in the field were held also regarding possibilities of reducing the administrative burden in the public procurement procedures for medical devices in relation to the submission of quality assurance documentation by using the SAM maintained and publicly available LATMED database for medical devices in the procurement process.

Last year SAM also held a meeting with representatives of manufacturers of medicinal products and medical devices from Kazahstan in order to discuss opportunities for further cooperation. Officials from the Ministry of Health, representatives of the largest pharmacy networks in Latvia and professionals from pharmaceutical companies also participated in the discussion.

Special events and campaigns

In 2016, several public informative seminars were also organised. Students from schools in Daugavpils, Ogre, Ādaži and Riga visited SAM on Shadow Day and were introduced with the daily work of the Director of SAM and senior expert–analyst at the SAM Medicines Examination Laboratory. They gained new knowledge about chemistry, marketing authorisation and quality control of medicines. SAM organised also an open lecture for students – future pharmacists, as well as an

Open-Door Day when anyone interested had the opportunity to find out more about the SAM field of operation.

In November 2016, the State Agency of Medicines implemented a social media campaign to promote reporting of adverse drug reactions. The campaign was executed as part of the information week on adverse drug reactions on a European level. Two previously initiated campaign activities were continued in 2016: "Reveal the other side of medicines!", as well as the campaign on risk of falsified medicines when purchasing medicines online, including providing information regarding the introduction of a common logo for all of the EU pharmacies offering consumers to buy medicines online. Thereby, SAM participated in the implementation of a European-wide campaign – provided information regarding the common logo not only in press releases, but also using video materials, banners, images and other materials. The introduction of the common logo is laid down by the Directive of the European Parliament and of the Council relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products. In 2016, information regarding SAM operation in the format of presentations and discussions was provided also at events organized by other organisations.

Two-way communication, feedback

SAM communication activities are not based solely on a one-way provision of information, but SAM also gives the opportunity for SAM cooperation partners, clients and employees to express their opinion about the quality of SAM client service and provided services. The information received is used for the improvement of the quality of SAM operations. In 2016, SAM organised two surveys:

1) **SAM client survey** regarding SAM operation and services with the purpose of improving the quality of client service and the provided services, based on the obtained data

2) **SAM employee survey** with the purpose of obtaining information regarding employee opinion on organisation of work and collaboration within SAM, job satisfaction and other important aspects of work that could help to identify priorities in working with personnel and make reasonable and considerate decisions with respect to employees

To enquire the opinion of SAM website visitors, five surveys were conducted in 2016 (the results of these surveys are available on SAM website, in the section "Homepage" > "Survey archive"). Website visitors answered the following questions:

- How does the pharmacist inform you about the dosage and regimen of the medicines indicated by the doctor on the prescription (e-prescription)?
- In your opinion, what indicates that the purchased medical device is qualitative and safe?
- Do you find out the price of medicines before going to the pharmacy?
- There are five licenced online pharmacies in Latvia. Have you purchased medicines at these pharmacies?
- Do you verify that medicines are intended for use in children before giving them to your child?

Events for promoting internal communication

In 2016, internal communication was promoted at the State Agency of Medicines by organising events for employees and offering employees to participate in events organised by other organisations, thus, promoting awareness about SAM, strengthening the sense of community at SAM and involvement in work processes, as well as motivating to

bring forward initiatives. The long-term commitment of SAM employees was celebrated at the event commemorating 20 years since the establishment of SAM by awarding certificates for gratitude of service to SAM employees who have worked at SAM for five, ten and twenty years to express gratitude for their contribution to SAM.

In order to promote good physical and mental health and to strengthen the sense of community, a team of SAM employees and their family members participated in the 18th Health Days for healthcare professionals in Latvia organised by the Latvian Red Cross and supported by the Ministry of Health of the Republic of Latvia, Latvian Medical Association and Trade Union of Health and Social Care Employees of Latvia. In 2016, for the third year in a row SAM employees and their family members participated in the basketball tournament organised by the Pharmacists' Society of Latvia. A collective SAM event "Big Clean-up" was also organised.

6. DEVELOPMENT PRIORITIES OF THE STATE AGENCY OF MEDICINES IN 2017

Potential SAM priorities were assessed during planning of SAM operations in accordance with Cabinet of Ministers and Ministry of Health issued documents for policy planning in the field, as well as taking into account the main strategic operational directions of the EMA and Heads of Medicines Agencies (HMA). In 2017, SAM will develop the operational strategy for 2017-2019. During the following years, special attention will also be paid to the availability of medicines, safety, rational use of medicines and development of SAM:

- Participate in the improvement of normative acts, as well as develop other options to promote prompt availability of appropriately assessed medicines in segments where the availability of medicines does not correspond to the needs of public health.
- Contribute to the preparation of normative acts and policy documents both on a national level and international level, giving special consideration to the impact of the regulatory framework on the long-term affordability of qualitative, safe and effective medicinal products and efficient use of SAM resources. Implementation of the requirements of the Regulations regarding clinical trials, medical devices, as well as prevention of falsification of medicinal products will be initiated in 2017.
- Take actions to minimise the risks to public health created by disruptions in supply of medicines, as well as minimise the denial of entry to the market in Latvia for authorised and necessary medicinal products.
- Improve the compliance evaluation process in the field of pharmaceutics and healthcare within the competency of the Agency by appraising and, as possible, implementing risk assessment based compliance evaluation.
- Implement educational measures (seminars, consultations, information on website and printed information, and others) and cooperation with the industry according to the wishes and needs of the target audience, paying particular attention to issues that promote the safe and rational use of healthcare products, amendments to legal acts, new or improved methods and tools in the safety surveillance of medicines.
- Expand proactive participation of the Agency in EMA's formal work-sharing procedures, as well as informal work-

sharing initiatives, contribute to international forums.

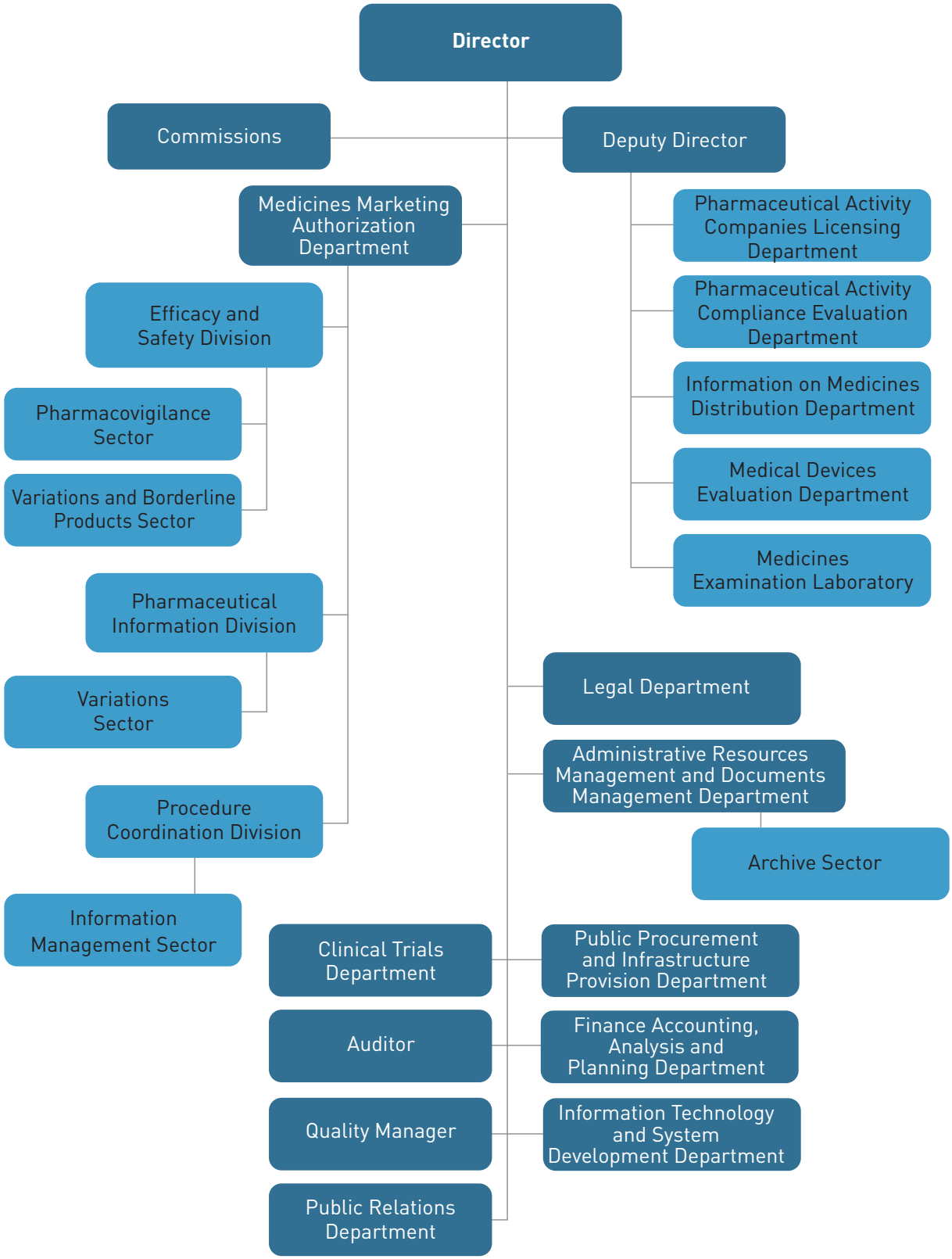
- Develop mutual cooperation with persons conducting scientific activity, paying particular attention to mutual exchange of information and knowledge.
- Continue to develop employee competencies, paying particular attention to scenarios regarding future development of medicinal products. As part of the task, it is necessary to make comprehensive use of the EMA established EU Network Training Centre and the opportunities offered by Joint Action in health programs and PIC/S.
- Within the realm of possibility, implement and improve opportunities for non-material motivation of employees.
- Plan and implement ICT projects and changes with the objective of increasing process efficiency. This would include promoting the development of e-services.

In 2017, SAM will face several external assessments. The periodic Pharmaceutical Inspection Co-operation Scheme audit is planned to take place in the first half of 2017 and it will assess the harmonised implementation of good manufacturing practice standards in Latvia and SAM quality systems in the field of compliance evaluation.

At the end of 2017, for the fourth time the State Agency of Medicines will participate in the mutual benchmarking of medicines agencies in EU member states with regard to results of operation and best practices. The audit will be conducted by independent observers and auditors from other medicines agencies in EU member states and it will provide additional information and future vision of improvements to the institutional processes and administrative capacity.

7. ANNEXES

7.1. Annex. SAM Structure



7.2. Annex. Budget and Expenses of the State Agency of Medicines

No.	Title of position	2014	2015	2016	
		Budget implementation EUR	Budget implementation EUR	Budget estimate EUR	Budget implementation EUR
1.	Resources for covering expenses (income)	5 452 798	5 170 617	4 856 107	4 892 390
1.1.	Paid services and other own income	5 421 136	5 127 338	4 856 107	4 892 390
1.2.	Transfers from the State budget	31 662	43 279		
2.	Expenses (total)	5 111 696	4 858 019	7 102 813	6 170 476
2.1.	Maintenance expenses	4 422 829	4 064 523	6 532 356	5 762 004
2.1.1.	Regular expenses	3 809 713	4 064 523	4 889 529	4 119 177
2.2.	Transfers for maintenance expenses	613 116		1 642 827	1 642 827
2.3.	Expenses for capital investments	688 867	793 496	570 457	408 472
	Financial balance	341 102	312 598	-2 246 706	-1 278 086
	Financial resources	- 341 102	-312 598	2 246 706	1 278 086
	Increasing (-) or decreasing (+) change in surplus of financial resources from paid services and other independent income	-341 102	-312 598	2 246 706	1 278 086

A REPORT BY INDEPENDENT AUDITORS

Riga

The date of the document is the date of the electronic signature on the document **No.1/2016**

To the State Agency of Medicines

Our opinion on the financial report

We have conducted an audit of the State Agency of Medicines' (hereinafter - Agency) financial report of 2016. The attached financial report includes:

- A report on the financial situation of the Agency on 31 December 2016 – form No. 1 "Balance"
- A report on the financial results of operation in 2016 - form No. 4-3.
- A report on the changes in own capital (net assets) in 2016 - form No. 4-1.
- A report on the flow of financial resources in 2016 - form No. 2-NP.
- Annexes of the financial report laid down in Clause 4.5 of the Cabinet of Ministers of the Republic of Latvia Regulation No. 1115 of 15 October 2013 "Procedure for Preparation of the Annual Report", description of the basic principles of accounting, explanations of reports, explanation of the financial report.

In our opinion, the attached financial report provides a truthful and clear overview of the financial situation of the State Agency of Medicines on 31 December 2016, as well as of the financial results of its operation and flow of financial resources in the year concluded on 31 December 2016, in accordance with the requirements of the Cabinet of Ministers of the Republic of Latvia Regulation No. 1115 of 15 October 2013 "Procedure for Preparation of the Annual Report".

Justification of the opinion

In accordance with the Law on Sworn Auditors of the Republic of Latvia, we carried out the audit in compliance with the International Standards on Auditing (hereinafter – ISA) recognised in the Republic of Latvia. Our responsibilities laid down by these standards are described below in the section *Responsibility of the auditor with regard to the financial report audit* of our report.

We are independent from the Agency in accordance with the requirements of the Code of Ethics for Professional Accountants established by the International Ethics Standards Board for Accountants (IESBA Code) and the independency requirements included in the Law on Sworn Auditors that are applicable to the financial report audit conducted by us in the Republic of Latvia. We have also complied with the other professional ethical standards and requirements for impartiality laid down in the IESBA Code and the Law on Sworn Auditors of the Republic of Latvia.

We are of the opinion that the evidence obtained as a result of our audit provides sufficient and appropriate justification of our opinion.

Reporting of other information

The Administration of the Agency is responsible for other information. Other information is made up by the Administration Report that is reflected in the "Administration report" section of the annual report – ZINO.

Our opinion of the financial report is not applicable to other information included in the annual report and we do not provide any sort of verification for it, excluding the one indicated in the section "Other reporting requirements in accordance with the requirements of the legal acts of

the Republic of Latvia" of our report.

In relation to the audit of the financial report, our responsibility is to familiarise with other information and, by doing so, assess whether this other information does not differ significantly from the information in the financial report or from our knowledge that we obtained during audit or does not include any other significant discrepancies.

If, based on the work conducted and taking into account the knowledge and understanding of the Agency and its operational environment obtained during audit, we conclude that other information contains significant discrepancies, it is our responsibility to report such circumstances. No such circumstances have come to our attention that would require reporting.

Other reporting requirements in accordance with the requirements of the legal acts of the Republic of Latvia

In addition, in accordance with the Law on Sworn Auditors of the Republic of Latvia it is our responsibility to provide an opinion on whether the Administration report has been prepared in accordance with the requirements of the Cabinet of Ministers of the Republic of Latvia Regulation No. 1115 of 15 October 2013 "Procedure for Preparation of the Annual Report".

Based only on the procedures conducted as part of our audit, we are of the opinion that:

- The information provided in the Administration report on the year of review, that the financial report is prepared for, conforms to the financial report, and
- The Administration report is prepared in accordance with the requirements of the Cabinet of Ministers of the Republic of Latvia Regulation No. 1115 of 15 October 2013 "Procedure for Preparation of the Annual Report".

In addition, taking into account the knowledge and understanding of the Agency and its environment obtained during the audit, it is our responsibility to report, if we have identified significant discrepancies in the Administration report. No such circumstances have come to our attention that would require reporting.

Responsibility of the Administration and persons entrusted with the supervision of the Agency with regard to the financial report

The Administration is responsible for the preparation of a financial report providing truthful and clear reflection in accordance with the requirements of the Cabinet of Ministers of the Republic of Latvia Regulation No. 1115 of 15 October 2013 "Procedure for Preparation of the Annual Report", as well as for the maintenance of an internal control system that, in the opinion of the Administration, is necessary for preparation of a financial report, which does not contain significant discrepancies due to fraud or error.

When preparing the report, the Administration is responsible for assessing the Agency's ability to continue operation, providing information regarding circumstances related to the Agency's ability to continue operation and application of the principle of continuing operation, unless the Administration is planning to liquidate the Agency or discontinue its operation, or the Administration has no other real alternative than to liquidate or discontinue the operation of the Agency.

Persons entrusted with the supervision of the Agency are responsible for the supervision of the preparation process of the Agency's financial report.

Responsibility of the auditor with regard to the financial report audit

Our objective is to obtain sufficient certainty that overall the financial report does not contain significant discrepancies due to error or fraud and provide an auditors' report expressing an opinion. Sufficient certainty is a high level of certainty, but does not guarantee that the audit conducted in accordance with ISA shall always reveal significant discrepancies, if such exist. Discrepancies may arise due to fraud or error and they are considered significant, if it can be justifiably considered that any of these discrepancies alone or all of these discrepancies together could affect economic decisions made by users, based on this financial report.

Upon conducting the audit in accordance with ISA, during the whole audit process we shall make professional judgements and maintain professional scepticism. We shall also:

- Identify and assess risks of significant discrepancies due to fraud or error being present in the financial report, establish and conduct auditing procedures for minimisation of such risks, as well as obtain audit evidence that provides sufficient and appropriate justification for our opinion. The risk that significant discrepancies due to fraud will not be identified is higher than the risk that significant discrepancies due to error will not be identified, because fraud may involve secret agreements, falsification of documents, intentional withholding of information, fictitious reflection of information or violations of internal control;
- Gain understanding of internal control which is important for conduct of audit in order to establish audit procedures appropriate for the specific circumstances, but not for providing an opinion on the efficiency of the Agency's internal control;
- Assess the compliance of applied accounting policies and validity of accounting estimations and relevant information supplied by the Administration;
- Draw conclusions regarding compliance of the principle of continuing operation applied by the Administration and, based on the existence or non-existence of major uncertainty with regard to events and circumstances that may create significant doubts, regarding the Agency's ability to continue operation. If we conclude that significant uncertainty exists, the auditor report shall draw attention to the information regarding these circumstances provided in the financial report, or if no such information is provided we shall provide a modified opinion. Our conclusions are justified with audit evidence obtained until the date of the auditors' report. However, the Agency may discontinue operation depending on future events or circumstances;
- Assess the overall structure and content of the financial report, including the information and explanations disclosed in the annexes, and whether the financial report truthfully reflects the transactions and events which the financial report is based on.

We shall contact the persons entrusted with supervision of the Agency and, among other things, shall provide information regarding the scope and time of the audit, as well as important audit observations, including significant internal control deficiencies identified during audit.

LLC „Auditorfirma Padoms"
Licence No. 68

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Vaira Šķibele
Chairperson of the board
Sworn auditor
Certificate No. 24

THIS DOCUMENT HAS BEEN SIGNED WITH A SECURE ELECTRONIC SIGNATURE AND CONTAINS A TIME STAMP

Vaira Šķibele 29239651
info@auditorfirmapadoms.lv

7.3. Annex. SAM History

1996

Establishment of the non-profit organisation - state joint stock company "State Medicines Agency" with the following tasks:

- Evaluation, authorization, monitoring, control and regulation of distribution of medicines and pharmaceutical products
- Issuance of authorisations for conduct of clinical trials
- Approval of directions for serial preparation of medicines at pharmacies
- Issuance of authorization for distribution of medicinal herbs purchased from physical persons

General director and Chairman of the board – Jānis Ozoliņš
Laboratory of Quality Control of Medicines (until 2006)

1998

Medicines Examination Laboratory
Clinical Trial Inspection Department

2000

The Medicines Examination Laboratory is accepted into the international network of Official Medicines Control Laboratories (OMCL).

2001

Evaluation and approval of medicinal product advertising (until 2009)
Adverse Drug Reaction Monitoring Department

2002

Development of Quality Management System, internal audit
The 5th EU meeting of associated drug regulatory authorities takes place in the Agency

2004

"State Medicines Agency" is reorganized as the public agency "State Agency of Medicines" (SAM)

2005

Inguna Adoviča becomes Director of SAM
Introduction of medicinal product price monitoring systems

2006

Participation within the Pharmaceutical Inspection Cooperation Scheme (PIC/S)
Pharmaceutical Activities Compliance Evaluation Department
Meeting of the medicines agencies of the Baltic states in Riga
The authorisation of veterinary medicines and monitoring their circulation (until 2010)

2007

Initiation of licensing of pharmaceutical activity companies

2009

Medicines Examination Laboratory – compliant with the requirements of the ISO 17025 standard

2010

The function of compliance evaluation, registration and safety monitoring of medical devices
The compliance evaluation and surveillance of procurement and storage organisations of tissues, cells and organs, blood establishments, hospital blood banks and the State Blood Donor Centre

2012

SAM integrated management system - compliant with the requirements of the ISO 9001:2008 and ISO 27001 standards

2014

New functions in the field of manufacturing, import and distribution of active substances and initiation of registration of persons conducting brokering with medicines

2015

SAM events during the Latvian Presidency of the EU Council: (meetings of the Heads of Medicines Agencies (HMA), HMA Clinical Trails Facilitation Group (CTFG), HMA Working Group of Quality Managers (WGQM), HMA Working Group of Communication Professionals (WGCP), as well as meetings of the European Medicines Agencies Cooperation on Legal and Legislative Issues (EMACOLEX), Competent Authorities for Medical Devices (CAMD) and the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh))

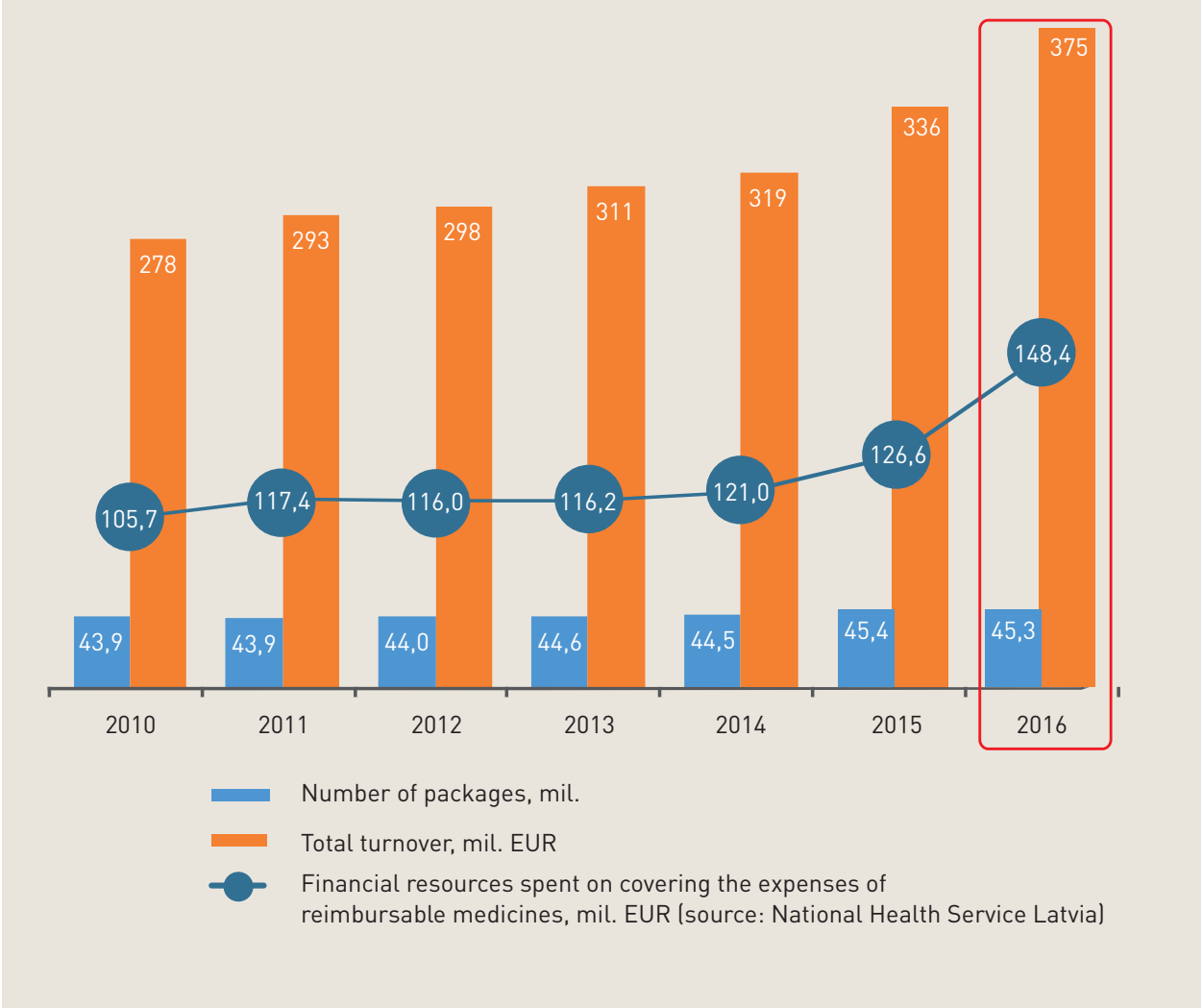
Svens Henkuzens becomes Director of SAM

SAM integrated management system – recertified as compliant with the requirements of ISO 9001 and ISO 27001 standards

2016

STATE AGENCY OF MEDICINES 20 YEARS

7.4. Annex. Total Turnover of Medicines in Latvia



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