State Agency
of Medicines
Republic of Latvia

STATE AGENCY OF MEDICINES

ANNUAL REPORT

2017

CONTENT

INTRODUCTION

Dear reader,

upon completing the previous three-year strategic planning cycle (2014–2016), a new mid–term strategy for the State Agency of Medicines was approved and is to be implemented until 2019. The Agency has developed a new operational strategy that is based on the achievements in the previous years and is aimed towards the availability of safe, qualitative and effective medicines in Latvia, paying special attention to contributing to a sustainable healthcare system and sustainable development of the Agency. Taking into account the important role of international collaboration in the daily work of the Agency, the strategy has been established keeping in mind the strategic initiatives and priorities of the network of European medicines agencies and the European Medicines Agency.

The achievements of the State Agency of Medicines in 2017 were internationally recognised within several collaboration forums:

Firstly, the Agency was compared with other European agencies according to the criteria of Benchmarking of European Medicines Agencies IV which include strategic management and leadership, interaction with non-governmental organisations, quality and risk management, scientific evidence based decision-making. Taking into account the Agency's longstanding and purposeful operation in compliance with ISO standards, most of the criteria showed a very high level of performance, furthermore, performance in all of the assessment criteria was above average.

Secondly, a scheduled audit as part of the Joint Audit Program was conducted in the field of competent authorities of Good manufacturing practice to assess the Agency's capacity to conduct compliance evaluation of Good manufacturing practice in accordance with the standards within the European Economic Area. Based on the assessment, trust

Svens Henkuzens, Director of the State Agency of Medicines

was gained regarding harmonised compliance evaluation of medicines manufacturers in the European Economic Area and countries that have mutual recognition agreements in place with the European Union, for example, Canada, Japan, Australia, soon to be joined also by USA. As a result of the audit, confidence was gained regarding implementation of high standards and requirements for supervision of medicines manufacturers in Latvia that are equivalent to the international practice.

Thirdly, competent authorities in the field of compliance evaluation of blood, tissues and cells are also moving in the direction of increased collaboration and harmonisation. A pilot project for comparative assessment of competent authorities is being developed with the support of the European Commission, and the State Agency of Medicines applied to be one of the first countries to be assessed as part of the pilot project. The benefits were two-sided – we made a substantial contribution to the development of the project and received feedback regarding the strengths of the Agency and potential for improvement.

Last year there was a substantial increase in the Agency's activity in the European

Medicines Agency. With regard to procedures, the participation of experts from Latvia's Agency has increased almost by 80% both in the assessment preparation for centrally authorised medicines and pharmacovigilance issues. Please see further details regarding centralised and decentralised procedures in the marketing authorisation section of the Annual report.

In order to strengthen collaboration and dialogue with the target audience among professionals several informative events for representatives of the pharmaceutical field were organised in 2017 – both regarding issues related to marketing authorisation of medicines and regarding the regulation for clinical trials and medical devices. The "Consult first" principle was and will continue to be implemented in the State Agency of Medicines and our collaboration partners have expressed their approval on this matter.

With regard to activities in the field of international collaboration, it should be mentioned that in 2017 we have joined the World Health Organization certification scheme on quality of pharmaceutical products moving in international commerce. Participation in the scheme allows third countries to verify the authenticity and contents of the certificates issued in Latvia. Certificates issued by the Agency are important for export of products manufactured by medicines manufacturers in Latvia to third countries.

In 2017, the Agency also initiated a two-way collaboration with the medicines agencies in Denmark and Norway to strengthen the capacity of SAM. This is the first step towards collaboration and exchange of best practices on expert level over the next three to four years.

These achievements would not be possible without the dedicated work and perseverance of Agency employees to ensure the development of this organisation, and it will be particularly important in 2018 when new challenges will be presented by the United Kingdom withdrawing from the European Union.

"With regard to activities in the field of international collaboration, it should be mentioned that in 2017 we have joined the World Health Organization certification scheme on quality of pharmaceutical products moving in international commerce. Participation in the scheme allows third countries to verify the authenticity and contents of the certificates issued in Latvia"

ABBREVIATIONS

ADR	Adverse drug reaction
BEMA	Benchmarking of European Medicines Agencies
CAP	Centralised authorisation procedure
CDPC	Centre for Disease Prevention and Control
CHMP	European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use
CM	Cabinet of Ministers
CPP	Certificate of Pharmaceutical Product
DCP	Decentralised authorisation procedure
EMA	European Medicines Agency
EU	European Union
FDA	USA Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
IMS	Integrated management system
INCB	International Narcotics Control Board
ISO	International Organization for Standardization
JAP	EMA Joint Audit Programme
LATMED	Electronic database of the Registers of Medical Devices
MAH	Marketing authorisation holder
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
SoHO	Substances of human origin
VIC	Vaccine-induced complications
WHO	World Health Organization

1. ABOUT THE STATE AGENCY OF MEDICINES

1.1 LEGAL STATUS

The State Agency of Medicines (hereinafter also SAM) is a state institution under the supervision of the Minister of Health and its operation is regulated by the State Administration Law, the Law on Public Agencies, the Pharmaceutical Law, Medical Treatment 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 also CM) Order No. 403 "Regarding the Non-profit Organisation State Joint Stock Company "State Medicines Agency"".

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.

Our vision is to become one of the leading institutions among the equivalent institutions on a national and international level by implementing the delegated functions and building our development on knowledge, efficacy, quality and collaboration.

1.2 FUNCTIONS OF THE STATE AGENCY OF MEDICINES

- Evaluation and authorisation of medicines, expertise on quality of medicines, development of the Medicinal Product Register of the Republic of Latvia;

"Our vision is to become one of the leading institutions among the equivalent institutions on a national and international level by implementing the delegated functions and building our development on knowledge, efficacy, quality and collaboration"

- Pharmacovigilance and vigilance of other medical products;
- 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 release of specially supplied medical devices on the market, as well as authorisations for conduct of clinical trials with medical devices;

- Issuance of compliance certificates to hospital blood banks, blood establishments and the State Blood Donor Centre;
- Issuance of authorisations for utilisation of human tissues, cells and organs to hospitals and higher education institutions implementing an accredited medical studies program;
- Issuance of licences for pharmaceutical activity;
- Compliance evaluation of active substance manufacturers, distributors and importers with the requirements of Good Manufacturing Practice and Good Distribution Practice and issuance of compliance certificates;
- Registration of manufacturers, importers and distributors of active substances;
- Registration of persons conducting international business transactions (brokers) with medicines for human use;
- Collaboration with professional organisations of doctors and pharmacists, non-governmental organisations in the field, and foreign and international institutions;
- 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 network by participating in work-sharing, complying with the collective standards and procedures and cooperating with other European and international organisations.

In 2017, the State Agency of Medicines was operating as a public agency not financed from the state budget and its operation was financed by income received from paid services in accordance with the Cabinet of Ministers Regulation No. 873 "Publicly Available Paid Service Pricelist of the State Agency of Medicines" adopted on 17 September 2013.

1.3 MAIN TASKS IN THE YEAR OF REVIEW

Operation was planned in accordance with the relevant policy documents issued by the Cabinet of Ministers and the Ministry of Health, as well as taking into account the strategic operational directions of the European Medicines Agency and Heads of Medicines Agencies, and developmental priorities were established.

In 2017, SAM established the operational strategy for 2017–2019, paying special attention to the availability, safety, rational use of medicines and development of the institution.

The main tasks in the year of review were as follows:

- Participate in improving the normative acts, as well as develop other opportunities to promote timely availability of appropriately evaluated medicines in segments where availability of medicines does not meet the demands of public health;
- Contribute to the preparation of normative acts and policy documents on both the national and international level, giving particular consideration to the impact of the regulatory framework on the long-term affordability of qualitative, safe and effective healthcare products and efficient use of SAM resources;
- Begin transposition of the requirements of the Clinical Trial Regulation, Medical Device Regulation, as well as Falsified Medicines Regulation;
- Minimise the public health risk created by disruptions in supply of medicines, as well as the risk of not releasing authorised and necessary medicines on the market in Latvia;
- Improve the process of compliance evaluation of the pharmaceutical and

healthcare field in the competency of SAM by acknowledging and implementing compliance evaluation based on risk assessment whenever possible;

- Ensure educational activities (seminars, consultations, online and printed information) and collaborate with the industry according to the wishes and needs of the target audience, paying particular attention to the issues that promote the safe and rational use of medicines, amendments to legal acts, new and improved methods and instruments in the monitoring of safety of medicines;
- Expand proactive participation in the EMA formal work-sharing procedures, as well as in the informal work-sharing initiatives, contribute to international forums;
- Develop mutual collaboration with scientific workers, paying particular attention to mutual exchange of information and knowledge;
- Continue to improve employee competence, paying particular attention to future scenarios of medicinal product development – it is necessary to fully utilise the EU Network Training Centre established by EMA, the opportunities offered within the Joint Action Health Program and PIC/S;
- Plan and implement ICT projects and changes with the objective of increasing process efficiency, including promoting e-service development.

2. RESULTS OF OPERATION OF THE STATE AGENCY OF MEDICINES

2.1 MEDICINES

2.1.1 MARKETING AUTHORISATION OF MEDICINES

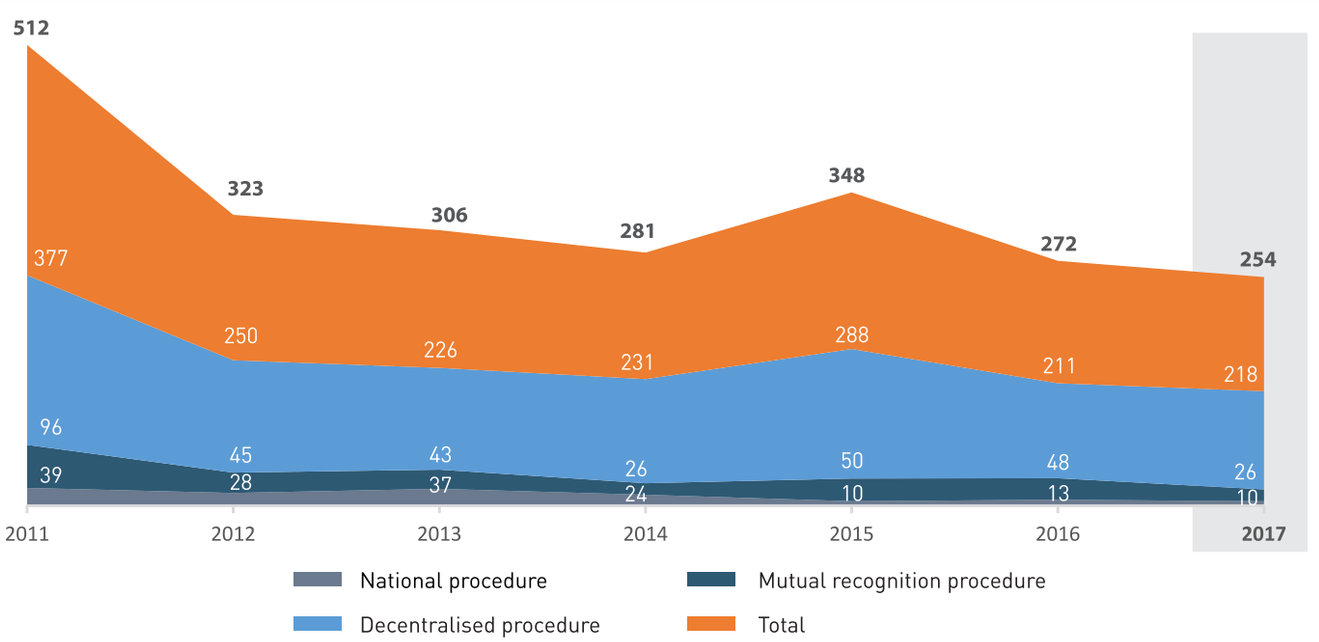
Taking into account the latest trends in the evaluation of marketing authorisation documentation for medicines in the European Union using an approach based on risk assessment, in 2017, the departmental functionality was improved. As a result, the duration of the national phase in procedures where Latvia was a concerned member state was shortened. On average, the State Agency of Medicines carried out the regulatory authority function in the national phase within 31 days.

For the first time the informative seminar for merchants in the industry organised by the Medicines Marketing Authorisation Department was available in a video format. All of the interested parties may learn about the topics discussed in the seminar on the website and in the Youtube channel of the State Agency 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 2017, by conducting the quality, safety and efficacy assessment within marketing authorisation documentation the State Agency of Medicines evaluated more than 8 000 applications for marketing authorisation, renewal and variations to marketing authorisation documentation. Evaluation was conducted also for general, chemical, pharmaceutical, preclinical and clinical, as well as pharmacovigilance documentation.

In 2017, assessment reports regarding 29 medicinal products were prepared for the

MARKETING AUTHORISATION OF MEDICINES



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 relation to the entries in the paid service pricelist of the State Agency of Medicines with an applicable 90% discount, SAM also received documents that were noncompliant with the normative acts, thus, adoption of a positive decision regarding marketing authorisation of these medicines was not possible. In 2017, SAM had to adopt a negative decision in 13 national marketing authorisation procedures.

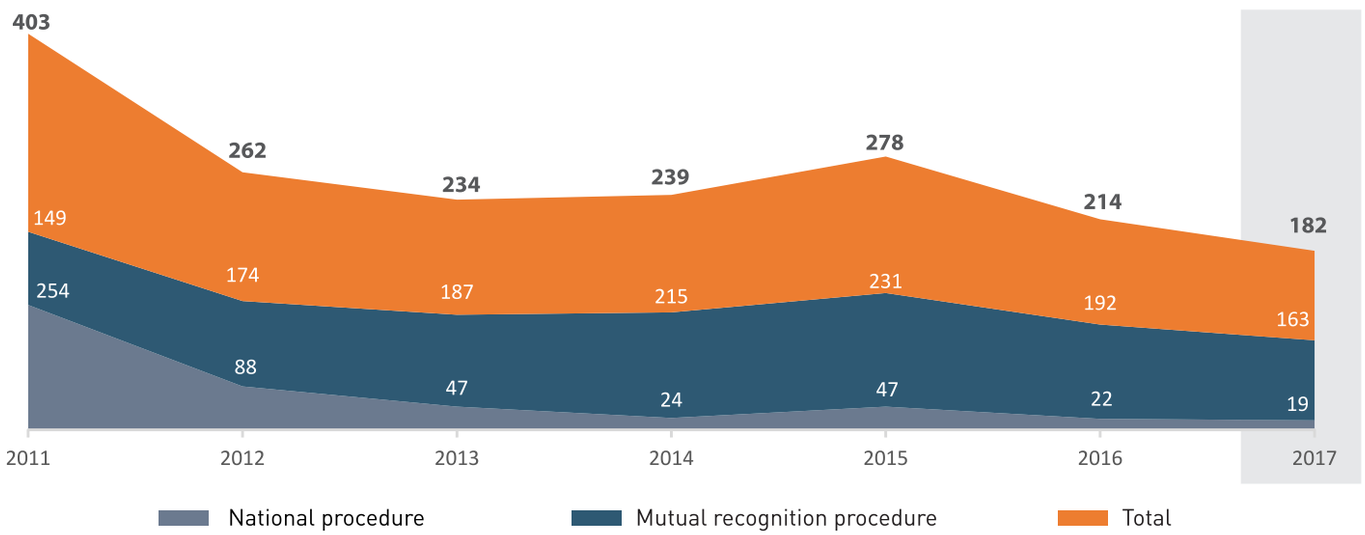
In 2017, Latvia successfully completed one mutual recognition procedure (MRP) and five decentralised marketing authorisation procedures (DCP) as the Reference Member State. In 2017, Latvia also took over the responsibilities of the Reference Member State from other countries for 24 medicinal products.

Assessment reports regarding

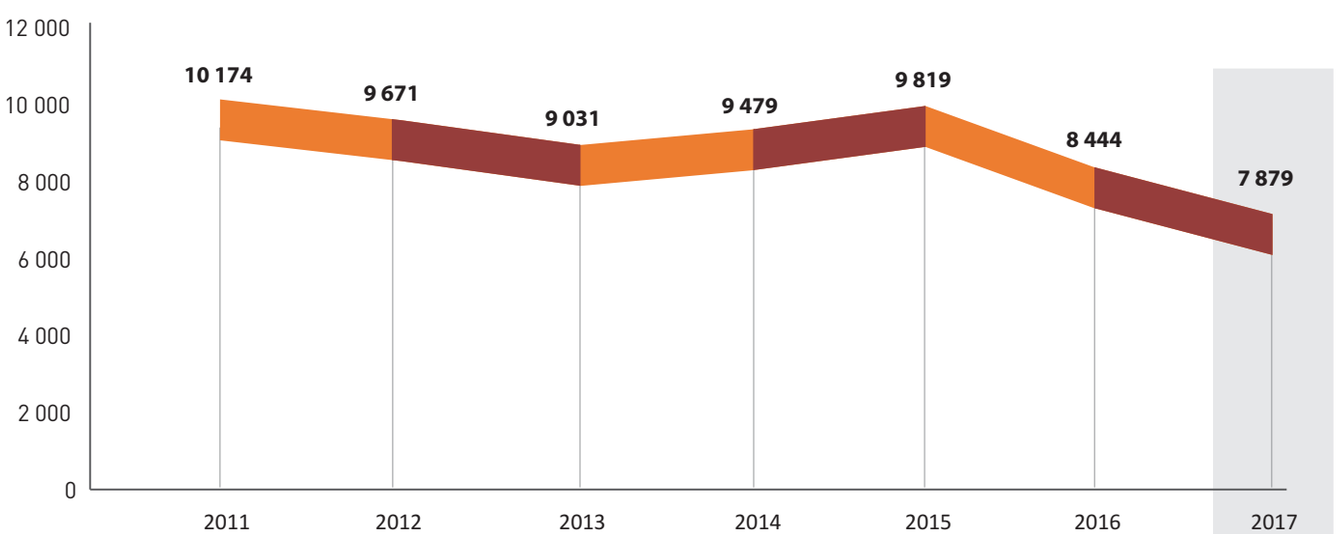
29

medicinal products were prepared

RENEWAL PROCEDURE OF MEDICINES



VARIATIONS TO THE MARKETING AUTHORIZATION PROCEDURE



At the end of the period of review, SAM was responsible for:

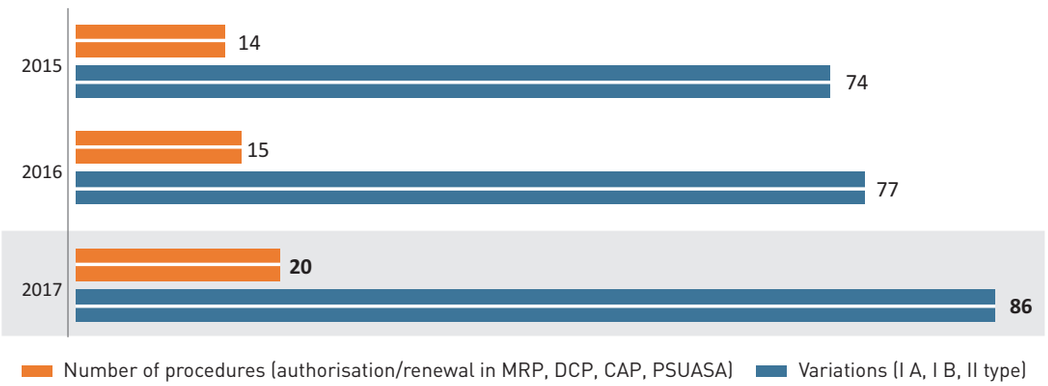
6
medicinal products centrally authorised by the European Medicines Agency

63
medicinal products authorised in DCP/MRP as the Reference Member State

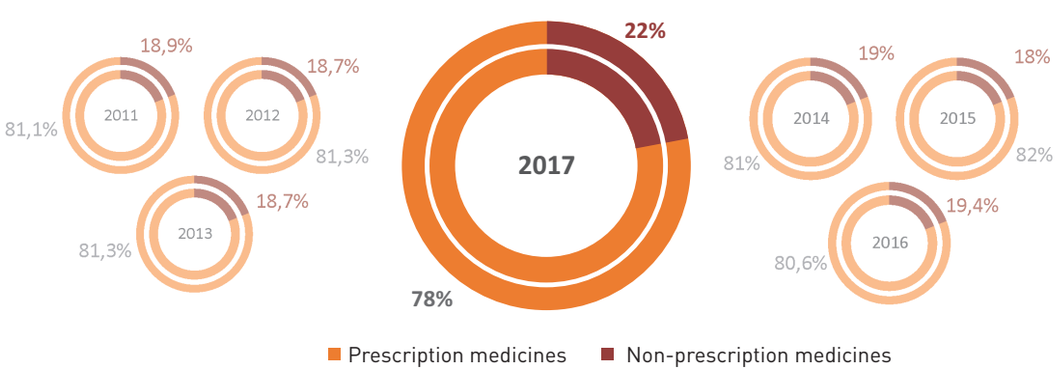
20
active substances as the member state responsible for signal monitoring

10
active substances as the leading member state in the assessment of periodic safety update reports

AUTHORISATION OF MEDICINES AND VARIATIONS (LATVIA AS REFERENCE MEMBER STATE)



THE PROPORTION OF PRESCRIPTION AND NON-PRESCRIPTION MEDICINES



In the year of review, the State Agency of Medicines successfully concluded 254 MRP/DCP and national authorisation procedures, 182 renewal procedures, and approved 7477 variations and denied 402 variations to marketing authorisation documentation.

Owing to the increasing professionalism of our experts, the State Agency of Medicines takes up more responsibilities in the common EU work-sharing and the work of scientific committees. In 2017, Latvia participated in the EMA Committee for Medicinal Products for Human Use (CHMP) by evaluating eight centralised marketing authorisation

Informative seminar on authorisation of medicines related issues on 18 May 2017
Participants: the collaboration partners

procedures. In three of these centralised marketing authorisation procedures SAM fulfilled the peer review function, in another three procedures – SAM was the responsible rapporteur (one of them continues in 2018) and in two procedures – the corapporteur (one of them continues in 2018). Independently of the peer review function, in two of the procedures our team was the responsible rapporteur in the Pharmacovigilance Risk Assessment Committee (PRAC). Latvia was the responsible rapporteur for two type II variation procedures for centrally authorised medicinal products.

Latvia was the leading member state in the single assessment procedures of periodic safety update reports (PSUR) regarding seven active substances. Latvia was represented within the EMA Paediatric Committee and participated in 11 primary Paediatric Investigation Plan (PIP) assessment procedures, 8 PIP modification assessment procedures and 4 EMA Scientific advice preparation procedures. A representative of SAM in the EMA Committee for Orphan Medicinal Products (COMP) prepared two decisions regarding proposals to apply orphan medicinal product status to medicines. In 2017, by regularly participating in the work sessions of the European Directorate for Quality of Medicines (EDQM) as external experts, two MMAD experts evaluated the compliance of more than 70 medicinal products with the monographs of the European Pharmacopoeia (CEPs).

At the end of the period of review, SAM was responsible for:

- 6 medicinal products centrally authorised by the European Medicines Agency;
- 63 medicinal products authorised in DCP/MRP as the Reference Member State;
- 20 active substances as the member state responsible for signal monitoring;
- 10 active substances as the leading member state in the assessment of periodic safety update reports.

In the year of review, 26 applications were evaluated for product compliance with the definition of a medicinal product and SAM issued its opinion regarding the status of these products.

Twenty public assessment reports for nationally authorised medicines were prepared, coordinated with marketing authorisation holders and published in 2017.

The proportion of prescription and non-prescription medicines included in the Medicinal Product Register of Latvia has remained unchanged for many years – with approximately 80% prescription medicines and 20% non-prescription medicines. In 2017, the precise proportion was 77.6% and 22.4%, respectively.

2.1.2 AUTHORISATIONS FOR DISTRIBUTION OF MEDICINES

In 2017, the State Agency of Medicines ensured expertise on applications and documentation in accordance with the normative acts for:

- 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 2017, SAM issued 7248 authorisations for import, export, transit and distribution of medicines. In addition, SAM carried out expertise on applications and documentation and issued 5 licences and authorisation cards to precursor operators and 6 authorisations for use of plants, substances and medicines included in the I, II and III list of narcotic, psychotropic substances and precursors controlled in Latvia. Variations were made to distribution authorisations of 235 parallel imported medicines.

Information regarding consumption and price of medicinal products was assembled monthly and published on SAM website www.zva.gov.lv. In 2017, with the help of the previously established list of disruptions

"In order to improve the availability of centrally authorised medicines in Latvia, on 14 July 2017 the European Medicines Agency decreased the administrative fees for parallel distribution of centrally authorised medicines for the period of one year. Thus, in 2017, applications were submitted for parallel distribution of 12 centrally authorised medicines, 8 of which were submitted after the administrative fees were decreased in July 2017"

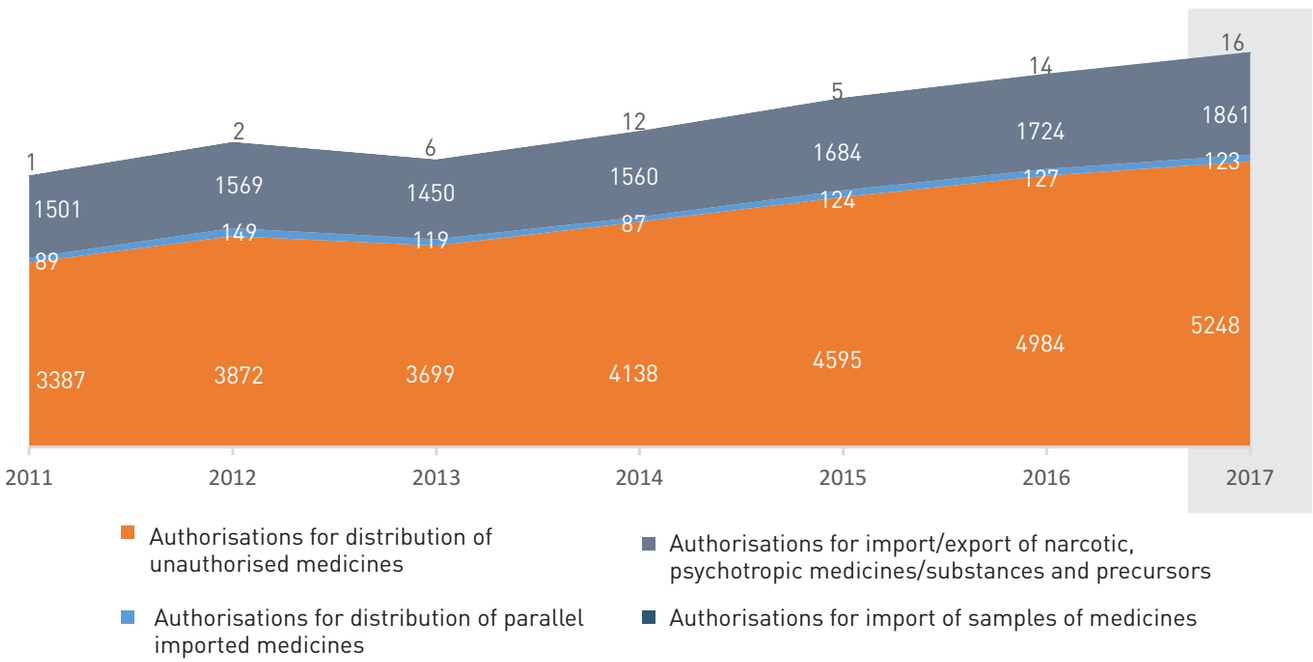
in the supply of medicines and other tools publicly available in the "Register" section of SAM website, public involvement was ensured in the provision of information regarding disruptions in the supply of medicines via a report form available on SAM website.

The annual publication "Statistics on Medicines Consumption 2016" was prepared, based on the statistical information regarding sales of medicines submitted by wholesalers.

In 2017, SAM also ensured 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.

In order to improve the availability of centrally authorised medicines in Latvia, on 14 July 2017 the European Medicines Agency decreased the administrative fees for parallel distribution of centrally authorised medicines for the period of one year. Thus, in 2017, applications were submitted for parallel distribution of 12 centrally authorised medicines, 8 of which were submitted after the administrative fees were decreased in July 2017. From 2007 until 2016, a total of 24 centrally authorised medicines were distributed in Latvia via the parallel dis-

NUMBER OF AUTHORISATIONS FOR IMPORT, EXPORT AND DISTRIBUTION OF MEDICINES FROM 2011 UNTIL 2017



tribution procedure. Parallel distribution of medicines means that medicines authorised via the centralised authorisation procedure and supplied by a European Economic Area country are released on the market in Latvia, provided that they are released by a medicines wholesaler that is not the manufacturer, marketing authorisation holder of these medicines or their authorised representative.

2.1.3 CLINICAL TRIALS WITH MEDICINES

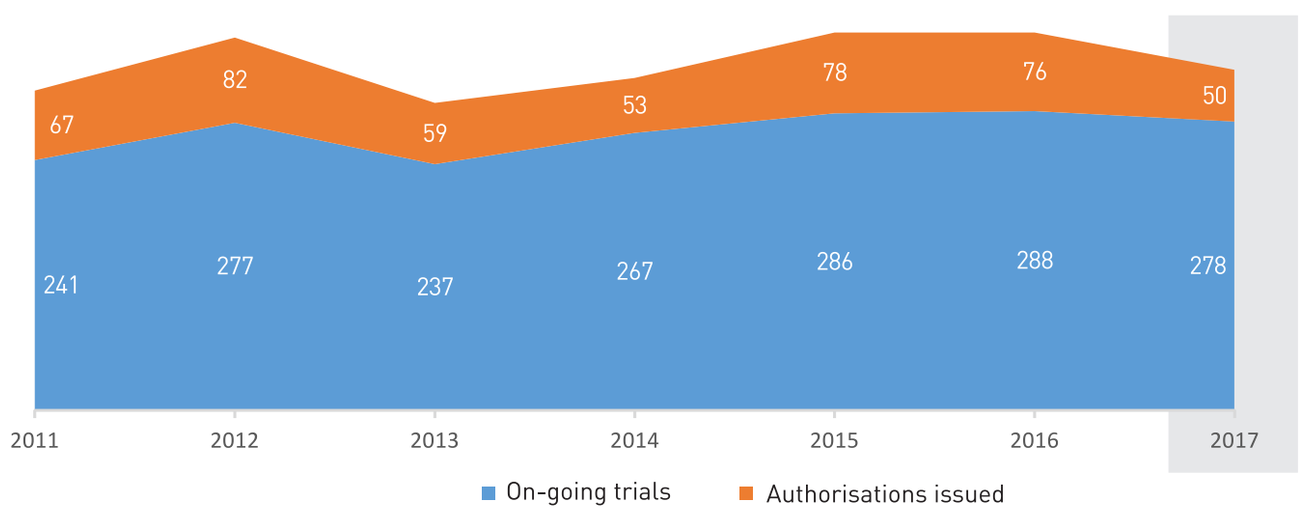
In accordance with the Cabinet of Ministers Regulation No. 289 of 23 March 2010 "Regulations Regarding the Procedures for Conduct of Clinical Trials and Non-interventional Trials of Medicinal Products, Labelling of Investigational Medicinal Products and the Procedures for Assessment of Conformity of Clinical Trial of Medicinal Products with the Requirements of Good Clinical Practice" and legal acts of the European Union, in 2017 the State Agency of Medicines received 59 clinical trial projects for review, 20 of which were submitted for evaluation as part of the International Harmonisation Procedure.

In 2017, the State Agency of Medicines issued authorisations for the conduct of 50 clinical trials with medicines, including 14 clinical trials within the International Harmonisation Procedure. One of the authorised clinical trials was approved with limiting conditions. In 2017, the State Agency of Medicines granted 298 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 other countries.

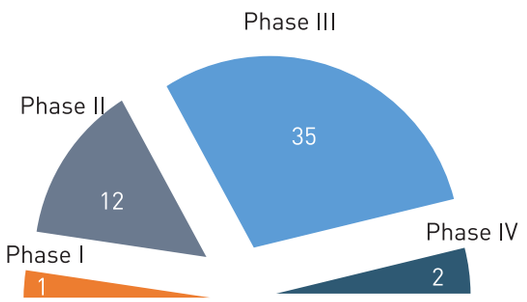
In comparison with the previous year, in 2017, there was a slight decrease in the number of authorised clinical trials, but their complexity has increased with regard to both

"In comparison with the previous year, in 2017, there was a slight decrease in the number of authorised clinical trials, but their complexity has increased with regard to both the molecules to be investigated and the study design. The number of clinical trials (278) being conducted in 2017 was stable with respect to the previous years. At the same time, the number of submitted and authorised amendments to clinical trials increased."

NUMBER OF AUTHORISATIONS ISSUED AND ON-GOING CLINICAL TRIALS (2011–2017)



NUMBER OF CLINICAL TRIALS AUTHORISED IN 2017 ACCORDING TO TRIAL PHASE



NUMBER OF CLINICAL TRIALS AUTHORISED IN 2017 ACCORDING TO MEDICAL SPECIALITY

Speciality	Number of trials
Oncology	8
Gastroenterology	7
Rheumatology	6
Pulmonology/Allergology	5
Infectology	4
Cardiology	4
Urology/Nephrology	4
Traumatology/Orthopedics/Surgery	3
Dermatology	3
Gynaecology	2
Neurology	2

the molecules to be investigated and the study design. The number of clinical trials (278) being conducted in 2017 was stable with respect to the previous years. At the same time, the number of submitted and authorised amendments to clinical trials increased.

Information regarding applications for clinical trials with medicinal products, the time of their authorisation, the dates of approval of applications for substantial 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

A total of

278

clinical trials were conducted in Latvia in 2017 and

52

projects were completed during the year, one of the projects was withdrawn before its initiation

TRIAL SITES OF CLINICAL TRIALS WITH MEDICINAL PRODUCTS AUTHORISED IN 2017

Trial site	Number of trials
State LLC "Pauls Stradins Clinical University Hospital"	28
Riga Eastern Clinical University Hospital • Clinic "Gailezers" • Latvian Oncology Center • Clinic "Bikernieki"	21 14 5 2
LLC "Daugavpils Regional Hospital"	11
LLC "Veselibas centrs 4""	8
LLC "Liepaja Regional Hospital"	6
LLC "Vidzeme Hospital"	6
LLC "Riga 1st Hospital"	6
State LLC "Children's Clinical University Hospital"	5
Other clinical trial sites (83 in total)	1–4 trials at each site

trials in Latvia to clinical trial sponsors that had submitted safety reports in the Clinical Trial Module of the EudraVigilance database in accordance with the local and European normative requirements. During the year of review, 42 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, reviewed and registered 147 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 the assessment format established by the safety sub-group of the European working group on promotion of clinical trials.

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

A total of 278 clinical trials were conducted in Latvia in 2017 and 52 projects were completed during the year, one of the projects was withdrawn before its initiation.

The authorised clinical trial projects were sponsored by 32 foreign pharmaceutical companies. In accordance with the power of attorney from the sponsors, 14 contract research organisations were involved in organising and ensuring the quality of conduct of clinical trials in Latvia in 2017.

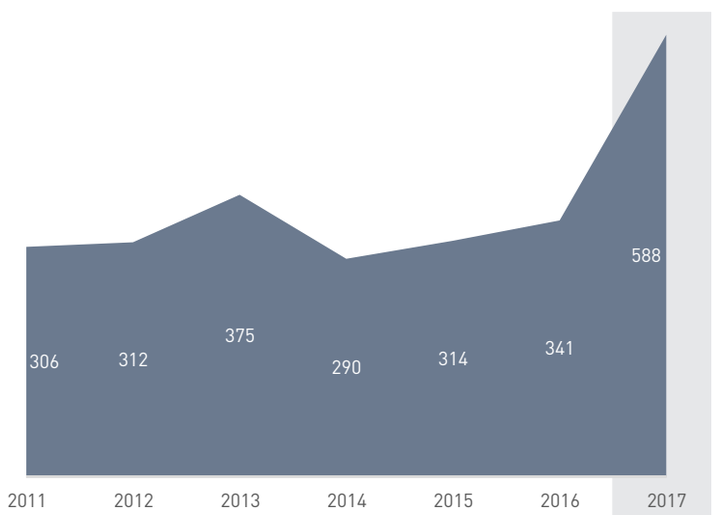
A total of 7 inspections of clinical trial compliance with good clinical practice were carried out in 2017, five of these were conducted at trial sites in Latvia, but two – in foreign countries, including one inspection upon request from EMA. Both major and minor deficiencies were discovered during the inspections.

In the year of review, employees of SAM Clinical Trials Department participated in the preparation of the 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.

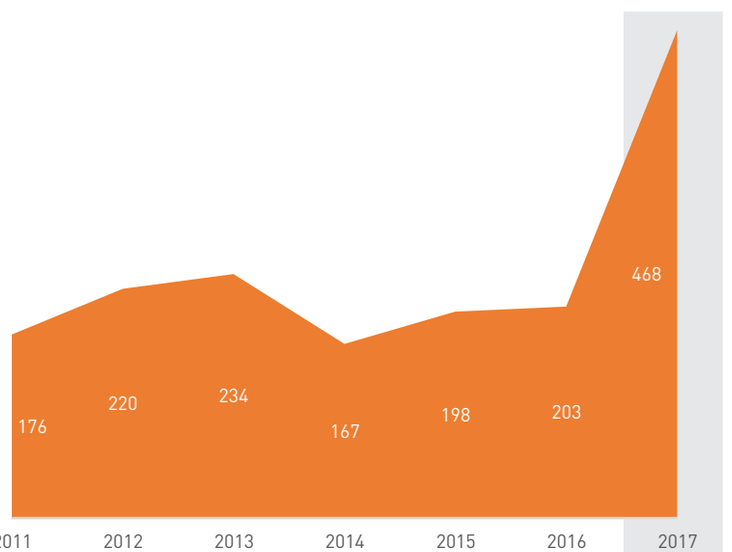
2.1.4 MONITORING OF ADVERSE DRUG REACTIONS AND RISK MINIMISATION

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.

ADVERSE DRUG REACTIONS REPORTS 2011-2017



CLINICAL CASES OF ADVERSE EVENTS WITH MEDICINES 2011-2017



"A pharmacovigilance expert representing Latvia actively participates in the meetings of the EMA Pharmacovigilance Risk Assessment Committee (PRAC). SAM informs the public, marketing authorisation holders and doctors in Latvia regarding all current issues in Europe related to medicinal products that are being reviewed within PRAC"

In 2017, the number of adverse drug reaction reports received in Latvia reached 588. In relation to the new reporting system introduced in in EudraVigilance 2017 and laid down in European normative acts, the number of reports submitted by marketing authorisation holders also increased.

Doctors and pharmacists submitted 49 reports. The Centre for Disease Prevention and Control (CDPC) submitted 34 reports on adverse reactions to vaccines.

The number of clinical events reported to SAM in 2017 increased, reaching 468 events.

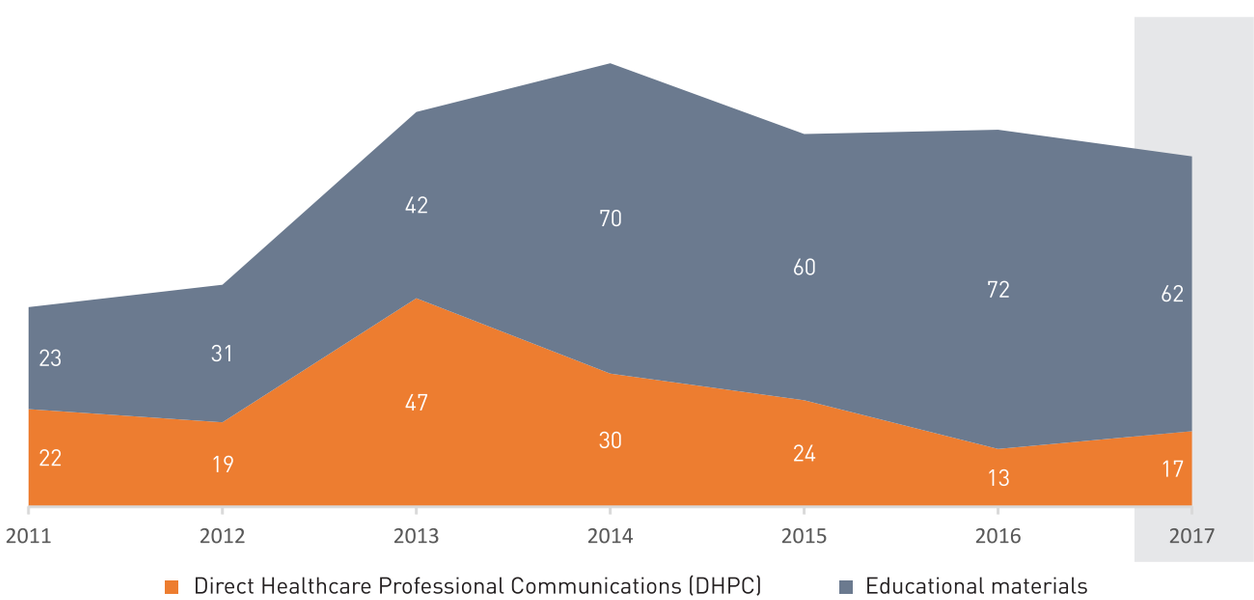
In 2017, SAM carried out five Good Pharmacovigilance Practice inspections of marketing authorisation holders.

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 2017, Latvia was a reference member state in 7 single assessment procedures. PSURs were evaluated for 13 nationally authorised medicinal products that were not included in the EU single assessment procedure, and the assessments with recommendations regarding required action were forwarded to the marketing authorisation holders.

Since 2017, 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 monitoring of the safety information regarding these products.

Regular evaluation of risk management plans (RMPs) is ensured by pharmacovigilance experts participating in marketing authorisation/renewal, as well as variation procedures. A total of 37 RMPs and related documentation were evaluated.

APPROVAL OF ADDITIONAL RISK MINIMISATION MEASURES FROM 2011 UNTIL 2017



During the period of review, SAM collaborated also with the MAH Qualified Persons Responsible for Pharmacovigilance. This ensured that the MAH established risk minimisation measures were implemented in Latvia, including the required communication with healthcare professionals, patients and the public regarding the safe use of medicines. SAM approves the MAH submitted Direct Healthcare Professional Communication (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 62 EMs and 17 DHPCs submitted by MAHs.

A pharmacovigilance expert representing Latvia actively participates in the meetings of the EMA Pharmacovigilance Risk Assessment Committee (PRAC). SAM informs the public, marketing authorisation holders and doctors in Latvia regarding all current issues in Europe related to medicinal products that are being reviewed within PRAC.

Information regarding the current medicinal product safety issues and recommendations regarding the required risk minimisation measures is regularly published on SAM website and in the informative bulletin "Cito!".

In 2017, the State Agency of Medicines conducted a study to assess the efficacy of educational materials intended for valproate risk minimisation, including analysis of consumption data, survey of healthcare professionals and 11 interviews with heads of professional associations of doctors in Latvia and other leading specialists – psychiatrists, neurologists, general practitioners and gynaecologists. The study results indicated that the educational materials in Latvia are not being used in accordance with the requirements with regard to prescription of valproate to women with reproductive potential. Doctors provided substantial information in their interviews regarding alternative medicines that could be used in pregnant women and women with reproductive potential instead of valproate and regarding the introduction of contraindication for valproate use in pregnant women and women not using effective contraception. Based on the opinion of doctors in Latvia, SAM submitted recommendations for the repeated valproate review procedure being conducted by the EMA.

2.1.5 QUALITY CONTROL OF MEDICINES

In 2017, SAM Laboratory carried out analysis of 119 samples of medicines. In the process of analysis 759 quality criteria were tested. 349 volumetric solutions, indicators and reagents were prepared upon request from pharmacies. 97 samples of purified water produced in pharmacies were selected and tested in 2017. Noncompliance with the requirements of the European Pharmacopoeia was discovered in one sample of purified water. Upon request from the SAM Medicines Marketing Authorisation Department, expertise was carried out on documentation submitted for marketing authorisation of 17 medicinal products by evaluating the methods for analysis of the active substance and/or the final product and their validation. In comparison to 2016, last year there was an increase in the number of samples of medicinal products tested (119) and a slight decrease in the number of volumetric solutions, indicators and reagents prepared upon request from pharmacies (349). The number of tested purified water samples (97) remained at the same level as in 2016.

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

- Parallel imported medicinal products
- Information from the EU or the Health Inspectorate regarding withdrawal of the medicinal product
- Low intensity manufacturing
- Unstable medicinal product
- Consumers – special patient groups
- Medicinal products for which samples have not been tested in the last 5 years
- Recently authorised medicinal products
- New endproduct manufacturer

"In 2017, the Laboratory participated in an audit within the European Joint Audit Program which included evaluation of both the quality system and technical procedures in place at the Laboratory. The operational organisation of the Laboratory received high recognition in the evaluation"

- Changes in the manufacturing process
- Changes in the quality specification

SAM Laboratory regularly participates in international programs for quality control of medicines and professional level assessment programs. In 2017, 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. In 2017, Laboratory specialists participated in the program for establishment of European Pharmacopeia standards ("Establishment of dexamethasone sodium phosphate CRS 7").

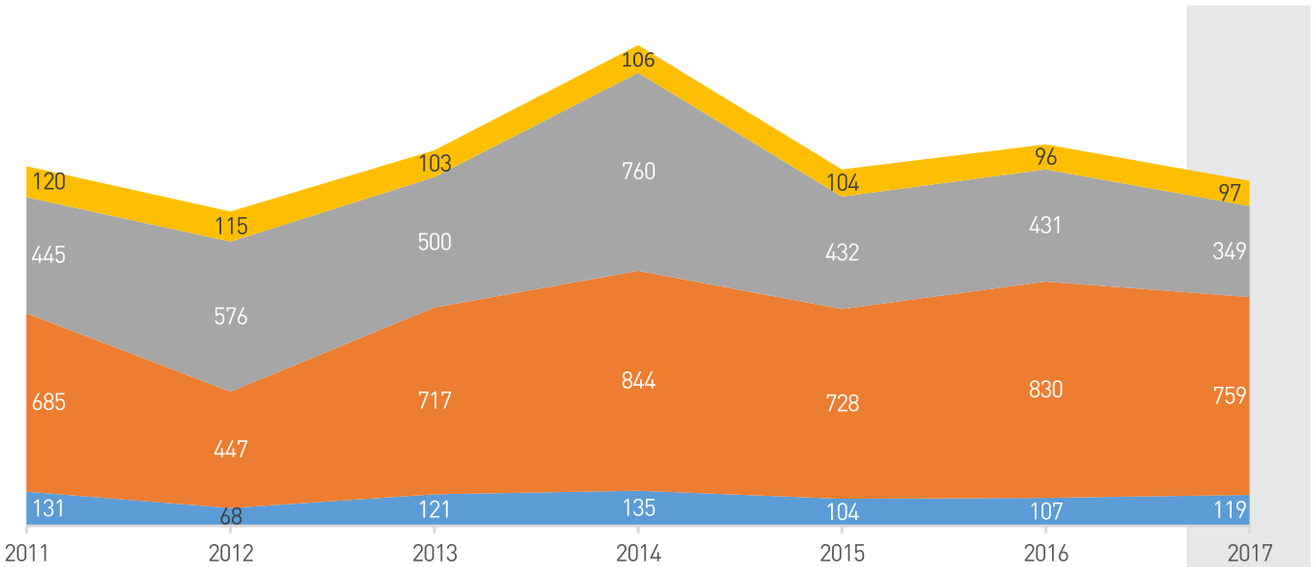
A routine monitoring visit by the Latvian National Accreditation Bureau took place on 10 May 2017. The Laboratory maintained accreditation regarding compliance with the requirements of the LVS EN ISO/IEC 17025:2005 standard in the following areas:

- Physical and physicochemical 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, thus, the reaccreditation is scheduled to take place in spring of 2018.

In 2017, the Laboratory participated in an audit within the European Joint Audit Program which included evaluation of both the quality

RESULTS OF THE MEDICINES EXAMINATION LABORATORY



system and technical procedures in place at the Laboratory. The operational organisation of the Laboratory received high recognition in the evaluation.

In 2017, software updates were ensured for 5 liquid chromatography systems and the atomic absorption spectrometer.

2.2 MEDICAL DEVICES

In 2017, in accordance with the Cabinet of Ministers Regulation No. 581 "Procedures for Registration, Conformity Assessment, Distribution, Operation and Technical Supervision of Medical Devices" adopted on 2 August 2005 and in force until 1 December 2017, SAM carried out expertise on documentation of 4 products as part of registration procedure for medical devices manufactured in the Republic of Latvia. SAM also carried out expertise on registration documentation of one specially supplied medical device not labelled with the CE compliance marking. In 2017, 253 reports were submitted within the notification procedure and were added to the LATMED, Latvia's medical devices database. Furthermore, information regarding purchase of safety group I and II medical devices was also entered in LATMED – 3034 reports, regarding variations to utilisation of the aforementioned medical devices – 3757 reports. SAM received 1008 primary reports about accidents with medical devices and corrective actions/ withdrawals within the vigilance system. In 172 cases, identification and implementation of safety measures was ensured with regard to noncompliant medical devices in operation in the Republic of Latvia. In the year of review, SAM issued authorisation for 5 clinical trials with medical devices and 2 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

On 1 December 2017, the Cabinet of Ministers Regulation No. 689 of 28 November 2017 "Procedures for Registration, Conformity Assessment, Distribution, Operation and Technical Supervision of Medical Devices" came into effect, stipulating various changes to decrease the administrative burden and improve the business environment for the local merchants.

REGISTRATION, CLINICAL TRIALS AND SAFETY MONITORING OF MEDICAL DEVICES IN 2017

Position	Number
Number of primary applications for registration of medical devices manufactured in the Republic of Latvia	4
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	1
Number of notifications of release on the market submitted within the notification procedure and registered in the LATMED database	253
Registration of information provided by MD holders regarding purchase of safety group I and II MDs in the LATMED database (number of documents received)	3034
Registration of information provided by MD holders regarding changes in utilisation of safety group I and II MDs in the LATMED database (number of documents received)	3757
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 reports received - Number of primary reports	 2130 1008
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	 194 58
Primary applications for authorisation of clinical trials with medical devices	5
Primary applications for authorisation of amendments to clinical trials with medical devices	9
Applications for variations to previously issued MD authorisations	0

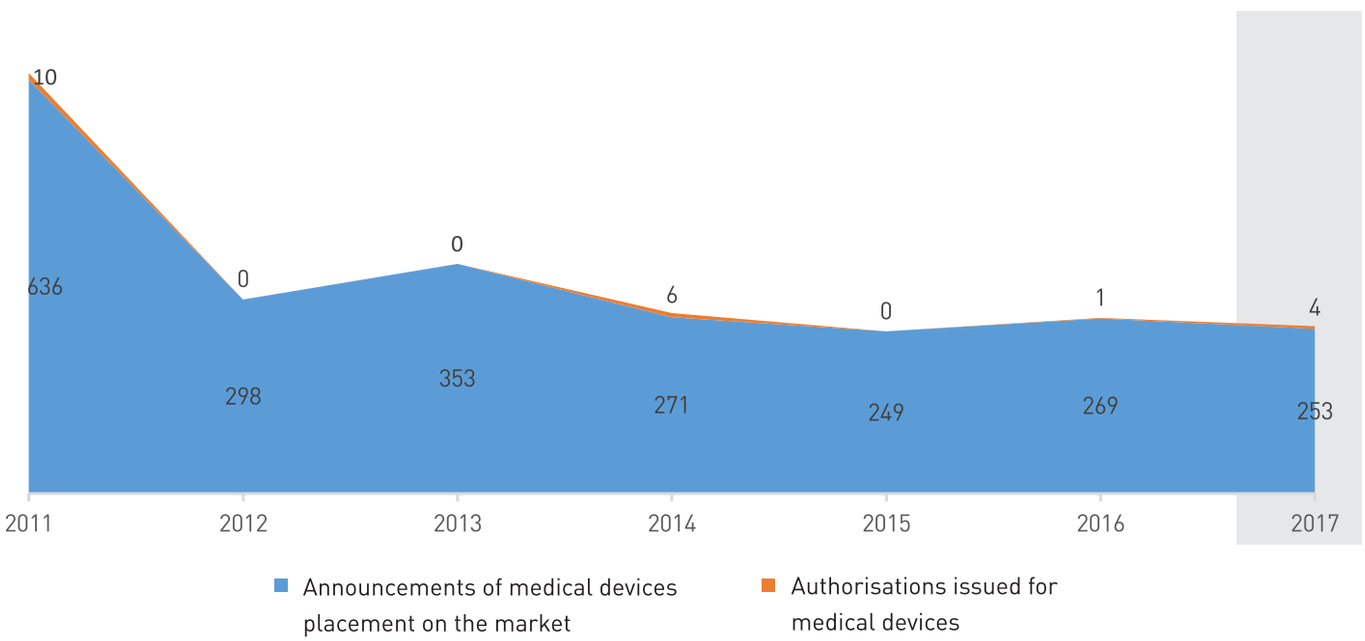
Trial with Medical Devices Intended for Human Use".

The Regulation (EU) 2017/745 of the European Parliament and of the Council (5 April 2017) on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC and the Regulation (EU) 2017/746 of the European Parliament and of the Council (5 April 2017) on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU came into force on 25 May 2017. It is predicted that with the introduction of the two aforementioned regulations better patient health and safety protection will be implemented and legal certainty will be achieved, and an environment supportive of innovations will be promoted.

On 1 December 2017, the Cabinet of Ministers Regulation No. 689 of 28 November 2017 "Procedures for Registration, Conformity Assessment, Distribution, Operation and Technical Supervision of Medical Devices" came into effect, stipulating various changes to decrease the administrative burden and improve the business environment for the local merchants.

To inform merchants regarding the main changes in the normative acts pertaining to the field of medical devices in Europe and Latvia, on 5 December, 12 December and 19 December SAM organised seminars for medical device manufacturers, authorised representatives, importers, distributors and healthcare institutions. In these seminars, experts from SAM Medical Devices Evaluation Department together with representatives of the Ministry of Health and Health Inspectorate presented the new European and Latvian medical device regulation, as well as answered the questions from participants.

NUMBER OF AUTHORISATIONS ISSUED TO MEDICAL DEVICES MANUFACTURED AND NUMBER OF NOTIFICATIONS RECEIVED BY SAM REGARDING RELEASE OF MEDICAL DEVICES ON THE MARKET IN THE REPUBLIC OF LATVIA 2011–2017



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 current normative acts.

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 licensing process are reviewed by the Commission on Licensing of Pharmaceutical Activity (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 15 Commission meetings were held in 2017.

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 2017, 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 (102), prepared draft decisions (533) for issuance, renewal, suspension or annulment of special permits (licences) or authorisations of manufacturers, importers and distributors of active substances and other decisions.

"In comparison to 2016 when seven new medicines wholesalers were established in Latvia, in 2017, the number of new medicines wholesalers increased. The State Agency of Medicines adopted the decision to issue licences to 11 new medicines wholesalers. Special permits (licences) for manufacturing or import of medicines were issued to two new medicines manufacturing/import companies. Licences were issued also to three new general type pharmacies, two of which were opened in places where before there were no general type pharmacies or pharmacy branches, but one pharmacy was opened where before there was a branch of a general type pharmacy that discontinued its pharmaceutical activity in this area"

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 2017, SAM carried out expertise on documents submitted by 1207 licence holders. SAM renewed (issued) special permits (licences) for pharmaceutical activity to 343 pharmaceutical activity companies (274 pharmacies, 46 medicines wholesales, 19 medicines manufacturing or import companies, 4 companies manufacturing active pharmaceutical ingredients). The majority of licensing documents submitted for renewal of special permits (licences) were related to replacement of pharmacy managers, respon-

SAM renewed special permits for pharmaceutical activity to

343

pharmaceutical activity companies

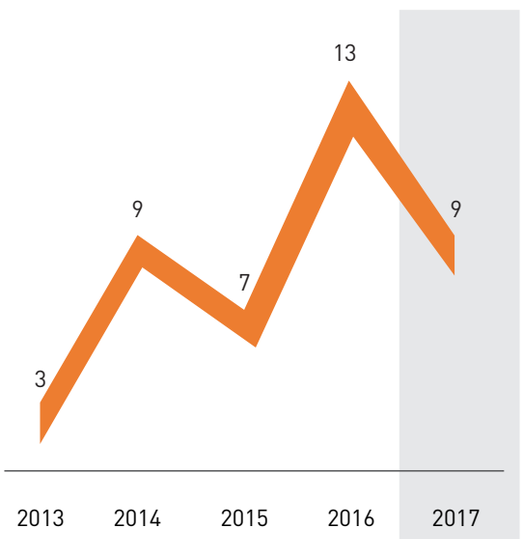
sible officials, change of legal address of licence holder, relocation of pharmaceutical activity, initiation or termination of new special activity conditions, change of address of pharmaceutical activity location in accordance with the decision of the Construction Board.

In 2017, SAM adopted decisions regarding authorisation or authorisation of variations to 9 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.

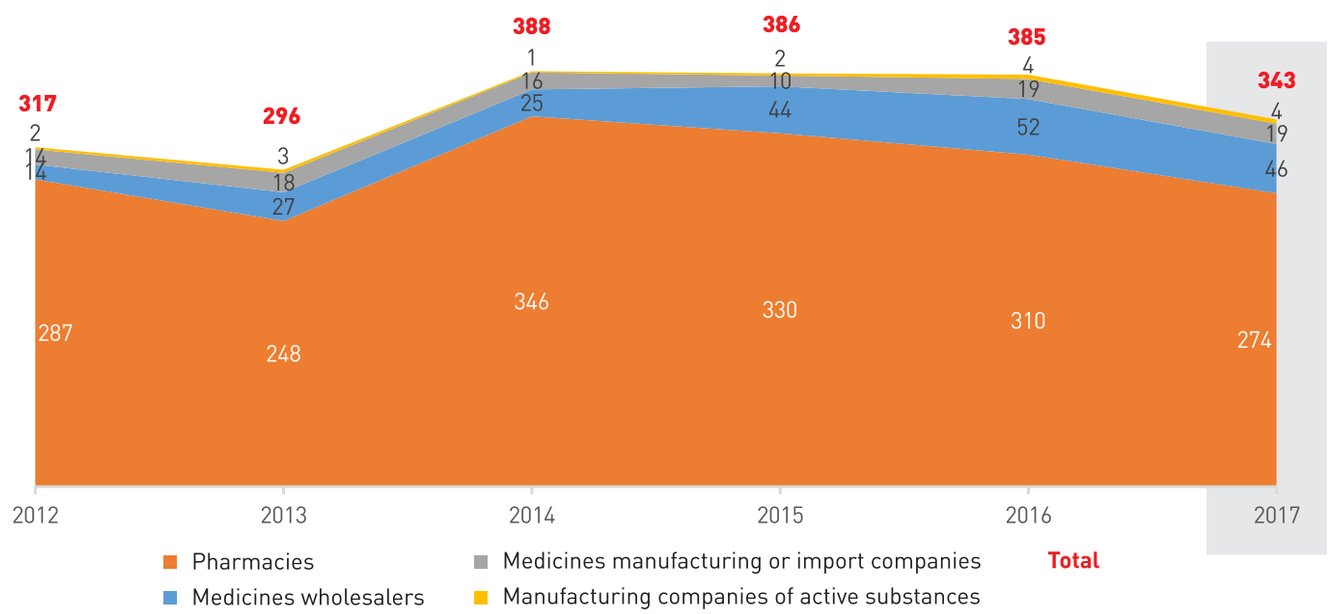
In comparison to 2016 when seven new medicines wholesalers were established in Latvia, in 2017, the number of new medicines wholesalers increased. The State Agency of Medicines adopted the decision to issue licences to 11 new medicines wholesalers. Special permits (licences) for manufacturing or import of medicines were issued to two new medicines manufacturing/import companies. Licences were issued also to three new general type pharmacies, two of which were opened in places where before there were no general type pharmacies or pharmacy branches, but one pharmacy was opened where before there was a branch of a general type pharmacy that discontinued its pharmaceutical activity in this area.

In 2017, the Pharmaceutical Acitvities Company Licensing Department actively verified the addresses of pharmaceutical activity company locations against the information published in the State Address Registry www.kadastrs.lv, by collaborating with the State Land Service and obtaining data from the information system of the National Real Estate Cadastre regarding groups of pharmacies/ branches.

REGISTRATION OF ACTIVE SUBSTANCE MANUFACTURERS, IMPORTERS AND DISTRIBUTORS (INCLUDING PRIMARY REGISTRATIONS AND RENEWALS)



LICENCES FOR PHARMACEUTICAL ACTIVITY COMPANIES



The daily operation of the department is managed to allow issuance of special permits (licences) for pharmaceutical activity in accordance with the current normative acts, as well as ensure that updated information regarding the licensed pharmaceutical activity companies is available to the public and Agency clients on the website www.zva.gov.lv, section: "Register > Licensed pharmaceutical activity companies."

2.3.2 COMPLIANCE EVALUATION

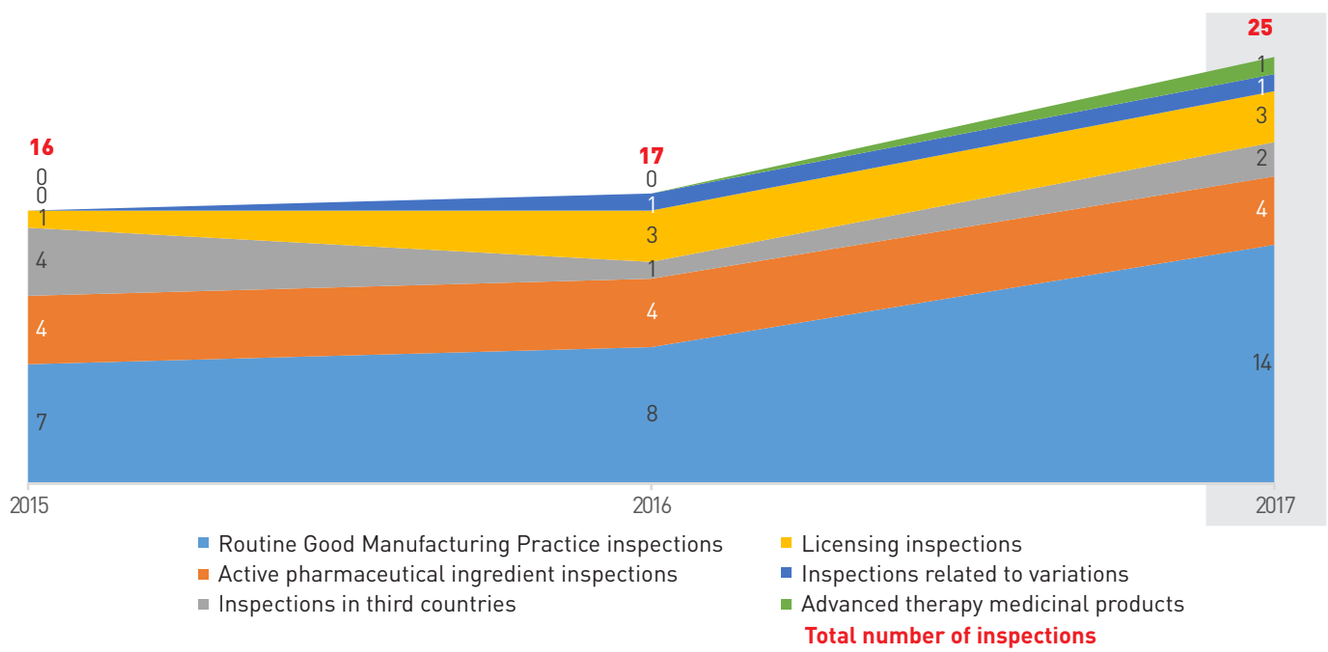
In 2017, the work of the Pharmaceutical Activity Compliance Evaluation Department of the State Agency of Medicines (inspection practice, including cooperation with other regulatory authorities) was assessed in three international audits:

- In the field of Good Manufacturing Practice inspections of the EMA Joint Audit Program. Furthermore, this audit was observed by representatives of the USA Food and Drug Administration in relation to the Mutual Recognition Agreement of Good Manufacturing Practice compliance between the European Union and the United States of America;
- Within the Common European SoHO Inspection Programme (CESIP) as part of the Joint Action project VISTART;
- Within BEMA, evaluating fact-based decision-making and efficacy of collaboration between various SAM functions (for example, between medicinal product evaluation, marketing authorisation and inspection functions – Good Manufacturing, Distribution, Pharmacovigilance and Clinical Practice).

"As a result of the audits, it was concluded that the competence of the State Agency of Medicines inspectors and the inspection practice introduced by the department was compliant with the performance standards laid down for European member states in all areas of operation and ensure an equivalent and harmonised application of these requirements in practice"

As a result of the audits, it was concluded that the competence of the State Agency of Medicines inspectors and the inspection

NUMBER OF GOOD MANUFACTURING PRACTICE INSPECTIONS



practice introduced by the department was compliant with the performance standards laid down for European member states in all areas of operation and ensure an equivalent and harmonised application of these requirements in practice.

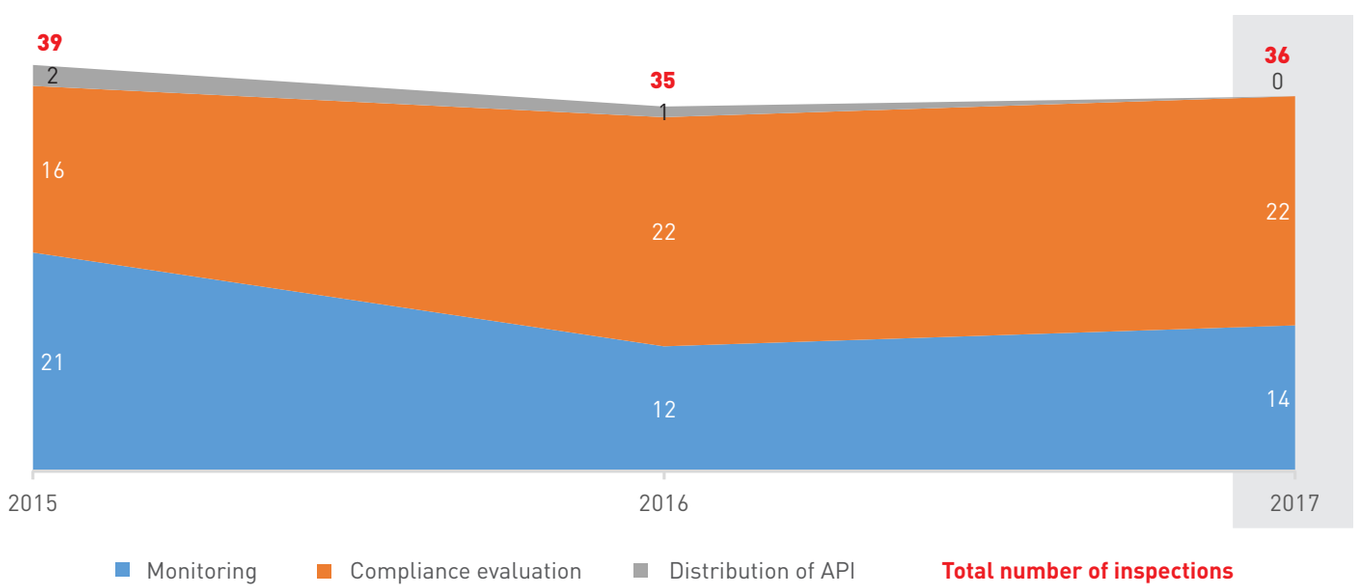
In 2017, the State Agency of Medicines conducted 25 inspections of medicines manufacturing/import companies – this required a total of 75.5 person-days. Two of the inspected medicines manufacturing companies were located in countries outside of the EEA, four inspections were related to inspection of active substance manufacturing, one inspection was related to inspection of manufacturing of advanced therapy medicines and another inspection was conducted at a contract laboratory. Overall, inspections were conducted for manufacturing of 7 chemically synthetized substances and one biologically active pharmaceutical substance. Employees of the Pharmaceutical Activities Compliance Evaluation Department together with the Pharmaceutical Activities Company Licensing Department implemented variations to 6 already registered manufacturers, importers and distributors of active substances. During inspections at manufacturing companies 13 (medicinal) product samples and 8 labelling samples were obtained for compliance evaluation. In addition, two document evaluation inspections were conducted in relation to inclusion of new contract manufacturers or laboratories and new third country manufacturing sites (for import of medicines) in the licence. Seven of these inspections were unscheduled.

In the year of review, 22 Good Manufacturing Practice certificates were issued to medicines manufacturing/import companies. Upon request from medicines manufacturers and wholesalers in Latvia, 218 certificates of pharmaceutical products and 30 certificates of free sale were issued in 2017 in order to promote export and marketing authorisation of medicines manufactured in Latvia in countries outside of the EU or EEA.

According to the agreement signed with the Food and Veterinary Service (FVS) in 2017 for exchange of experience, an expert from FVS observed three Good Manufacturing Practice inspections conducted by SAM.

36 compliance evaluations of medicines wholesalers, including 22 inspections related to issuance or renewal of licences for operation of wholesaler, as well as 14 Good Distribution Practice inspections of medicines wholesalers were conducted in 2017. One inspection was conducted for evaluation of documentation in relation to licence renewal of medicines wholesaler. The conduct of these inspections required a total of 55.5 person-days. In the year of review, 16 Good Distribution

NUMBER OF GOOD DISTRIBUTION PRACTICE INSPECTIONS



Practice certificates were issued to medicines wholesalers.

COMPLIANCE EVALUATION AND MONITORING INSPECTIONS OF SUBSTANCES OF HUMAN ORIGIN (SOHO)

In 2017, 21 applications for compliance evaluation of utilisation activity of human organs, tissues and cells were reviewed:

- 20 applications for tissue centres, including 14 related to changes in activity;
- One application related to changes in activity of a higher education institution.

In the year of review, 17 permits for utilisation of tissues and cells were issued to tissue centres and one permit – to a higher education institution, including 14 related to changes in activity. One permit for utilisation of tissues and cells was annulled upon request from the institution and two administrative cases regarding permits for utilisation of tissues and cells were concluded.

In 2017, two applications for compliance evaluation and receipt of certificate for a new blood bank were reviewed and one new compliance certificate was issued to the blood bank.

In the year of review, following compliance monitoring inspections a compliance certificate was issued to the State Blood Donor Center, compliance certificates were issued to 4 blood establishments and 18 blood banks that had received temporary compliance certificates within the previous period of review.

7 compliance monitoring procedures for human blood and blood component establishments and 22 inspections of hospital blood banks were performed in 2017, including 20 inspections of compliance of activity. One compliance evaluation inspection was conducted at the Latvian Transplant Centre, one – at a higher education institution, as well as 17 inspections at tissue/cell procurement establishments and tissue centres, including 4 inspections related to changes in activity and 6 inspections to ensure monitoring of compliance of tissue centre activity, implementing the procedures for haemovigilance and biovigilance surveillance.

Department specialists prepared the annual reports to the European Commission regarding serious adverse reactions and serious adverse events in the field of blood, tissues and cells, assembled and clarified the data submitted by tissue centres for the EUROCET reports on utilisation of tissues and cells, as well as prepared information for the surveys included in the Joint Action project VISTART, and the survey received from the European

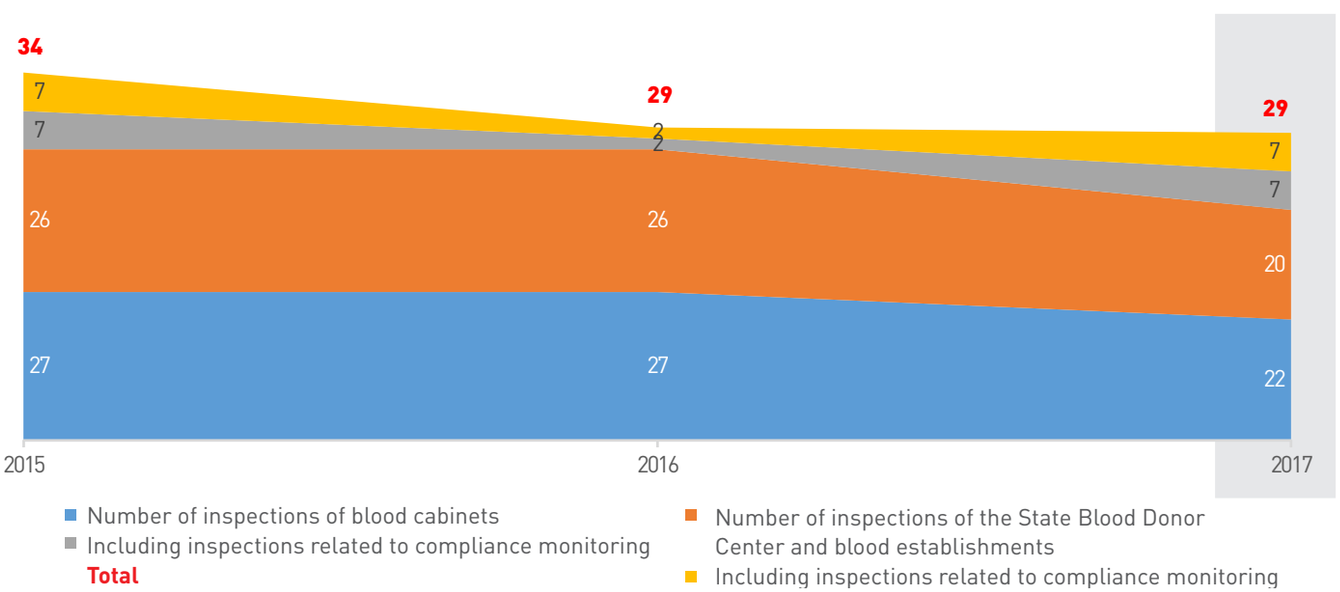
218

certificates of pharmaceutical products and

30

certificates of free sale were issued in 2017 in order to promote export and marketing authorisation of medicines manufactured in Latvia in countries outside of the EU or EEA

NUMBER OF INSPECTIONS OF BLOOD BANKS, STATE BLOOD DONOR CENTER AND BLOOD ESTABLISHMENTS



Commission Directorate General for Health and Food Safety (DG-SANTE) regarding assessment of the regulation for blood, tissues and cells. Department experts actively evaluated and commented on the draft amendment prepared by the Ministry of Health for the transposition of the new EU directive in the field of blood in relation to Good Practice principles (including approval of the translation of the "Good Practice Guidelines for Blood Establishments" with the State Language Centre and Ministry of Health), as well as checked the understanding within hospitals regarding the application of the Single European Code to tissues and cells and compliance with the principles for establishment of code sequences.

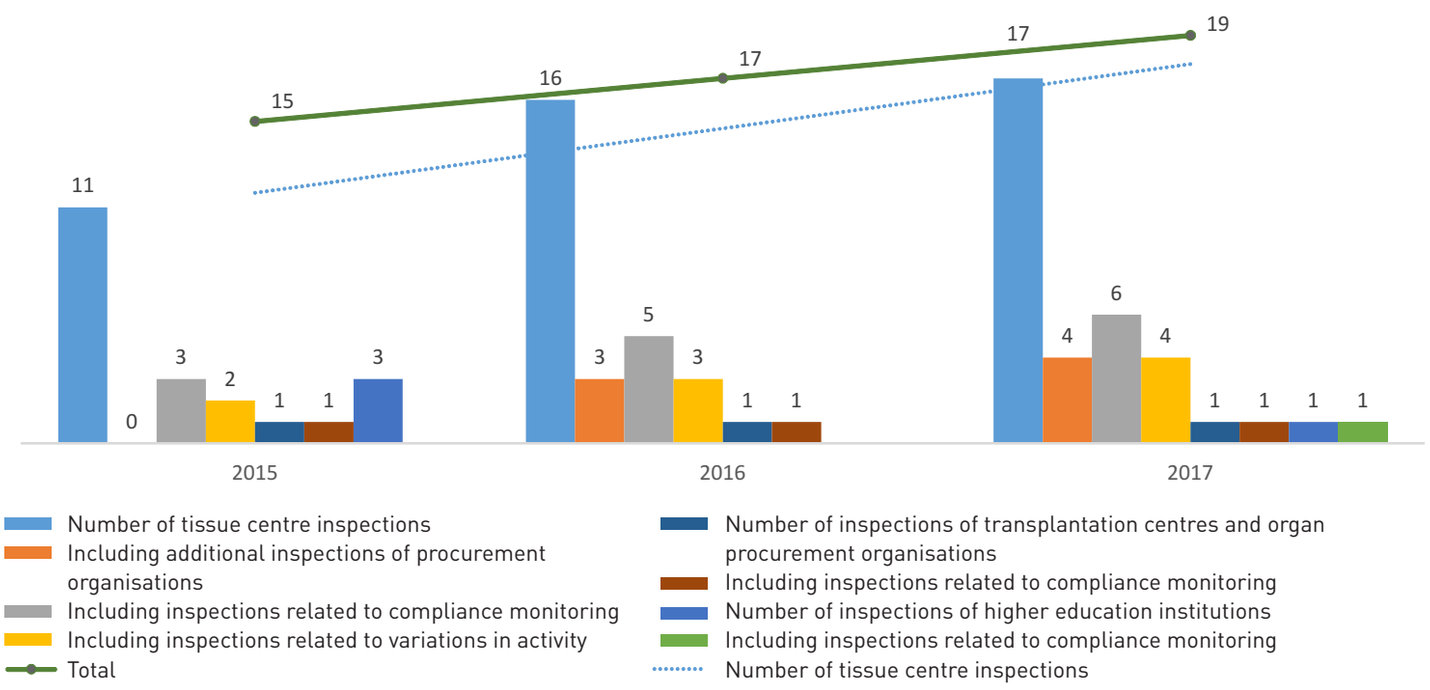
Department experts ensured verification of information and, if required, collaboration with the Health Inspectorate in relation to the information received by SAM regarding potential unauthorised activity in the field of tissues and cells.

In collaboration with IT specialists, a section was established on SAM website for information regarding the application of the Single European Code to tissues and cells, and online access was ensured for hospitals for submission of Urgent reports regarding serious adverse reactions and events related to utilisation of blood, tissues and cells and organs. The online reporting in the field of haemovigilance was also presented at the meeting of the Association of Transfusiologists which was attended by the responsible employees from the State Blood Donor Center, hospital blood establishments and blood banks.

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 VISTART) and working group meetings (VISTART) 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.

As part of the Joint Action project (VISTART), work package 9 (WP9), the first audit by the inspectorate compliance evaluation and monitoring of the field of tissues, cells and blood took place and it was conducted by representatives of the WP9 coordinator – the Health Products Regulatory Authority (HPRA) in Ireland.

NUMBER OF INSPECTIONS ON UTILISATION OF HUMAN ORGANS, TISSUES AND CELLS



3. INTERNATIONAL COOPERATION

The State Agency of Medicines is a part of the network of national medicines agencies in Europe and the successful performance of Agency's functions and tasks is closely related to participation in the common European medicines regulatory network – it entails cooperation with the EMA, European Commission and more than 47 regulatory institutions in the pharmaceutical field within the European Economic Area. 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 Latvia's Agency, qualified human resources, as well as financial resources are undoubtedly necessary. In 2017, SAM employees were involved in cooperation with the European Commission and Council working groups, European Commission Directorate General for Health and Food Safety (DG SANTE), WHO, the Uppsala Monitoring Centre (UMC), European Pharmacopoeia Commission, PIC/S, European Directorate for the Quality of Medicines & Healthcare (EDQM), as well as in other directions for collaboration.

In the year of review, the activity of Agency experts in international procedures was higher than in the previous year. In 2017, Latvia participated in the EMA Committee for Medicinal Products for Human Use (CHMP) by evaluating eight centralised authorisation procedures for medicinal products. In three of these procedures, the State Agency of Medicines assumed the peer review function, in three other procedures the Agency was the responsible rapporteur and in the remaining two procedures – the corapporteur. In 2017, Latvia participated in two re-evaluation procedures of centrally authorised medicines as the responsible PRAC rapporteur. Latvia was the leading Member State in four Periodic Safety Update Report single assessment (PSUR SA) procedures. Experts of the Medicines Marketing Authorisation Department together with external experts actively participated in the work of the Committee on Herbal Medicinal Products. In 2017, evaluation of the Community herbal monograph was conducted.

> *"In 2017, the HMA/EMA Task Force on Availability of Authorised Medicines for Human and Veterinary Use (TF AAM) began its operation and a representative from the State Agency of Medicines also took part in this task force"*

In 2017, the State Agency of Medicines participated in the assessment audit of the Estonian medicines agency as part of the EU Joint Audit Program (JAP) with the participation of representatives from the USA Food and Drug Administration (FDA), regarding the compliance of processes organised and practical activities (inspections) conducted by SAM with the international requirements for compliance evaluation of Good Manufacturing and Good Distribution practice for medicines.

In 2017, the administration of the State Agency of Medicines participated in EMA Management Board meetings where the agenda included involvement of EMA 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, exchange of information related to the development of the common EU portal and database for clinical trials, data assembly within the system for safety monitoring of medicines and other relevant issues.

In 2017, the HMA/EMA Task Force on Availability of Authorised Medicines for Human and Veterinary Use (TF AAM) began its operation and a representative from the State Agency of Medicines also took part in this task force. In order to promote better availability of medicines in the European Union, the task force operates in the following directions:

- Improving availability of authorised medicines that have not been released on the market for any reason or were previously on the market, but are no longer released;
- Disruptions in the supply chains of medicines that are authorised and currently on the market.

For several years now, SAM has been involved in the cooperation for surveillance of medical devices, blood and its components, tissues and cells. SAM is the competent authority for 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.

SAM has a binding collaboration agreement with the medicines agencies in Estonia and Lithuania aiming to promote closer cooperation between the medicines agencies of the Baltic States in the field of medicinal product regulation. The trilateral meeting to be organised by the Estonian medicines agency and scheduled to take place in 2017 was postponed and will take place in 2018.

In 2017, several international auditor visits took place at the State Agency of Medicines, and these visits allowed to gain experience and contribute to the adoption of best practice and transfer of best practice on an international level:

- The EMA and FDA EU Joint Audit Program (JAP) audit regarding the compliance of SAM processes and practical operations (inspections) with the international requirements for compliance evaluation of Good Manufacturing Practice and Good Distribution Practice of medicines;
- The European Commission VISTART project audit regarding the compliance of regulatory action with the requirements for compliance evaluation of procurement and utilisation organisations of human tissues and cells;
- BEMA included a thorough evaluation of SAM operation, highlighting the collaboration among the competent authorities in the Baltic States as one of its strengths.

BEMA IV auditors visit at SAM on September 2017

4. GENERAL GOVERNANCE OF THE STATE AGENCY OF MEDICINES

In 2017, the State Agency of Medicines prepared a new mid-term operational strategy for 2017–2019. It was established in compliance with the national priorities and objectives in public health, as well as international priorities reflected in the strategy and operational plan for 2016–2020 established by the network of European medicines agencies.

The strategy emphasises that in order to improve and ensure qualitative services for public health in Latvia in the longterm, the following operational directions have been established for 2017–2019:

- Service direction with the objective of ensuring qualitative implementation of the functions delegated to SAM by promoting availability of effective, safe and qualitative medicines and other healthcare products on the market in Latvia;
- Collaboration and information direction with the objective of promoting efficient collaboration between the Agency and stakeholders in Agency's services and collaboration;
- Sustainable development direction with the objective of continuous development of the State Agency of Medicines as the centre for exchange of knowledge by managing knowledge responsibly and improving the learning process within the organisation in order to ensure high quality of the delegated functions and services in the longterm.

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 defense of the Agency's interests in courts, thereby, reiterating the legality of the decisions adopted by SAM within the administrative process, if necessary. In 2017, eight of the decisions adopted by the Agency were contested at the Ministry of Health and none of the contested decisions were repealed. Thus, the proportion of repealed decisions to adopted decisions was 0.

In 2017, the State Agency of Medicines in collaboration with the Ministry of Health prepared amendments to several normative acts which were adopted by the Cabinet of Ministers in 2017, for example:

- Cabinet of Ministers Amendment of 17 January 2017 to the Cabinet of Ministers Regulation No. 344 of 25 June 2013 "Procedure for Import and Distribution of Active Substances" came into force on 1 March 2017 and supplements the requirements of this regulation with references to European Union guidelines on Good Manufacturing and Distribution Practice of active substances.
- Cabinet of Ministers Amendment of 14 March 2017 to the Cabinet of Ministers Regulation No. 1176 "Procedure for Utilisation of Human Tissues and Cells" came into force on 29 April 2017. The draft amendment to this regulation was prepared in order to transpose into national normative acts the requirements related to the Single European Code, import and export of tissues and cells laid down in the Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells and

⇨ *Service direction*

⇨ *Collaboration and information direction*

⇨ *Sustainable development direction*

the Commission Directive (EU) 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.

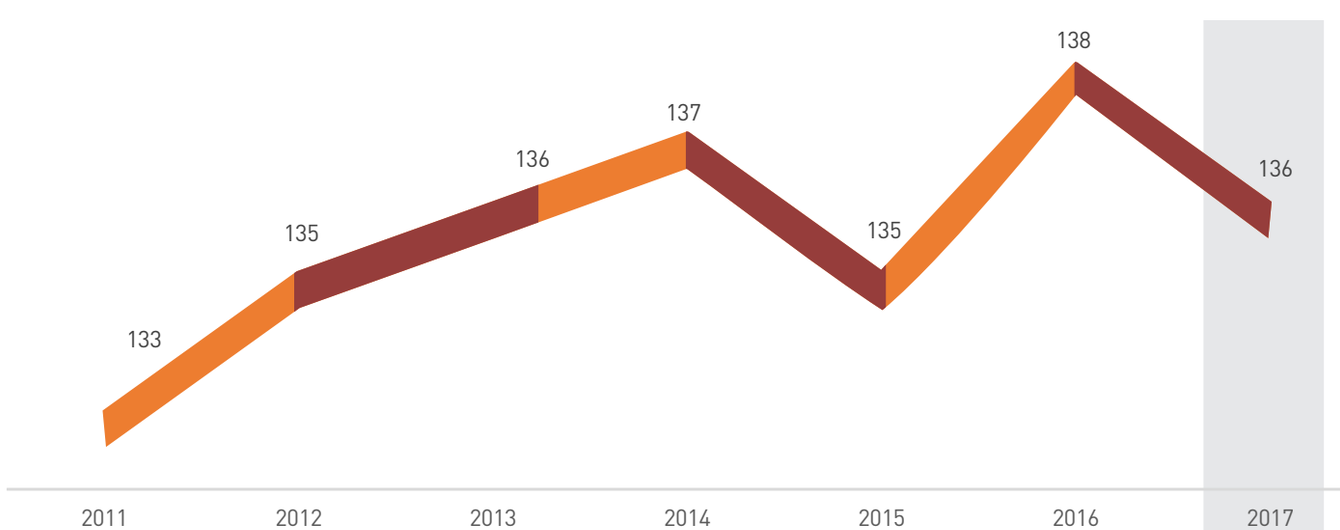
- As a result of collaboration between the Ministry of Health and the State Agency of Medicines, a new regulation was established in the field of medical devices and it was reviewed and adopted by the Cabinet of Ministers on 28 November 2017 – Regulation No. 689 "Procedure for Registration, Compliance Evaluation, Distribution, Utilisation and Technical Surveillance of Medical Devices" and the related Cabinet of Ministers Regulation No. 690 of 28 November 2018 "Amendments to the Cabinet of Ministers Regulation No. 873 of 17 September 2017 "Publicly Available Paid Service Pricelist of the State Agency of Medicines"". The aforementioned regulation came into force on 1 December 2017. In accordance with the adopted regulation, the State Agency of Medicines shall be entitled to issue a Certificate of Free Sales for medical devices upon request from manufacturers whose place of commerce is registered in the Republic of Latvia, because certificates confirming the free sale of products are requested in many countries and they essentially certify that the relevant product is authorised for free sale in Latvia. Furthermore, the regulations entail registration of manufacturers of medical devices in Latvia. The new regulations also optimised several functions of the State Agency of Medicines – the Agency no longer has to evaluate the technical documentation of medical devices manufactured in Latvia having the lowest risk prior to the release of the devices on the market. From now on healthcare institutions no longer have notify the Agency regarding medical devices purchased from distributors in Latvia. This information shall be assembled and submitted to the State Agency of Medicines as part of vigilance cases.

4.2 STAFF AND HUMAN RESOURCES MANAGEMENT

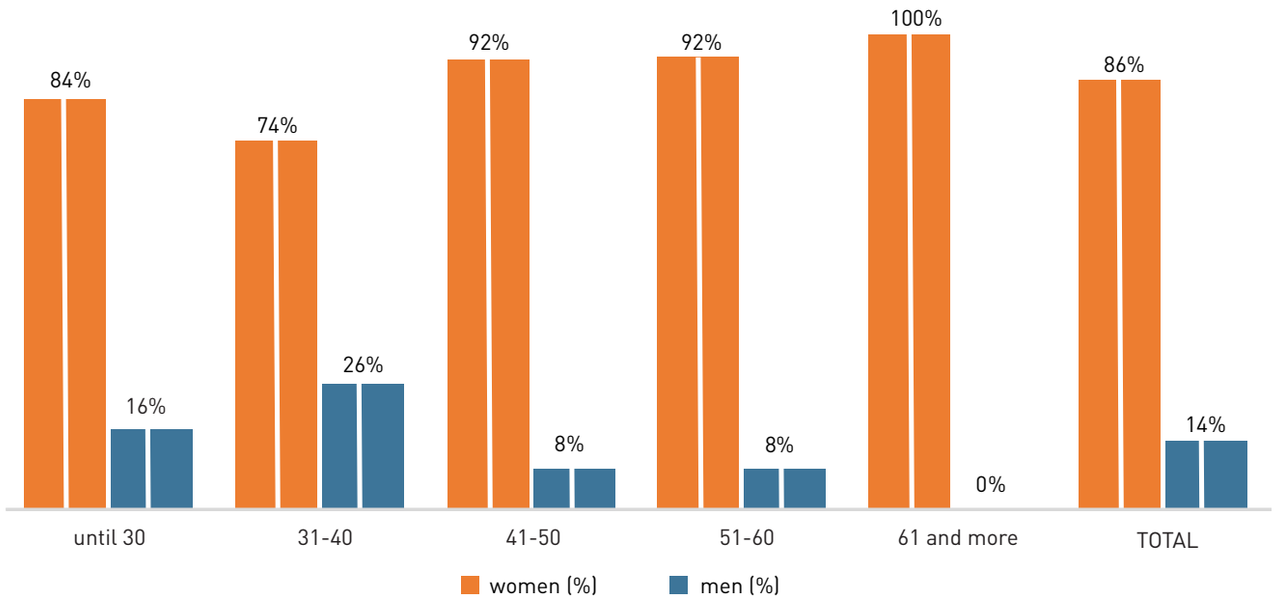
Management of human resources is ensured by the Administrative Resources and Documents Management Department, which resolves issues of human resources management, ensures the work processes for enlistment, selection, assessment and development of personnel, as well as processes personnel related documentation.

At the end of the 2017, there were 136 civil servants and employees actually working at SAM. In total, 145 persons were in a civil service or an employment relationship with SAM in 2017. Changes in the number of employees from 2013 until 2017 are shown in image, distribution of employees according to age and gender – in next image.

CHANGES IN THE NUMBER OF ACTUAL EMPLOYEES FROM 2011 UNTIL 2017



DISTRIBUTION OF EMPLOYEES ACCORDING TO AGE AND GENDER



In 2017, 6 new employees (3 civil servants and 3 employees) began their employment at the Agency, but 6 persons terminated their civil service and 6 persons terminated their employment. Detailed information regarding the reasons for termination of civil service or employment are shown in table.

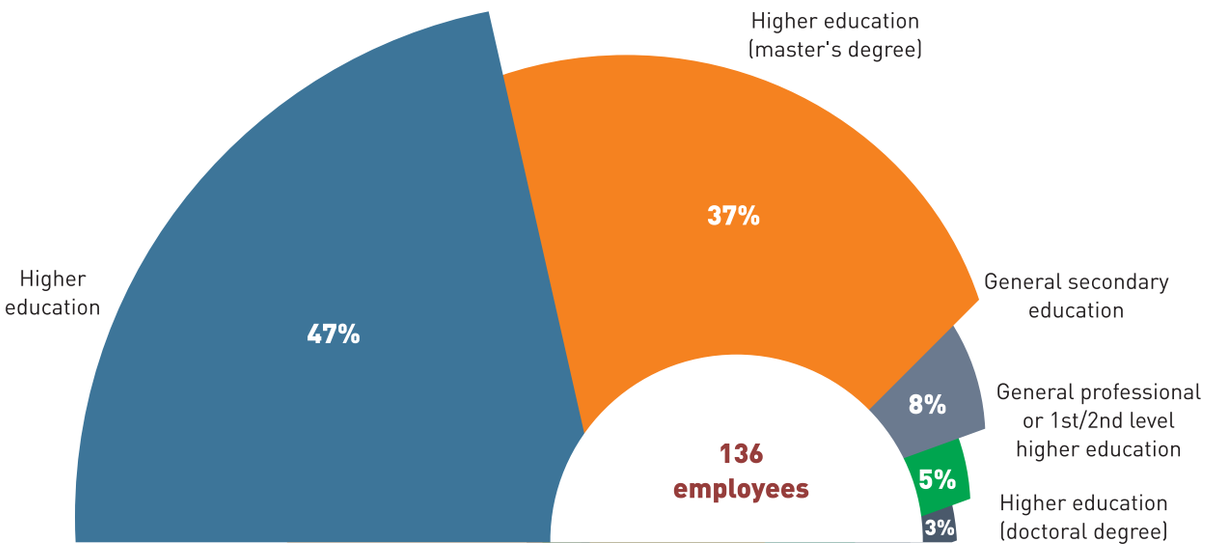
In 2017, the average staff turnover quotient was 9% (*staff turnover = number of staff members who have terminated employment in a definite time period/ average number of staff members in the same time period*), complying with the personnel strategy and showing a 1% decrease in comparison with the previous year. Even though the staff turnover is not very high, when implementing various personnel management processes and planning personnel development it is important to pay attention to issues related to incorporation of new employees within the staff, training for new work tasks, development and training of professional and personal competencies, mutual exchange of knowledge.

Well educated, competent and highly qua-

REASONS FOR TERMINATION OF CIVIL SERVICE OR EMPLOYMENT

Reasons for termination of civil service or employment	Legal basis	Skaits
Notice of termination by an employee	Section 100 of the Labour Law	4
Agreement between employee and employer	Section 114 of the Labour Law	1
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
Based on his or her own will	Section 41, Paragraph 1, Clause a of the State Civil Service Law	5
Transfer to another office at another institution, if the duties of the official position require a civil servant with special qualification or experience	Section 37, Paragraph 1 of the State Civil Service Law	1

DISTRIBUTION OF EMPLOYEES ACCORDING TO THE LEVEL OF EDUCATION

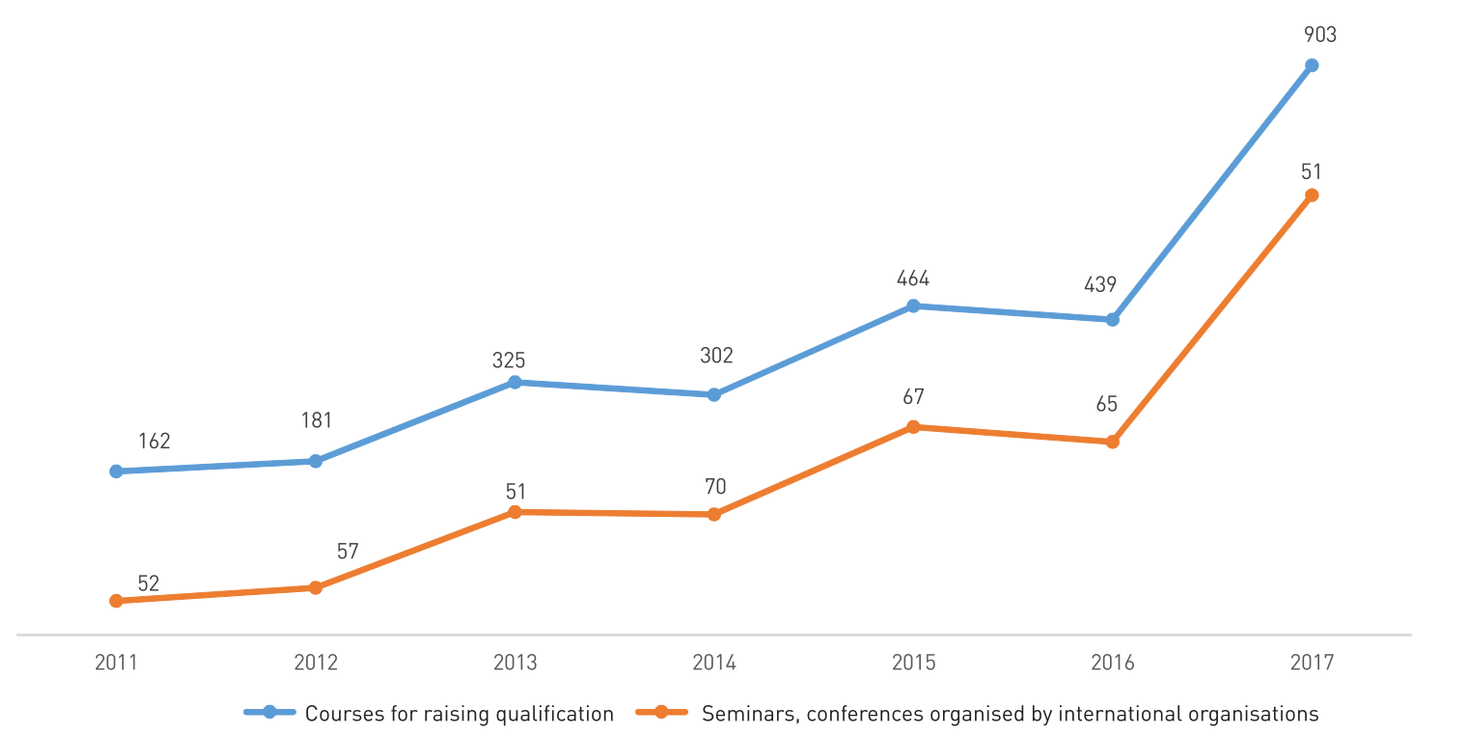


lified specialists are required to successfully ensure the functions assigned to the Agency. The overall level of education of SAM staff members is high – 127 or 88% of SAM employees have higher education, five of these staff members have a doctoral degree.

One of the ground principles of Agency 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 2017, SAM employees attended 903 training events, including seminars, conferences and forums organised by international organisations (51). Statistical information regarding events for personnel development over the previous years is shown in the image.

For automatization of the management

RAISING PERSONNEL QUALIFICATION FROM 2011 UNTIL 2017



of training process organised for employees by the EMA and other competent authorities in the field, EMA Training Centre established and implemented the Learning Management System (EU NTC LMS). In 2017, SAM employees participated in 44 EU NTC LMS organised learning sessions. With the introduction of EU NTC LMS as a collective training platform, the proportion of extramural learning (webinars) increased substantially – in 2017, 68 Agency employees participated in 34 extramural learning courses.

In preparation for the BEMA IV assessment, the Agency ensured English lessons for 17 employees.

In collaboration with the University of Latvia, the Agency organised a special learning course led by L. Civjane, associate professor at the Faculty of Medicine, on the topic "Principles for statistical and scientific evaluation of research studies and preparation of assessment reports". This course was attended not only by Agency employees, but also employees from the Ministry of health, State Blood Donor Center, State Sports Medicine Center and National Health Service.

In 2017, improvements were made to the record system for registration of training sessions attended by Agency employees, a new report table was established providing updated information to employees and heads of structural units. Starting from 2017, internal training organised by the State Agency of Medicines is also included in the training report, including training led by mentors of new employees, internal seminars and presentations regarding latest topics in the industry or work organisation.

Taking into account the knowledge and qualification of Agency experts and based on the collaboration contracts signed between the Agency and European institutions, in 2017, 38 experts and 5 employees with a supportive function participated in the performance of tasks delegated by European institutions – the Agency received financial resources after qualitative and timely completion of 7 procedures.

4.3 INTEGRATED MANAGEMENT SYSTEM AND AUDITS

In 2017, the compliance of the operation of SAM management system was evaluated in 8 external audits, as well as within the Benchmarking of European Medicines Agencies (BEMA) and by the World Health Organisation. SAM management system was recognised as compliant with the external and internal requirements.

In June 2017, the European Medicines Agency together with the USA Food and Drug Administration (FDA) conducted an audit within the EU Member State Joint Audit Program (JAP) regarding the compliance of processes organised and practical activities conducted by SAM with the requirements for compliance evaluation of Good Manufacturing and Good Distribution Practice.

In August 2017, in preparation of the audit program within the European Commission VISTART project for EEA countries regarding the compliance of their regulatory activities with the requirements for compliance evaluation of procurement and utilisation organisations of human tissues and cell, an external audit was conducted at SAM which was also the first mutual EU international audit in this field. The

"Another important event was the assessment of the Agency operation conducted by the World Health Organisation. As a result of this assessment, in September 2017, SAM received confirmation of its compliance with the requirements of and its inclusion in the WHO Certification Scheme on Quality of Pharmaceutical Products Moving in International Commerce"

experience gained from this audit will be used to establish a new international audit system and to train auditors.

During the year of review the Ministry of Health audited SAM in the following areas:

- Organisation of finance management;
- Organisation and management of the marketing authorisation process;
- Organisation and management of provision of state administration services.

Furthermore, in order to establish compliance with the requirements for ISO standard certification and accreditation maintenance, organisation and management of SAM process in governance, basic operation and supportive processes were evaluated in 3 external audits inspecting the following areas:

- ISO 9001:2015 "Quality Management Systems",
- ISO 27001:2013 "Information technology. Security techniques. Information Security Management Systems",
- ISO/IEC 17025:2005 "General requirements for the competence of testing and calibration laboratories" (Medicines Examination Laboratory regarding physical and chemical testing of medicines, pharmaceutical active ingredients, excipients, as well as purified water prepared at pharmacies),

and were found to be compliant with the requirements of these standards.

In September 2017, as part of the Benchmarking of European Medicines Agencies (BEMA IV) a thorough evaluation of SAM operation (compliance of management system and main functions with the requirements of normative acts, guidelines, standards and good practice) was conducted, highlighting the collaboration among the competent authorities in the Baltic States as one of its strengths.

Another important event was the assessment of the Agency operation conducted by the World Health Organisation. As a result of this assessment, in September 2017, SAM received confirmation of its compliance with the requirements of and its inclusion in the WHO Certification Scheme on Quality of Pharmaceutical Products Moving in International Commerce. This confirmation shows the highest appreciation of the longterm work of SAM management and employees in Latvia in establishing and maintaining a system for Good Manufacturing Practice compliance evaluation that is compliant with international requirements.

4.4 INFORMATION TECHNOLOGIES

In 2017, 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; use of new tools for business analysis was initiated providing data visualisation possibilities. A new ICT solution for secure processing and exchange of electronic information and data with partners outside of Agency, including external experts, was introduced.

The algorithms for selection and processing of information in the ZVAIS and LATMED information systems were refined, and significant improvements were made in accordance with the requirements of the Cabinet of Ministers Regulation No. 442 of 28 July 2015 "Procedure for Ensuring Compliance of Information and Communications Technology Systems with Minimal Security Requirements."

The improvements made to the Agency's website provide new important information search options, as well as expand availability and comprehensibility of information. On the website, Agency clients are provided with the opportunity to conduct a convenient and clear search for information in the Medicinal Product Register of Latvia regarding the maximum price of medicines in pharmacies, to select biosimilar medicines, search medicines according to disease group, using the ATC classification; the current information on marketing authorisation holders is reflected dynamically, and other solutions improving client experience have been introduced,

including a substantial increase in the speed of operation of the Medicinal Product Register. In addition, a solution for electronic submission of biovigilance reports to the State Agency of Medicines was introduced – report forms on biovigilance adverse effects and adverse events, as well as improved pharmacovigilance report forms for patients and healthcare professionals were created. The information on Agency's website regarding submissions from pharmaceutical activities merchants and decisions adopted by the Agency is refreshed several times a day.

In 2017, 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 and a subscription was made for a solution in self-learning and knowledge testing in ICT security.

In the year of review, collaboration in the exchange of information was continued with different European institutions, competent authorities in other countries by using the collective ICT solutions, for example, the European clinical trial database EudraCT, the secure e-mail (EudraMail) and data exchange (Eudralink) system, the pharmacovigilance system EudraVigilance and data analysis system EVDAS, 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, as well as the Common Repository for marketing authorisation documentation in the centralised procedure, the Periodic Safety Update Report (PSUR) Repository and others.

To continue implementation of the tasks laid down by the Ministry of Health Order No. 141 of 22 July 2013 "Regarding Establishment of Main Tasks for the Ministry of Health and Institutions Under the Supervision of the Ministry of Health in Management of Information and Communication Technologies for 2013–2015" (amendments – order No. 189 of 18.12.2015., No. 13 of 11.01.2017.) with regard to ICT centralisation within the field of health, the ICT infrastructure used by the Ministry of Health and five institutions under supervision of the Ministry of Health was maintained and support was provided to ICT specialists in these institutions.

"The improvements made to the Agency's website provide new important information search options, as well as expand availability and comprehensibility of information. On the website, Agency clients are provided with the opportunity to conduct a convenient and clear search for information in the Medicinal Product Register of Latvia"

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 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 facilities;
- 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 2017, SAM announced 13 procurement procedures, as well as made procurements where, in accordance with the contract fees stipulated by law and other exemptions stipulated by law, the provisions of the Law on Public Procurement are not applicable.

Contracts for supply, services and construction were signed as a result of public procurement procedures. The most important contracts were signed to ensure functions related to information technologies and infrastructure, for example:

- Security for the buildings and territory on Jersikas Street 15 in Riga, as well as for the rented facilities on Daugavpils street 62/66 in Riga;
- Rent facilities for office space and archive purposes;
- Construction and renovation of the roofing over the oval section of the administrative building, construction work of the steps leading to the administrative building and archive building;
- Reconstruction of the driveway on SAM territory and implementation of the reconstruction project for the administrative and archive facilities;
- MS licence subscription;
- Maintenance of IT infrastructure and its availability;
- Massive modernisation of discs;
- IS security inspection and consultation services.

5. PUBLIC INFORMATION AND COMMUNICATION

In 2017, the State Agency of Medicines continued to broaden the spectrum of its external communication activities and channels with various collaboration partners, thus, providing independent and objective information on the issues within the competency of SAM. Special attention was paid to communication with professional associations and other non-governmental organisations in the industry, at the same time not forgetting about patient organisations and state institutions.

In 2017, the State Agency of Medicines provided information to the public and carried out communication activities in accordance with the "Operational Strategy of the State Agency of Medicines 2017-2019". The aim of the direction of collaboration and information laid down in the strategy is to promote efficient interaction between the Agency and the stakeholders in its services and collaboration.

One of the priorities in the year of review was to contribute to the public understanding of safe and rational use of medicinal products and promote awareness among healthcare professionals regarding the role of monitoring in ensuring quality, safety and efficacy.

In March and April 2017, SAM in collaboration with the organisation "Health Projects for Latvia" implemented the informative campaign "How not to overpay for medicines?" in order to inform the public regarding the option to choose several alternative medicines from the wide range of medicinal products with the same active substance, but different price. With the help of informative materials, a message was forwarded to doctors and the general public (every patient) informing them about what are generic or patent-free medicinal products, their benefits and whether they are safe. The State Agency of Medicines prepared an informative brochure for doctors "Rational choice of medicines" and distributed it to industry professionals. An informative website www.generiskaszales.lv was created where all the campaign-related information is available electronically.

On 21–24 November 2017, the State Agency of Medicines participated in a social media campaign taking place across Europe by providing information not only via press releases, but also using animations, banners and other materials. Adverse drug reaction reporting activity is insufficient in

MEDIA PUBLICITY

In 2017, 45 various press releases were prepared and distributed to media representatives and more than 180 answers were provided to queries from the media, the public, merchants in the industry, as well as the Ministry of Health and institutions under its supervision.

To promote more purposeful external communication, in 2017, the State Agency of Medicines organised the following informative campaigns:

"One of the priorities in the year of review was to contribute to the public understanding of safe and rational use of medicinal products and promote awareness among healthcare professionals regarding the role of monitoring in ensuring quality, safety and efficacy"

45
press releases

180
queries from the media

5
infographics

2
campaigns

all EU Member States, therefore, the aim of the campaign was to inform the public and promote reporting. The campaign was executed as part of a Europe-wide information week regarding adverse drug reactions and its main focus was over-the-counter medicines. The adverse drug reaction information week was created within the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) project in Europe. One of the main aims of this project is to increase understanding of national systems for reporting of adverse drug reactions. This social media campaign was also supported by the WHO Uppsala Monitoring Centre.

In 2017, five infographics were prepared to show information in a more comprehensible manner:

- "How to purchase medicines wisely?"
- "Consumption of medicines in Latvia in 2016"
- "Unauthorised medicines: what should patients know?"
- "Price of medicines in focus"
- "Life-cycle of medicines"

The infographics were distributed to the media, in the Agency's informative bulletin "Cito!", published on the website www.zva.gov.lv, in Agency's social media profiles on Facebook and Twitter, as well as distributed to individual stakeholders.

Following the medicinal product regulation in Europe and Latvia and evaluating information regarding the safe use of medicines, regular news updates in Latvian and English were published on Agency's profiles on Facebook, Twitter, LinkedIn and YouTube.

As a result of the communication activities

WHAT WERE THE MAIN NEWS TOPICS?

Topic	Conclusions expressed in publications, TV and radio programs
Which country will be the new host of EMA?	• Have the responsible state institutions – Ministry of Health, SAM been active enough to ensure that the European Medicines Agency could move to Latvia? • What are the chances of Latvia becoming EMA host country? • What should be done to ensure this and by whom?
Within the publication cycle "Invisible power of pharmaceutics": domination over the pharmacy network in Latvia	• Pharmacy distribution and opportunities for patients to purchase medicines • Does it affect the price of medicines and how? • Availability of pharmacies in regions • Legislative framework
Distribution of pharmacies in the city and power of the municipal government	• During the period before municipal government elections the issue of "municipal pharmacies" and "where seniors would have access to cheaper medicines" has been raised. • The normative acts clearly stipulate the conditions and criteria for opening a new pharmacy and who can do it, however, some municipal government representatives benefited from maintaining an illusion of election promises.
Publicity for the campaign "How not to overpay for medicines?"	• Why is it important to clarify the active substance in medicines? • What are generic medicines? • What determines the price of medicines? • How to search for information in the Medicinal Product Register and elsewhere?
Consumption of medicines	• Medicines consumption data • Sales of medicines manufacturers in Latvia • Total turnover of medicinal product wholesalers

of the State Agency of Medicines in 2017, there were 352 publications in various media channels mentioning the State Agency of Medicines. For example, last year the news agency "LETA" published 1150 articles mentioning "State Agency of Medicines" as one of the keywords. Even though it may seem like a high number, it has to be mentioned that the State Agency of Medicines was not the initiator of all of these articles. This includes also topics proposed by other institutions, for example, in relation to amendments to normative acts in the pharmaceutical field, as well as material (stories, programs) prepared by journalists and including commentary or clarification of situation by the Agency.

At the same time in 2017, regular updates were made to the information on Agency's website www.zva.gov.lv. In the age of technology, maintenance of the website is not only one of the most cost effective tools for communication, but also allows to provide information directly to the target audience browsing the world wide web.

The State Agency of Medicines regularly invited the general public to use the information on medicinal products available on the website www.zva.gov.lv more actively. For example, view the contents of the Public Assessment Report (PAR). The PAR not only certifies the compliance of the documentation submitted for marketing authorisation with the requirements of the normative acts in Latvia and Europe, but also contains important information regarding the quality, efficacy and various safety aspects, as well as the risk-benefit assessment of the relevant medicinal product. Therefore, SAM invited all of its stakeholders to find out more about medicines by viewing the contents of the Public Assessment Report.

According to the Google Analytics data, SAM website was visited 538 662 times in 2017, which is a substantial increase in the number of visits in comparison with 2016. During one of the months in the year of review, the website was visited 40 000 times, and the most popular section was the Medicinal Product Register. Maintenance of the website is an effective way to ensure official and current information regarding the operation of the State Agency of Medicines and news in the industry.

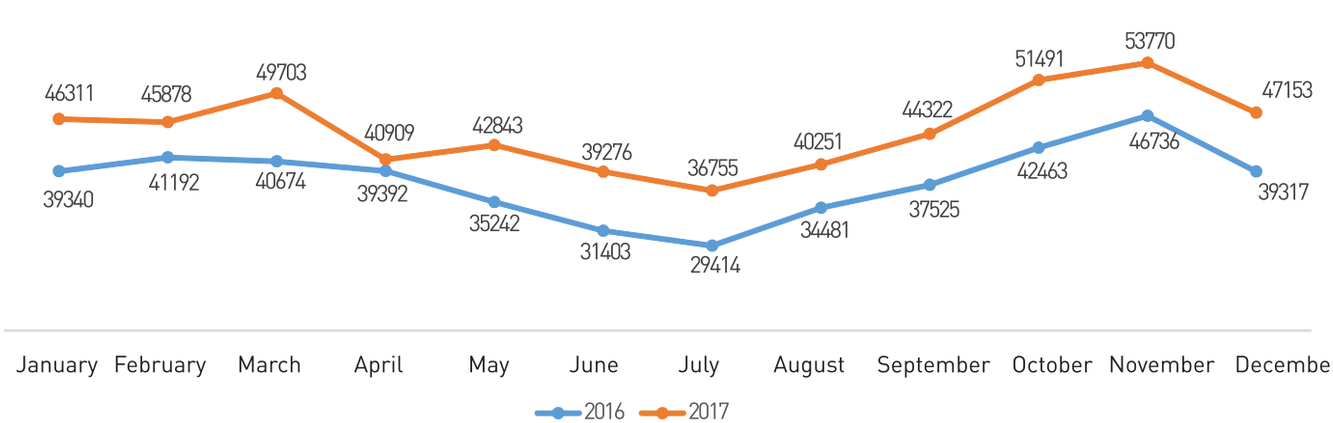
In 2017, the layout, functionality and design of Agency's website was transformed to ensure a user-oriented presentation of information for the various target audiences of SAM in separate sections of the website – for healthcare professionals, marketing authorisation holders and patients. Furthermore, in 2017 the project for the new website design was prepared and the programming work was initiated. It is planned that in 2018 the State Agency of Medicines will have a website with a new design that will be even more suitable to the needs of the visitors.

According to the Google Analytics data, SAM website was visited

538 662

times in 2017

NUMBER OF VISITORS OF THE WEBSITE WWW.ZVA.GOV.LV IN 2016 AND 2017



WEBSITE IMPROVEMENTS

In 2017, the functionality of the search form in the Medicinal Product Register of Latvia was improved substantially, making the search for information faster and more convenient. A new search parameter "Disease group (by ATC)" was added to the expanded search form, allowing to search for medicines according to a specific disease group. In addition, new functionalities were introduced in both of the online search forms (simple and expanded) – the option to "choose medicines with a listed price". All of the authorised medicines are included in the Register, including the medicines that are not being distributed in Latvia for various reasons and do not have a listed maximum price at a pharmacy, thus, the new parameter allows for a more purposeful search. The Medicinal Product Register search form also allows to sort the selected list of medicines according to the maximum pharmacy price and availability. For example, now the list of selected medicines can be sorted starting from the lowest price and in an ascending order. In addition to these improvements, the speed of operation of the Medicinal Product Register was also increased in 2017.

In order to improve healthcare professional access to information regarding the potentially biological origin of medicines and implementation of normative acts, as well as to allow other users of the Medicinal Product Register to navigate the range of medicines included in the register, the State Agency of Medicines introduced a new symbol for "biosimilar medicines" visible next to the name of active substance. Since 2017 "Biosimilar medicines" is also available as a search parameter in the expanded search form of the Medicinal Product Register.

In order to promote more active reporting of adverse drug reactions, the procedure for patient reporting of adverse reactions was simplified and made faster. That is, since 2017 by activating the banner "Reveal the other side of medicines" you may complete the report form without authentication through the portal Latvija.lv.

In order to make the reporting process faster and more modern, since 2017 healthcare institutions may submit electronic Vigilance reports related to human blood, tissues, cells and organs on SAM website. Healthcare institutions may submit information regarding adverse events creating risks for donors or recipients of blood, blood components, organs, tissues or cells on the website www.zva.gov.lv, "section Services – Evaluation of the State Blood Donor Center, blood establishments, blood banks, procurement and storage centres for tissues, cells and organs".

PUBLICATIONS OF THE STATE AGENCY OF MEDICINES

In order to inform doctors, pharmacists and other healthcare professionals regarding the news in the pharmaceutical industry and in the operation of the State Agency of Medicines, as well as safety of medicines, several informative publications were prepared in 2017. 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 printed (electronic) SAM publications provide updated, objective, verified and focused information to the interested parties who wish to follow the most important developments in pharmaceutics and the industry.

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 2017.

The Medicinal Product Register of the Republic of Latvia is an official and inde-

pendent source of information for doctors and pharmacists, 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 version, 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.

To provide information regarding trends in the consumption of medicines, in 2017, the annual statistical report on the consumption of medicines in Latvia was published. 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 medicines with the highest sales in Latvia and further information was provided about the market of medicines manufactured in Latvia.

The annual report was published also in 2017, summarising information regarding operation of SAM in 2016.

SPECIAL EVENTS AND INFORMATIVE SEMINARS

On 30 June 2017 representatives of the State Agency of Medicines participated in the discussion festival "LAMPA" regarding the topic "Independent information on medicines. Safety of medicines". SAM colleagues invited the festival attendees to discuss the following

PUBLICATIONS	COPIES
• Bulletin "Cito!"	5600
• Medicinal Product Register of the Republic of Latvia	200
• Brochure regarding issues related to quality and safety of medicines "Rational choice of medicines"	1500
• Brochure for the public "How not to overpay for medicines?"	39 500
• Poster for the campaign "How not to overpay for medicines?" (A1)	1000
• 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 2016 (Latvian and English version) – electronic version only	

* Provided by SAM upon request

topics: what is the Medicinal Product Register, where to find information regarding prices of medicines, what is safety of medicines and why is it important to report adverse drug reactions to state institutions? The aim and motivation for SAM participation in this event was to inform the public so that it would be able to make informed decisions in the interests of their healthcare. Our colleagues not only talked about the safe and rational use of medicines and options for finding information, but also answered questions and participated in discussions. The visitors of our tent together with the representatives of the organisation "Health Projects for Latvia" were introduced to the slogans and information of the SAM informative campaign "How not to overpay for medicines?". The State Agency of Medicines also provided visual materials – infographics, animations, videos, brochures and posters.

In February 2017, Shadow Day took place in SAM, allowing students from various cities in Latvia to see the daily work of a senior expert-analyst at the Medicines Examination Laboratory, thus, broadening their perspective on the work and career of a chemist. The students were also informed about the work specifics of the Information on Medicines Distribution Department.

On 22 September 2017, SAM experts participated in the Latvian Congress of Physicians. Collaboration and communication with healthcare professionals is one of the priorities of the State Agency of Medicines. The experience of doctors regarding use of medicines in real-life/daily clinical practice is important for the SAM safety assessment and safety profile establishment for medicinal products, thus, providing maximum benefit to patients. In 2017, SAM once again promoted the activities in relation to the European Antibiotic Awareness Day (18 November) and World Antibiotic Awareness Week (13-19 November), inviting everyone to pay attention to the correct and safe use of antibiotics that should always be implemented in accordance with the doctor's recommendations. The slogan of the Antibiotic Awareness Day was "Keep antibiotics working" (#KeepAntibioticsWorking). Materials of the WHO World Antibiotic Awareness Week were distributed as part of the informative campaign, and the latest data on antimicrobial resistance in Europe assembled by the European Centre for Disease Prevention and Control (ECDC) was published in the publication of 15 November 2017.

SAM supported the initiative "Consult first". The administration of State Agency of Medicines alongside other state administration institutions signed a Memorandum of Agree-

Conversation "Independent information on medicines" on 30 June 2017 in Cēsis

ment on the introduction of the "Consult first" principle. The aim of this initiative is to improve the collaboration between supervisory authorities and merchants, thus, decreasing the administrative burden and introducing the principle of good administration.

One of the SAM communication directions in 2017 were informative seminars – for manufacturers of medicines and medical devices, medicines marketing authorisation holders and other representatives of the pharmaceutical industry.

On 18 April 2017, a meeting took place at the State Agency of Medicines bringing together experts from professional associations in the pharmaceutical industry and the Agency on issues related to marketing authorisation. At the meeting discussions were held on specific issues regarding various authorisation procedures (national, mutual recognition, decentralised, centralised), electronic submission of documents, heading towards common marketing authorisation applications in the European Union, as well as towards the introduction of a unique identifier – a two-dimensional barcode. The meeting was attended by 38 participants. On 18 May 2017, a seminar was organised at SAM regarding marketing authorisation issues, with 72 participants in attendance. On 8 and 13 September 2017, a meeting took place where SAM administration and experts informed the 30 participants regarding the principles for review of Agency's paid service pricelist. On 27 October 2017, a seminar was held on issues of Good Clinical Practice with 55 persons in attendance. In collaboration with the Medical Devices Evaluation Department three seminars were organised regarding the new regulation in the field of medical devices: on 5, 12 and 19 December with a total of 160 participants.

OTHER EVENTS

SAM also promoted internal communication and employee participation in events organised by other organisations, thus, increasing employee understanding of common goals and a unified work culture, strengthening the sense of community at SAM, as well as motivating initiatives. 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 19th 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.

"Consult first" – an initiative signed on 15 June 2017

556

respondents replied to questions on SAM website

FEEDBACK

SAM communication activities are not based solely on one-directional provision of information, but SAM also gives the opportunity for SAM collaboration 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 2017, SAM organised several surveys:

- SAM client survey regarding SAM operation and services with the purpose of improving the quality of client service and the provided services, including distribution of two separate surveys – to industry representatives and the general public;
- SAM employee survey with the objective 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 motivating development of pesonnel resources.

To enquire the opinion of SAM website visitors, five surveys were conducted in 2017 (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 regime of the medicines indicated by the doctor on the prescription (e-prescription)?
- Why, in your opinion, is it important to know the active substance in medicines?
- Do you have any experience with the use of e-prescriptions and what are their benefits, in your opinion?
- Do plan to vaccinate against the flu this season?
- What will you do, if you experience an adverse reaction after using medicines?

556 respondents replied to these questions.

6. PRIORITIES IN DEVELOPMENT IN 2018

In 2017, the State Agency of Medicines established a new midterm operational strategy laying down the main operational directions and priorities for 2017–2019.

Taking into account the state administration reform plan until 2020, in 2018, there will be a greater emphasis on optimal use of human resources, particularly in the supportive structural units of the Agency, as well as on review of processes, following a result-oriented approach.

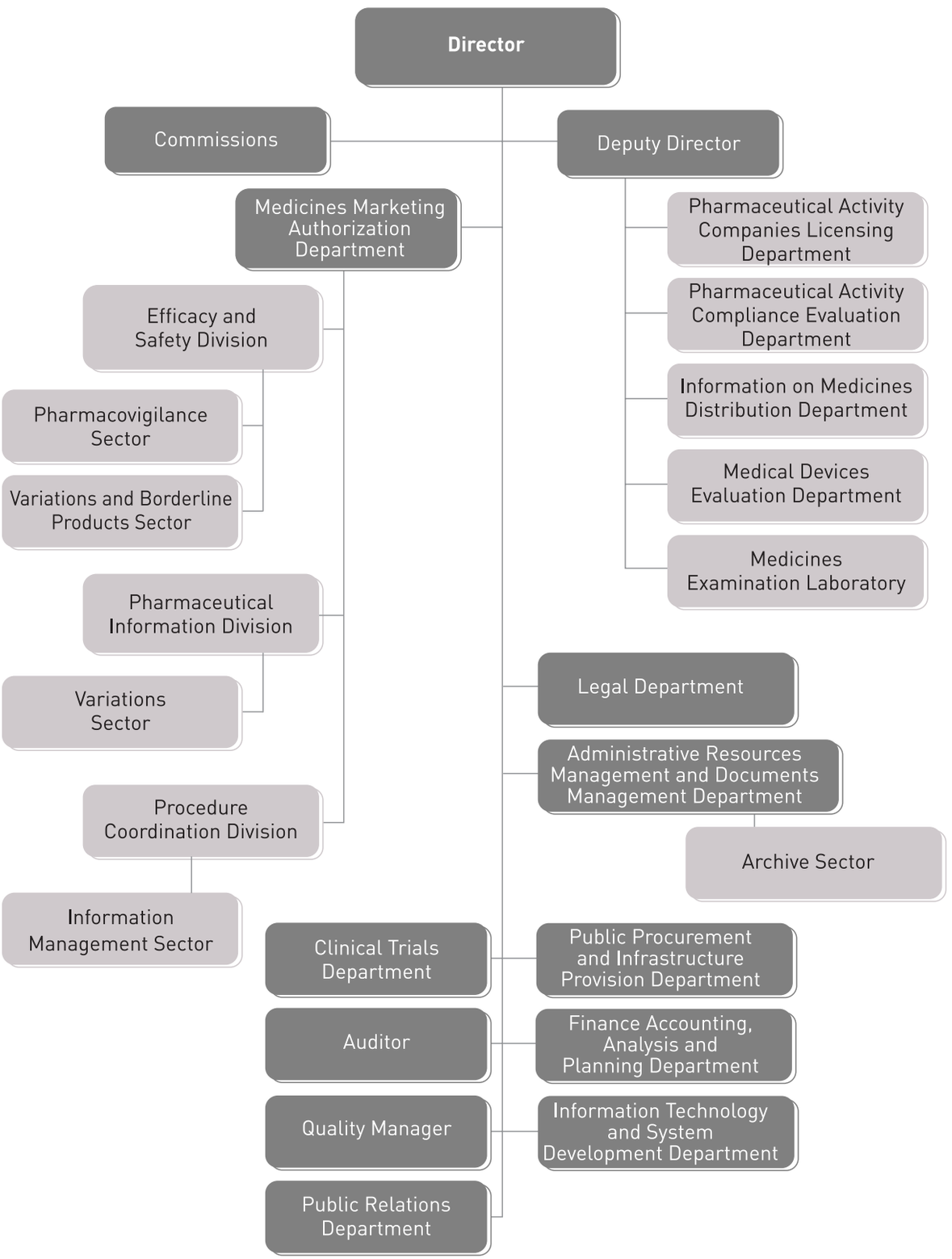
The network of European medicines agencies is preparing for the withdrawal of the United Kingdom from the European Union, and this means that the work carried out by the Medicines Agency in the United Kingdom (approximately 30% of the total work) will be distributed among the agencies in other member states. Therefore, additional resources will be allocated to structural units responsible for marketing authorisation and safety monitoring, and the professional qualification of experts involved in assessment of innovative medicines will be strengthened.

The State Agency of Medicines has put forward the following operational priorities for 2017–2019:

- Promote availability of appropriately evaluated medicines, as well as minimise shortterm and longterm shortages of medicines;
- Increase application of risk assessment principles in compliance evaluation of the pharmaceutical field, the field of procurement and storage of human blood, tissues, cells and organs, as well as the field of clinical trials and ensure a more thorough utilisation of the capacity of SAM in compliance evaluation;
- Contribute to the public understanding of safe and rational use of medicines and promote awareness of healthcare professionals of the role of monitoring in ensuring quality, safety and efficacy of medicines;
- Improve the use of ICT solutions in support and main processes, as well as ensure a secure environment for exchange of information with clients. This priority shall be implemented in accordance with the general development priorities in the field of ICT established by the Ministry of Health;
- Continuously increase the knowledge and professionalism of experts and SAM personnel.

7. ANNEXES

7.1 ANNEX. SAM STRUCTURE



7.2 ANNEX. BUDGET AND EXPENSES

BUDGET AND EXPENSES OF THE STATE AGENCY OF MEDICINES

Nr. p.k.	Title of position	2015	2016	2017	
		Budget implementation EUR	Budget implementation EUR	Budget estimate EUR	Budget implementation EUR
1.	Resources for covering expenses (income)	5 170 617	4 892 390	4 856 107	4 832 185
1.1.	Paid services and other own income	5 127 338	4 892 390	4 856 107	4 832 185
1.2.	Transfers from the State budget	43 279			
2.	Expenses (total)	4 858 019	6 170 476	5 459 986	4 109 039
2.1.	Maintenance expenses	4 064 523	5 762 004	5 071 566	3 968 819
2.1.1.	Regular expenses	4 064 523	4 119 177	5 071 566	3 968 819
2.2.	Transfers for maintenance expenses		1 642 827		
2.3.	Expenses for capital investments	793 496	408 472	388 420	140 220
	Financial balance	312 598	-1 278 086	-603 879	723 146
	Financial resources	-312 598	1 278 086	603 879	-723 146
	Increasing (-) or decreasing (+) change in surplus of financial resources from paid services and other independent income	-312 598	1 278 086	603 879	-723 146

A REPORT BY INDEPENDENT AUDITORS

Riga

No.1/2017

The date of the document is the date of the electronic signature on the document

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 2017. The attached financial report includes:

- Report of 31 December 2017 on the financial situation of the Agency – the form No. 1 "Balance" stipulated by the Cabinet of Ministers Regulation No. 1115 of 15 October 2013 "Procedure for Preparation of the Annual Report" (hereinafter – form),
- A report on the financial results of Agency operation in 2017 – form No. 4-3,
- A report on the changes in own capital (net assets) in 2017 – form No. 4-1,
- A report on the flow of Agency's financial resources in 2017 – form No. 2-NP,
- Annexes of the financial report stipulated 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,
- 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 2017, as well as of the financial results of its operation and flow of financial resources in the year concluded on 31 December 2017, 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 Audit Services of the Republic of Latvia ("Law on Audit Services"), we conducted 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*.

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 Audit Services applicable to the financial report audit conducted by us in the Republic of Latvia. We have also complied with other professional ethical standards and requirements for impartiality laid down in the IESBA Code and the Law on Audit Services 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, and whether it 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 Audit Services 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 with 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 that is truthful and clear 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.

> *"Financial report provides a truthful and clear overview of the financial situation of the State Agency of Medicines on 31 December 2017, as well as of the financial results of its operation and flow of financial resources in the year concluded on 31 December 2017"*

Persons entrusted with the supervision of the Agency shall be 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 as a whole 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.

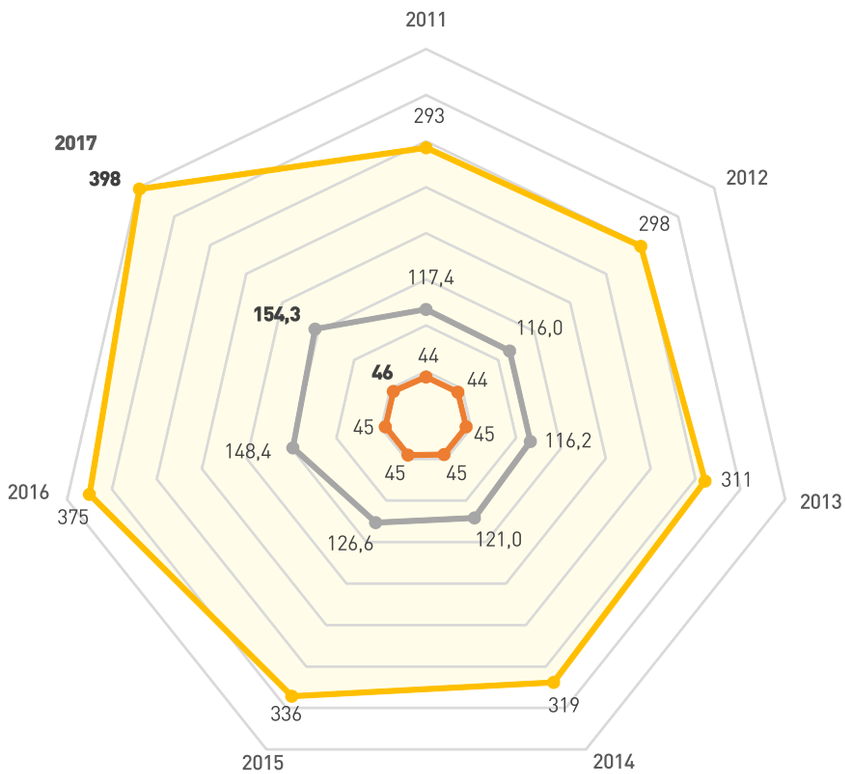
We shall contact the persons entrusted with supervision of the Agency and, among other things, shall provide information regarding the scope and time of the audit, as well as important audit observations, including significant internal control deficiencies identified during audit.

LLC „Auditorfirma Padoms"
Licence No. 68

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. TOTAL TURNOVER OF MEDICINES IN LATVIA



Address: Jersikas iela 15, Riga, LV-1003
Phone: 67078424
Fax: 67078248
E-mail: info@zva.gov.lv
Homepage: www.zva.gov.lv