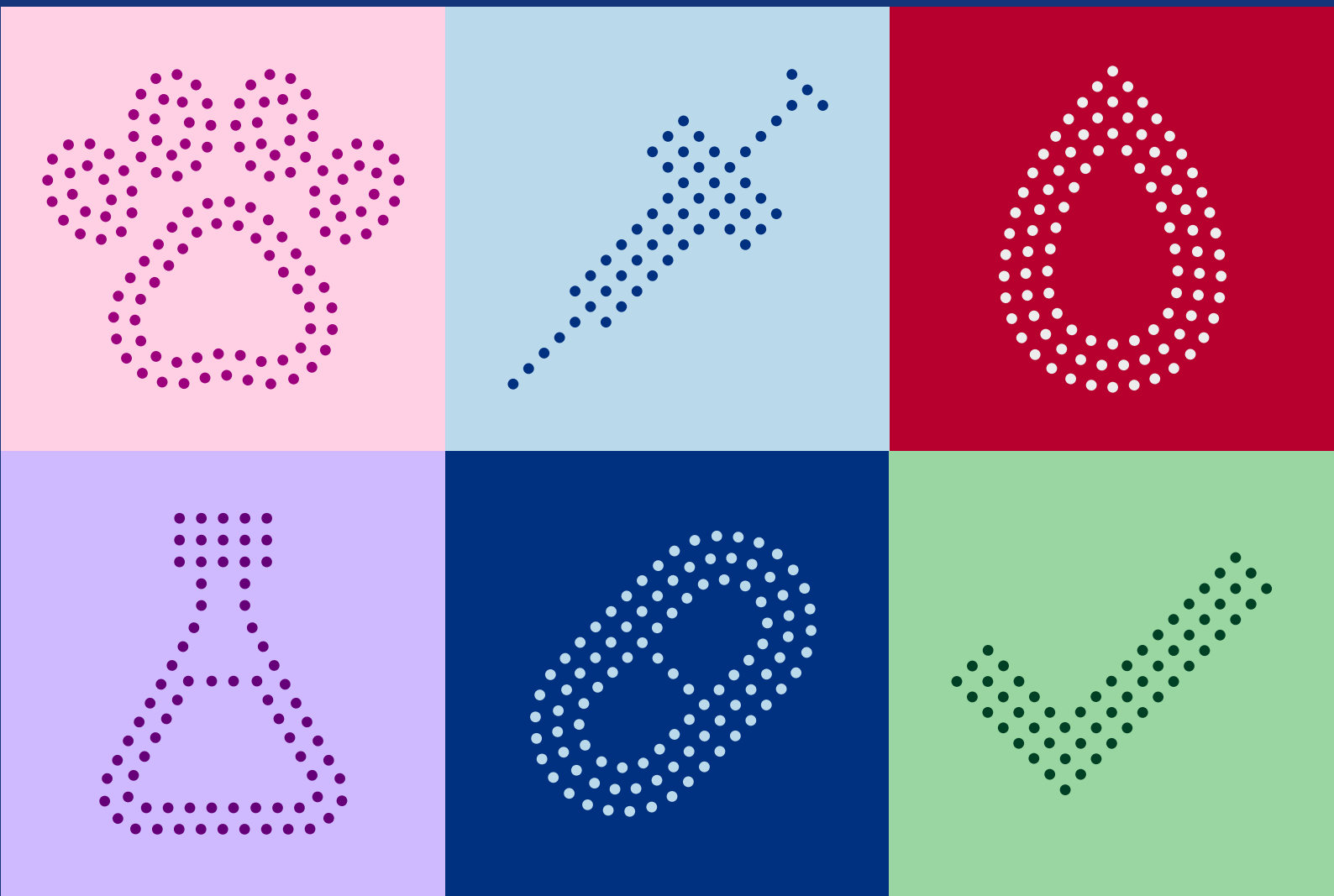
RAVIMIAMET

2024

YEARBOOK



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The past is behind us and we must look to the future. However, we must remember the past to choose the right path forward. This is a review of 2024 for the State Agency of Medicines. The annual review considers both our mandated activities, as well as activities we chose to do because of their perceived importance for our society. We aim to deliver more than is expected of us.

We take part in shaping the future both here in Estonia, as well as globally. Be it more effective state supervision, improving availability of novel and innovative services or contributing to discussions concerning public health or new European Union pharmaceutical regulations. We do everything in our power to support healthcare in Estonia, using all our available expertise, data and analytical capability.

Just as a successful pharmaceutical manufacturer is not made of only brick, mortar and laboratory equipment, but also encompasses effective quality systems and a lot of smart people, our Agency is not an abstract shell and we do not act without considering the effects and importance of our oversight and enforcement decisions. We have always emphasized reason, honesty and ethics in our cooperation efforts. It is crucial for managing expectations, communicating and supporting each others' work. Equally important is that we maintain a human aspect in our work, both in designing human-centred services and our communications and outlook.

I would like to thank all our colleagues and partners for their dedication, professionalism and positive attitude!

With sincere gratitude, Katrin

2024 in numbers for the State Agency of Medicines

Imported **662** authorised veterinary medicines

290 supply difficulty notices

Issued **446** adverse event reports

Conducted **390** laboratory tests

55 transition requests

Our laboratory analysed **63** authorised medicinal products

36 Initial approvals for clinical trials

There are **26** pharmaceutical manufacturers in Estonia

163 information requests from press

We were involved in **17** legal cases

274 new marketing authorisations for human medicinal products

59 new marketing authorisations for veterinary products

9 clinical trial inspections

450 young people visited the Agency

27 posts in our new blog

157 social media posts

We had **10** new employees join us

The Agency is an innovative and valued partner

Ott Laius

According to our current development strategy, we strive to support companies with any new ideas they have for improvements or innovations. This is not always easy for a public organization, as any innovation always comes with uncertainties and potential dangers. This includes dangers for patients, protection of whom is the core purpose of our Agency.

On the other hand, it is clear that improvements and innovations are necessary to improve patient care. We need to find a balance - protect the interests of patients without inhibiting innovation or development of the Estonian pharmaceutical sector in general.

There were several cases in 2024 where the goals set in our development strategy helped us focus and choose the right course to properly balance patient safety and pharmaceutical interests. Most of these cases are detailed in chapters below, but I would like to take this opportunity to also give some examples.

Last year, Estonian hospitals made several innovations which involved consultation with our specialists. CAR-T cell therapy is a potentially effective advanced therapy for certain tumours, which could initially benefit tens of Estonian patients, with potential for application in many more cases in the future. We are looking for ways to implement this therapy in Estonia in cooperation with hospitals, pharmaceutical companies and the Estonian Health Insurance Fund. I am happy to say we are making significant progress with this project. In order to expedite implementation of this and other advanced therapies, we have submitted a proposal to amend the regulation for hospital exemptions.

Another advanced therapy introduced in Estonia last year was phage therapy. This is an antibacterial therapy where pathogenic bacteria are infected with bacteriophage viruses. While the effectiveness of phage therapy is difficult to prove using the regular proof of effectiveness methods, there is certainly scientific evidence to support it. We also approved a hospital exemption for an exciting new medicinal product produced from the patient's mesenchymal stem cells, which will hopefully prove effective for the treatment of patients with critical lower limb ischaemia.

Last year, pharmacies made progress with testing 3D printed medicinal products in both hospital and retail pharmacies. This significantly simplifies extemporaneous preparation of certain drugs, as preparing patient-specific powder dose is extremely time-consuming. We helped adjust this practice to the Estonian legal framework and our laboratory contributed by evaluating test batches.

We are also glad to see new pharmaceutical manufacturers established in Estonia. Domestic drug manufacturing is good for the economy as well as overall security of supply, and provides professionals of the field an opportunity to apply themselves closer to home. We can't deny, however, that our manufacturing supervision capability was stressed by this development. With our resources optimised for the previous lower amount of supervision work, our pharmaceutical manufacturing inspectors put in an extraordinary effort to support Estonian entrepreneurs in their ambitions. We reassigned resources internally and secured permissions for creating new jobs to ensure that pharmaceutical manufacturers have all the support and oversight they will need in the future.

Last year, a preliminary proposal for expanding the range of services offered in Estonian retail pharmacies was drafted. The changes described therein will enable pharmacists to increase their participation in primary healthcare via prevention, immunization and additional pharmaceutical counselling. We believe all proposals merit discussion. Anything can be done if all stakeholders can agree on what services need to be provided and what kind of training is needed. After all, the goal is to improve patients' access to health services.

Last year a decision was made to expand (or restore, as medical devices were previously overseen by the Agency up until 2010) the Agency's area of supervision to medical devices. This is obviously a very wide and varied area, which will include plenty of constructive discussions with importers and device manufacturers. We are excited to re-enter the field this year.

I would like to thank all my colleagues for their efforts last year and in the future. You help make the Agency an innovative partner always open for new ideas. Our partners are not afraid of bringing new ideas to the table, and they have not come to expect stubborn resistance or refusal to work towards a solution. Of course, public health is our primary concern. While we cannot say yes to everything and occasionally have to impose additional restrictions, all parties need to feel and be heard. So let's keep an open mind!

Timeline of key events in 2024

January

- Improved transparency of clinical trials information - data on clinical trials recruiting participants in Estonia are now published in the Estonian open data portal
- In capacity of WHO partners, Agency experts Katrin Lambing, Marje Zernant and Aet Viispert advised the Ukrainian Health Ministry and Ukrainian pharmaceutical authorities on the development of a quality management system, scientific evaluation of drug data, and sharing of pharmaceutical information
- The Agency started issuing scientific advice in the area of pharmaceutical development

March

- Helerin Eiche from our Bureau of Quality Assessment participated in two panel discussions on green and sustainable pharmaceutical manufacturing at the Drug Information Association (DIA) Europe conference in Brussels
- Maia Uusküla, head of our Bureau of Pharmacovigilance, consulted the evaluation of the drug and vaccine safety monitoring system in Uzbekistan

April

- Maia Uusküla, head of our Bureau of Pharmacovigilance, consulted the evaluation of the drug and vaccine safety monitoring system in Turkmenistan
- Keiu Heinla, head of our Bureau of Clinical Assessment, participated in the “Clinical Research in Central and Eastern Europe: New Approaches for the Next Level of Development” conference in Poland with her talk on regulatory initiatives, and participated in the panel discussion titled “Clinical trials in Europe – regulatory perspective”

May

- We held an information day for pharmaceutical manufacturing activity license holders
- We held an information day for pharmacists
- The Agency gained the status of WLA WHO Listed Authority via the relevant EU network, attesting to the competence, reliability and transparency of the Agency and the state regulatory system as a whole

June

- Pille Säälik from our Department of Biologicals represented the EMA Committee for Advanced Therapies (CAT) at the International Society of Gene and Cell Therapy (ISCT) conference in Vancouver. Pille participated in three panel discussions on artificial intelligence, potency testing of cell and gene therapies and induced pluripotent stem cell therapies

July

- An amendment to the Medicinal Products Act came into force, authorising the Agency to discretionally permit the marketing of unauthorised medicines in case of shortage impacting an authorised medicine
- Alar Irs, our clinical advisor, participated at an event on the application of clinical practice guidelines in Frankfurt, speaking on the role of the pharmacovigilance system in ensuring the quality of scientific data

August

- Katrin Tagel, one of the inspectors from our Department of Supervision, was a member of the EMA inspection team conducting central clinical trial inspection in Georgia

September

- The Schengen certification service was transferred from the Agency to pharmacies
- The Agency conducted the “Travel smart, healthy and safe!” public communication campaign
- The Agency’s expert commission on pharmacological terminology celebrated its 25th year
- The annual meeting of Nordic pharmacy inspectors took place in Tallinn on September 5th-6th
- We held an information day for cell, tissue and organ procurers and processors
- The Agency received a new visual identity
- Katrin Tagel, one of the inspectors from our Department of Supervision, was a member of the EMA inspection team conducting central clinical trial inspection in Brazil

October

- The Agency website received a new report form for reporting drug quality issues, inaccurate drug information and possible counterfeits
- Laivi Saaremäel, head of our Bureau of Quality Assessment, joined a working group of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as an expert chosen by the European Commission
- On October 8th, the Nordic-Baltic Conference in Pharmacovigilance took place in Helsinki, with our Director of Pharmacovigilance Maia Uusküla talking on the subject of risk mitigation measures
- Helerin Eiche from our Bureau of Quality Assessment talked on the subject of green and sustainable pharmaceutical manufacturing at the meeting between EMA Biologics Working Party and pharmaceutical manufacturers

November

- We held an information day for marketing authorisation holders
- Agency Director General Katrin Kiisk attended a panel discussion at the Health Care Summit 2024 held by POLITICO in Brussels. The discussion was centred on solving issues with drug availability and supply chains
- Triin Suvi, head of the Agency's Department of Biologicals, attended a meeting on hospital exemptions held by the European Commission and talked about hospital exemption criteria in Estonia
- Publication of the Agency's Statistical Yearbook 2024
- Katrin Tagel, one of the inspectors from our Department of Supervision, was a member of the EMA inspection team conducting central clinical trial inspection in the United States of America

December

- Estonian drug utilization research methodology received international recognition in the book titled "Drug Utilization Research. Methods and Applications. (Second Edition)" - it is considered a prime example in the European region

Adverse reaction report numbers fell to pre-Covid level, and reporting awareness has increased in the field of veterinary drugs

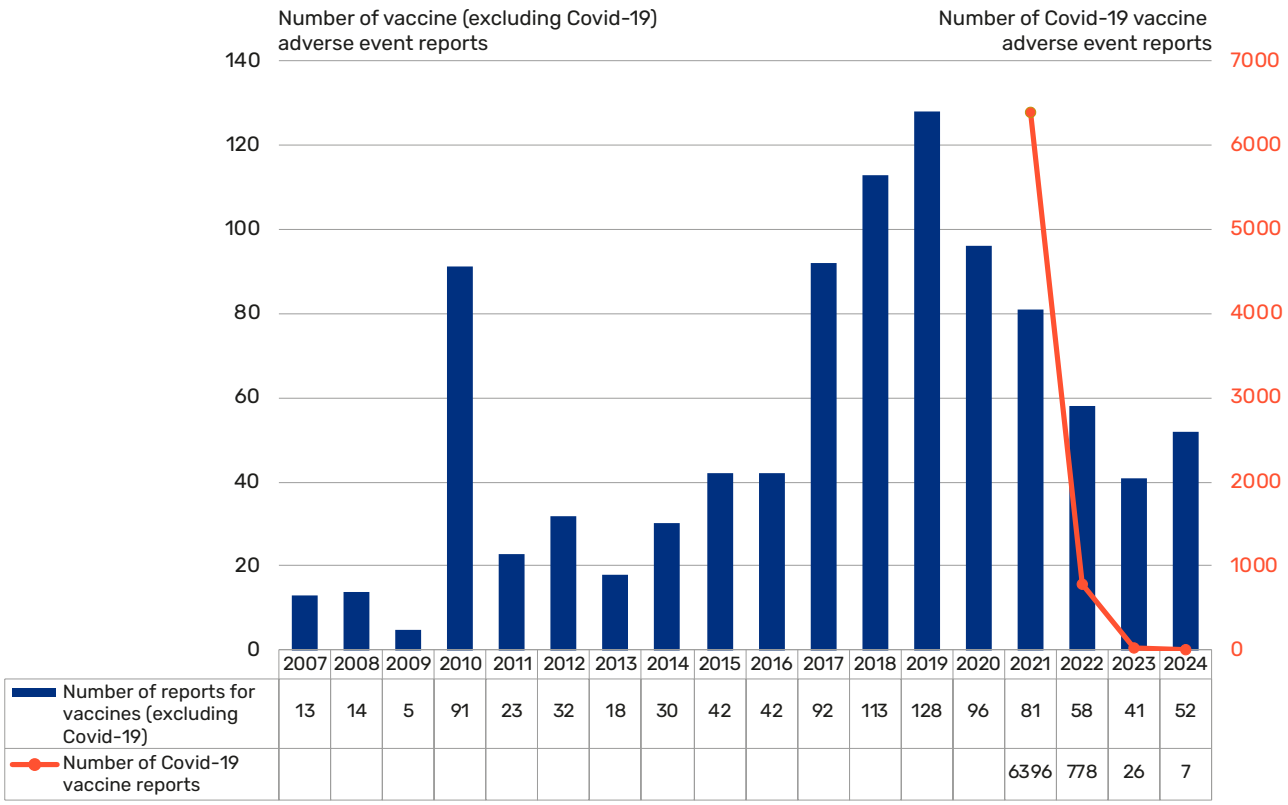
Maia Uusküla

The department of post-authorisation safety is responsible for collecting, evaluating and disseminating drug safety information to healthcare professionals, as well as educating patients about the risks associated with medicinal products.

The goal of collecting and evaluating reported adverse reactions associated to medicinal products (including vaccines) during marketing is to quickly identify any new adverse reactions or changes in their frequency or severity.

In 2024, the Agency received 446 reports:

57 reports of adverse events following immunisation and inefficacy, including		**389 reports** of potential adverse reactions or lack of efficacy of medicinal products, including	
52 reports of adverse events following immunisation;	**5 reports** of vaccine inefficacy (4 concerning rotavirus vaccine, 1 concerning flu vaccine).	**382 reports** of potential adverse reactions;	**5 reports** of lack of therapeutic effect (pregnancy / ectopic pregnancy with contraceptives).



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Number of reports for vaccines (excluding Covid-19)	13	14	5	91	23	32	18	30	42	42	92	113	128	96	81	58	41	52
Number of Covid-19 vaccine reports															6396	778	26	7

Figure 1. Number of vaccine adverse event reports 2007-2024.
Because the number of Covid-19 vaccine reports is graphed on a separate scale (line graph (orange), 2021-2024).

Vaccines – 52 reports of adverse events following immunisation, including 12 associated with hexavalent vaccine (diphtheria, tetanus, whooping cough, poliomyelitis, type B Haemophilus influenza infection, hepatitis B), followed by influenza vaccine (8 reports), mRNA COVID vaccine (5 reports, with 3 cases vaccinated in 2021 and 2 cases in 2023), and tick-borne encephalitis vaccine (5 reports).

Serious adverse events were reported in 12 reports. In four of these cases, the Agency determined a probable or potential causal association (WHO class A1): one case of hypersensitivity reaction and one case of fever and cough after influenza vaccination, blood in stool after rotavirus vaccination, and lymph node abscess after tuberculosis vaccination. In one case, the Agency determined a potential causal association – procedural complication (WHO class A3) – injection site infection after meningococcal vaccination. In all other cases, the Agency determined that causal association between the vaccination and the adverse event was unlikely.

Medicinal products – there were 382 reports of potential adverse reactions. 147 reports described serious adverse events. 45 reports described potential adverse reactions not currently associated with the drug (101 previously unknown serious adverse reactions).

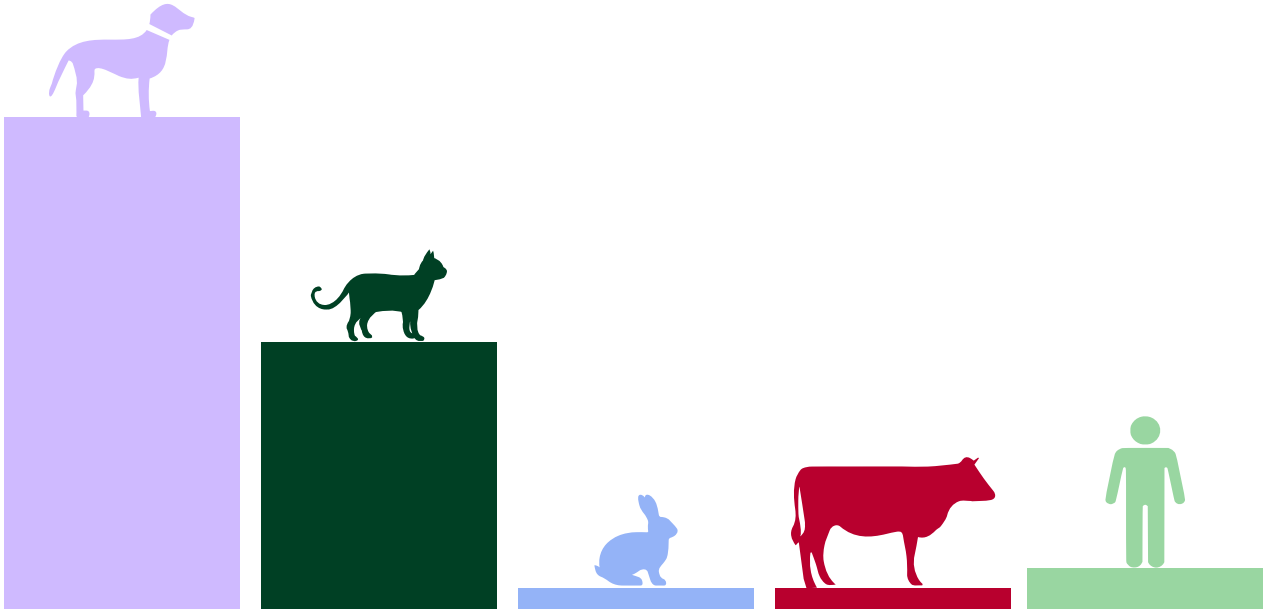
Assessment of vaccine injury claims

In 2024, the Agency received 14 applications to assess the causal association between vaccine and health injury (11 cases of COVID-19 vaccine and 3 cases of other vaccines) from the Estonian Health Insurance Fund (Tervisekassa). The Agency provided 39 assessments of probable causality or lack thereof in 2024. Of these, 2 assessments (5.1%) reflected the Agency's position that a causal association between vaccine and injury was probable (positive assessment):

- in one case, the Agency concluded that there was a matching causal association with vaccination (WHO class A1), a known adverse reaction causally associated with the vaccine (listed on the label):
  - tuberculosis vaccine (BCG Vaccine) – BCG lymphadenitis.
- in one case, the Agency determined that causal association was probable (WHO class B1) - the adverse reaction is not causally associated with the vaccine (i.e. not listed on the label) and there is insufficient proof to say the vaccine causes this reaction, but there was a temporal association with vaccination; other potential causes were ruled out and there exists a plausible pathophysiological mechanism - a potential signal (while this reaction is not currently causally associated with vaccine, this may constitute a new, unknown adverse reaction):
  - mRNA COVID-10 vaccine (Comirnaty) – sub-acute giant cell myocarditis

Adverse events associated with veterinary medicinal products

In 2024, Agency received 41 reports of potential adverse effects identified on animals.



24 reports for dogs

13 reports for cats

1 report for rabbits

1 report for bovines

2 reports adverse effects in humans after contact with a veterinary medicinal product

29 reports regarding drug safety issues	**8 reports regarding drug efficacy issues**	**4 reports regarding both safety and efficacy issues**
Drug safety issues 23 reports described adverse events probably or potentially associated with the drug in question in the opinion of the Agency. Six reports described adverse events for which causality could not be determined due to lack of information or for which causality was deemed to be unlikely.	Drug efficacy issues All eight reports described a lack of therapeutic effect (in six cases after administering an antiparasitic, in one case after administering a dermatological preparation, and in one case a lack of analgesic effect).	Drug safety and- efficacy issues Three reports described lack of efficacy and emergence of adverse effects after administering antiparasitics, and one report was for the same after administering a dermatological preparation.

Our laboratory - ensuring the quality and reliability of medicines

Aune Ahman

Laboratory testing of medicinal products is an important part of the Agency's national supervision activities. Our laboratory is responsible for the quality testing of medicinal products used in Estonia, providing an additional control beyond the batch testing conducted by manufacturers. Our laboratory applies 20 chemical-pharmaceutical testing methods, enabling QC of several parameters of various dosage forms.

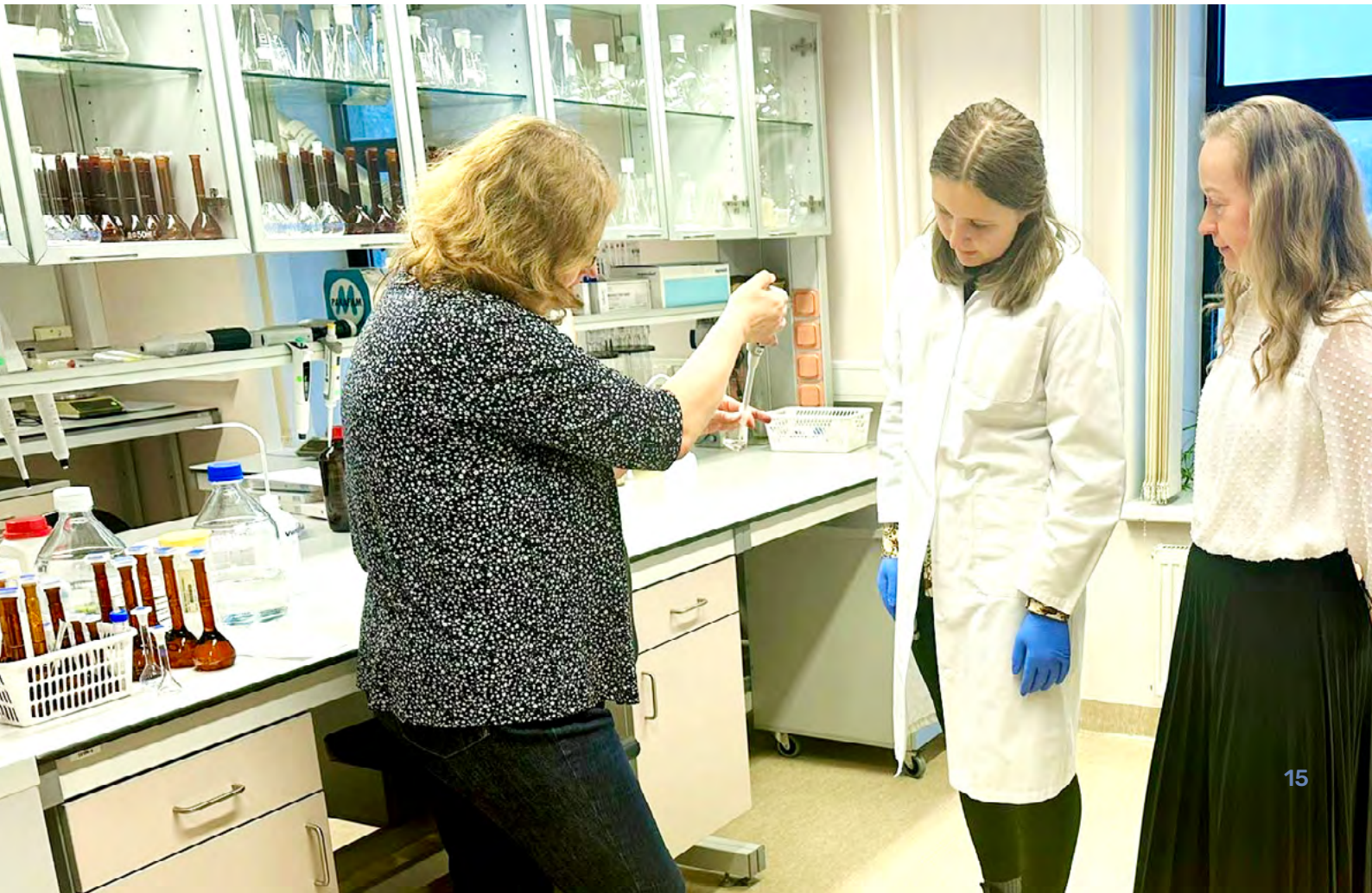
Methods used in our laboratory:

- Liquid chromatography
- Infrared spectroscopy
- Potentiometric titration
- UV-VIS spectrophotometry
- Thin-layer chromatography
- Quality control of purified water used for drug manufacturing
- Karl Fischer Method of Moisture Detection
- Loss on drying
- Sub-visible particle counting
- Volumetric titration
- pH measurement
- Uniformity of dosage content
- Single-dose Determination of single-dose average mass and uniformity of mass
- Release of active ingredient
- Determination of tablet disintegration time
- Determination of liquid density
- Determination of tablet parameters and hardness
- Determination of solution volume
- Determination of endotoxins, loss on drying, tablet fiability
- Determination of active pharmaceutical ingredient dissolution
- Sterility (subcontracted)

In 2024, our laboratory analysed a total of **63 medicinal products marketed in Estonia**, 7 of which were analysed as part of collaborative projects with other European Union member states. We also participated in **9 international proficiency testing studies**. Proficiency testing studies are designed to assess the competence of testing laboratories, and involve analysing identical samples across different laboratories and followed by a statistical comparison of the results. In total, we performed **390 tests** during 72 analyses. On average, 6-7 methods were used for assessing the quality of each medicinal product. **The laboratory identified 7 medicinal products that did not meet quality standards.** The non-compliances involved parameters such as volume, active ingredient content, number of doses, clarity of solution, description, tablet ¼ splitting, and mass uniformity. Based on the findings, the Agency issued the following decisions:

- 2 medicinal products were recalled, i.e. prohibited from being distributed in pharmacies and on the wholesale level;
- In five cases, the non-compliances identified did not pose a risk to patients' life or health, and the Agency allowed these products to remain on the market.

Quality control of medicinal products also includes international cooperation. Our laboratory is a member of the Network of Official Medicines Control Laboratories (OMCL), coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM). This cooperation network provides international recognition for analysis results, and includes most laboratories within European medicines agencies. Our laboratory is accredited by the Estonian Accreditation Centre as a testing laboratory in the field of medicinal product analysis.



Last months of the clinical trials transition period and the beginning of a new era

Keiu Heinla

2024 was the final year of the transition period for clinical trials. From January 31st of this year, all clinical trials conducted in the European Union are required to follow the new Clinical Trials Regulation and be registered in the Clinical Trial Portal (Clinical Trials Information System, CTIS). We received 55 transition applications in 2024. Overall, Estonia had a smooth and timely transition to the new legislation.

European Commission conducted Union Control audit in all member states to make sure state activities meet the requirements of the Clinical Trials Regulation. Estonia passed the audit successfully with no additional questions.

Last year, the Agency only received 34 initial clinical trial applications. We acted as the reference member state (RMS) in three clinical trial application assessment procedures. That meant the State Agency of Medicines had a large role in providing a scientific opinion, including writing an assessment report which other member states will base their own decisions on.

Similarly to previous years, most were applications for phase III trials - 26 applications. Phase III trials have a significantly larger number of subjects compared to earlier phases. The goal of phase III trials is to gather more information about the drug candidate's efficacy and safety. Phase III trials often involve comparing the investigational product with another, previously approved medication.

Compared to phase III trials, there were significantly fewer applications for phase II trials (6 applications): phase II trials are conducted on a smaller number of subjects and often involve studying the efficacy of different dosing regimens.

For phase IV (post-authorisation studies) and phase I (initial phase) trials, there was just one application for each.

The most active clinical areas were oncology and infectious diseases (7 applications each) and gastroenterology (4 applications).

Clinical trials

Last year there were a total of nine clinical trial inspections, including two inspections conducted in regard with the European Commission marketing authorisation procedures. We inspected sites and sponsors in Georgia, Brazil and US.

Opinion of the ethics committee has an important role in clinical trial evaluations. Our three-year cooperation with our previous partner was coming to a close. We held an open call to assemble a new committee

Marketing authorisations and expert assessment requests on the rise

Aet Viispert

Before a medicinal product becomes available to patients, healthcare professionals or veterinarians, the Agency provides a scientific assessment of the substantial evidence submitted by the pharmaceutical company. Marketing authorisation is granted only if the medicinal product is proven safe, effective and of high quality and its potential benefits outweigh the risks associated with it. In the course of assessing the marketing authorisation application, a summary of product characteristics (SPC) for doctors or veterinarians, a Package Insert (PI) for patients and a draft package design are prepared in Estonian. Upon completion of this process, a marketing authorisation for the medicinal product is issued, and the medicinal product is entered into the Register of Medicinal Products.

The Department of Marketing Authorisations evaluates and processes applications throughout the product life-cycle from medicinal product development to the end of marketing. Pharmaceutical development and oversight must follow scientific and technological developments - companies are constantly updating their manufacturing processes and post-marketing pharmacovigilance results in new important safety information which must be included in SPCs and PIs. Accordingly, our experts evaluate applications for amending, renewing, transferring or withdrawing marketing authorisations, and applications for parallel import of human and parallel trade of veterinary products, as well as applications to amend or withdraw these authorisations.

There are several procedures established to receive a marketing authorisation for a medicinal product: **the national procedure, the mutual recognition procedure** (MRP) **and the decentralised procedure** (DCP). Both MRP and DCP involve submitting applications in several EU member states simultaneously, one of these being the reference member state (RMS) which will prepare the scientific assessment of the medicinal product. The other countries are concerned member states (CMS) the main role of which is to review the assessment provided by the RMS.

In 2024, new marketing authorisations were issued for 374 human medicinal products. This includes:

- 66 new marketing authorisations from the national procedure, including 53 parallel import authorisations;
- 60 marketing authorisations via MRP;
- 223 marketing authorisations via DCP where Estonia was a CMS;
- 25 marketing authorisations were issued to medicinal products where Estonia (represented by the Agency) was the RMS in DCP.

Antihypertensives and various cholesterol medications had the highest number of new authorisations.

In addition to the above procedures, there is also the centralised procedure, coordinated by the European Medicines Agency and resulting in a marketing authorisation issued by the European Commission, valid in all countries of the European Economic Area. Such marketing authorisation applications are evaluated by the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Veterinary Medicinal Products (CVMP) of the European Medicines Agency. The evaluation is led and scientific assessment is prepared by experts from the member states.

Last year, the centralised marketing authorisation procedure was initiated for five human medicinal products where the Estonian State Agency of Medicines was one of the scientific assessment providers. Most of these applications were for biological medicinal products.

In 2024, European Commission issued marketing authorisations for 7 medicinal products where the Agency was one of the evaluation providers. These included four oncological products, one haematological product, an infusion solution for treating hypotension in neonates, infants and children, and an oral preparation containing several active ingredients for treating hypertension.

Last year, marketing authorisations were issued for **59 veterinary medicinal products:**

- one marketing authorisation via national procedure;
- eight marketing authorisations via MRP;
- 49 marketing authorisations via DCP where Estonia was a CMS;
- one marketing authorisation where Estonia (represented by the Agency) was the RMS in DCP.

For new veterinary medicinal products, antiparasitics and analgesics were the most represented classes.

Based on the safety data submitted in the marketing authorisation application, medicinal products are classified as over-the-counter or prescription drugs. Drug classification may change in the post-marketing phase based on new safety and usage data. A medicinal product's over-the-counter or prescription status may also depend on its package size. Last year we changed the classification for two human medicinal products. Eye drops containing 40 mg/ml chromoglycic acid used for symptomatic treatment of allergic ocular inflammation in adults and children above the age of 4 will be marketed as over-the-counter drugs. Vaginal tablets containing 10 µg of estradiol (24 pcs per package) indicated for the treatment of vaginitis caused by low oestrogen levels in postmenopausal women also received over-the-counter status.

For veterinary medicinal products, two antiparasitics for cats received over-the-counter status: two- and four-tablet containing packages of 4 mg + 10 mg and 16 mg + 40 mg tablets of milbemycin oxime and praziquantel.

Let's help veterinarians provide animals with the treatment they

Epp Ülevaino

Availability of veterinary medicinal products and efficient use thereof remain important concerns, especially regarding antimicrobials and antiparasitics.

As of the end of 2024, there were a total of listed on 1532 veterinary products in the Estonian Register of Medicinal Products, of which 742 were distributed in Estonia. Last year, 662 different authorised medicinal products were marketed in Estonia.

One of the long-term goals of these ongoing changes is to improve the availability of veterinary medicinal products. There remain occasional cases where no authorised human or veterinary medicinal product is available and the only option to help the patient is to use an unauthorised human medicinal product.

Last year, veterinarians received permission from the Agency to use unauthorised human medicinal products in 99 cases, with applications concerning 27 active ingredients in total. For clarity, the number of applications is not the same as the number of patients treated. Most applications are not for a specific patient - a single permission from the Agency may enable the veterinarian to treat many patients.

To the credit of Estonian veterinarians, most applications are very well researched and reasoned, which is why such a large majority receive the permission requested. The large number of applications, on the other hand, indicates that availability of veterinary medicinal products and authorised human medicinal products is not sufficient to meet the treatment needs of veterinary patients.

Indeed, unauthorised human medicinal products are mostly used for the treatment of pets, particularly those with rare conditions. The largest number of applications have been for ocular drugs - a total of 30 applications for four active ingredients. An unmet treatment need is also evident for oncological conditions. There were a total of 12 applications for oncological drugs containing three different active ingredients. There was also a marked increase in applications for neuroactive ingredients - in total, veterinarians submitted 15 applications for using three active ingredients indicated for various behavioural disorders (mostly anxiety and fear) in small animals. The increased number of applications for neuroactive ingredients was mostly due to the shortage affecting an authorised human medicinal product last year.

Introduction of a new, more compact veterinary prescription form in spring of 2024 was an important and long-awaited event. The new form is significantly more user-friendly, clear and easy to fill out for veterinarians and pharmacists. Veterinarians no longer need to provide a reasoning cascade for the choice of drug - ticking the relevant box is sufficient. Indication is not needed on the veterinary prescription.

Last year, we held four information days in Rakvere, Tartu, Pärnu and Tallinn in cooperation with the Agriculture and Food Board, to inform veterinarians about veterinary medicinal products and our Agency. We also contributed to educating future veterinarians by giving lectures to veterinary students in the Estonian University of Life Sciences concerning veterinary medicinal products, their use and the relevant legislation. We hope to continue this cooperation in the future. Veterinary medicinal products and changes concerning their use were also a subject of an information day for marketing authorisation holders last fall.

We are happy to announce that the veterinary medicinal products section of our website received an overhaul, and veterinarians and pharmacies should now have easier access to even more thorough information. We are seeing more and more information requests. These are very welcome and have led to interesting discussions which have helped both the requester and us gain important insights.

Pharmacies now conveniently provide Schengen certificates and other new services

Katrin Kõiv

As of 1 January 2025, there were 475 general pharmacies in Estonia, including 105 branch pharmacies and five online pharmacy providers. There were 24 hospital pharmacies and two veterinary pharmacies, with one of the latter's activity license temporarily suspended at the initiative of the pharmacy. Hospital pharmacies suplly medicinal products to hospitals and ambulance service providers, whereas general pharmacies provide medicines to individuals as well as to companies and institutions that need them for their activities. Veterinary pharmacies sell veterinary medicinal products exclusively.

In 2024, 20 general pharmacies were opened and 17 were closed. This included seven branch pharmacies that were closed and reopened by another owner at the same location. One hospital pharmacy was closed. Most pharmacy closures have little or no impact on the availability of medicinal products, as they are either replaced by another pharmacy or alternative local pharmacies are available. The small town of Rõuge was left without a pharmacy for half of the year, but another one was opened before the s end of the year.

A pharmacy should provide medicinal products along with relevant and evidence-based advice. It is also important that pharmacies carry a wide selection of medicinal products, including more affordable discount-rate medicines. To ensure this, we conducted 80 inspections in general pharmacies, 12 in hospital pharmacies, and two in veterinary pharmacies last year. We observed that pharmacies increasingly use automated electronic systems to monitor and log the storage conditions of medicinal products. Medicines verification has become a routine part of pharmacy work, and availability of discount-rate medicines has continued to improve over the past years. Unfortunately, we also initiated two misdemeanour proceedings related to the dispensing of expired medicinal products.

We are committed to issuing newsletters to pharmacists to help them stay up to date with relevant developments. Last year, we published nine newsletters covering topics such as the principles of patient-centric advice, new veterinary prescription forms, drug quality issues, and shortages. We also published several articles in the proffesional magazines "Apteek TÄNA" and "Eesti Rohuteadlane" and organized an information day for pharmacists focused on changes in pharmaceutical regulations.

The most important legislative change affecting pharmacy services came into effect on 1 September and related to travelling with narcotic and psychotropic drugs – the responsibility for issuing Schengen certificates was transferred from the Agency to pharmacies.

To communicate this transition, the Agency organised a public awareness campaign on travelling with medicinal products in cooperation with pharmacies.

The campaign included videos shared on social media channels, advertisements displayed in pharmacies and other healthcare institutions, and booklets handed out to pharmacy customers. In order to help pharmacists prepare, the Agency published two in-depth newsletters and held an information day in September primarily addressing the issuing of Schengen certificates. We are pleased to report that, according to both the Agency and pharmacists, the transition went smoothly, making the service more convenient and accessible for the people of Estonia.

In the spring, we reviewed the pharmacies' existing drug substitution practices and updated our relevant guidelines. The goal was to avoid situations where patients are unable to receive the medicines they need. Pharmacists are qualified to substitute medicines without consulting the patient's doctor or receiving a new prescription. Such situations may arise during supply shortages or when a pharmacy is unable to restock in a timely manner, resulting in the patient needing to schedule another visit to obtain a new prescription. Drug substitutions at the pharmacy level are appropriate if the substitute differs only in name, active ingredient content per unit (but not per dose) or pharmaceutical form only, without any change to the route of administration or treatment outcome (including time to effect and duration of effect). This makes use of pharmacists' professional expertise to reduce the burden on patients and the time physicians spend on consulting substitutions or rewriting prescriptions.

We are pleased to see that the pharmacy sector is actively exploring opportunities to adopt new technologies. 3Dprinted medicinal products have been administered to first patients at the Tartu University Hospital, and phage therapy has also been used to treat at least one patient. Our Agency participates in the European working group on 3D printing of pharmaceuticals, which is tasked with developing common principles for all member states and monitoring the latest developments in the field.

In 2024, the Agency's supervisory activity focused on hospital pharmacies, once again confirming that hospital pharmacists are committed to improving service quality and open cooperation. A striking example is the set of quality guidelines voluntarily adopted by hospital pharmacies, the drafting of which was led by the Estonian Association of Hospital Pharmacists. The guidelines offer detailed support in ensuring the quality of services provided by hospital pharmacies, while maintaining compliance with regulatory requirements.

Among general pharmacies, we are seeing growing interest in technological solutions for the individualised l packaging of medicinal products. This service is likely to become a mark of quality for nursing institutions in the near future, encouraging more pharmacies to adopt this approach and offer individualisedpackaging services. For several years, only two pharmacies provided this service, but the number has now now increased to four. In 2025, the Agency will focus on this area to provide pharmacies with the necessary guidance to ensure the delivery of high-quality and safe services to Estonian patients.

ositive developments in Estonian pharmaceutical manufacturing and less bureaucracy in international pharmaceutical trade

Liis Prii

As of January 1st, Estonia has 26 pharmaceutical manufacturers active in 27 locations in total (9 producing medicinal products, 3 producing active ingredients, 1 producing medical gases, 4 producing herbal substances, 1 importing medicinal products from third countries, and 9 labelling and/or packaging medicinal products). We had the addition of one manufacturer of sterile veterinary medicinal products and one medicinal product packager. One medical gas producer was reorganised to a medical gas wholesaler. Several manufacturers expanded or updated their facilities or reassigned the competent persons responsible for manufacturing. We partially suspended a manufacturer's activity license due to critical non-compliances. One herbal substances manufacturer discontinued activity in January 2025. We are happy to see that several manufacturers are expanding their activities in the field of both biological and chemical products or active ingredients.

All Estonian pharmaceutical manufacturers follow Good Manufacturing Practice (GMP) to ensure drug quality, safety and efficacy. In order to check GMP compliance, we conducted 27 inspections with Estonian manufacturers and issued 8 GMP certificates to 7 locations. Out of all these inspections, 10 were associated with one new pharmaceutical manufacturer and one pharmaceutical packager entering the market. In one company, the GMP compliance inspection resulted in a partial suspension of activity license and issuing of several precepts. Consecutive inspections revealed several critical and material non-compliances, and therefore we could not be assured of the quality of veterinary medicinal products manufactured there. The first step was to halt the sales of these medicinal products, followed by a review of the manufacturer's remedial actions to ensure that they produce high-quality medicinal products.

As of January 1st 2025, there were 56 pharmaceutical wholesalers in Estonia (36 handle human medicinal products, 2 handle veterinary medicinal products, 18 handle both, and 29 have right of storage). In 2024 we issued two additional wholesale licenses to companies previously licensed for pharmaceutical manufacturing, so that they could continue selling other manufacturers' medicinal products as well. We also temporarily suspended two wholesale licenses, which were reinstated after the non-compliances were remedied. Activity license changes were mostly associated with change of competent person or change of secondary conditions.

All Estonian wholesalers of medicinals products apply the Good Distribution Practice (GDP), in order to ensure that medicinal products reaching pharmacies have the same level of quality as when they are supplied from the manufacturer. We conducted 20

inspections of GDP compliance, including five to check non-compliances identified in previous inspections, and two initial GDP inspections.

GMP and GDP certificates are valid for three and five years respectively. In addition to being preconditions for an activity license, they provide confidence that the company is regularly inspected for compliance with pharmaceutical regulations. In addition to the Eudra GMDP database, all Estonian companies' GMP and GDP certificates are now available in the Agency's register of activity licenses along with manufacturing and wholesale license information.

With a backlog of non-renewed and provisionally extended GMP and GDP certificates from the Covid-19 pandemic expiring at the end of 2024 and several new companies entering the market, we had to work hard to verify all companies in a timely manner. We consider it our duty to be there for companies, helping them identify opportunities for improvement and prevent non-compliances affecting quality of medicinal products by systematic application of good practices.

In addition to meeting them during supervisory activities, we held an information day for[1] pharmaceutical manufacturers and would like to continue this tradition after a several-year pause. We are committed to supporting the growth of the pharmaceutical sector by providing expert advice and expedient supervision, which means training an additional manufacturing inspector over the next few years in addition to supporting ongoing development of our existing pharmaceutical manufacturing and wholesale inspectors.

The long-awaited changes in the procedures for medicinal product import and export license application and notification of cross-border movement of medicinal products came into effect in late 2023, significantly reducing red tape for both companies and the Agency - in many cases, post-fact notification is sufficient instead of applying for a permit beforehand, and in some cases even notification is not needed. For example, this expedites the import of non-authorised medicinal products authorised in other European states, export of non Estonian authorised medicinal products manufactured in Estonia to non-EU countries, and medicinal products used in clinical trials. The permit is still required for importing from non-EU countries, as well as for narcotic and psychotropic drugs. Post-fact notification is significantly more flexible, facilitating smooth logistics for companies and faster responses to unexpected supply chain changes. Quarterly wholesale statistics provide a good overall picture of movement of medicinal products.

Long-term supply difficulties resolved and new options for mitigating supply disruptions

Marko Tiisler

A medicinal product has supply difficulties if supplies do not meet clinical demand - the demand exceeds suppliers' capabilities. Planning of manufacturing volumes, availability of active ingredients and management of relevant risks are up to pharmaceutical manufacturers. If a pharmaceutical manufacturer realises that they are unable to maintain sufficient supply in Estonia, they need to notify us.

In 2024, we received 290 such notification, five of which concerned veterinary medicinal products and the rest human medicinal products. What is important is whether the medicinal product in shortage has potential alternatives, and what kind of condition it is for.

Shortages are mainly caused by manufacturing issues, unexpected spikes in demand, and in some instances logistical issues, inaccurate forecasts or commercial reasons. In rare cases, the cause lies in quality issues. Unfortunately, there are more frequently cases of shortages where the reason is unknown or unspecified by the marketing authorisation holder.

The positives from last year include improvements in the availability of the widely published semaglutide solution for injection, with the medicinal product constantly available at pharmacy and wholesale level. Long-term shortages of hospital thrombolytics were also resolved. Effective cooperation with the Estonian Pain Society and the Estonian Psychiatric Association helped to alleviate shortages of pain medication (oxycodone), antidepressants (fluoxetine, bupropion) and antipsychotics (quetiapine). For several medicinal products, the shortage was resolved by introduction of a new medicinal product on the market (e.g. paediatric amoxicillin).

The State Agency of Medicines does not order medicinal products and does not stockpile medicines. We publish the shortage's information in the Register of Medicinal Products, as well as on our website for more complicated cases or those impacting many patients, adding information regarding potential replacements. We may temporarily authorise marketing the medicinal product in foreign language packaging or authorise doctors to prescribe alternatives which are not authorised for sale in Estonia, based on the doctor's or a medical association's request.

As a result of the amendment to the Medicinal Products Act, which came into force last year, we are also able to permit the use of unauthorised medicines on our own initiative

in case of a shortage. We took this action in five cases to reduce administrative burden on medical associations and accelerate the access of necessary medicinal products for patients. Prohibiting the export of the medicinal product in shortage is another option, reserved for exceptional cases. Last year's shortages impacting a diabetes medication forced us to extend the export limits

on three medicinal products with the same mechanism of action and indication. The shortage remains active in the Register of Medicinal Products until imports and stockpiles recover.

Solutions to human medicinal product shortages in 2024 (in some cases a combination of measures was applied):

59% (170 medicinal products)

of the cases had essentially no effect on patients, as there was an alternative from another manufacturer available at the time of notification about the shortage.

15% (45 medicinal products)

of the cases involved a medicinal product which could be replaced by using two medicinal products instead of a single combined drug, splitting tablets to provide the suitable dose, lowering the dosage regimen, using another medicinal product with identical indication, etc. While these situations may alarm patients and increase the workload of doctors due to having to fill out new prescriptions, they do not result in discontinuation of treatment.

26% (75 medicinal products)

of the cases had no alternative at the time of receiving the shortage notification.

Solutions

26% of shortages were therefore more critical, and cooperation with marketing authorisation holders, wholesalers, doctors and pharmacists was needed to make sure patients receive continued treatment. Solutions used for shortages with no alternative medicinal product:

30 cases involved a short-term shortage covered by stockpiles held by local wholesalers or otherwise not significantly impacting the continued supply of the medicinal product to patients;

- 23 cases where the Agency permitted use of an unauthorised medicinal product based on a medical association's request or on its own initiative;
- 7 cases were resolved by marketing the impacted medicinal product in foreign packaging;
- 4 cases were resolved by permitting the marketing of the impacted medicinal product in foreign packaging as well as without a marketing authorisation;
- 6 cases involved a medicinal product with limited use/demand and were resolved on a patient-by-patient basis or on the healthcare institution level;
- 4 cases involved the doctors having to significantly adjust treatment regimens to use medicinal products with different mechanisms of action (shortages impacting all of Europe, late notifications);
- 1 case involved a non-critical medicinal product (over-the-counter medicine);
- 1 case was resolved by releasing the stocks of the Estonian Stockpiling Agency.

Last year, there were also some cases where medicinal products in foreign packaging or without marketing authorisation had to be permitted because while alternatives with the same active ingredient and strength or other suitable alternatives were available, they would not have covered the entire period of shortage. There were a total of 20 cases of permitting medicinal products in foreign packaging and 35 cases of permitting unauthorised medicinal products to alleviate the impact of shortages.

The Agency also issues permits for marketing medicinal products in foreign packaging in the case of hospital medicines and medicines for which there are no alternatives in Estonian packaging due to low demand in Estonia (e.g. medications for rare diseases). In 2024, foreign-packaged marketing permits were issued for 397 medicinal products, which is 110 more than in 2023.

At the end of 2023, additional authority was granted to limit the quantities which can be sold in pharmacies or diagnoses for which a specific medicinal product can be issued, if there are no other solutions to ensure continuity of supply of a particular medicinal product. We have not applied these measures yet as of now. However, in some cases we have recommended that pharmacists issue smaller quantities and doctors limit prescribing the impacted medicinal product if suitable alternatives are available for the patient.

The Agency appreciates the cooperative efforts of all involved parties, which have helped us resolve shortages in a timely manner and ensure all patients get the treatment they need even if authorised medicinal products are not available in sufficient quantity.

We supported development of cell therapy and are preparing for changes in the field of substances of human origin

Triin Suvi

Substances of human origin (SoHO) includes donor cells, tissues, organs and blood which are used for patient treatment. Procurement, processing, storage and issuing of SoHOs to doctors for transplantation requires the relevant activity license issued by the Agency. Currently, 25 such licenses have been issued, 11 of which are for procuring and/or handling of cells, tissues and organs, and 14 are for handling blood. In 2024, we issued an activity license to a new site storing and distributing blood derivates.

In Estonia, various cells and tissues are procured and handled: blood stem cells, therapeutic cells (T-lymphocytes and peripheral blood mononuclear cells), reproductive cells and embryos, cord blood and tissue, skeletal tissues, cornea and amnion membrane, teeth and vascular tissue. Organs procured and handled include kidneys, liver, lungs, pancreas and heart.

Blood establishments use collected donor blood to produce red cell suspension, fresh frozen plasma, thrombocyte concentrate and cryoprecipitate. Plasma not used for transfusion is sent to a plasma fractionator, to be used to manufacture various medications.

All 25 establishments are subject to our supervision and inspection, with 15 inspections conducted last year.

Establishments are reporting all serious incidents (including patient adverse reactions) to us.. This reporting system is called haemovigilance in the case of blood, and biovigilance in the case of cells, tissues and organs. We analyse all cases - if necessary, we request additional information and ask the establishment about the measures taken to prevent recurrence of the incident, in order to ensure patient safety. Last year we were notified of 84 haemovigilance incidents and 14 biovigilance incidents. Previous years had similar numbers of such reports. Incident reporting shows that establishments are vigilant regarding abnormalities and adverse events, and grasp the importance of case analysis and prevention.

Last year, a new human-derived material EU regulation was adopted, which will enter into force in August 2027, and which our experts also actively contributed to.

The new regulation will replace the current directives regulating blood, cells and tissues, but will also regulate various additional human-derived materials used in medicine, including breast milk, serum-based eye drops, and faecal microbiota. We have lots of work ahead of us in the coming years to prepare for changes associated with the new regulation.

Advanced therapy medicinal products

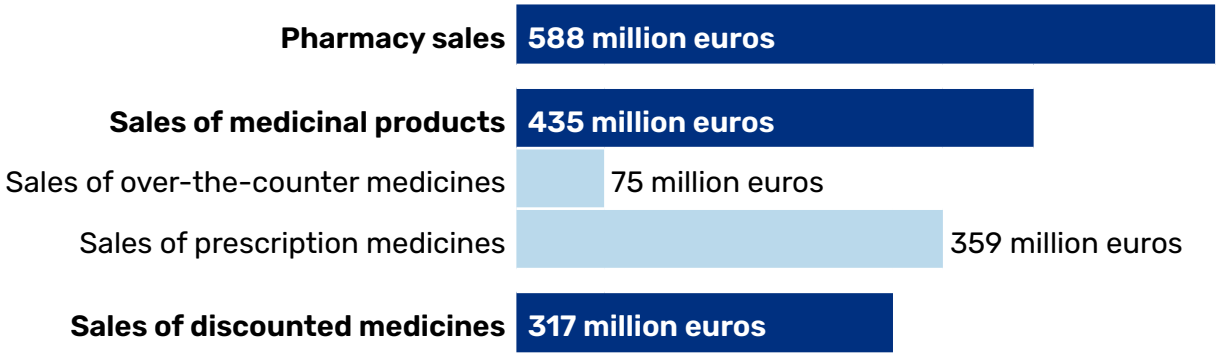
Advanced therapy medicinal products (ATMP) are biological medicines containing viruses, live cells and/or tissues. Cells and tissues used in ATMPs are substantially manipulated or used to perform different essential function. It is a distinct small group of drugs with its own set of regulations and good manufacturing practices. This is because they carry particular risks which do not enable classification as cells, tissues, blood or biological medicines. Advanced therapy medicinal products reach patients in the same way as other medicinal products - they need marketing authorisation. All ATMPs marketed have been issued a European Commission marketing authorisation valid in the entire EU.

Unlike with other medicinal products, provisions have been made to prepare ATMPs without marketing authorisation within the scope of hospital exemption. Hospital exemption means the making and use of a custom-made ATMP in Estonia on non-routine basis for an individual patient in a hospital and under the professional responsibility of a doctor. Such exemptions enable the preparing of ATMPs in cases where there is no authorised medicinal product available or where there is potential for developing an entirely new drug.

Last year, we permitted a hospital exemption to prepare a drug from the patient's own mesenchymal stem cells, to be used for the treatment of critical lower limb ischaemia caused by lower limb atherosclerosis.

Statistics

Pharmacies 2024



Human medicinal products 2024

Market size of human medicinal products: **514 million euros**

Human medicinal products sold by **27 whole-salers**

TOP groups of medicines by revenue

Antitumor and immunomodulating substances
26% 134 million euros

Gastrointestinal and metabolic medicines
14% 72 million euros

Systemic antibiotics
10% 52 million euros

*Together, these three ATC groups made up 50% of the human medicines market by revenue in 2024

1438 active ingredients
Top five active ingredients:

1. rosuvastatin (cholesterol medication)
2. ramipril (blood pressure medication)
3. atorvastatin (cholesterol medication)
4. omeprazole (stomach medication)
5. acetylsalicylic acid + magnesium oxide (blood thinner)

4891 medication packages

3 million total packages sold

834 million tablets/capsules

76 t creams/gels/ ointments

700000 vaccine doses

Veterinary products 2024

Veterinary medicines market size **20 million euros**

Veterinary products sold by **9 whole-salers**

TOP groups of medicines by revenue

Antiparasitics (QP)
25% 5,1 million euros

Immunologicals (QI)
21% 4,2 million euros

Antibiotics (QJ)
18% 3,5 million euros

64% of total veterinary product sales

372 active ingredients
Top five active ingredients:

1. Oclacitinib (dermatitis)
2. circovirus (porcine inactivated virus vaccine)
3. fluralaner (acaricide)
4. flumethrin + imidacloprid (acaricide)
5. *Escherichia coli* (piglet vaccine)

791,701 packages sold

4.3 million tablets

0.9 t of ointments

17.1 million vaccine doses

21,500 drug collars

A dynamic and productive year of IT development for the Agency

Märt Roogna

In 2024, the Agency made significant strides in digital development, successfully completing participation in an international project and making continued progress with its own information systems. Structural changes, new tools and the proficiency of our teams have laid a strong foundation for high-quality data-based healthcare services.

An important milestone was the completion of the UNICOM project. One of the goals of this international project initiated in December 2019 was to support member states' medicines agencies in transitioning to a single ISO IDMP data standard enabling unambiguous identification of medicinal products and automated data exchange. Our participation in the project was highly successful - since 2022 the new information system is used for processing authorised drug information and authorisation applications, and interfaces with various information systems (e.g. the SPOR database of the EMA) ensure data quality and help us work more efficiently. The quality and standardisation of drug information becomes increasingly important to ensure patient safety and improve medical services. The Agency has made great progress to ensure that Estonian drug information meets the growing demands.

The Agency's Samtrack information system is in ongoing development - last summer, it entered its second phase targeting the automation of processing of shortages, unauthorised medications, import and export notifications and special permits. Another important achievement was reaching the final stretch in developing the Samtrack clinical trials module. Completion of this innovative tool interfaced with the EMA's CTIS information system will significantly simplify processing clinical trial information.

Establishing data descriptions went according to plan - we harmonised the Agency's data descriptions with the national data description standard. This is an important step for ensuring data quality and reliability and will support further digitalization efforts.

Last year, the Agency underwent a reorganization - two ancillary teams were merged into a new Development and Administration Department. Our people also participate in working groups coordinated by the Ministry of Social Affairs, helping shape digital solutions and data management strategies.

We adopted the new PlanPro application to facilitate monitoring of cross-domain targets and management of Agency workflows and the professional development of our staff.

We have a dedicated and professional development team whose competence and novel ideas have helped strengthen our digital capabilities. Work is well-organised within the team, contributing to smooth and effective development processes. Any institution relies on its administrative team to ensure that everyday work goes smoothly.

Our goal is to provide the Agency with all the innovation and technological solutions it needs to do its job well. The progress made in 2024 shows that we are well on our way towards smarter, faster and more data-centred pharmacovigilance.

It was a varied year of significant development

Carmen Katariina Sikk

Last year we mostly focused on proactive or preventative communication to ensure availability of drug information to patients and healthcare professionals. Pharmaceutical safety was another subject of focus.

During the first half of the year we conducted a user friendliness survey on the Agency website. Results of the survey were used to improve the availability of information for patients on our website. At the beginning of the year, we also added a blog to our website to clarify current issues regarding medicinal products or use thereof. Our blog posts have been referenced in press, and the blog has become an important source of information for the general public. Not limited to the blog, our communication efforts included articles published in news outlets and professional journals, as well as appearances in various radio and TV shows.

Last year we extended our outreach to schoolchildren, because they are at a stage of developing knowledge about medications and use thereof. Based on the Agency's educational videos, we developed worksheets and shared them with schools and subject teachers. They are now available on our website and the Teaduskool website. We received over 400 high school student visitors in our office to attend exciting workshops on the subject of various medicinal products and the work we do at the Agency.

We held information days for pharmacists, wholesalers and medicinal product manufacturers, and published articles in the "Ravimiteave Ravimiametilt" column of the Eesti Arst professional journal. Our specialists attended several Estonian and foreign conferences as speakers.

In addition to our own media communications, our specialists responded to more than 160 information requests from media outlets last year. The number of information requests was highest in the areas of shortages, pharmaceutical safety, adverse effects and rational use of medicines.

The role of social media is ever-increasing, as many people receive information from social media platforms. This led to developing a new social media strategy in cooperation with the VividStudio agency, improving our visibility on the modern media landscape. While this strategy is a work in progress, results are already apparent in marked improvements of our reach and engagement.

To a large degree, the success in social media is due to our new visual identity - one of the major changes last year. We developed a modern and distinctive visual identity in cooperation with the Velvet creative agency, to help us stand out with our messages. Visual identity is not just how we look - it is a reflection of our work.

The new identity immediately found its use in our first major public communication campaign “Travel smart, healthy and safe”, focused on the regulations applicable to travelling with medications. Held in September 2024, the campaign included educational videos and informational materials handed out in pharmacies, general practices, bus and train stations, student workbooks and our social media channels, including YouTube. The ads reached people via social media, as well as radio. We also discussed the subject in five radio shows. Here, I would like to extend our thanks to our partners Poison Information Centre, Police and Border Guard, Highway Administration and Association of Estonian Provisor Pharmacists, who helped extend our reach.

In addition to the subject of travelling with medications, our communication efforts involved antibiotic resistance, adverse effects, unused medicines, and dangers associated with purchasing medicines online. The latter being an ongoing issue, as there are individuals engaged in illegally selling pharmaceuticals via social media groups. The only proper place to buy medicinal products is a pharmacy or an official online pharmacy - uncontrolled products sold online are a health hazard. In cooperation with the online activities counsellor of the Estonian Health Board, we keep an eye on such ads and help remove them if possible. We have also helped inform people about the fact that reselling

or giving away unused medicines is illegal and people could be unknowingly committing a crime by engaging in such activity.

In 2024, we initiated preparations for a European public communication campaign on pharmaceutical safety. The campaign is planned for 2025 in cooperation with medicines agencies of Spain, Netherlands, Sweden and France.

Promoting pharmaceutics in Estonia

Triin Suvi, Liis Prii, Aet Viispert, Keiu Heinla

Domestic pharmaceutical manufacturing has an important role in ensuring continuity of national healthcare systems, especially with regard to improving availability and reducing dependence on international supplies. Supporting local pharmaceutical development stimulates economic growth, creating new jobs in manufacturing, research and marketing. It also encourages innovation and helps develop qualified workforce in the sector.

Supporting development of pharmaceutics is part of the Agency's mission, and therefore our everyday work. We want to use our expertise to support Estonian pharmaceutical developers and manufacturers on their journeys and lend credibility for cooperation abroad. Navigating regulatory and scientific standards is not easy and we do not expect developing companies to handle this on their own.

It is not just startups and innovators needing support. Many academical clinical trials are motivated by a lack of information necessary in everyday work, for example dosing information for children. We are able to help Estonian medical professionals with planning and conducting clinical trials.

Clinical trials of medicinal products

It is important for us that clinical trials in Estonia are planned and conducted according to best practices and international standards. Last year, we updated the clinical trials section of the Agency website to improve its searchability and make sure it has all the necessary information. In cooperation with the ethics committee, we updated participant informed consent forms to make the information clearer and easier to understand for participants. Our partners have provided feedback which we used for the updates. We thought of pharmaceutical manufacturers who need quick access to country-specific requirements, as well as academic researchers looking for practical guidelines and requirements for conducting clinical trials for medicinal products.

Last year we advised academic researchers in four cases. They contacted us for advice on the regulatory, practical and scientific aspects of conducting clinical trials. In most cases, providing legal advice is not time-consuming. Scientific advice, on the other

hand, requires thorough research into the planned trial and properties of the medicine, involving tens of hours of work by our experts.

A good indicator of successful cooperation is the percentage of academic clinical trials, which has increased in Estonia over the past few years, while it has stagnated or even decreased elsewhere in the European Union. Between 2016 and 2021, the percentage of academic trials (including those initiated by foreign academic sponsors) of all applications submitted stayed between 1-8%, but in 2023 they made up 12% and in 2024 11% of the total number of initial applications.

Information on ongoing trials is easier to find since January of last year - the Estonian open data portal now includes information about currently recruiting clinical trials. This helps patients and their doctors keep an eye on clinical trials to join.

New veterinary medicinal product manufacturer

A new veterinary medicinal product manufacturer joined the Estonian pharmaceutical sector in 2024. The company has engaged with us for several years now to help ramp up their new manufacturing site. The activity license issued in early 2024 has been amended five times to permit all the manufacturing steps required by the company in its three units (sterile veterinary drug manufacturing, microbiology laboratory and chemistry laboratory). We have also conducted inspections of good manufacturing practices in all these units, and issued a GMP certificate to the company.

A pharmaceutical manufacturing license requires a lot more than just a building and a manufacturing line. In order to reach the desired result, the company and the Agency have had to conduct nine inspections (16 days in total) and around a dozen meetings, as well as exchange a large number of messages and phone calls. It has been an exciting and challenging journey, with all parties making sure the new manufacturing site meets both national requirements as well as the good manufacturing practices the European Union requires from the pharmaceutical industry.

Advice prior to submitting a marketing authorisation request

Developing a new drug is a long journey and pharmaceutical companies may encounter both scientific as well as regulatory questions. It's good to see that domestic pharmaceutical developers, manufacturers, and local representatives of global companies are more prepared to contact us, including in early stages of product development. This facilitates the steps needed to apply for a marketing authorisation after receiving an activity license. In 2024, there were approximately ten meetings where companies received advice on what documentation to include with their marketing authorisation requests. There were various subjects from active ingredient manufacturing data to information on the validation method applied to the finished product, as well as submitting research results based on which the expiry date of the medicinal product is determined.

Nearly every day we respond to information requests on whether a product is classified as medicinal, or whether a medicinal product requires full safety and clinical trials or if it is sufficient to refer to published research or trials conducted with a similar medicinal product already on the market.

Scientific advice involves processing large amounts of information. We have been offering such service to applicants for over a year now, and one applicant has used the service.

Enquiries regarding novel technologies are especially interesting, and we handle these with our colleagues in the European cooperation network.

Phage therapy first introduced in Estonia

In the world of pharmaceutics, phages are classified as biologicals. For phage therapy, a bacterial sample taken from the patient is used to identify a suitable phage or combination of phages. Each phage therapy patient receives a customised phage cocktail.

This kind of personal approach to pharmaceutical manufacturing differs from current standard practices in the pharmaceutical industry. For example, it is difficult to test phage therapy in clinical trials, because different patients' infections are generally caused by different bacteria and it can be hard to find a sufficient number of patients whose diseases are sufficiently similar to allow for reliable comparison. For this reason, no human phage therapies are currently authorised for marketing in Europe.

Due to the biological nature of phages, there are currently no globally recognised guidelines, but there is published research as well as thorough overviews of phage therapy quality and instructions for use by manufacturers. Based on these, it is possible to establish rules for preparing and administering phage therapies. Such activity requires permission from the Agency. Last year, the Agency permitted the Tartu University Hospital pharmacy to process and use phage therapies.

A supportive regulatory framework

Besides supporting pharmaceutical developers with practical issues, we also have an important role in shaping the relevant regulatory framework. In 2024, we started drafting amendments to provisions regulating hospital exemption.

A hospital exemption means the making and use of a custom-made ATMP in Estonia on non-routine basis for an individual patient in a hospital and under the professional responsibility of a doctor. The current Medicinal Products Act allows hospital exemptions for treating up to ten patients or for two years, whichever is earlier. At the time of drafting this hospital exemptions regulation, it could not be foreseen that hospital exemptions would become more and more common in various member states in the years to follow.

The new pharmaceutical directive also sees the hospital exemption as an opportunity to improve the access of innovative medicines to patients. Early last year, we met with stakeholders to discuss

the shortcomings of current hospital exemption regulation and tried to come up with solutions together. In late spring, we submitted our draft amendments to the Ministry of Social Affairs. Discussions on the draft amendments are ongoing at the time of writing this yearbook.

Activities in the development strategy

1. area of focus - adding value with drug information

Keiu Heinla

For some patients, clinical trials are the only option to receive treatment. Therefore, it is important that patients and doctors have good access to clinical trial information. It is equally important to make sure participants' rights are protected and the transparency of clinical trials isensured. In 2024, we updated the clinical trials section of our website, as well as the participant informed consent forms in cooperation with the ethics committee. Information on ongoing clinical trials is more accessible since January last year - details of clinical trials recruiting participants are now published in the Estonian open data portal.

In 2024, we surveyed Estonians on the user friendliness of the Agency website. The survey resulted in useful ideas to improve the selection of information. We also reorganised and adjusted the menu structure to help with information accessibility and usability.

Our communication efforts now focus more on reaching the future users of medicinal products (young people) and the elderly. We prepared written educational materials (worksheets) for schools to improve public knowledge of medicinal products. These worksheets cover a wide selection of practical issues: biologicals, clinical trials, adverse effects, patient information leaflet, the road from drug candidate to marketed drug, medicinal products derived from blood, and pharmaceutical quality assurance. We published information on these worksheets in Estonian educators' journal Õpetajate Leht, as well as via direct contact. The information and materials are also posted on the University of Tartu Youth Academy website. We have been invited to give lectures and workshops on medicinal products in schools. Students are welcome to join us as job shadows and we conducted youth workshops in cooperation with the University of Tartu Institute of Pharmacology, attended by nearly 450 young people last year.

There were educational campaigns and information weeks all year round.

Information on medicinal product shortages is available in the Register of Medicinal Products, and we updated this information with suitable alternatives and estimates for when supply will resume.

2. area of focus - being an innovative and valued partner

Jana Danilovitš

There is a growing trend of active ingredient specific nitrosamines finding their way into medicinal products - therefore it is important to test medicinal products in order to minimise risks. Unfortunately there are few EU laboratories testing for nitrosamines, and therefore we need to develop this competence in our Agency laboratory. We evaluated possibilities for expanding our laboratory's capabilities, and determined that our mass spectrometric (MS) testing capability could be developed to enable testing nitrosamine content and unauthorised medicinal products. We analysed the investment needed and potential alternatives.

An advisory role best practices document was prepared to support the Agency's advisory role. These best practices will be introduced to our people later this year.

The service of providing scientific advice has been defined and the definition is available on our website in Estonian and English. We evaluated options for expanding our competence in areas where we lack expertise, but there is great demand on the EU level. Information on pharmaceutics promotion activities in Estonia may be found in the "Promoting pharmaceutics in Estonia" chapter.

We have made proposals to improve and amend both national and EU pharmaceutical regulations: 16 in Estonia and 81 on the European level. Our proposals are drafted with enough flexibility to allow for adjustments in response to future developments. We try to avoid excessive regulation and reduce administrative burden for both our Agency and our clients and partners. Some examples: Schengen certification was transferred from the Agency to pharmacies. Clearly, this is a more accessible and quicker solution for consumers. Patients travelling with larger quantities of narcotic or psychotropic medicinal products no longer have to carry a permit issued by us. A doctor's letter or a copy of the prescription is sufficient. The limits on the amount of over-the-counter and prescription drugs carried when travelling were increased. Due to the new EU regulation of marketing authorisation amendments, we only need to be notified of amendments once a year.

3. area of focus - durable national capability for directing and developing the field of pharmaceutics

Reelika Jõgi

The goal of this development area is to create a motivating and balanced professional environment where everyone feels valued and which is centred around sustainability and consistent development of the organisation.

Workplace fatigue is a major challenge for the Agency. In 2024 we mapped workloads by departments and submitted proposals for improving the situation. We also reviewed staff substitution plans to enable our experts to take their vacations without having to worry about important projects left on standby or not meeting deadlines. This is an ongoing process and we will continue to map the situation in the years to come.

The Agency employs top industry experts. In order for new employees to develop into experts, they need constant support and direction in addition to time and motivation. We want our people to have a clear development path and all opportunities to hone their professional skills. That›s why we started developing a roadmap to expertise, which outlines the necessary skills, a training plan and the trainings they need to complete to advance. Last year we created a draft roadmap in cooperation with Agency experts and department managers, and development will continue in 2025.

A sustainable organisation needs empathy. In 2024, we organised several social events and included our Tallinn office as much as possible. Together, we visited theatre plays, played paddle ball, monitored our physical activity and acquired new knowledge based on thematic months. In order for our employees to feel cared for, last year we started a new project with the goal of creating an automated workplace satisfaction assessment system.

We care about our employees as well as the environment. This year the Agency conducted its first greenhouse gas (GHG) emissions audit. With our experts valued all over the world, air travel was our largest source of GHG emissions. Another major factor is our electric energy consumption, but we managed to reduce this by switching to green electricity last March.

Our goal is to be attractive for current and future employees, our partners, and the public. Last year we updated our visual identity, focused on developing our social media strategy, and improved the user experience of our website.

We will continue to strive to a motivating, balanced and sustainable working environment.

International and EU cooperation

Much of the Agency's work is done outside Estonia - preparing assessment reports, conducting monitoring, as well as developing regulations and guidelines and providing expert opinions.

We actively participate in the European Council and Commission legislative processes and contribute to work done by the European Medicines Agency (EMA), World Health Organisation (WHO), European Directorate for the Quality of Medicines and Healthcare (EDQM) and other organisations. Our experts contribute by advising legislators in the pharmaceutical field, coordinating the drafting of guidelines, and making sure Estonia is heard at international events, which includes sharing our best practices.

The European Commission has initiated one of the most significant EU pharmaceutical legislation reforms in two decades, which should improve the availability and affordability of medicinal products, including innovative ones. Availability of medicinal products and small countries' interests in EU legislative processes are important subjects for the Agency, which is why our Legal Department director Kaili Semm was sent to represent Estonian expertise at the European Commission Directorate-General for Health and Food Safety in 2022. She has been involved in matters of EU pharmaceutical legislation for over 20 years in Estonia and abroad. Kaili Semm participates in the Commission's work on the pharmaceutical reform, primarily representing small member states' interests in achieving the goals of the reform and contributing the highest level of expertise available at our Agency. Agency experts also help defend Estonian interests in negotiations concerning the reform at the EU Council Working Party on Pharmaceuticals and Medical Devices.

The area of biologicals has seen rapid development over the past decade. They increasingly provide treatment options supplementing conventional chemically synthesized drugs. A small subset of biologicals, cell and gene therapies are further classified as advanced therapy medicinal products. In addition to their role as Agency biologicals experts, Helerin Eiche and Pille Säälik also participate in working parties of the European Medicines Agency (EMA). Helerin Eiche is a member of the Biologics Working Party, and Pille Säälik works in the Advanced Therapies Committee. Helerin has stepped up as leader of the EMA phage therapy work group. The goal is to develop new quality guidelines for phage therapies. This involved a meeting with pharmaceutical manufacturers, where Helerin led the discussion on environmentally friendly and sustainable pharmaceutical development. Helerin spoke on the same subject at two panel discussions at the DIA Europe conference in Brussels in March 2024.

Pille Säälik was invited to represent the EMA Committee for Advanced Therapies at the International Society of Gene and Cell Therapy (ISCT) conference in Vancouver. The major conference had several parallel sessions and was attended by researchers, regulators and pharmaceutical companies. In addition to the presentations, there were more than 50 panel discussions. Our colleague Pille took part in three of them.

In addition to biologicals, discussions at the European level increasingly focus on clinical drug trials. On April 15th-16th, our Bureau of Clinical Assessment director Keiu Heinla attended a conference organised by the Cancer Drug Development forum titled “Clinical Research in Central and Eastern Europe: New Approaches for the Next Level of Development”. Held in Kraków, the conference was attended by international experts from various national research institutions and regulators, pharmaceutical industry, academical institutions and patient advocacy organisations. The two days were filled with discussions and dialogues on how to promote clinical trials and expand treatment options for patients in Eastern and Central Europe, outlining potential challenges and issues as well as opportunities for increased international cooperation.

Agency Director General Katrin Kiisk attended a panel discussion at the Health Care Summit 2024 held by the POLITICO news outlet in Brussels. Focusing on hot topics in healthcare, the two-day summit was attended by European healthcare experts, policymakers and pharmaceutical industry representatives. Main talking points included improving availability of medical services and medicinal products, competitiveness in the area, preparation and forecast strategies, and innovative digital solutions. Katrin Kiisk attended a panel discussion on medicinal product availability, preventing shortages, resolving supply chain disruptions, and critical future pharmaceutical regulations.

Since Estonia's accession into the European Union, the Agency's medical counsellor Alar Irs has been a member of the European Medicines Agency's Committee on Human Medicinal Products and Cardiovascular Working Party, latter of which he has chaired since 2022. Last year he participated in the Cardiovascular Round-table held by the European Cardiology Association, bringing together researchers, patient advocates and healthcare technology industry representatives to discuss current topics. Focused on the subject of implementation of clinical guidelines, the event took place in Frankfurt in July and he spoke of the role of pharmacovigilance in ensuring quality of clinical research data. Later last year he helped prepare for the next event in the series, to be held this year and titled CRT meeting with EMA on Unmet Medical Needs Focusing on Patient-Benefit Risk and Patient-Reported Outcomes.

Alar was also invited to the High Level Ministerial Conference on Cardiovascular Health organised in July as part of the Hungarian EU Presidency. A direct result of the conference was the December 3rd Conclusion by the Council of the European Union in which the Council invites the Commission to take extensive measures to help reduce the prevalence of cardiovascular disease in EU, emphasising the importance of promoting healthy lifestyles, prevention, screening, early detection, treatment, rehabilitation, and research and innovation. The document was also referred to by sitting Commissioner for Health Olivér Várhelyi in his proposals to develop a European cardiovascular health plan.

Last year we got to cheer on the director of our Bureau of Quality Assessment Laivi Saaremäel, who became the first Estonian to be invited to represent the European Commission at the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) working group updating the guidelines for investigating stability of medicinal products. This important milestone strengthens Estonia's role in international cooperation and improves our international communication in the pharmacological field. Laivi is tasked with protecting the interests of European Union medicines agencies in the global working group.

The World Health Organisation (WHO) supports developing countries' efforts to build and improve their pharmacovigilance systems. In 2024, Maia Uusküla, director of our Department of Post-authorisation Safety, attended two such missions as an expert: in Uzbekistan and in Turkmenistan.

Marje Zernat also lends her expertise to the WHO by evaluating the quality of active ingredients at the Geneva head office. WHO prequalification of medicinal products was first established in 2001 in response to the HIV/AIDS pandemic, and was later expanded to other medicinal products. The goal is to expedite availability of critical medicines to those who need them in cooperation with national regulators. This is achieved by evaluating medicinal products and their active ingredients and by conducting inspections (of manufacturing and clinical trials).

While there is no common European pharmacy regulation, there is cooperation in this area. In early December last year, a meeting of Nordic medicines agencies' pharmacy inspectors

was organised by Estonia in Tallinn. The meeting was attended by representatives from Finland, Sweden, Norway, Denmark, Iceland and Estonia. The annual meeting is held to help industry specialists share expertise and experiences. National representatives give an overview of salient issues during the past calendar year (e.g. changes in pharmacy regulation, challenges and focus areas in pharmacy inspections, common non-compliances and violations) and discuss on previously agreed-upon topics. In 2024, the focus areas included personalized packaging of medicinal products, personalized manufacturing, sale to minors, substitution, etc.

Such meetings and exchanges should provide a better overview of developments in a field where, unlike in other pharmaceutical areas, there is no EU mandated network.

A year of improving legislation

Andrus Varki

We are primarily engaged in three kinds of legal activities:

- advising our colleagues and conducting internal legal trainings to ensure that all our actions and decisions are legally correct;
- helping with legislative processes and implementation of legislation concerning medicinal products, as well as representing the Agency in legal issues and cases;
- expert opinions regarding EU medicinal products regulations and participation in the EU legislative process in the area of medicinal products.

One of the key focus areas of our activities last year was working on legal framework to ensure the availability of medicinal products in various crisis situatsions – for example during supply shortages, through regulatory changes concerning the exceptional preparation and use of medicines in hospitals (hospital exemption), and by enabling hospitals to procure medicinal products from wholesalers in other EU member states.

Another important activity in 2024 was preparing draft amendments to legislation to transfer the field of medical devices to the Agency starting January 1st 2025.

We were involved in 17 court proceedings. Five cases were concluded with final decisions, four of which in our favour. 12 cases are ongoing.

To a large extent, our international activities were associated with developing the new European Union medicinal products regulation. We also contributed to shape Estonia's positions on the application of pharmaceutical law in preliminary ruling procedures before the Court of Justice. In 2024 we were involved in formulating Estonia's positions in two cases referred to the Court of Justice. One of them concerned the justification for the simplified marketing authorisation procedures in decentralised procedures, and the other involved preparing medicinal products in pharmacies.

We also share our knowledge and experience in the European Medicines Agencies' Co-operation on Legal and Legislative Issues (EMACOLEX) working group.

Hybrid work can be engaging, too

Mari Kompus

As of the end of last year, we have 114 people working with us. We have pharmacists, doctors, chemists, veterinarians, cellular biologists, gene technologists, nurses, lawyers, and other professionals.

It is becoming increasingly important for people to know who to turn to for reliable information on medicinal products, and the Agency has a crucial role in this area. Last year, we introduced the Agency and its activities in social media. We posted clear and simple explanations of the duties of unauthorised medicinal products specialists, shortage specialists, inspectors, etc. People were also able to visit us and see what we do. Last year we were visited by more than 400 schoolchildren. We also visit schools to talk about our organisation and work.

There›s a good balance of seniority - both experienced people and new recruits. In 2024 we were joined by 10 new people. That meant the year involved a lot of learning, instruction, and adjusting.

We held several group trainings: scheduling, values, workplace stress. We also try to teach and learn from each other. For example, we held internal trainings on the subjects of administrative proceedings, activity licenses, restrictions in public service, conflicts of interest, external activities, and lobby.

Nearly half of our people work from home. Hybrid work is also popular, but we all consider it important to touch base at office. We also value time spent together outside of work. For example, we have gone orienteering and hiking, taken part in marathons, and had biscuit tastings.

Every spring we give out awards for those who best exemplify our values. This year, too, all Agency employees are able to vote for our Competence guide, Reliability ward, Cooperation master and Efficient worker. These titles are highly valued in our institution.

We are not just colleagues. We are a group of friends!

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