State Agency
of Medicines
Republic of Latvia

STATE AGENCY OF MEDICINES
ANNUAL REPORT

2021

CONTENTS

FOREWORD

Ilze Bude,

Acting Director of the State Agency of Medicines

2021 has been a year of change for the State Agency of Medicines (hereinafter – Agency). Most of the changes have been related to the requirements associated with the COVID-19 pandemic and movement towards the Agency's development, ensuring the Agency's ability to adapt to future needs.

It brings me great joy that despite the impact of the ever-changing and complex outer environment a lot has been achieved at the Agency, and the collective work was aimed not only at fulfilling Agency's functions, but also at reaching strategic goals and improving quality of work. This was certainly facilitated by establishment of an appropriate internal work environment and culture that received high praise from employees in the annual survey: more than 95 % of survey's respondents consider the Agency to be a modern institution with very good internal communication, work environment and provision of information.

Both process rearrangement and flexible approach to working remotely, e-training and improving employee wellbeing has provided the opportunity to move towards the Agency's strategic goal – sustainable development. Last year, the Agency also received the highest evaluation in Latvia's e-index dimension "Internal institutional processes and inter-institutional collaboration/ internal process efficacy" and was among the 10 institutions characterised as agile organisations in the engagement survey conducted by the State Chancellery of Latvia, i.e., organisations that are able to change their operational customs sufficiently quickly and appropriately with

respect to the dynamic environment and client demands.

An important part of Agency's work is its involvement in international collaboration. Last year, considering the COVID-19 pandemic, in addition to regular marketing authorisation processes substantial amount of work was done in the committees of the European Medicines Agency (EMA) in order to evaluate safety and efficacy data for marketing authorisation of vaccines and in their post-authorisation period. The Agency has been a rapporteur at the EMA safety committee in the evaluation of the marketing authorisation application for the mRNA COVID-19 vaccine "Curevac". Agency's specialists have worked intensively in EMA scientific committees and working groups, e.g., Committee for Medicinal Products for Human Use (CHMP), Biologics Working Party, COVID-ETF (COVID-19 EMA pandemic Task Force), safety committee (PRAC), etc.

Last year, the Agency ensured continuous and long-term safety monitoring of medicinal products. The number of reports on suspected adverse drug reactions received in 2021 increased ten-fold – almost 3000 adverse reaction reports were received in relation to COVID-19 vaccines alone. This confirms that during this time public awareness has been directed towards vaccines, therefore, Agency's experts ensured independent and data-based information regarding COVID-19 vaccines and their safety as part of interviews given to the public media, as well as in response to individual patients and healthcare specialists, and to medical professionals at various events. At the same time, the Agency alongside other healthcare institutions took part in working groups established by the Ministry of Health concerning vaccination and restricting viral spread.

In collaboration with the medicines agencies in Estonia and Lithuania, the Baltic states initiated a pilot project where product information for medicines used only in the hospital setting was provided only in electronic format. The aim of the pilot project is to assess whether the use of electronic package leaflets ensures safe use of medicines and whether it may improve availability of medicines used in hospitals.

In response to the consequences and challenges of the COVID-19 pandemic, the Agency took care of the continuity of medicinal product availability in Latvia in order to allow distribution of authorised medicines also in packaging intended for other European Union (EU) member states, if necessary. Furthermore, in cases where medicines included in the Medicinal Product Register of Latvia were not available

the Agency issued permits for distribution of medicines not authorised in Latvia. In comparison to pre-pandemic times, this number increased by 10 %. The Agency also ensured restrictions on export of critically important medicines in Latvia during the state of emergency and issued permits for export of medicines for which the state had signed a co-financing agreement with the supplier.

Upon initiation of comprehensive state-wide testing of students and employees using rapid SARS-CoV-2 antigen self-tests, there was a substantial increase in the number of notifications received via the notification procedure about the release of SARS-CoV-2 antigen self-tests on the market in Latvia. Considering the importance of maintaining the export capacity of local manufacturing companies in Latvia during the COVID-19 pandemic, the number of certificates of free sale issued to local medical device manufacturers in Latvia increased by 18 % in 2021, in comparison to 2020. The Agency also continued preparation for the implementation of the new medical device regulation (EU) 2017/745 and in vitro diagnostic medical device regulation (EU) 2017/746.

In 2021, the Agency successfully participated in the establishment of the Clinical Trials Information System of EU and European Economic Area (EEA) countries. Extensive work was done to ensure implementation of the regulation on clinical trials with human medicines ((EU) No 536/2015) and to initiate simultaneous evaluation and approval of clinical trials in several countries from January 2022 by member states working in a unified information system.

I invite you to view precise and comprehensive information about Agency's functions, achievements and news in 2021 in this public report.

"I would like to thank every employee of the Agency for the work they have done individually and we have achieved collectively to ensure the availability of qualitative, effective and safe medicines and medical devices to the residents of Latvia. I wish to express gratitude to collaboration partners and clients for their support and involvement that allowed the Agency to not only fulfil its tasks, but also to improve and develop in order to continue to successfully achieve its goals in the ever-changing environment."

ABOUT THE AGENCY

The State Agency of Medicines 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, the Medical Treatment Law, the Cabinet of Ministers Regulation No. 537 "Statutes of the State Agency of Medicines" adopted on 31 July 2012 and other normative acts. The Agency was established on 9 October 1996, based on the Cabinet of Ministers Order No. 403 "Regarding the Non-profit Organisation State Joint Stock Company "State Medicines Agency"".

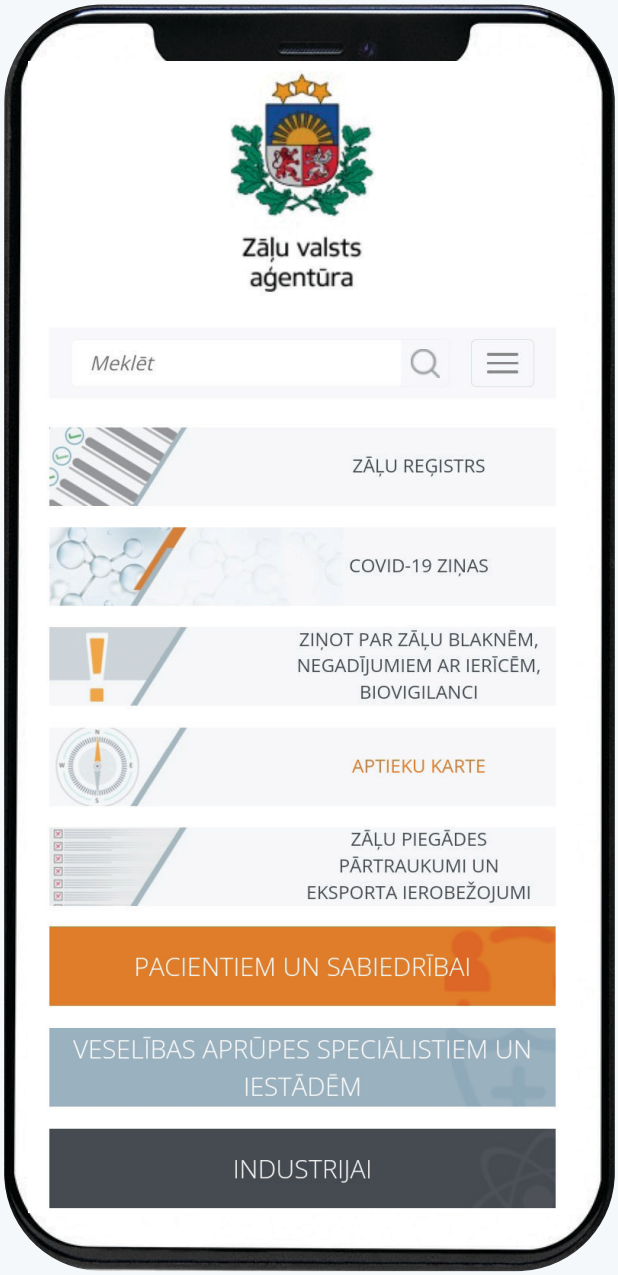
The mission of the Agency has been included in the objective of its activities determined by the Cabinet of Ministers of the Republic of Latvia

> to ensure qualitative and justified services in the evaluation of medicinal products used in healthcare, centres for procurement and utilisation 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.

Vision

It is our vision to become one of the leading authorities among equivalent national and international institutions by implementing functions delegated to the Agency and basing our development on knowledge, efficacy, quality and collaboration.

Functions



- evaluation and authorisation of medicines
- establishment and maintenance of the Medicinal Product Register
- expertise on quality of medicines
- pharmacovigilance of medicines
- vigilance of medical devices
- issuance of authorisations for conduct of clinical trials with medicines and medical devices
- compliance evaluation of Good Clinical Practice, Good Manufacturing Practice and Good Distribution Practice
- issuance of permits for import, export, transit, distribution and utilisation of medicines
- assembly and provision of information regarding medicines consumption
- issuance of licences for pharmaceutical activity
- analysis of cost-effectiveness of medicines and medical devices
- approval of medical technologies used in healthcare
- other functions

In 2021, 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. 641 “Publicly Available Paid Service Pricelist of the State Agency of Medicines” adopted on 10 December 2019.

SUMMARY OF IMPLEMENTATION OF THE AGENCY'S STRATEGY 2020-2022 IN THE YEAR OF REVIEW

Results achieved in 2021 as set forth for the planning period 2020-2022, considering also the operational strategy of the EMA and Heads of Medicines Agencies (HMA), may be taken as a confirmation of the Agency's movement towards attaining the objective set out in its vision.

Agency's operation in the year of review

Main events affecting the Agency's operation in the year of review

1) National state of emergency declared in Latvia and the SARS-CoV-2 pandemic. Due to its impact in 2021, the Agency acted as follows:

- Considering the increasing interest of local merchants to release on the market medical devices used for individual protection in healthcare and for identification of the SARS-CoV-2 virus, the Agency provided consultations to merchants regarding requirements of normative acts applicable to classification, manufacturing, release on the market and commissioning of the aforementioned medical devices.
- The Agency continued to participate in EMA working groups, evaluate information and data in order to ensure availability of medicinal products, including vaccines, as well as participated and prepared assessment reports in centralised marketing authorisation procedures for medicines.

- Provided independent and scientific fact-based information regarding vaccines and medicines against COVID-19 authorised in the EU, as well as distributed the latest EMA information regarding progress in vaccine research, evaluation and approval and the role of regulatory authorities in vaccine approval, ensuring public awareness in Latvia regarding safe and rational use of medicinal products.
- Continued safety monitoring of medicines, including vaccines, evaluation of adverse drug reaction reports, promoting awareness of healthcare specialists regarding medicinal product use and adverse reaction management. In 2021, the Agency initiated in-depth evaluation of causal relationships in cases when a suspected adverse reaction report was received regarding a patient's death after administration of a vaccine against the COVID-19 infection.
- Streamlined the work environment and maintained solutions for working remotely, in order to ensure continuity of operation and substantially decrease health risks for employees and clients.

2) Development of the pharmaceutical industry, including implementation of a new EU regulation

- The Agency established a Data Analytics Division within the Medicines Marketing Authorisation Department with the main task to participate in international working groups regarding use of big data in the post-authorisation surveillance period of medicines and to implement data gathering, collection, processing and analysis with respect to effective and safe use of medicines in their post-authorisation period, as well as to perform impact analysis of regulatory decisions on the use and availability of medicines according to the priorities set forth by the Medicines Marketing Authorisation Department.
- Participation was ensured in the establishment of the common EU member state and EEA country Clinical Trial Information System (CTIS). CTIS will be the only place where regulatory authorities will evaluate submitted clinical trial information, including a work space for clinical trial sponsors and collaborative organisations.
- Participation was ensured in the development of the new European Medical Device Database (EUDAMED) which will improve management and coordination of information regarding medical devices available on the EU market. The new database will include various electronic systems: for medical device registration and

unique identification of medical devices (UDI) (available from 4 October 2021), for merchant registration (available from 1 December 2020), for notified bodies and certificates (available from 4 October 2021), for clinical trials, for vigilance and post-marketing surveillance, for medical device market surveillance.

- In 2021, active work was continued to streamline the Agency's information system and establish a client service platform, evaluating the most appropriate solutions in order to link Agency's information system ZVAIS with the new platform.

Measures to implement operational directions set forth in the Agency's strategy

Last year, the Agency continued actively working to reach the goals set forth in the mid-term operational strategy for 2020-2022.

In order to strengthen the public belief in health as a value, the following Agency's strategical operation directions have been set from 2020 to 2022:

- **Public health interest direction** with the purpose of facilitating availability of appropriately evaluated medicinal products, as well as safe, effective and economically-sound pharmacotherapy;
- **Readiness for future necessities and external circumstances**, considering the required competencies related to release of new and innovative medicinal products on the market, as well as opportunities provided by data in development and evaluation of medicinal products;
- **Direction for sustainable and productive development of the Agency** with the purpose of organising the work environment and expand automatization of certain steps in processes in order to minimise the administrative burden and increase effective work-load of highly-qualified employees in areas where their professional knowledge would provide the highest added value to public health.

The following operational priorities were put forward:

1) Promote availability of appropriately evaluated medicinal products, including minimisation of short-term and long-term disruptions in availability of medicinal products;
2) Increase patient and healthcare specialist knowledge about resources providing independent and qualitative information regarding medicinal products;
3) Purposeful professional development of employees, considering the trends in

development of medicinal products and maintenance of current competencies;

4) Promote competency and understanding of potential uses of Real World Data[1] in decision-making;

5) Review of processes with the purpose of maximising rational use of resources by determining risk-based priorities;

6) Use of Agency's resources in a rational and environmentally-friendly manner.

In order to achieve the goals of the Agency's strategy in the period of review, 6 strategic working groups established in 2020 continued their work:

- Options for improving the medicinal product marketing authorisation process and minimising obstacles in establishing multilingual packaging were explored by participating in the working group of the EMA Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh), as well as the Multilingual Packaging Group by providing comments and opinions regarding specific situations and at the meetings of Baltic medicines agencies.
- Marketing authorisation holders were approached in order to identify medicines not included in the Medicinal Product Register of Latvia, but necessary to ensure the medical treatment process and regularly imported in Latvia as unauthorised medicines.
- Structured, LEAN-based streamlining and optimisation of Agency's operational processes was continued using the knowledge and skills obtained by employees during LEAN method practical training.
- The tool for appraisal of employee competency was streamlined. This tool allows collection of information regarding current and future needs for competencies in order to ensure purposeful raising of competencies based on future needs and succession of competencies.
- An environmentally friendly policy was streamlined and maintained, continuing to substantially decreased the amount of paper consumed, ensuring circulation of documents with digital solutions in more than 90 % of cases, increasing energy efficiency and decreasing the CO_2 footprint.

[1] Electronic medical records, registries, adverse drug reaction reporting data.

MARKETING AUTHORISATION OF MEDICINES

Elita Poplavska,
Head of Medicines Marketing Authorisation Department:

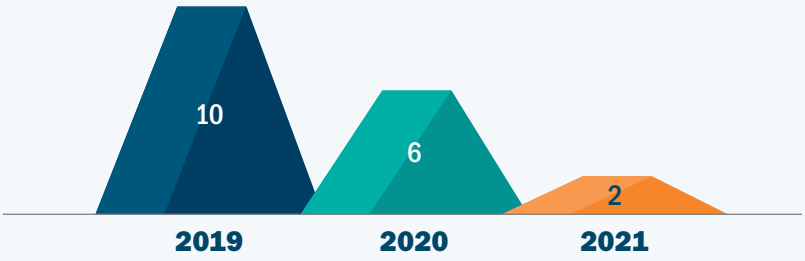
"The work undertaken by Agency's specialists in scientific committees and working groups of the European Medicines Agency, giving priority to and actively evaluating safety and efficacy data regarding COVID-19 vaccines and treatments to ensure their marketing authorisation and simultaneously continuing evaluation of submitted data regarding medicinal products for other diseases, was the cornerstone to ensuring availabiity of qualitative, safe and effective medicines in Latvia also during the pandemic.

In addition, last year Agency's specialists undertook careful and rigorous work to ensure qualitative implementation of the European Medicines Agency's approved pharmacovigilance plan for COVID-19 vaccines in the vaccine post-authorisation period in Latvia.

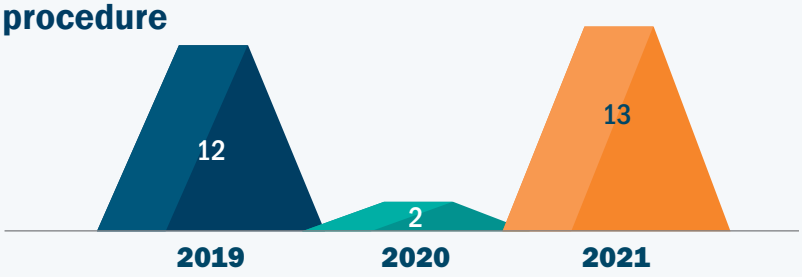
Agency's participation in the collective work-sharing procedures of the European Medicines Agency is our duty and an important additional responsibility, which in 2021 was mainly aimed at fighting the COVID-19 pandemic and ensuring also continuous scientific evaluation and monitoring of other medicines in the EU."

In 2021, the Agency evaluated more than 8346 applications for marketing authorisation, renewal and variations to marketing authorisation documentation of medicines by reviewing marketing authorisation documentation related to quality, safety and efficacy.

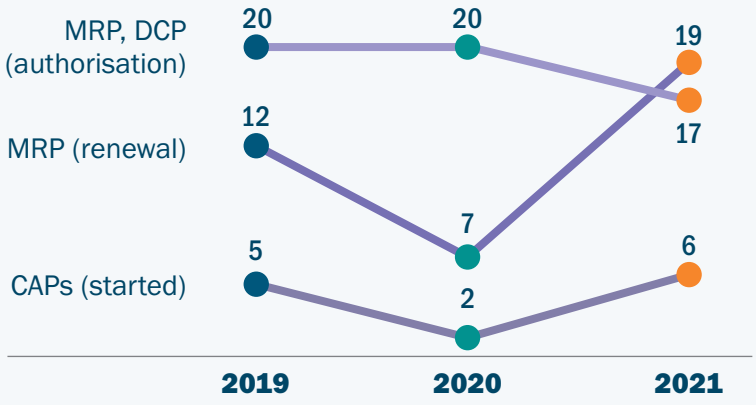
Marketing authorisations via national procedure with a positive outcome



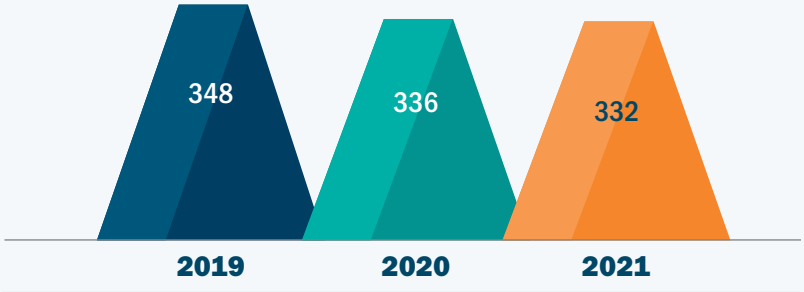
Medicinal product renewals via national procedure



Marketing authorisations and renewals (Latvia as a Reference Member State)



Marketing authorisations and renewals (Latvia as a Concerned Member State) with positive outcome



Reviews included also administrative information, as well as chemical, pharmaceutical, preclinical and clinical sections of the documentation and pharmacovigilance documents.

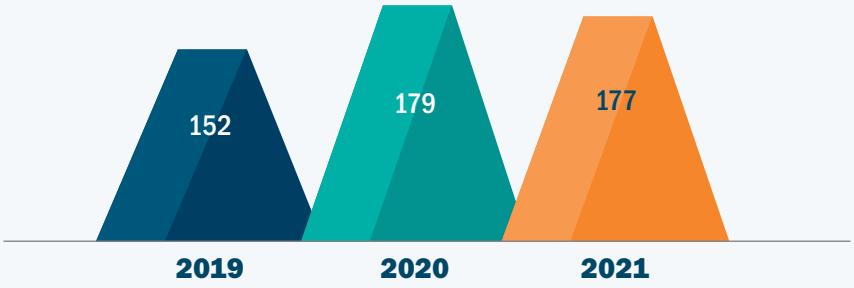
Last year, Latvia ensured marketing authorisation and renewal of 36 medicinal products via mutual recognition procedures (MRP) and decentralised procedures (DCP) as a Reference Member State.

Latvia also participated in 377 MRP and DCP marketing authorisation and renewal procedures as a Concerned Member State.

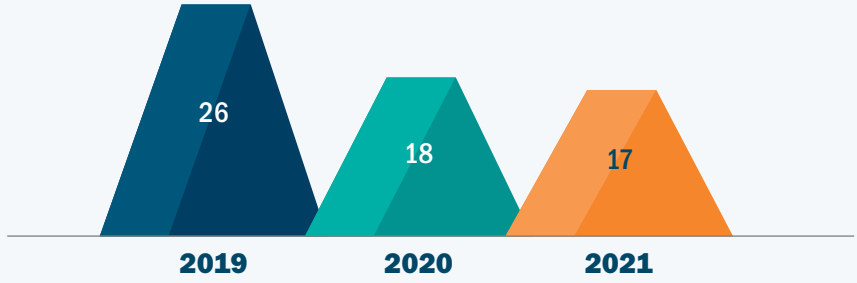
In addition, in 2021 the experts of the Agency prepared assessment reports for 6 centralised marketing authorisation procedures (CAP) as the co-rapporteur.

Last year, the activity of Agency's experts in international procedures was very significant, similarly as in the previous years. Latvia was represented in the EMA Paediatric Com-

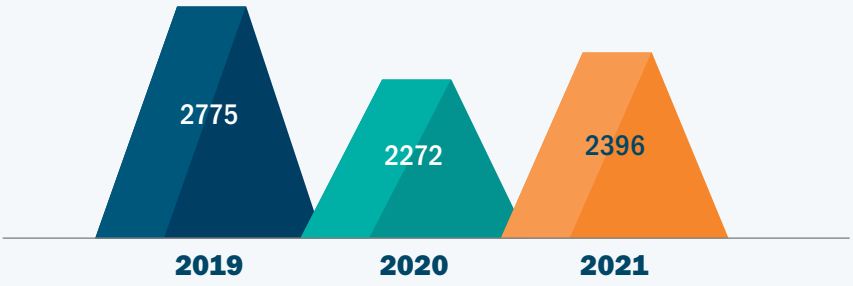
Type IA/IB variations (Latvia as a Reference Member State) with a positive outcome



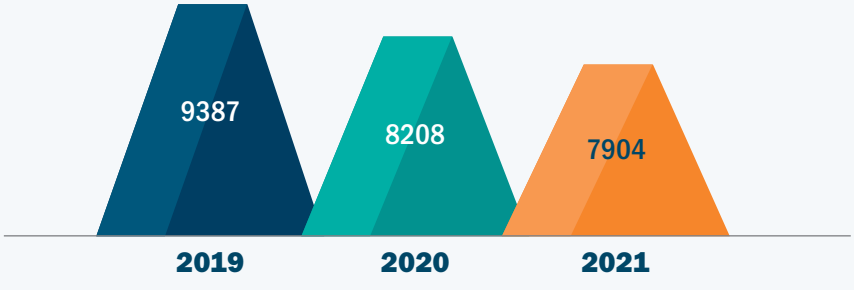
Type II variations (Latvia as a Reference Member State) with a positive outcome



Variations via national procedure



Variations to marketing authorisation documentation



mittee and participated in evaluation procedures for 38 primary paediatric investigation plans (PIP) and for 28 PIP modifications.

Experts from the Medicines Marketing Authorisation Department together with external experts actively participated in the work of the Committee for Advanced Therapies, Committee on Herbal Medicinal Products and other committees. Experts regularly participated in the work sessions of European Directorate for the Quality of Medicines (EDQM) as external experts.

In 2021, there was no change in the number of variations to marketing authorisation documentation of medicines evaluated in DCP and MRP procedures at the Agency where Latvia was the Reference Member State (177 type I variations and 17 type II variations).

Overall, the number or variations has decreased slightly which could be related to the internatio-

nal restrictions related to COVID-19 that have affected operation of pharmaceutical companies.

Agency experts evaluated 3 applications and issued their opinion on product compliance with the definition of medicines.

Last year, the Agency also issued 14 Certificates of Free Sale and 157 Certificates of Pharmaceutical Products, thus, promoting export of medicinal products authorised in Latvia to countries outside of EU. These certificates verify that companies manufacture medicines in compliance with Good Manufacturing Practice – according to strict and common quality standards and requirements.

By the end of the period of review, the Agency had:

- authorisations and renewals of **383** medicinal products;
- evaluated **7904** applications for variations to marketing authorisation documentation of medicines.

MEDICINAL PRODUCT DISTRIBUTION

Katrīna Lukša,
Head of Information on Medicines Distribution Department:

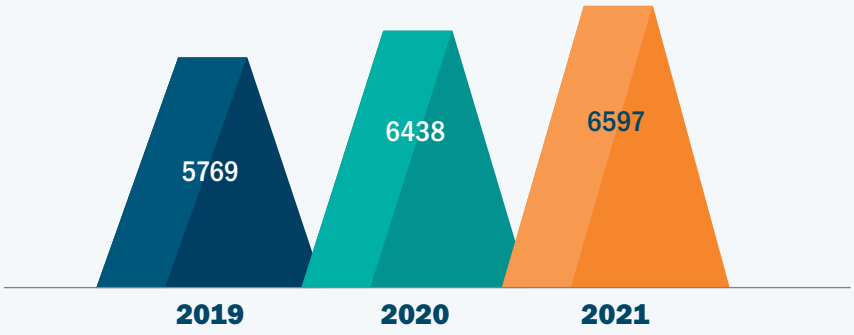
"One of the main problems worldwide, in Europe and in Latvia is the lack of availability and disruptions in the supply of medicines, thus, one important goal of the Agency is not only to evaluate and authorise medicines ensuring the possibility for safe and qualitative medicines to enter the market, but also to ensure prompt assessment of applications and issuance of permits for import and export of medicines. It is also important to provide useful, reliable and updated information regarding the availability of medicines on the medicinal product market in Latvia. Therefore, the previously undertaken project regarding remaining stock of medicines at wholesalers was particularly valuable and has proven itself also in practice – pharmacies and healthcare institutions can obtain information in the Medicinal Product Register not only about the availability of specific medicines, but also about medicinal product wholesalers where the medicines in question may be ordered."

2021 was filled with challenges created by the COVID-19 pandemic and its consequences. In order to ensure availability of medicines intended for treatment of COVID-19 and whose availability was affected, countries worldwide, including European Union member states, put in place various internal market protection measures that complicated the supply of active pharmaceutical ingredients, manufacturing and distribution of medicines, thus, creating risks for the capacity of the healthcare system and for patient health and life. Therefore, mention has to be made of the various amendments to normative acts where the Agency, including the Information on Medicines Distribution Department, actively participated in their preparation with proposals and risk assessments.

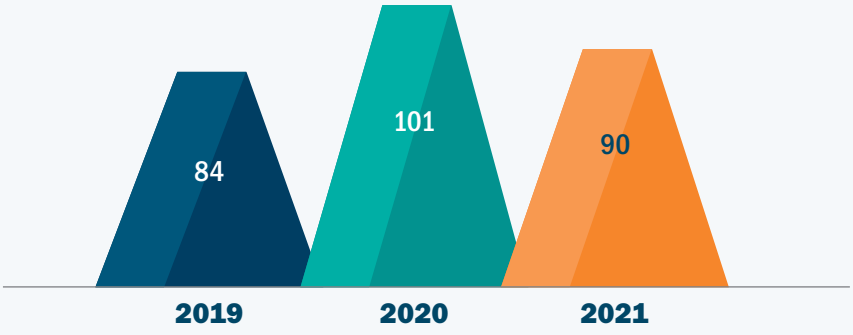
In reaction to the consequences and challenges of the COVID-19 pandemic, Agency's operation was aimed at improving availability of medicines, decreasing the administrative burden for import of medicines authorised in Latvia in a packaging intended for another European Union member state, issuing permits for export of medicines for which the state has signed a co-financing agreement with the supplier, etc., all of which together with other measures allowed to decrease the potential effects of the COVID-19 pandemic.

In 2021, the Agency issued 9117 permits for import, export, transit and distribution of medicinal products.

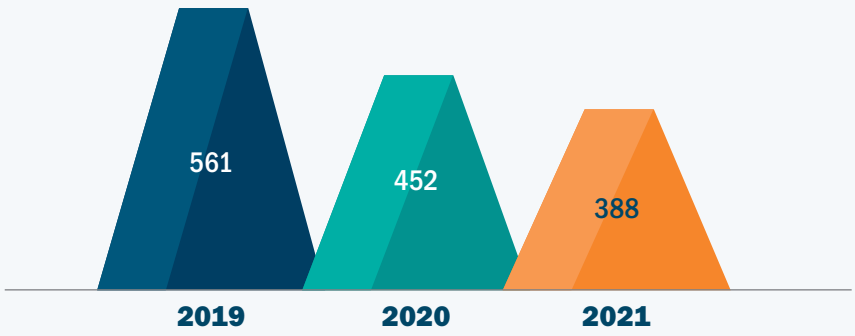
Permits for distribution of unauthorised medicines



Number of permits for parallel import



Number of variations to permits for parallel import



The Agency ensured expertise on applications and documentation related to distribution of the following medicinal products in accordance with the normative acts:

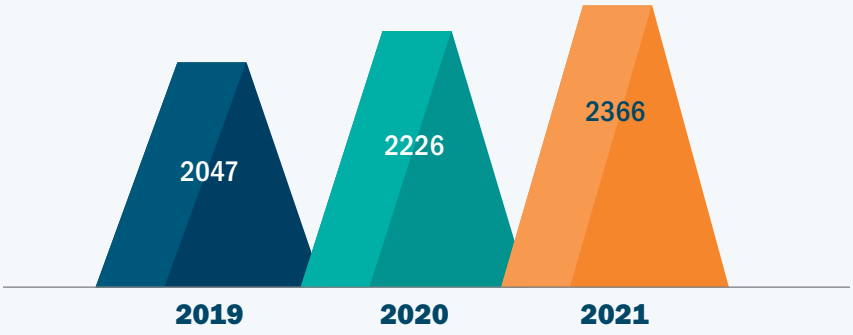
- for import and export of psychotropic, narcotic medicinal products/ substances, as well as precursor;
- for distribution of unauthorised and parallel imported medicinal products;
- for import of medicinal product samples.

In addition to the aforementioned, the Agency performed expertise on applications and documentation and issued 8 licences and registration cards for precursor operators and 1 authorisation for medical scientific

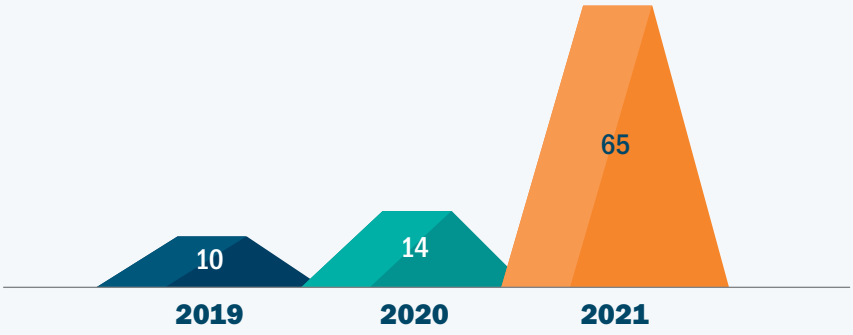
research on herbs, substances and medicinal products included in the I, II and III list of narcotic substances, psychotropic substances and precursors controlled in Latvia.

Every month the Agency collected information regarding consumption and pricing of medicinal products and published this information on its website. Based on information regarding sales of medicinal products provided by wholesalers, the Agency prepared its annual publication "Statistics on Medicines Consumption 2020".

Permits for import/ export of narcotic, psychotropic medicines/ substances and precursors



Permits for import of samples of medicines



In 2021, the Agency also ensured recording 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 addition, the Agency participated in the expert working group on Precursors of narcotic substances, as well as in the 62nd session of the UNODC Narcotics Control Committee.

Proposals were submitted for amendments to normative acts regulating circulation of medicines, including proposals related to circulation of narcotic and psychotropic substances and medicines, as well as precursors, the procedure for import and export of medicines, distribution and quality control of medicines, medicinal product labelling, etc.

CLINICAL TRIALS WITH MEDICINES

Jana Migliniece,
Head of Clinical Trials Department:

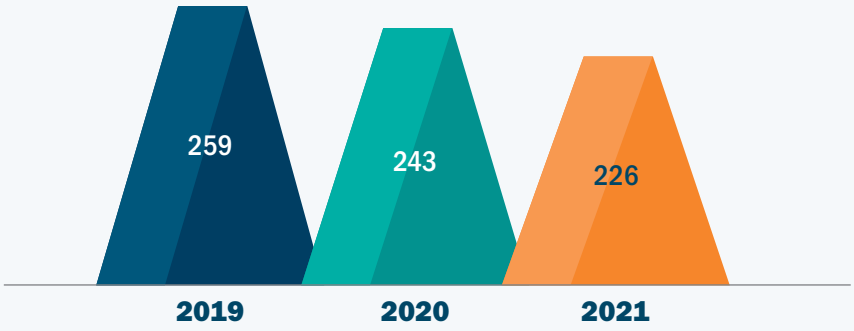
"In preparation for the work within the European Commission clinical trial Regulation 536/2014, the Clinical Trials Department became familiar with the Clinical Trials Information System (CTIS), submitted proposals to the Ministry of Health regarding the required amendments to national legal acts, collaborated with independent ethics committees in order to strengthen their capacity by operating in the new clinical trial Portal. Last year, experts from the Clinical Trials Department participated in international expert groups: clinical trial expert working groups established by the European Commission and Heads of Medicines Agencies in order to contribute to the harmonisation of clinical trial authorisation in Europe, and in the EMA Good Clinical Practice Inspectors Working Group in order to harmonise inspection procedures."

In 2021, the Agency issued 53 authorisations for conduct of clinical trials in Latvia, including 6 clinical trials authorised as part of the Voluntary Harmonisation Procedure (VHP) in Europe and 2 of the authorised clinical trials have been proposed by academic sponsors.

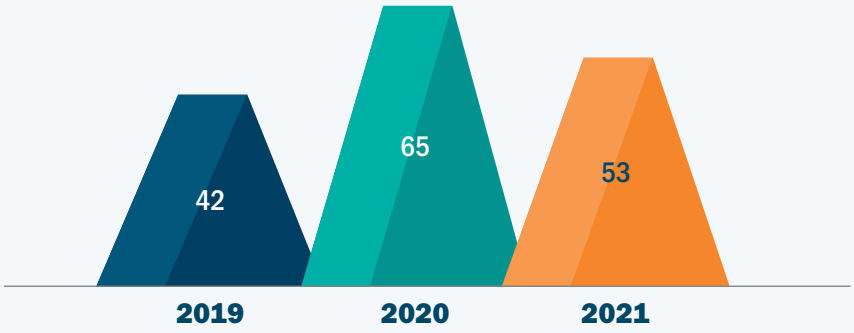
Latvia was the Reference Member State in 2 procedures, performing an important role in ensuring the overall evaluation process for investigational medicinal products in Europe.

Last year, 4 Good Clinical Practice (GCP) compliance inspections were carried out in Latvian trial sites and the GCP inspector participated in the inspection of the sponsor in Denmark.

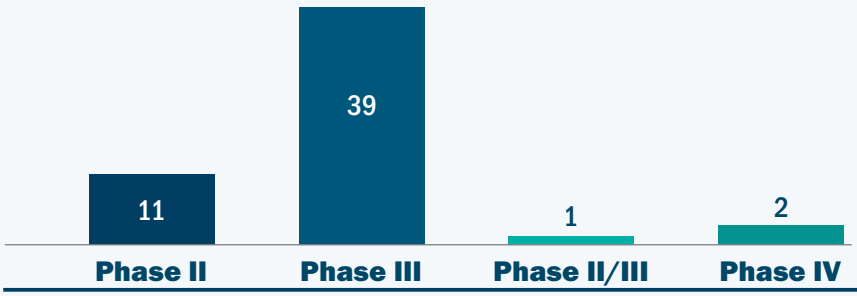
Total number of clinical trials conducted in Latvia



Authorisations for clinical trials



Number of clinical trials authorised in 2021, according to trial phase



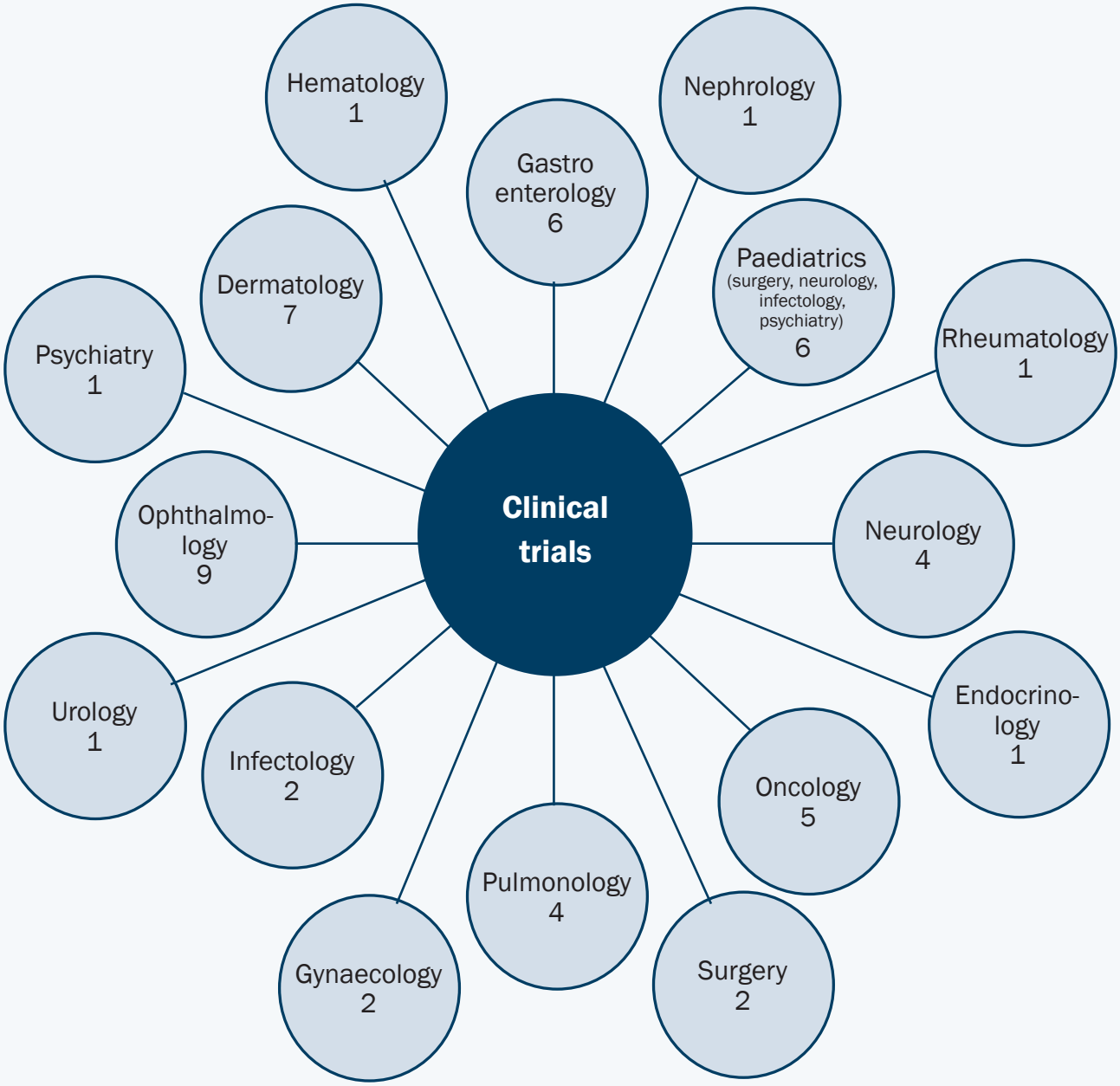
Information regarding applications for clinical trials with medicinal products, their authorisation, the dates of approval of applications for substantial amendments, opinions of ethical committees, completion of clinical trials, as well as inspections of Good Clinical Practice was regularly entered into the European clinical trial database EudraCT. Regular entry of this data is required to ensure maintenance and updating of the European Clinical Trials Register.

In the year of review, the Agency received 8 primary and 21 follow-up reports regarding serious unexpected adverse events potentially related to investigational medicinal products.

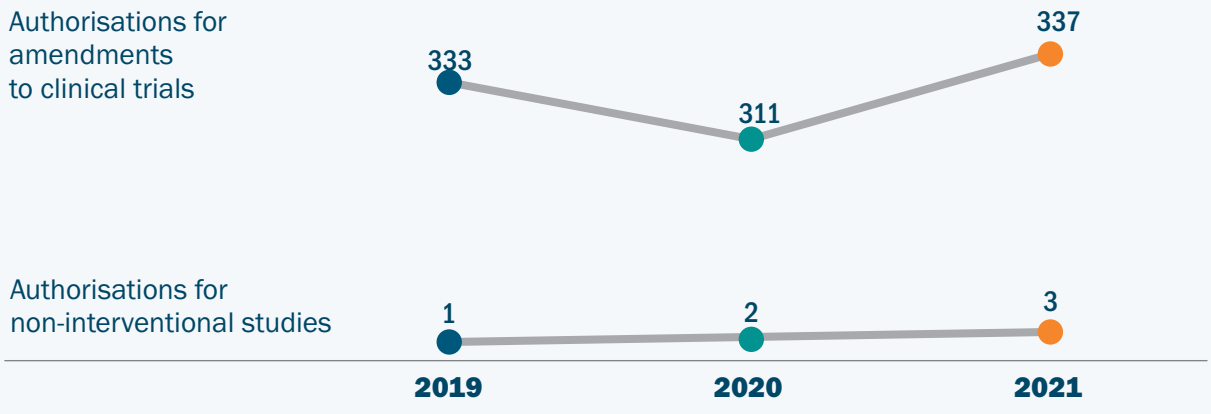
Trial sites of medicinal product clinical trials authorised in 2021

Trial site	Number of trials
State LLC “Pauls Stradins Clinical University Hospital”	31
Riga Eastern Clinical University Hospital	17
“Veselības Centrs 4”	12
LLC “Riga 1st Hospital”	10
State LLC “Children’s Clinical University Hospital”	8
LLC “Daugavpils Regional Hospital”	8
Aija Šmite medical practice in dermatology	6
LLC “J. Ķīsis”	5
Other clinical trial sites (82 in total)	1-4 trials at every site

Number of clinical trials authorised in 2021, according to medical specialty



Authorisations for amendments to clinical trials and authorisations for non-interventional studies in 2021



The Agency received and reviewed 123 annual safety reports from sponsors related to clinical trials with medicinal products conducted in Latvia. Experts of the Clinical Trials Department together with experts from other European medicines agencies have been involved in the review of these safety reports as part of the work-sharing process. As a result, in-depth analysis of some of the annual safety reports was conducted and the assessment was reflected in the assessment form designed by the safety subgroup of the European Clinical Trials Facilitation Group.

The authorised clinical trials with medicinal products were sponsored by 44 foreign pharmaceutical companies. In 2021, 17 contract research organisations were involved in the organisation and quality assurance of clinical trials conducted in Latvia according to authorisation issued by sponsors.

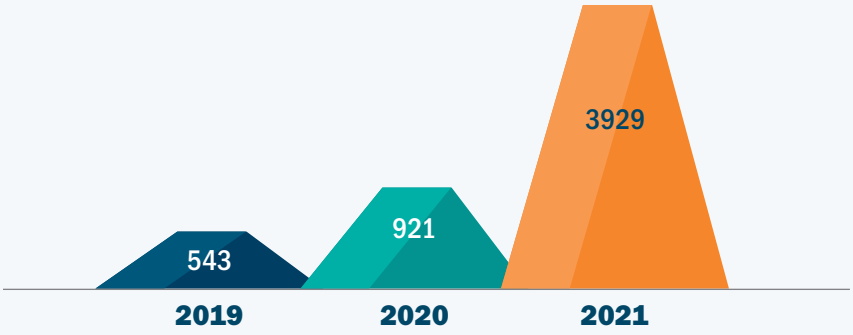
MONITORING OF ADVERSE DRUG REACTIONS AND RISK MINIMISATION

Zane Stade,
Head of Pharmacovigilance Department:

"The challenge for the Pharmacovigilance Department in 2021 was the monitoring of COVID-19 vaccine safety related to a substantial increase in the number of adverse drug reaction reports and increased public interest in vaccine safety. A large focus was put on regular provision of the latest information to doctors and the public regarding questions related to COVID-19 vaccines. Last year, in-depth evaluations of specific adverse drug reaction reports were initiated in relation to "events of special interest" and reports of fatalities in the time period following vaccination against COVID-19. Clinicians from certain specialties were also invited to participate in the process of evaluating complex cases, providing substantial support in the evaluation of reported events using their knowledge and experience. I assign high importance to promoting further Agency collaboration with clinical specialists. Furthermore, I would like to mention the contribution of pharmacovigilance experts in the 7-month-long project for translation of MedDRA terminology in Latvian. The workload in 2021 has been very large, but, despite certain limitations like working remotely, pharmacovigilance experts have completed all of their tasks in a timely manner with results of sufficiently high quality."

In 2021, the Agency received 3929 adverse drug reaction reports, including reports related to adverse reactions to vaccines, and this information was forwarded to the EudraVigilance database in the EU. 24 % of the reports were submitted by healthcare professionals and pharmacists, but 76 % reports – by patients.

Adverse drug reaction reports



Almost all adverse drug reaction reports were received in electronic format. Agency's pharmacovigilance experts and IT specialists worked on regular improvements to the electronic report form in order to facilitate data entry for doctors and improve the quality of submitted reports. The improved Adverse drug reaction report information system is now easy to use for daily work and collection of statistical data.

As part of the EU single assessment procedure, Agency's pharmacovigilance experts evaluate medicinal product Periodic Safety Update Reports (PSURs) regarding active substances where EMA has delegated Latvia as a reference member state. Agency performed 15 evaluation procedures in 2021.

In accordance with the EMA work-sharing procedure, in 2021 Agency's experts conducted monitoring for 31 active substances, i.e., regular surveillance of the safety information regarding these substances, as well as 2 in-depth evaluation procedures on a European level where Latvia assumed the role of the leading expert.

Last year, the Agency also evaluated risk management plans for 38 medicinal products authorised via national procedures. In addition, pharmacovigilance experts participated in centralised marketing authorisation procedures: 4 cases as Pharmacovigilance Risk Assessment Committee (PRAC) raporter and collaborated with clinical experts on safety issue assessment for 6 procedures.

In 2021, the Agency approved a total of 93 additional risk minimisation materials intended for doctors and patients prepared with the purpose of risk minimisation for specific medicines. 26 of these were Direct Healthcare Professional Communication letters submitted by marketing authorisation holders.

Agency's pharmacovigilance experts also actively participated in informing the public and healthcare specialists regarding the field of adverse drug reaction reporting and safety issues of medicines. The main emphasis during the COVID-19 pandemic was on safety issues of COVID-19 vaccines. These issues were repeatedly explained to the public, also by taking part in some TV and radio programs, by giving interviews to public media regarding the safety of COVID-19 vaccines, for example, to "Latvijas Avīze", TV program "Aizliegtais paņēmiens", TV "Delfi" , TV "Bez Tabu", TV program "Panorāma" (repeatedly), TV 24 program "Uz līnijas", "Ļičnoje ģelo", "Latvijas Radio" and others, as well as by participating in online events organised for doctors and nurses. Pharmacovigilance experts have provided a substantial contribution in the development of the new electronic format of the bulletin "Cito!".

The Agency also ensures regular exchange of pharmacovigilance-related information with EMA and European medicines agencies as reflected by the information provided in response to 18 information query documents from EU member states (NUI – nonurgent information).

A pharmacovigilance expert representing Latvia actively participated in PRAC working group meetings by regularly expressing opinion and presenting assessments performed by experts in Latvia. Information regarding decisions adopted by PRAC in relation to safety of medicines and recommendations for risk minimisation was provided to professional associations of doctors and medical specialists.

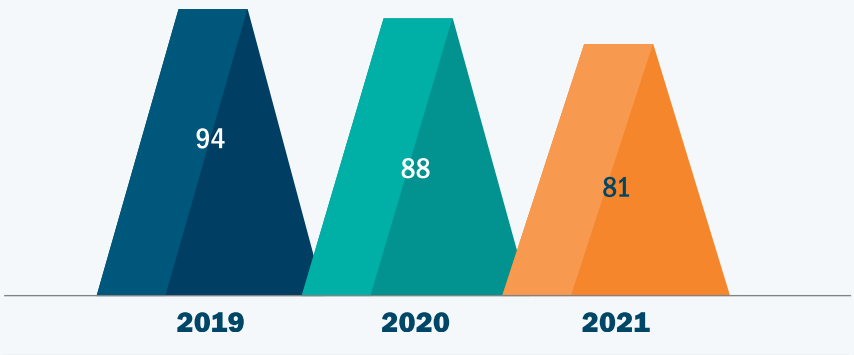
In 2021, Latvia together with several other EU countries (Denmark, Greece, the Netherlands, Portugal and Slovenia) participated in the EMA initiated study (Impact study) regarding effectiveness of communication related to the risk of TTS for COVID-19 vaccines Vaxzevria and Janssen. Experts of Pharmacovigilance Department in collaboration with Public Relations specialists prepared the information required for the study regarding communication conducted in Latvia and forwarded it to EMA.

QUALITY CONTROL OF MEDICINES

Guntars Kaspars,
Head of Medicines Examination Laboratory:

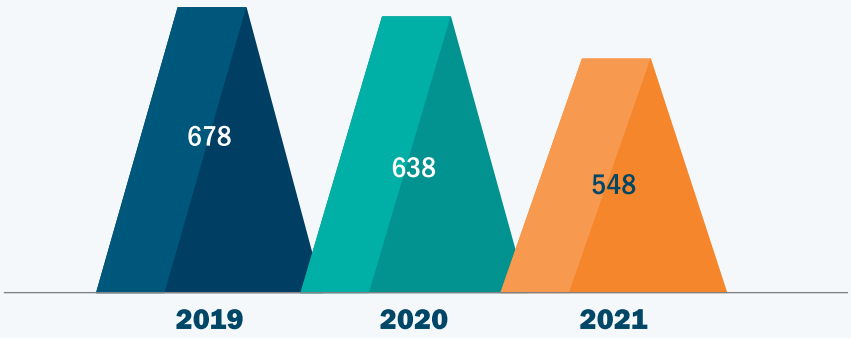
"In 2021, the Latvian National Accreditation Bureau (LATAK) conducted its routine monitoring visit, as a result of which the Agency maintained its accreditation for compliance with the requirements of the LVS NE ISO/IEC 17027:2005 standard in the following fields: physical and physicochemical testing of medicinal products, pharmaceutical active ingredients and excipients (fixed and flexible scope), physical testing of purified water (fixed scope). The successful audit is an important validation of the quality of Agency's professional operation. This annual confirmation of certification compliance ensures that our clients can have confidence in our work – industry professionals, collaboration partners in Latvia and other countries and the residents of Latvia may rely on the quality of the Agency's operation."

Number of medicinal product samples tested



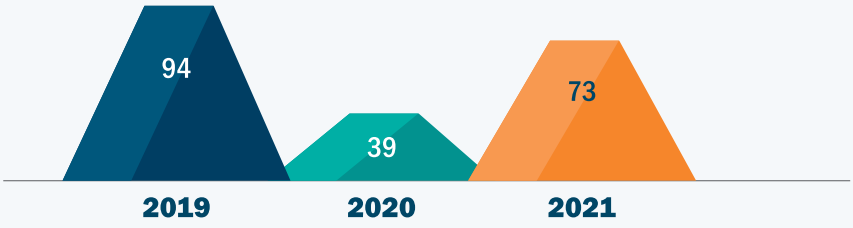
Given the epidemiological conditions that were established in the country, the Medicines Examination Laboratory was able to provide high quality testing of drug samples, it is proved also by the very small reduction in the

Number of medicinal product quality parameters tested

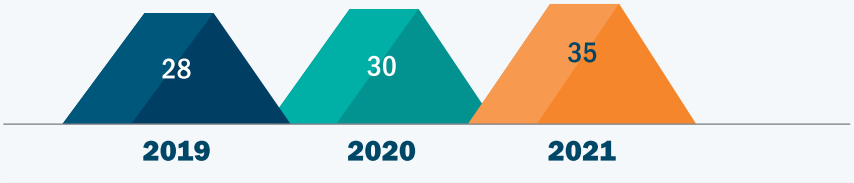


Number of volumetric solutions, indicators and reagents prepared upon request from pharmacies

Number of purified water samples tested



The conducted expertise for medicinal products upon request from the Agency's Medicines Marketing Authorisation Department, assessing the methods for analysis of active substances and/ or end-products and their validation



number of drugs tested.

In the Medicines Examination Laboratory were introduced electronic work journals, which were highly appreciated by LATAK evaluators. A new storage room for reagents/ standards and samples was put into operation, which in turn improves the working environment in the laboratory.

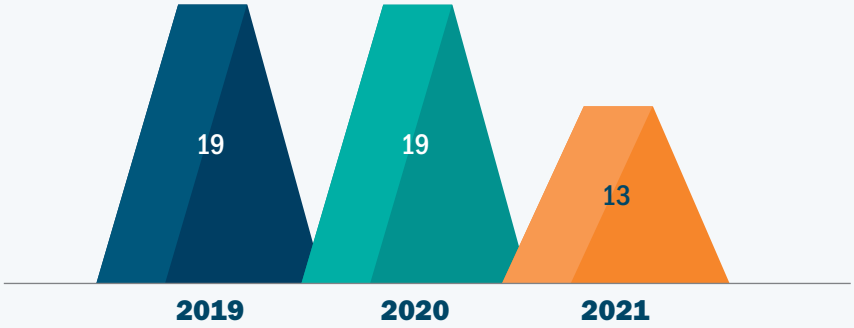
Laboratory's specialists participated in international programs for quality control of medicines and professional level evaluation programs, i.e. quality control programs for medicines authorised in the CAP, MRP/ DCP and national procedure as well as in the professional level evaluation programs provided by EDQM and Royal Dutch Pharmacists Association.

MONITORING, CLINICAL RESEARCH AND VIGILANCE OF MEDICAL DEVICES

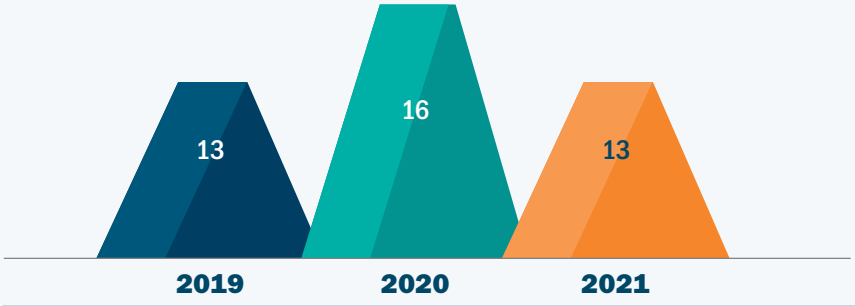
Andis Viļums,
Head of Medical Devices Assessment Department:

"Effective regulation of medical devices and strict requirements in this field are very important in ensuring a high level of health protection and safety for residents across the EU and Latvia. At the same time, strict and unified registration and safety monitoring of these devices is required. On 26 May 2021, the application of the new medical device Regulation (EU) 2017/745 was initiated, allowing for even greater safety for the people and greater assurances that the medical devices used in their treatment and care are working the way they were intended to."

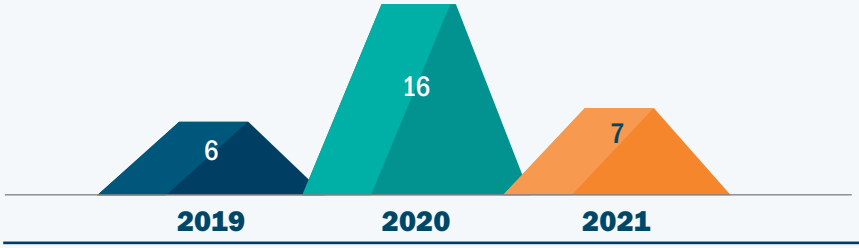
Latvian medical device manufacturers and their medical devices: information analysed and included in the Medical Device Database LATMED



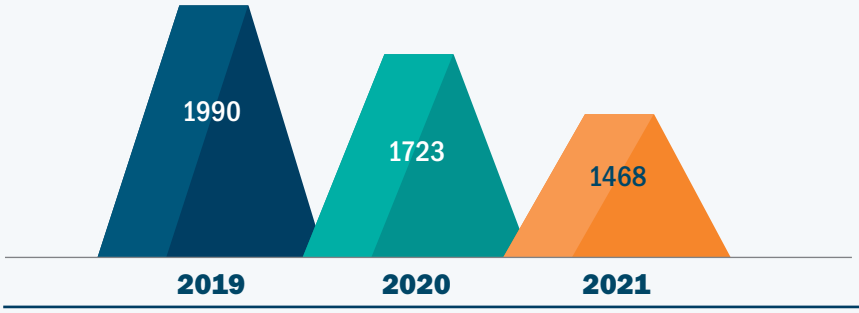
Authorised representatives of third country medical device manufacturers in the EU who have registered business in Latvia: information evaluated and included in the Medical Device Database LATMED



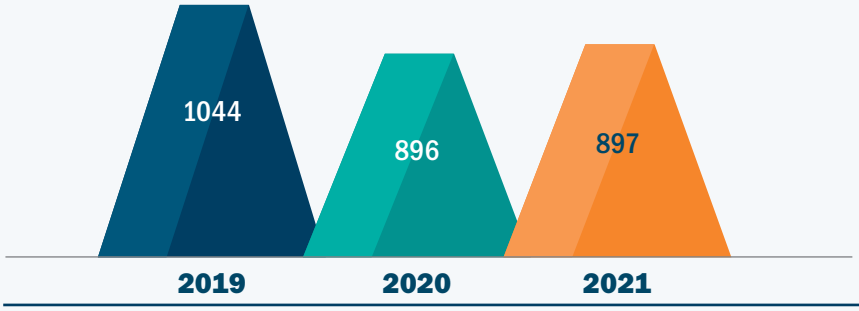
Authorisations for clinical trials with medical devices*



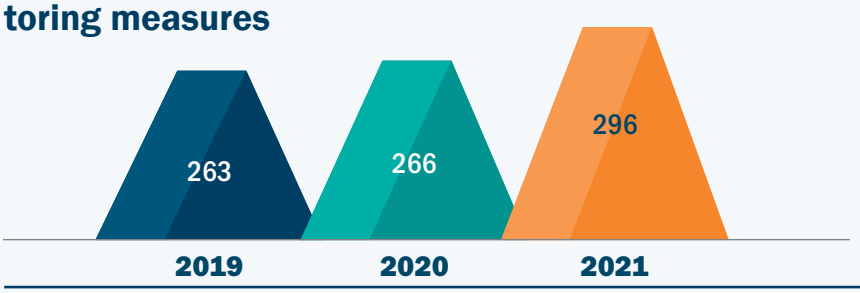
Vigilance reports regarding medical devices (total)



Primary vigilance reports regarding medical devices



Primary vigilance reports regarding medical devices located in Latvia and implementation of safety monitoring measures



To promote the export capacity of Latvian manufacturers outside of the EU, last year the Agency issued 28 certificates of free sale to medical devices manufactured in Latvia. In 2021, the number of certificates of free sale issued to local medical device manufacturers in Latvia increased by 18 % in comparison to 2020 when the number of these certificates had already increased five-fold during the pandemic.

*Authorisations for conduct of clinical trials with medical devices and authorisations for amendments to the research plans of clinical trials already being conducted.

HEALTH TECHNOLOGY ASSESSMENT

Antra Fogele,
Head of Health Technology Assessment Department:

> **"Despite working remotely, the department was able to ensure timely provision of opinions of an independent institution regarding the clinical and cost-effectiveness of new non-proprietary names of medicines, as well as take active part in the updating of the Database of Medical Technologies for Therapeutic Use. There was no decrease in the activity of applicants – marketing authorisation holders, healthcare institutions and professional associations."**

Opinion on clinical and cost-effectiveness of new non-proprietary names or new combinations of medicines

In 2021, the Agency received 44 applications and prepared 44 opinions.

Applications according to diagnostic groups

- Neoplasms – 22 applications (50 %)
- Diseases of the circulatory system – 3 applications (~7 %)
- Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism – 4 applications (~9 %)
- Diseases of the digestive system – 2 applications (~5 %)
- Infections (HIV/AIDS) – 1 application (~2 %)
- Mental and behavioural disorders – 1 application (~2 %)
- Diseases of the nervous system – 4 applications (~9 %)
- Diseases of the respiratory system – 2 applications (~5 %)
- Endocrine, nutritional and metabolic diseases – 2 applications (~5 %)

- Diseases of the musculoskeletal system and connective tissue – 2 applications (~5 %)
- Other diagnoses – 1 application (~2 %)

17 of all applications (39 %) were related to the treatment of orphan (rare) diseases.

In comparison, in 2020 the Agency received 42 applications and prepared 34 opinions.

As Agency's opinion is a required step towards the opportunity for reimbursement of new medicines from the state budget, according to the information available on the website of the National Health Service 30 applications, for which Agency's opinion was issued, have been submitted for inclusion in the system for reimbursement of medicinal product expenses.

Starting from 2021, we have initiated public participation in the evaluation process of medicines. After gathering information about experience in other countries and consulting with patient organisations and professional associations of doctors, we have established separate survey forms for healthcare professionals and patients where the interested parties may express their opinion regarding the role of the new medicinal product in the treatment process of a specific disease, the expected benefits and unmet needs.

Completion of this survey by patients and specialists is voluntary, but it may provide important information for the evaluations performed by the Agency.

Initially during the pilot project, surveys were created only for medicines for oncological diseases, but from 1 September 2021 such survey forms are being prepared and disseminated for every new application.

Out of the 44 opinions prepared in 2021, 11 surveys were disseminated to patient organisations via the Patient organisation network. Surveys regarding 14 new non-proprietary names of medicines or new diagnoses/ patient groups were sent to professional associations of doctors, including surveys regarding 11 medicinal products for treatment of tumours. Replies were received from specialists in 12 cases.

Information from these surveys is included in the prepared opinion on the clinical and cost-effectiveness of medicines.

Approval, supplementation and withdrawal of medical technologies (MT) and updating of the Database of Medical Technologies for Therapeutic Use

In 2021, the Agency received 30 applications for approval, supplementation or withdrawal of MTs and adopted 37 decisions, including 2 decisions to deny withdrawal of an approved transfusiology-related MT (see detailed information in the table below):

Name of medical technology group	Approved MTs	Supplemented MTs	Withdrawn MTs
Medical services in internal medicine and functional diagnostics	2		
Medical services in laboratory investigations	1		
Medical services in diagnostic and therapeutic radiology		8	
Medical services in anaesthesia, reanimatology, transfusiology and intensive care			17
Medical services in otorhinolaryngology	1		
Medical services in urology	1		
Medical services in pathology	1		
Medical services in physical medicine and rehabilitation	2		1
Medical services in complementary medicine	1		

In comparison, in 2020 the Agency received 10 applications for approval, supplementation or withdrawal of MTs and adopted 32 decisions on approval of MTs. We finalised work on the last of MT applications taken over from the National Health Service as part of the reorganisation in 2019 – 8 ultrasonography-related technologies were supplemented/updated in the MT group “Medical services in diagnostic and therapeutic radiology”.

The Medical Technology Assessment Committee, whose purpose is to evaluate the compliance of documentation regarding approval, supplementation and withdrawal of medical technologies submitted to the Agency with the requirements of normative acts and to provide an opinion to the Director of the Agency, held 5 meetings in 2021. The committee includes both Agency specialists and representatives from the National Health Service and the Health Inspectorate.

Utilising the opportunity provided by normative acts, we have asked for the opinion of the Latvian Society of Cardiology regarding a medical technology submitted for approval.

In 2021, work was continued on improvements to the content and updating of the Database of Medical Technologies for Therapeutic Use:

- More than half of the adopted decisions (17) were related to the MTs registered in the section "Preparation and quality control of blood and blood components" within the group "Medical services in anaesthesia, reanimatology, transfusiology and intensive care".
- We finalised the collaboration with Association of Latvian Rehabilitation Physicians started in the previous year, as a result of which the medical technology groups "29. Services in physical medicine" and "30. Medical services in rehabilitation" were merged, creating a new group "29./30. Medical services in physical medicine and rehabilitation" which corresponds to the guidelines of the European Society of Physical and Rehabilitation Medicine and the European Society of Physical and Rehabilitation Medicine Physicians.
- A new medical technology group "Medical services in algology (pain medicine)" was established including three medical technology descriptions from the section "Anaesthesia technologies" within the MT group "Medical services in anaesthesia, reanimatology, transfusiology and intensive care".

LICENSING OF PHARMACEUTICAL ACTIVITY COMPANIES

Signe Čudare,
Head of Pharmaceutical Activity Company Licensing Department:

"In 2021, the Agency provided services, delegated by the Pharmaceutical Law in the field of pharmaceutical activity licencing, in electronic format – issued special permits (licences) for opening general and closed-type pharmacies (activity), operation of medicinal product wholesalers, medicinal product manufacturing or import and manufacturing of active pharmaceutical ingredients. Last year, the proportion of documents received in electronic format reached 90 % out of all the pharmaceutical activity licencing services requested by clients.

As part of administrative reform, the Agency took measures to organise and renew data regarding licenced pharmaceutical activity companies and legal addresses by synchronising address data from the National Address Register with the data in the information system of the Enterprise Register of the Republic of Latvia.

We appreciate the fact that clients submit documentation in an electronic format, respond to Agency's requests for updating pharmaceutical activity company data reflected in the Pharmaceutical Activity Company Register. This allows Agency's employees to have prompt access to documents and provide the requested services to clients, decreasing resource consumption."

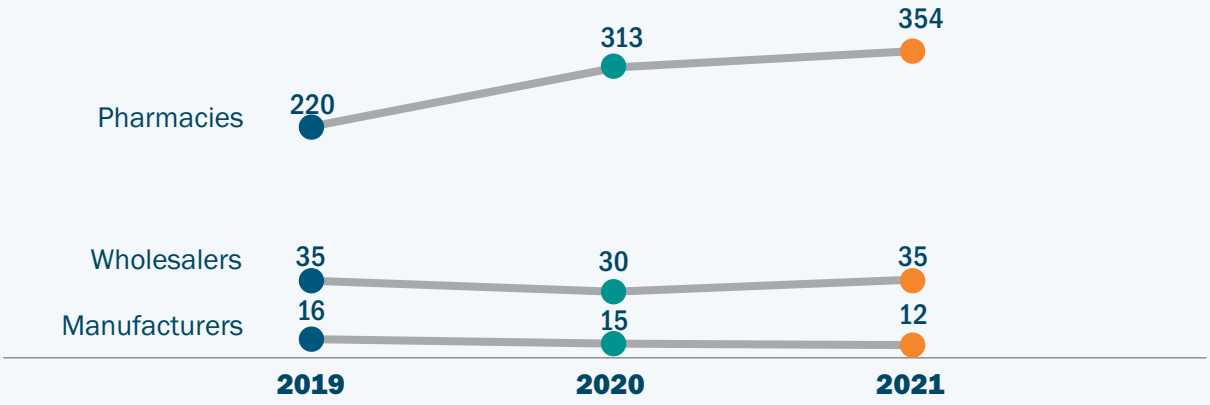
2021 was spent working remotely – a fact that was related to the national state of emergency, and the details of performing official duties and providing services had to be worked out promptly.

In 2021, the Agency renewed or issued licences for pharmaceutical activity for 415 pharmaceutical activity companies:

- 354 general-type pharmacies;
- 9 closed-type pharmacies;
- 35 medicinal product wholesalers;
- 12 medicinal product manufacturing or import companies;
- 4 active pharmaceutical ingredient manufacturing companies;
- 1 veterinary medicinal product wholesaler.

In 2021, the Agency renewed or authorised 6 active pharmaceutical ingredient manufacturing, importing or distribution companies.

Changes in licences for pharmaceutical activity

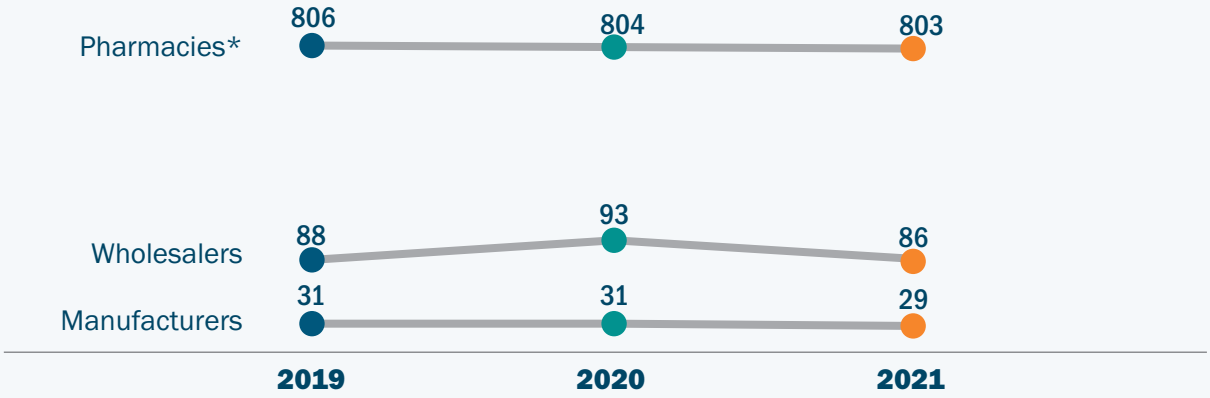


The Agency also assessed 34 cases related to new site (address) of operation of general-type pharmacies. In addition, the Agency issued 5 licences for new general-type pharmacies, 5 licences for new medicinal product wholesalers, 1 authorisation for manufacturing, import or distribution company of active pharmaceutical ingredients.

In 2021, changes were made to the operation of Agency's Pharmaceutical Activity Company Licencing Commission (hereinafter – Commission) – issues reviewed

by the Commission and outside of the Commission were separated in order to facilitate faster provision of services to clients. In 2021, the Pharmaceutical Activity Company Licensing Commission held 21 meeting, reviewing issues and adopting recommendations for issuance, renewal or suspension of pharmaceutical activity licences.

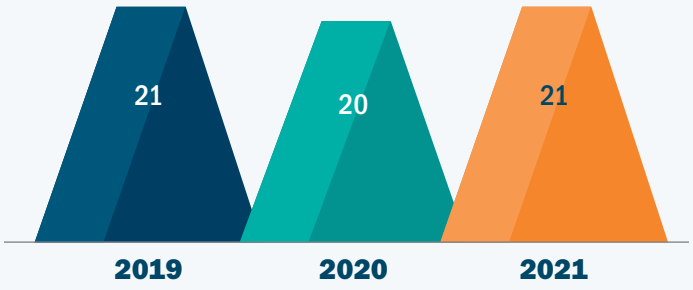
Total number of licensed pharmaceutical companies in Latvia



*Not counting pharmacies' structural units (in 2021 – 73 structural units; in 2020 – 77 structural units; in 2019 – 76 structural units).

Data: December, 2021

Total number of licensed of active substance manufacturers, importers and distributors (API) in Latvia



Authorisation of API (including primary authorisations and renewals)

The national state of emergency affected also the decision of many licenced merchants to discontinue pharmaceutical activity.

In 2021, the following special permits (licences) were annulled:

- 5 licences for opening a general pharmacy (activity);
- 1 licence for opening a closed-type pharmacy (activity);
- 12 licences for medicinal product wholesaler operation;
- 2 licences for manufacturing or import companies.

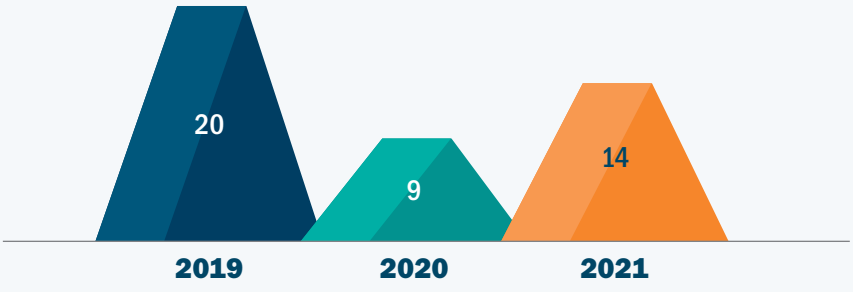
COMPLIANCE EVALUATION OF PHARMACEUTICAL ACTIVITY COMPANIES, HEALTHCARE AND HIGHER EDUCATION INSTITUTIONS

Iveta Vilcāne,
Head of Pharmaceutical Activities Compliance Evaluation Department:

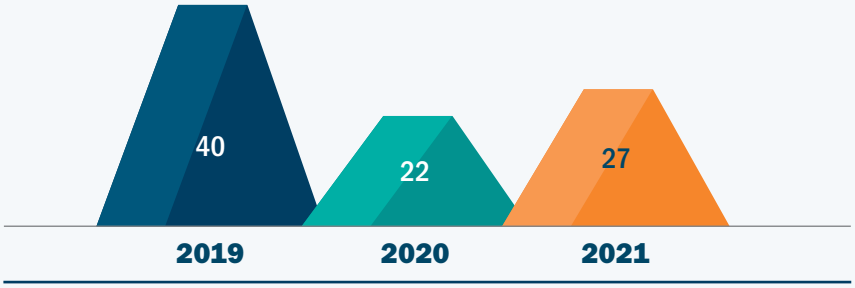
"In 2021, we successfully resumed and continued on-site inspections, utilising remote evaluation of documentation where possible – implementing EMA recommendations on principles of regulatory flexibility as much as possible."

In 2021, the Agency conducted Good Manufacturing Practice compliance inspections of 14 companies (including 7 inspections related to issuance or renewal of licence) and 2 additional inspections of documents related to licence renewal. Due to the COVID-19 pandemic and the related travel restric-

Good Manufacturing Practice inspections



Good Distribution Practice inspections



tions, in 2021, inspections outside of Latvia were conducted only upon request from the EMA (2 manufacturing sites). The Agency also conducted 27 inspections of Good Distribution Practice of medicinal product wholesalers, 16 of which were related to issuance or renewal of licences. In addition, support was provided to the Agency's Pharmaceutical Activities Company Licensing Department in relation to issuance or renewal of special permits (licences) for wholesale and manufacturing or import of medicinal products, as well as authorisation of manufacturers, importers and distributors of active substances.

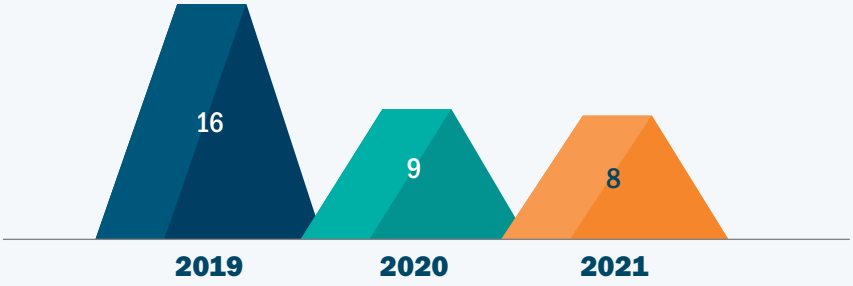
The Agency also conducted vigilance for utilisation of human biomaterial, collected data regarding the operation of tissue centres, procurement organisations/ transplantation centres of human organs, blood establishments and the State Blood Donor Centre and submitted reports to the European Commission, performed hemovigilance and biovigilance in relation to adverse reactions and adverse events reported to the Agency, as well as ensured exchange of information in relation to reports published as part of the Rapid Alert Systems for blood (RAB) and tissues and cells (RATC) where Latvia was a concerned member state.

In 2021:

- The Agency received 5 applications for compliance evaluation (4 for tissue centres, 1 for the higher education institution) and issuance of permits related to variations;
- The Agency issued 7 permits (5 for tissue centres and 1 for the State Blood Donor Centre and 1 for the higher education institution related to changes of operation);
- The Agency suspended the permit for 1 blood bank.

Last year, the Agency also conducted 4 compliance inspections of a human blood and blood component establishment, 10

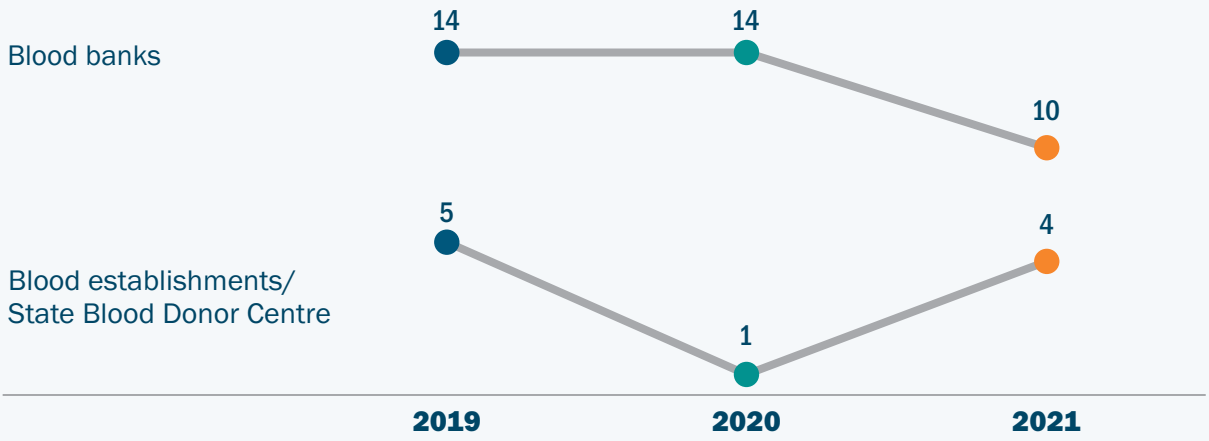
Inspections of tissue centres (and an organ transplantation centre*)



* In 2020, 1 tissue transplantation centre was inspected, but the remaining 8 inspections were conducted at tissue centres. In 2019, no organ transplantation centres were inspected.

inspections of hospital blood banks and 8 inspections of tissue centres (including 2 inspections of centres for procurement of tissues and cells), 3 inspections in higher education institutions providing a medical studies program (including 1 inspection related to the changes of operation). The Agency also conducted 6 compliance inspections of documents – at 5 tissue centres in relation to changes in operation and 1 inspection related to changes in operation of the State Blood Donor Centre.

Compliance inspections of human blood banks and blood establishments



As part of vigilance monitoring, collaboration was continued with specialists from the State Blood Donor Centre by initiating the annual mutual comparison of hemovigilance report data.

Experts from the Pharmaceutical Activities Compliance Evaluation Department prepared annual reports regarding serious adverse reactions and serious adverse events in the field of blood, tissues and cells, and submitted them to the European Commission. Agency also ensured communication with healthcare treatment institutions regarding Urgent reports of serious adverse reactions and events received online, as well as reports in the Rapid alert systems maintained by the European Commission in the fields of tissues and cells (RATC) and blood (RAB).

Department employees ensured representation of the Agency in the EMA Good Manufacturing and Distribution Practice Inspectors Working Group, in the activities of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and European Commission DG SANTE working groups on human blood and blood components,

tissues, cells and organs, and in working group meetings organised as part of the Joint Action project (GAPP).

The Pharmaceutical Activities Compliance Evaluation Department specialists actively participated in the preparation of normative acts and amendments, including participation in the targeted surveys and panel discussions organised by the European Commission regarding the review of the regulation in the field of substances of human origin and the pharmaceutical field, and also submitted proposals. Department experts also submitted proposals to the Vigilance Expert Subgroup of National Competent Authorities regarding vigilance issues related to the review of blood and tissue/ cell regulation. A department expert participated in an Advisory Board as a course program creator and teacher in the training organised by the European Directorate for the Quality of Medicines and Healthcare (EDQM) for vigilance experts of competent authorities, and, as part of which he initiated a proposal for the creation of an interactive tool for vigilance inspectors and actively participated in its development. EDQM submitted the established interactive PDF file (Survival kit) to the European Commission resulting in its approval and distribution to all national competent authorities in the field of blood and tissues.

INTERNATIONAL COLLABORATION

The Agency is a member of the network of the European medicines agencies. Successful implementation of Agency's functions and tasks is closely related to participation in this network – collaboration with EMA, European Commission and more than 47 European Economic Area authorities regulating the field of pharmaceutics. This collaboration network gives access to a wide range of experts, thus, allowing to ensure the best possible expertise for the regulatory environment of medicines in the EU. National experts participate in the work of EMA as members of working groups and scientific advisory groups, as well as scientific committees.

Full participation in common European work procedures, which constitute additional responsibilities and duties for the Agency, undoubtedly require qualified human resources, as well as financial resources. In 2021, Agency's employees have been collaborating with EMA scientific committees, European Commission and Council working groups, WHO, European Pharmacopoeia Committee, PIC/S, EDQM, etc. Last year, the Director of the Agency participated in the Management Group of the HMA.

The Agency also participated in the Drug Precursor Working Group, as well as in the 62nd session of the UNODC Narcotics Control Board. For several years now, the Agency has been involved in collaboration related to surveillance of medical devices and blood components. The Agency is the competent authority in Latvia for issuance of authorisations for clinical trials and safety surveillance of medical devices. Relevant Agency experts regularly participate in the meetings of representatives of national competent authorities for medical devices in Europe.

The Agency has entered into a binding agreement with the medicines agencies in Estonia and Lithuania promoting closer collaboration between the Baltic medicines agencies in the regulatory field of medicines.

See more information about the results of international cooperation from p.11 to p.30 of the report.

IMPLEMENTATION OF AND AMENDMENTS TO NORMATIVE ACTS

Decisions adopted by the Agency are balanced, legal and compliant with the requirements of normative acts. In 2021, only one out of the 9680 decisions adopted by the Agency was contested at the Ministry of Health, and none of the decisions adopted by the Agency in 2021 was repealed.

In 2021, the Agency participated in the development of more than 30 normative acts and provided its proposals and opinions to both the Ministry of Health and other public administration institutions. In 2021, the Agency, in collaboration with the Ministry of Health, developed amendments to several normative acts, which were reviewed and adopted in 2021, for example:

- **Amendments to the Pharmaceutical Law** were required to stipulate for a new permit authorising issuance of a permit for distribution of medicines unauthorised in foreign countries, but used in a European Union member state or a European Economic Area country or where international recommendations have been issued regarding their use and the medicines are intended for treatment, diagnostics or prevention of life-threatening or chronically debilitating diseases, and medicines included in the Medicinal Product Register of Latvia, as well as medicines authorised in foreign countries with a valid permit issued by the Agency for distribution of unauthorised medicines may not be used due to medical indications or their use is limited.
- **Amendments to the Medical Treatment Law** to clarify the definition of a medical device pursuant to Regulation No 2017/745 and the definition of an in vitro diagnostic medical device pursuant to Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. As the abovementioned regulations clearly distinguish medical devices and in vitro diagnostic medical devices, henceforth such separation shall be implemented in all national normative acts in Latvia.
- **Amendments to the Law on the Legal Trade of Narcotic and Psychotropic Substances and Medicinal Products**, and also Precursors to supplement the current delegation, laying down that precursor users must also sub-

mit information regarding use of precursors to the Agency as they are also participating in the precursor trade, as well as the contents of the information to be submitted. The abovementioned is pursuant to Regulation No 271/2004 which separates precursor users and lays down responsibilities applicable also to precursor users.

- **Amendments to the Cabinet of Ministers Regulation No 57** of 17 January 2006 "Regulations Regarding Procedures for the Labelling of Medicinal Products and the Requirements to Be Set for the Package Leaflet of Medicinal Products" to improve actual availability of medicines, decrease the burden on merchants related to distribution of foreign country medicinal product packaging when the packaging intended for Latvia is unavailable. The Agency in collaboration with the Estonian and Lithuanian medicines agencies has gotten involved in the initiative of the Baltic (Estonian, Latvian, Lithuanian) medicines agencies proposed by the Estonian medicines agency inviting marketing authorisation holders to participate in a pilot project for implementation of electronic package leaflets for medicines utilised only in hospitals. Therefore, regulatory standards for implementation of the pilot project, procedure for notification and criteria for medicines subject to exceptions regarding distribution of medicines to in-hospital medical treatment institutions without a paper format package leaflet in the packaging were integrated within the Regulation.
- **Amendments to the Cabinet of Ministers Regulation No 416** of 26 June 2007 "Procedures Regarding the Distribution and Quality Control of Medicinal Products" to promote availability of medicines continuing to allow remote ordering of medicines by private persons from a general type pharmacy and receipt of medicines at their place of residence, to permit also remote inspections of medicines wholesalers, as well as to not place an excessive burden on merchants and perform surveillance of the trade of medicines with less restrictive measures. Considering also the practice in other member states, licencing of temporary storage sites and customs warehouses storing medicines for up to 72 hours was abolished, whereas licencing of customs warehouses storing medicines for longer than 72 hours was postponed for one year in order to decrease the burden on merchants and competent authorities in compliance with the practice in other member states and considering the situation related to the spread of the COVID-19 infection.
- **Amendments to the Cabinet of Ministers Regulation No 641** of 10 December 2019 "State Agency of Medicines Paid Service Price List" to update the paid service price list of the Agency according to the actual costs, as well as to clarify the scope of services according to the actual costs to the institution and of the services performed.

COMMUNICATION AND COLLABORATION

Last year, one of the main priorities was to provide evidence-based and reliable information regarding approval and safety monitoring of COVID-19 vaccines and medicines. In 2021, explanations were provided regarding the fact that evaluation of these vaccines and medicines is performed in accordance with the same rigorous requirements for quality, safety and effectiveness as for any other medicine.

Last year, the Agency regularly and timely provided the latest information in Latvian regarding COVID-19 vaccines and medicines to the residents and public in Latvia. The Agency also provided information regarding the evaluation progress and marketing authorisation process of medicines against COVID-19, including vaccines, the role of regulatory authorities in their approval, evaluation and safety monitoring to the public, healthcare professionals, pharmacists and interested parties, as well as reported on press briefings and public discussions held by EMA regarding vaccines. An important part of providing information last year was giving news regarding reports on suspected adverse drug reactions of vaccines in Latvia and the evaluation of these reports.

Publications, press briefings and social media communication

In 2021, there was a substantial increase in the flow of information on Agency's website – **251 articles were published** in the "News" section.

Last year, intensive collaboration with the media was carried out and responses were provided all year round to media queries related to current regulatory issues of COVID-19 vaccines and medicines. On 19 March 2021, the Agency held a press briefing to provide information regarding the quality and safety evaluation of a vi-

ral vector vaccine. With this press briefing vaccination against COVID-19 with this particular vaccine was resumed in Latvia. The Agency also participated in press briefings held by other authorities, informing about COVID-19 vaccines.

Every press release regarding COVID-19 vaccines and medicines and other important information for public awareness was published on the Agency's page on the social media Facebook and Twitter.

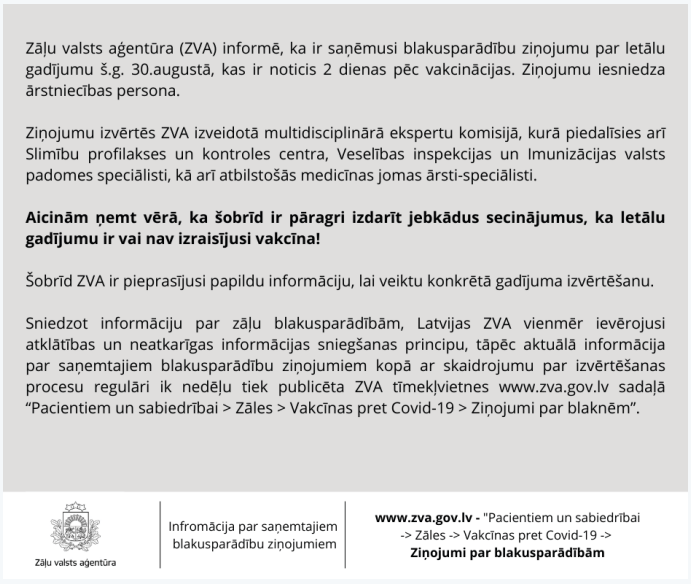
Examples of publications

1) Vaccine authorisation compliance with rigorous quality, effectiveness and safety standards

- Do not fall for 12 myths about COVID-19 vaccines! The Agency provides evidence-based information
- The Agency: COVID-19 vaccines are not experimental, they are authorised in compliance with strict standards

2) Suspected adverse drug reactions of vaccines

- Roughly 1 in 100 vaccinated people have reported an adverse drug reaction of a COVID-19 vaccine
- Every case of adverse drug reactions of COVID-19 vaccines is carefully evaluated
- The Agency: there are no fatalities in Latvia causally linked to COVID-19 vaccines
- The Agency encourages people to speak first with their doctor in case of suspected adverse drug reactions of COVID-19 vaccines
- Known adverse reactions of COVID-19 vaccines are being reported in Latvia; there are no confirmed fatalities
- Ongoing evaluation of adverse reaction reports received in Norway regarding COVID-19 vaccines



Zāļu valsts aģentūra (ZVA) informē, ka ir saņēmusi blakusparādību ziņojumu par letālu gadījumu š.g. 30.augustā, kas ir noticis 2 dienas pēc vakcinācijas. Ziņojumu iesniedza ārstniecības persona.

Ziņojumu izvērtēs ZVA izveidotā multidisciplinārā ekspertu komisijā, kurā piedalīsies arī Slimību profilakses un kontroles centra, Veselības inspekcijas un Imunizācijas valsts padomes speciālisti, kā arī atbilstošās medicīnas jomas ārsti-speciālisti.

Aicinām ņemt vērā, ka šobrīd ir pāragri izdarīt jebkādus secinājumus, ka letālu gadījumu ir vai nav izraisījusi vakcīna!

Šobrīd ZVA ir pieprasījusi papildu informāciju, lai veiktu konkrētā gadījuma izvērtēšanu.

Sniedzot informāciju par zāļu blakusparādībām, Latvijas ZVA vienmēr ievērojusi atklātības un neatkarīgas informācijas sniegšanas principu, tāpēc aktuālā informācija par saņemtajiem blakusparādību ziņojumiem kopā ar skaidrojumu par izvērtēšanas procesu regulāri ik nedēļu tiek publicēta ZVA tīmekļvietnes www.zva.gov.lv sadaļā "Pacientiem un sabiedrībai > Zāles > Vakcīnas pret Covid-19 > Ziņojumi par blaknēm".

Zāļu valsts aģentūra

Infromācija par saņemtajiem blakusparādību ziņojumiem

www.zva.gov.lv - "Pacientiem un sabiedrībai -> Zāles -> Vakcīnas pret Covid-19 -> **Ziņojumi par blakusparādībām**

The Agency ensured publications when **explanatory information** was required. For example, regarding the benefit and risk characterisation of viral vector vaccines in relation to very uncommon adverse drug reactions. Special informative activities were focused on providing information regarding **side effects of vaccines**. Furthermore, an evidence and scientific fact-based explanation was provided on the differences between vaccines, their mechanisms of action and methods for establishing effectiveness.

The Agency also **countered the spread of disinformation**, including on social media, in order to dispel public myths related to vaccines and their side effects. The Agency also published monthly reports in Latvian regarding the safety of every COVID-19 vaccine authorised in Latvia. These reports summarised results from the latest global safety data assessments conducted by the EMA safety committee, as well as information from reports of suspected adverse drug reactions that EMA considers during evaluation.

Information on Agency's website

In order for the general public and healthcare professionals to have easy access to reliable and science-based information on authorisation and safety monitoring of COVID-19 vaccines, the Agency regularly updated and published the latest information regarding vaccines and their approval process, including reliable and science-based facts on vaccines.

Reliable and non-commercial information sources about COVID-19 vaccines and medicines were provided to the public in the dedicated sections of the website – "Patients and Public" and "COVID-19 News", as well as to the healthcare professionals in the section "Healthcare Professionals".

Website traffic parameters:

- The number of Agency's website visitors (users) **increased by 122 % last year** in comparison to 2020. In 2021, Agency's website was visited by more than million unique users (1 121 619 users).
- In 2021, Agency's website was visited almost **7.8 million times** (7 786 102 times). The number of visits grew by 19.14 % in 2021 in comparison to the previous year.

- The following were the top 5 most visited sections of the website last year: frequently asked questions about COVID-19 vaccines, section on the viral vector vaccine in Russian, section on the viral vector vaccine in Latvian, adverse drug reaction report submission and the Medicinal Product Register.

Bulletins, infographics and videos

- Bulletin “In short about COVID-19 vaccines” in Latvian and Russian

  The bulletin contains evidence-based and reliable information about the mechanism of action and relevant side effects of currently authorised COVID-19 vaccines. It includes important information regarding COVID-19 vaccines, their development and approval, time interval between the first and second dose, safety and other relevant information.

- Infographic “COVID-19 vaccines in Latvia: marketing authorisation”
- Infographic “COVID-19 medicines”
- Infographic “Evaluation of suspected adverse drug reactions”
- Infographic “Achievements in 2020”
- Infographics “Consumption of patent-free and original medicines in 2020”

- Infographic about risks of falsified medicines
- Video “Vaccine safety monitoring and evaluation of submitted adverse drug reaction reports in the EU”
- Video series in collaboration with the WHO regarding the importance of reporting adverse reactions as part of Medicines Safety Week.

Campaigns

- Social media campaign during Medicines Safety Week

  In November 2021, together with 64 medicines agency across the world the Agency participated in Medicines Safety Week (#MedSafetyWeek 2021) during which healthcare professionals, workers in the national immunisation programs, as well as patients and relatives and carers were invited to report healthcare conditions observed after administration of any vaccine, including a COVID-19 vaccine. In order to promote reporting of suspected adverse drug reactions after vaccination the Agency implemented a social media campaign via its social media profiles distributing informative videos and infographics inviting the public to take care of their own health and that of other members of the public.

- World Antimicrobial Awareness Week

  In support of the World Antimicrobial Awareness Week activities, the Agency informed about the correct and safe use of antibiotics in order to increase awareness of bacterial resistance to antibiotics.

- European Immunization Week

  Campaign for vaccination against COVID-19, providing information from a vaccine regulatory perspective in collaboration with EMA and the European

Center for Disease Prevention and Control (ECDC) on an international level

As a result of this collaboration, regulatory information and explanations were provided, for example, on the fact that, as noted by EMA and ECDC, in September of the previous year there was no urgent need for additional and booster doses of COVID19 vaccines and on the ongoing assessment of data on heterologous vaccination.

Last year, the Agency conducted informative activities within two projects. One of these projects was the pilot project of Baltic medicines agencies for implementation of electronic package leaflets for medicines used only in hospitals. In 2021, the Agency also initiated distribution of informative materials for the project conducted by Lithuanian and Latvian experts "Pharmaceutical substances in waste water – amount, impact and options for minimisation" (MEDWwater).

Information for healthcare professionals and pharmacists

Last year, increased efforts were put into informing healthcare professionals and vaccination staff about COVID-19 vaccines and their potential side effects. Information was provided during seminars for healthcare professionals, in informative articles and distributed letters. For example, healthcare professionals were informed about the importance of reporting adverse reactions to vaccines, clinical recommendations on course of action in case of the thrombosis with thrombocytopenia syndrome and on vaccine expiration dates.

Informative bulletin "Cito!" for doctors and pharmacists

Last year, the Agency published the informative bulletin "Cito!" for doctors, pharmacists and other healthcare professionals. One issue in 2021 was dedicated to information resources on COVID-19 vaccines and the latest news.

Annual report

Last year, the annual report regarding Agency's operation in 2020 was published.

Collaboration with the industry

By implementing one of the priorities set for 2021 (providing explanation of normative act requirements), last year the Agency organised informative seminars for marketing authorisation holders, manufacturers, wholesalers, pharmacies and other industry and non-governmental organisation representatives. Last summer, a seminar was held on current issues in the industry: development of multilingual labelling during decentralised and mutual recognition authorisation procedures, the new regulation on medical devices and clinical trials, as well as options for providing scientific consultations. In December, a seminar was organised for healthcare institutions and closed-type pharmacies regarding the use of electronic package leaflets as part of a pilot project starting from 1 January of the following year. The industry was also informed about the implementation of the new clinical trials regulation and the clinical trials information system, as well as the EU regulation on medical devices from 26 May 2021 and other explanatory information about normative act requirements.

Feedback

- **Employee survey** – objective: to obtain information regarding Agency's employees opinion on organisation of work, environment and collaboration, job satisfaction and other important aspects of work that could help to identify priorities in motivating development of personnel resources.
- **Client and collaboration partner survey** – objective: to obtain opinion regarding Agency's work and provided services in order to improve client service and quality of services, based on this data.

The Agency also ensured provision of updated information on the platform for providing information to employees – on the Intranet.

MANAGEMENT OF THE INTEGRATED QUALITY MANAGEMENT SYSTEM

In order to implement the principles and fulfil the aims set out in the Agency's quality policy, in 2021 we continued maintenance and improvement of the quality management system by ensuring compliance with the requirements of the ISO 9001 "Quality Management System", ISO/IEC 27001 "Information Technology. Security Measures. Information Security Management Systems", ISO/IEC 17025 "General Requirements for the Competence of Testing and Calibration Laboratories" standards, as well as international guidelines and recommendations.

The quality management system helped to coordinate and manage Agency's operations to comply with the requirements of clients and normative acts and to continuously improve Agency's organisational efficacy.

Review of the completion of parameters within the quality management system indicated that, despite the fact that most of the institutions internal processes for service provision were organised remotely, the planned results were achieved and the deadlines for services provided were met.

In 2021, monitoring inspections continued to present challenges for the Agency in terms of meeting the deadlines of planned tasks as the epidemiological restrictions set forth during the COVID-19 pandemic prevented Agency employees and monitoring subjects to organise inspections within the previously agreed time-frames.

On the other hand, the flexibility and adaptability of work organisation in the field of

pharmacovigilance in response to a two-fold increase in work load (in comparison to 2020) with respect to timely processing and evaluation of adverse drug reaction reports and the initiation of a new type of evaluation regarding fatal cases after administration of a COVID-19 vaccine, should be recognised as a sign of the high level of readiness of the organisation to ensure continuity of operation even in the setting of public health crisis.

In the year of review:

- One out of the 9680 decisions adopted by the Agency was challenged, i.e., 0.01 % of all the decisions adopted by the institution as part of service provision;
- None of the decisions adopted by the Agency in 2021 was repealed.

In the annual client satisfaction survey, we received feedback regarding the collaboration experience with the Agency from 134 clients (in 2020 – from 144 clients) with the following conclusions:

- Client satisfaction with respect to fulfilling deadlines in service provision and provision of information regarding implementation of new normative requirements remains unchanged;
- There was an increase in client satisfaction in the other areas of assessment, most notably with respect to the following aspects:
  - 86 % of all clients gave a positive assessment of the collaboration with the Agency (very satisfied/ satisfied), compared to 81 % for 2020;
  - 83 % of all clients gave a positive assessment of the professionalism of Agency's staff, compared to 77 % for 2020;
  - 87 % of all clients gave a positive assessment of the quality of services provided, compared to 80 % for 2020.

Whereas in the annual Agency employee survey:

- 95 % of employees indicated satisfaction with the work environment;
- 99 % of employees indicated satisfaction with the solutions for personnel management issues and the availability of relevant information.

Results of the surveys reflect the unchangingly high level of professionalism of Agency employees and orderly internal organisational processes, as well as high level of leadership of Agency's administration in ensuring the delegated functions.

Results of the activities planned for the period of review:

I. planned: process streamlining for solutions for working remotely

The most time-consuming solutions to develop for improvements to the quality system ensuring increased efficacy of organisational operation, as well as more convenient solutions for clients were related to:

- continued total review and streamlining of the quality system documentation and processes for the Medicines Examination Laboratory, considering the improvements initiated in 2021;
- automatisation and standardisation with respect to ensuring circulation of information regarding imported medicines, including unified communication with clients, standardised online data exchange with the customs, as well as provision of information to the Food and Veterinary Service;
- review of internal flow for issuance of permits for import and export of unauthorised medicines, cutting the time from receipt of application to start of review by several hours;
- review and streamlining of the rapid alert process;
- introduction of a new IT support system;
- etc.

II. planned: streamlining of operational continuity assurance within the context of the COVID19 pandemic

Within the context of assuring operational continuity of the organisation, the main operational functions and the tasks within these functions were analysed in the year of review, and as a result a list for prioritisation of Agency's task completion was approved, considering various potential modes for operation.

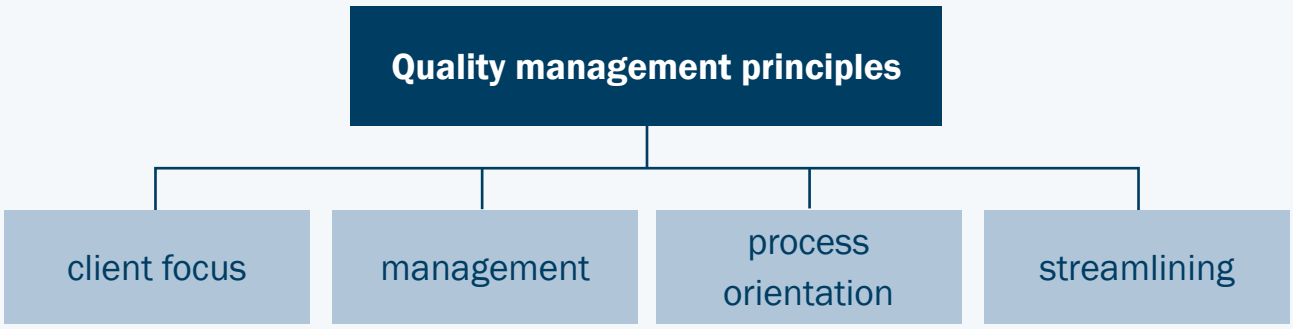
III. planned: preparation for the benchmarking of members of the network of European medicines agencies and other third-party inspections scheduled for 2022–2023

Considering that international audits and benchmarking were postponed to 2023, in 2021 preparatory work was done for the internal self-evaluation planned to take place in 2022.

With respect to internal audits, we maintained access for active internal control, primarily – information security management, considering the workload, changes in work mode and restrictions in tools for communication of the Agency employees involved in pandemic management.

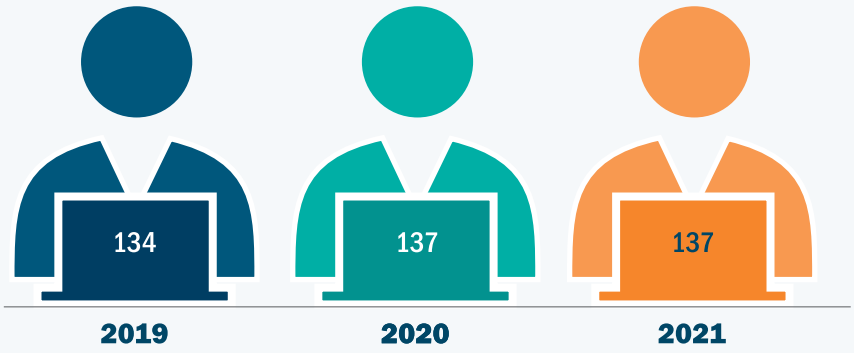
Activities planned during the next period of review:

- participation in the development of organisational strategy 2023–2025;
- ISO 9001 and ISO/IEC 27001 recertification;
- process streamlining;
- ensuring operational continuity and preparedness for public health crises;
- preparation for the third-party inspections and benchmarking of the members of the network of European medicines agencies.



PERSONNEL MANAGEMENT AND TRAINING

Actual number of employees



There were a total of 143 employees under employment or civil service at the Agency.

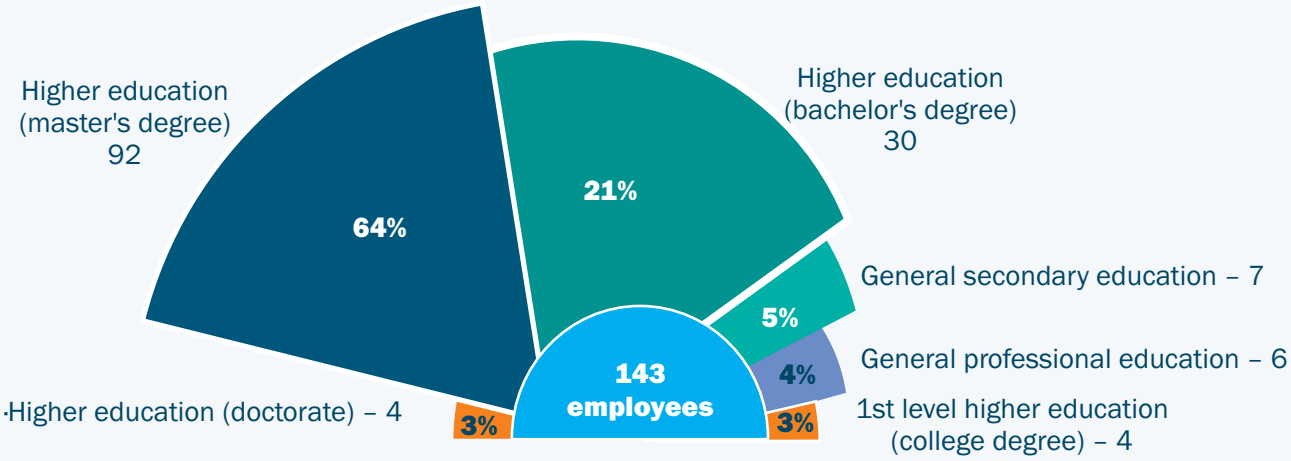
The overall level of education among Agency's staff is high – 130 employees (91 %) have a higher education, and 4 of these employees have a doctorate degree.

Staff turnover*

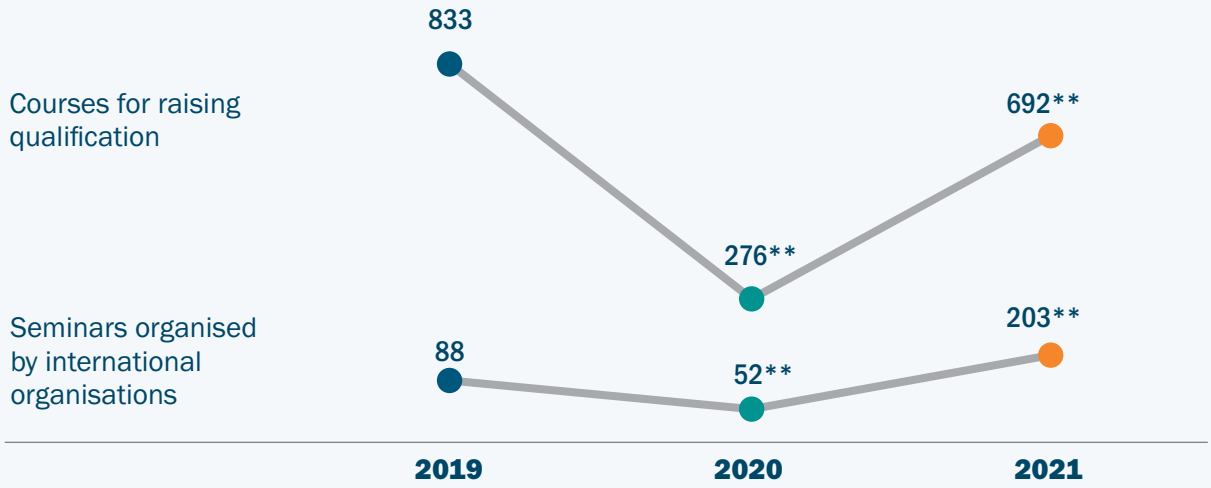
9 %

* Number of employees and civil servants, who have terminated employment, divided by the average number of staff members

Staff members according to the level of education (%)



Participation in courses for raising qualification and international seminars, conferences



** In 2021, staff participation in training and international events was ensured according to demand. Most of the events, including training and international collaboration events, were organised remotely and free of charge. Employees had a wide range of opportunities to utilise the available resources independently without absence or additional financial expenses for the Agency.

Results of the employee survey in 2021:

99 %
of employees

were satisfied with the solutions for personnel management issues and the availability of relevant information (applications for vacations and other absences, business trip organisation, consultations and support for other personnel management issues);

95 %
of employees

were satisfied with the work environment and solutions for household issues (work environment, technical condition of facilities, transport coverage).

MANAGEMENT OF INFORMATION AND COMMUNICATIONS TECHNOLOGY

In 2021, the Agency continued to develop and improve solutions for IS and information and communications technologies (ICT), as well as to improve their availability and management. Last year, the Agency implemented 57 applications for ICT changes that facilitated increase in work efficiency and provided substantial support to merchants, the public and employees.

Improvements to the Agency's website

Agency's website underwent several substantial changes.

- Last year, informative supplements were added to the patient adverse drug reaction report form – a separate functionality to receive information regarding adverse reactions to COVID-19 vaccines, the data is also forwarded to the Centre for Disease Prevention and Control, additional information added regarding patient's doctor and other improvements. The healthcare professional report form was modernised, improving its usability;
- The contents of Agency's website were separated from the data of Agency's information systems by creating a separate subdomain "dati.zva.gov.lv";
- The unified style of design, layout and colour palette of the Agency were applied to the separate sections of the new site.

In 2021, measures were taken to minimise IT security related risks, and regular employee training was conducted regarding IT security issues, a solution for self-training and testing of knowledge in the field of ICT security was used. Last

year, employee knowledge on ICT security was tested using the CloudStudy.eu solution where IT security training materials are available. Based on the analysis and testing results, employees were repeatedly instructed on measures to prevent computer infection with malware and/ or data leaks.

Last year, maintenance of ICT infrastructures utilised by the Ministry of Health and the institutions under its supervision was continued and support was provided to the ICT specialists of these institutions. In 2021, collaboration continued with various European institutions and competent authorities in other countries to exchange electronic information using common ICT solutions, for example, the European clinical trial database EudraCT, the secure e-mail EudraMail and the data exchange system Eudralink, the pharmacovigilance system EudraVigilance and the data analysis system EVDAS, the European medical device database EUDAMED, the Communication and Tracking system (CTS) solution for mutual recognition procedures for medicines, the Common European Submission Platform (CESP) for marketing authorisation documentation, as well as the Common Repository for marketing authorisation documentation in centralised procedures, the Periodic Safety Update Report (PSUR) Repository. A new EURS next generation program EURSnext was introduced in the medicinal product documentation evaluation system and user migration to its use in daily operation is taking place, allowing for more convenient and faster use of the necessary data.

PRIORITIES AND TASKS FOR THE NEXT STRATEGIC PERIOD

- Actively provide solutions to medicinal product availability issues, perform risk assessment regarding potential presence of nitrosamine impurities in medicines, participate in EMA scientific consultation procedures and implement projects such as Multilingual package project and the Electronic package leaflet (e-PIL) project.
- Continue to work on implementation of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC starting from 31 January 2022 and implementation of Commission Implementing Regulation (EU) 2022/20 of 7 January 2022 laying down rules for the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials.
- Continue work on introduction of Regulation (EU) 2017/745 of the European Parliament and of the Council and preparation for implementation of the new in vitro diagnostic medical device regulation – Regulation (EU) 2017/746 of the European Parliament and of the Council – from 26 May 2022.
- Promote availability of informative materials created by the Agency and raise patient and healthcare professional awareness of resources providing independent and qualitative information regarding medicines, as well as information on services provided by the Agency.
- Continue streamlining of ZVAIS with the aim of increasing its functionality by linking it with client self-service functionality, client relations management and e-service development.

- Promote sustainable development of the Agency by improving quality of work environment and effective work organisation, decreasing the risk of employee loss to the private sector, giving priority to establishment of a new remuneration system and balancing material compensation with the level within the pharmaceutical industry in Latvia, as well as increasing the level of motivation together with streamlining of personnel competency development based on future needs.
- Ensure conduct of compliance evaluation audits (ISO 9001, ISO/IEC 27001, ISO/IEC 17025, JAP (Joint Audit Programme)) at the Agency in order to confirm compliance of actions implemented by the Agency with the national and EU requirements, quality and safety standards.

Annex 1

BUDGET AND EXPENSES

		2019	2020	2021	
		Budget implementation, EUR	**Budget implementation, EUR**	**Budget estimate, EUR**	**Budget implementation, EUR**
1.	Resources for covering expenses (income)	5 161 435	6 102 023	6 401 033	6 733 920
1.1.	Paid services and other own income	5 110 759	5 265 476	4 903 201	5 364 714
1.2.	Foreign financial assistance	10 969	763 393	1 429 441	1 300 815
1.3.	Transfers from the State budget	39 707	73 154	68 391	68 391
2.	Expenses (total)	4 814 202	5 229 171	7 019 479	5 654 977
2.1.	Maintenance expenses	4 319 361	4 920 943	6 549 483	5 189 700
2.1.1.	Regular expenses	4 205 695	4 814 528	6 535 483	5 176 040
2.1.2.	Transfers for maintenance expenses	113 666	106 415	14 000	13 660
2.2.	Expenses for capital investments	494 841	308 228	469 996	465 277
	Financial balance	347 233	872 852	-618 446	1 078 943
	Financial resources	1 301 877	2 174 729		3 253 672

Annex 2

A REPORT BY INDEPENDENT AUDITORS

Riga

The date of the document is the date of the electronic signature on the document **No.01/2021**

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 included in the annual report of 2021. The attached financial report includes:

- Report on financial situation on 31 December 2021 (balance);
  - Report on the financial results of Agency's operation in the year concluded on 31 December 2021;
  - Report on the changes in own capital in the year concluded on 31 December 2021;
  - Report on the flow of Agency's financial resources in the year concluded on 31 December 2021;
  - Annexes of the financial report, including explanation of financial report positions, description of the principles for accounting, description of principles for preparation of annual report and description of risk management for financial instruments.

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 2021, as well as of the financial results of its operation and flow of financial resources in the year concluded on 31 December 2021, in accordance with the requirements of the Cabinet of Ministers Regulation No 344 of 19 June 2018 "Procedure for Preparation of the Annual Report".

Justification of the Opinion

In accordance with the Law on Audit Services, we conducted the audit in compliance with the international standards public sector audits (hereinafter – ISSAI) recognised in 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 (including International Independence Standards) and the independency requirements included in the Law on Audit Services applicable to the financial report audit conducted by us. We have also complied with other professional ethics standards and requirements for impartiality laid down in the Law on Audit Services and in the Code of Ethics for Professional Accountants (including other professional ethics principles and requirements for objectivity laid down by the International Independence Standards).

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 includes:

- Administration Report included in the annual report attached;

– Budget implementation report included in the annual report attached.

Other information does not include the financial report and our auditors' report regarding this financial report. Our opinion of the financial report is not applicable to such other information, 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 review other information and, by doing so, assess whether there are no significant discrepancies between this information and the information in the financial report or our knowledge that we obtained during this audit, and whether it does not include any other substantial discrepancies.

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

Other Reporting Requirements in Accordance with the Requirements of the Legal Acts of the Republic of Latvia

In accordance with the Law on Audit Services, 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 Regulation No. 344 of 19 June 2018 "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, for which the financial report is prepared, conforms with the financial report, and

– The Administration report is prepared in accordance with the requirements of the Cabinet of Ministers Regulation No. 344 of 19 June 2018 "Procedure for Preparation of the Annual Report".

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 provides a truthful and clear impression in accordance with the requirements of the Cabinet of Ministers Regulation No. 344 of 19 June 2018 "Procedure for Preparation of the Annual Report", as well as for an internal control system that, in the opinion of the administration, is required for preparation of a financial report, which does not contain substantial discrepancies due to fraud or error.

Upon preparation of 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 as required, unless there are plans in place to merge the Agency with another institution or to divide the Agency.

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 the financial report as a whole does not contain substantial 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 ISSAI shall always reveal substantial discrepancies, if such exist. Discrepancies may arise due to fraud or error and they are considered substantial, 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 conduct of the audit in accordance with ISSAI, during the whole audit process we make professional judgements and maintain professional scepticism. We also do the following:

- Identify and assess risks of substantial 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 substantial discrepancies due to fraud will not be identified is higher than the risk that substantial 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 the internal control which is important for conduct of the audit in order to establish audit procedures appropriate for the specific circumstances, but not to provide an opinion on the efficiency of 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 adequacy of the principle of continuing operation applied by the administration and, based on the audit evidence obtained, also regarding the existence or non-existence of major uncertainty with regard to events and circumstances that may create substantial concerns regarding Agency's ability to continue operation. If we conclude that substantial uncertainty exists, the auditor report shall draw attention to the information regarding these circumstances provided in the financial report. 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 its operation due to 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 inform the persons entrusted with supervision of the Agency of, among other things, the estimated scope and time of the planned audit, as well as important audit observations, including significant internal control deficiencies identified during audit.

LLC „Auditorfirma Šķibele un Partneri"
Licence No 164

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Baiba Jēkabsone
Member of the Board
Sworn Auditor
Certificate No. 195

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

Baiba Jēkabsone 26538700
info@skibeleunpartneri.lv

Contacts

State Agency of Medicines

Jersikas iela 15, Riga, LV-1003, Latvia

Phones: (+371) 67078424, (+371) 29447659,

E-mail: info@zva.gov.lv

www.zva.gov.lv