BULGARIAN DRUG AGENCY'S

ANNUAL REPORT

2019

CONTENT

1. INTRODUCTION

The Bulgarian Drug Agency (BDA) is the successor of the National Institute for Medicinal Products and was established by Council of Ministers Decree № 218 of 1999 as Administration at the Minister of Health. BDA's competences and powers are described in three acts - the Medicinal Products for Human Use Act (MPHUA), the Medical Devices Act (MDA) and the Blood, Blood Donation and Blood Transfusion Act (BBDBTA).

For achieving the goals set in these Acts, The Agency's activities include implementing the goals stated in the National Health Strategy of the Ministry of Health (MoH) and participation in the activities of the European Medicines Agency (EMA), the European Directorate for the Quality of Medicines and Health (EDQM), international bodies and organizations, as well as the implementation of international treaties.

The Agency's functions include:

• Expert evaluation and supervision of quality, safety and efficacy of the medicinal products;

• Pharmacovigilance;

• Expert evaluation and monitoring of clinical trials;

• Expert evaluation of medicinal products advertising;

• Control and supervision on the production, import and marketing of medicinal products and active substances;

• Expert evaluation, registration and market supervision of medical devices;

• Blood transfusion system supervision.

The structure of the Agency includes six departments of specialized administration and one department of general administration.

Specialized administration

• *Market Supervision and Inspections* Department;

• *Marketing Authorisations of Medicinal Products* Department;

• *Medicinal Products Analyses* Department;

• *Pharmacovigilance and Clinical Trials* Department;

• *Control of Blood Transfusion System* Department;

• *Medicinal Products Information and Noninterventional Researches* Department;

General administration

• *Legal, Administrative, Financial Services and Quality Management* Department.

2. RESULTS

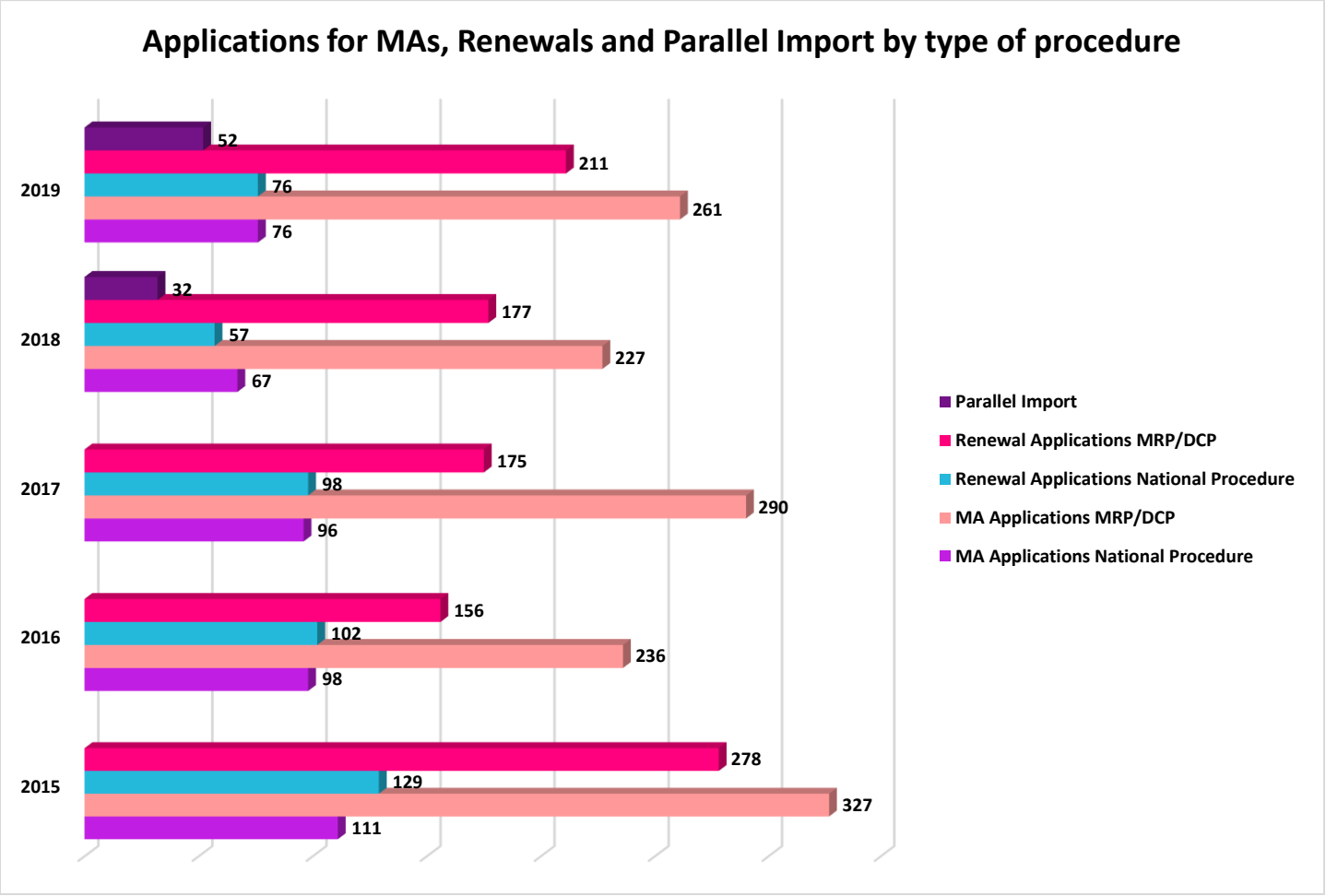
2.1. MARKETING AUTHORISATIONS OF MEDICINAL PRODUCTS

One of the BDA's main activities is the marketing authorisation (MA) of medicinal products in Bulgaria after expert assessment of their quality, safety and efficacy.

Received applications

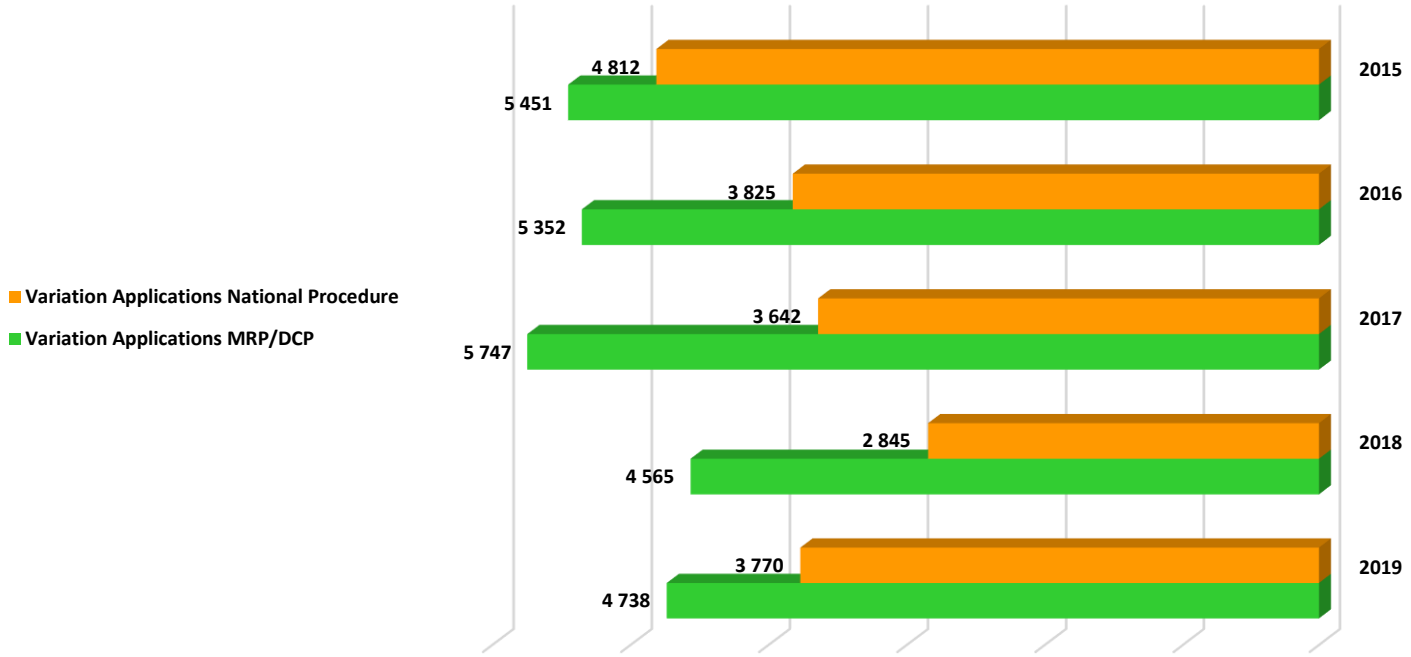
In 2019, there were received 9 184 applications for marketing authorisations, renewals, and variations under decentralized, mutual recognition and national procedures concerning 10 531 medicinal products (MPs).

The total number of applications consisted of 337 Marketing Authorisation Applications; 52 Applications for Parallel Import; 287 Renewals; and 8 508 Variations for 9 866 medicinal products. They are distributed as follows:

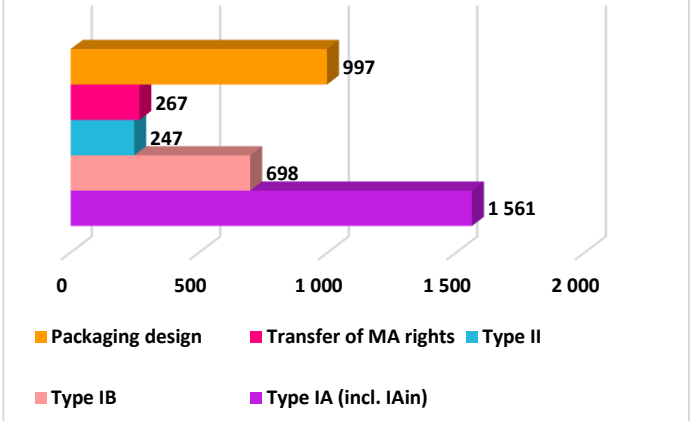


A significant part of the regulatory activity covers the assessment of variations in the marketing authorisations for medicinal products.

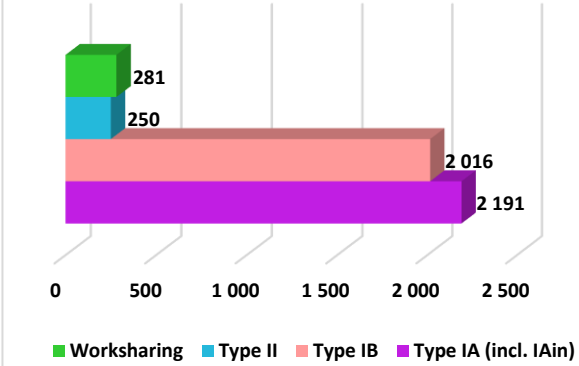
Applications for Variation by type of procedure



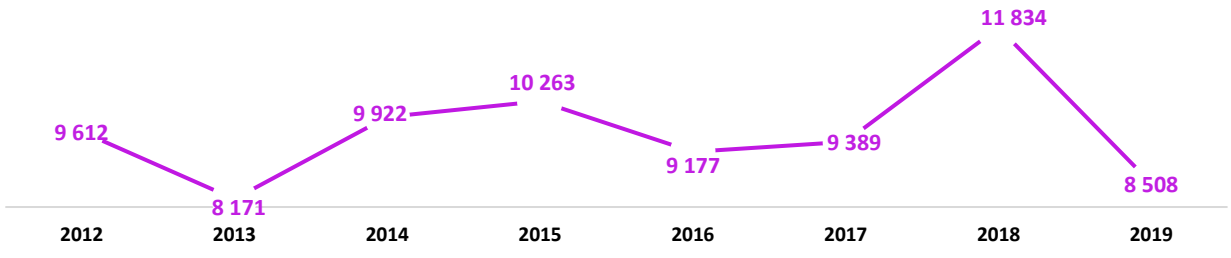
Variation Applications National Procedure by type for 2019



Variation Applications MRP/DCP Procedure by type for 2019



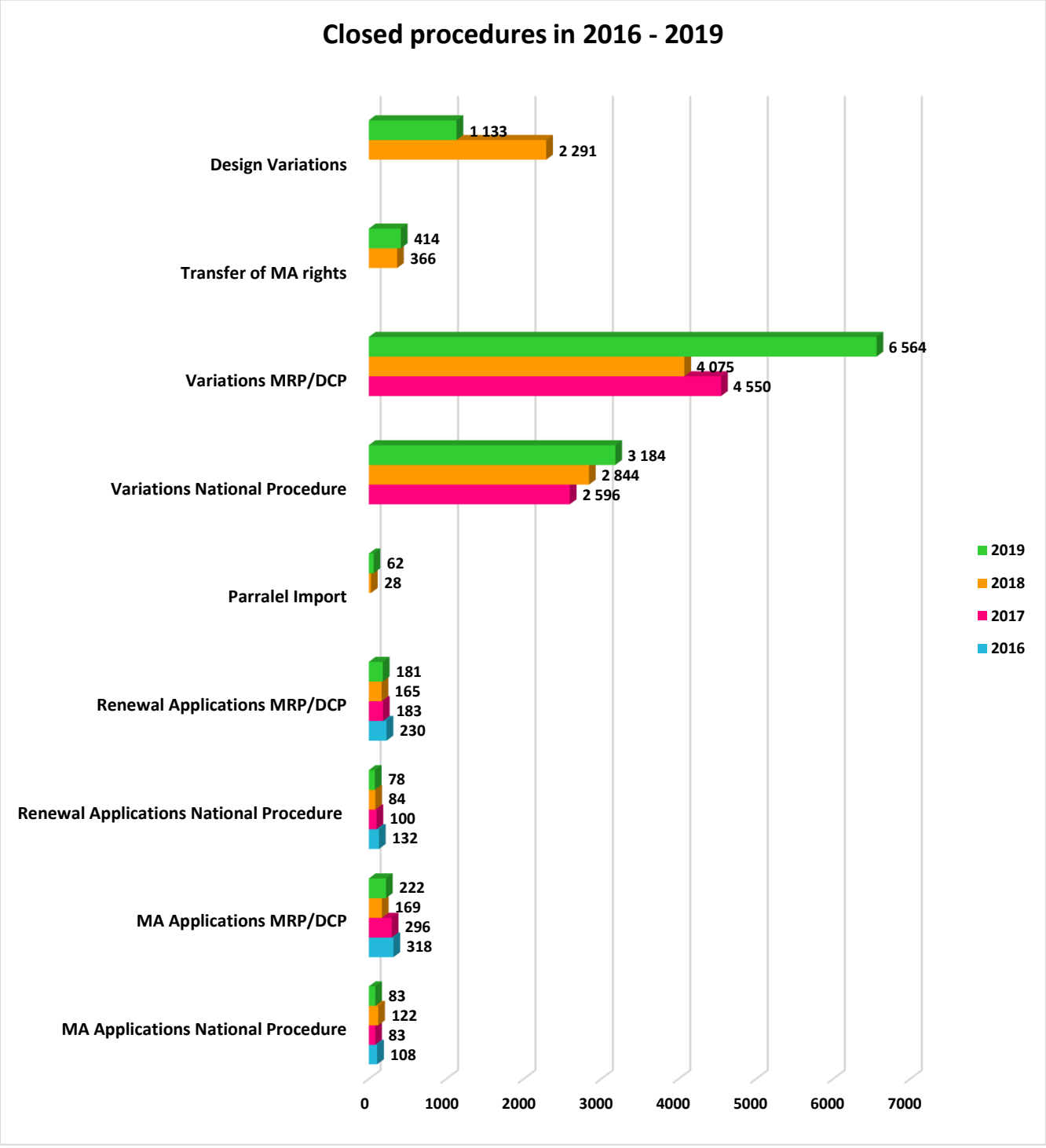
Variations Applications



In 2019, there is a decrease in the number of the applications for transfer of marketing authorisations rights, compared to the previous year. The peak in 2018 was largely due to the high number of applications for transfer of marketing authorisations rights and variants in packing design as a result from the preparatory steps for BREXIT and the legal requirement the MAHs to be located within the EU.

Closed procedures

The total number of the completed procedures in 2019 is 11 921.

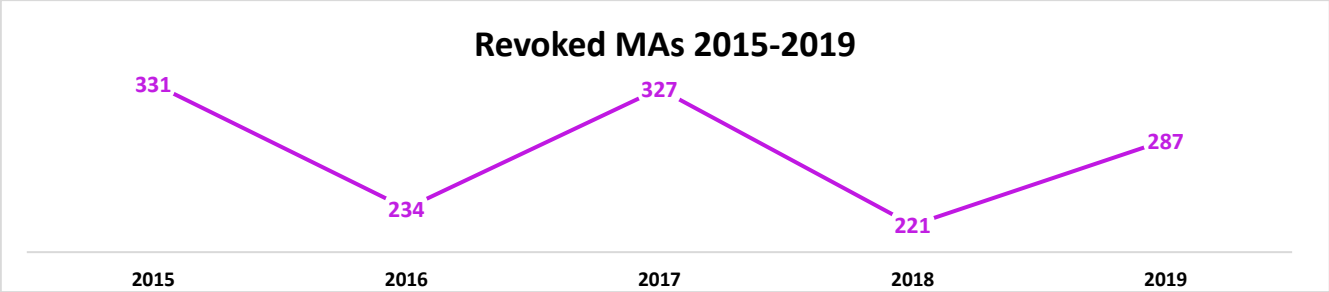


A total number of 11 295 Variations were completed for the year concerning 9 866 medicinal products, including 414 procedures for MA transfer as well as 1 133 variations to the package design and/or package leaflet; 4 678 variations Type IA, 4 015 variations Type IB and 1 054 variations Type II.

In August 2019 was announced a pilot phase for the introduction of CESP - a platform for EU Member States to submit electronic applications and marketing authorization documents. They accepted only the applications and the accompanying documentation for new MRP/DCP procedures. In the first half of 2020, it is planned inclusion of Renewal applications. From the start of the project until the end of 2019, have been submitted 89 MRP/DCP procedures through the CESP portal, which consist of 120 Applications for Marketing Authorisations.

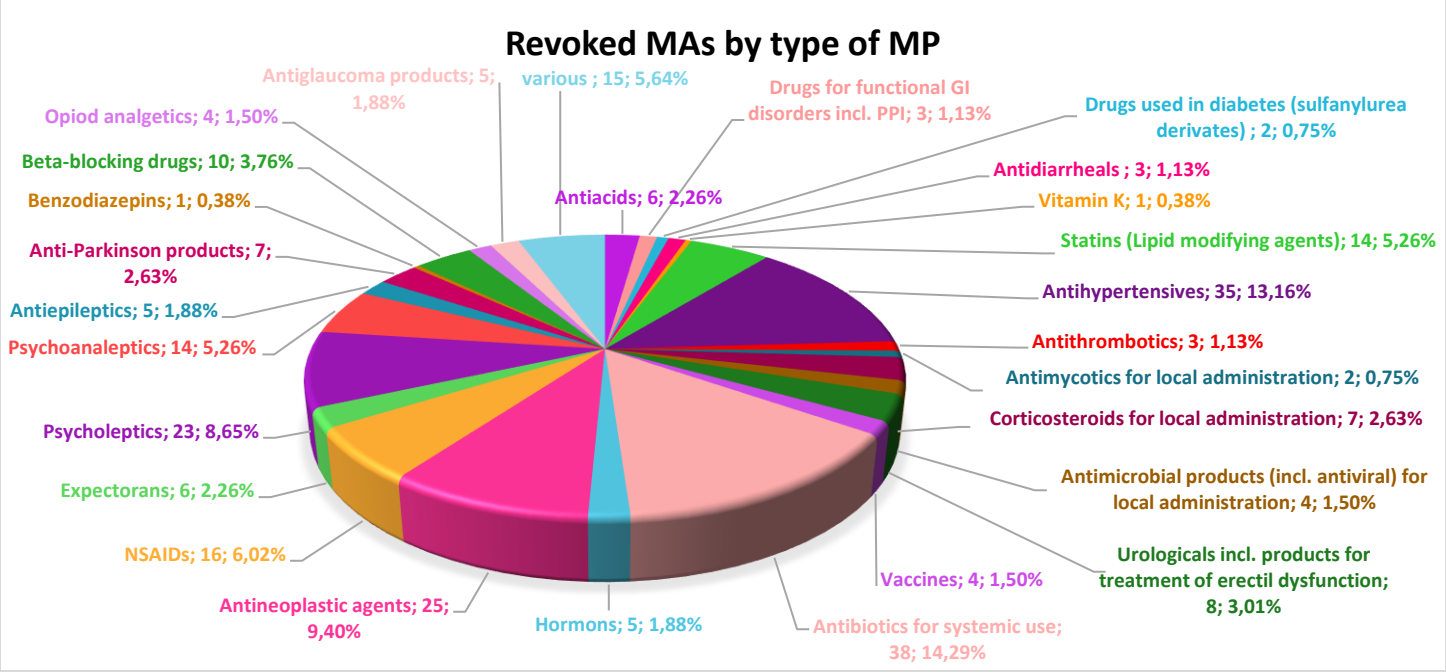
Revoked Marketing Authorisations

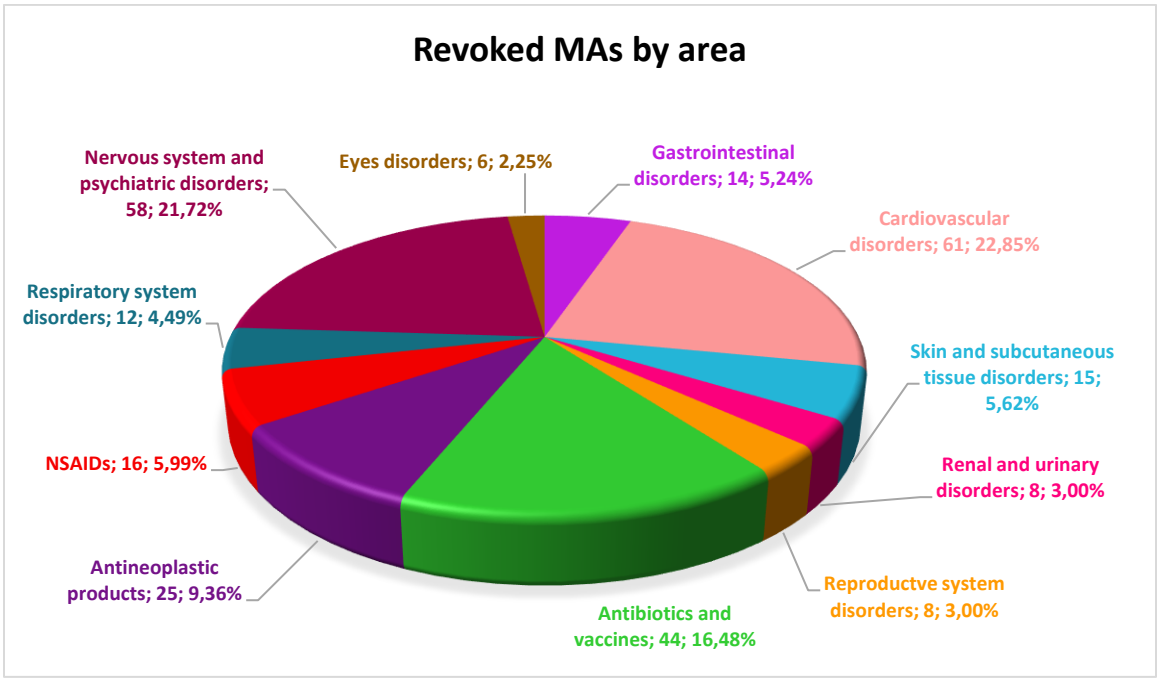
In 2019, 287 marketing authorizations of medicinal products were revoked as a result of the explicit request by the MAHs. On the CMDh recommendation, based on a recommendation by PRAC, authorizations for three medicinal products containing the active substance fenspiride were suspended in 2019 because of possible heart rate problems.



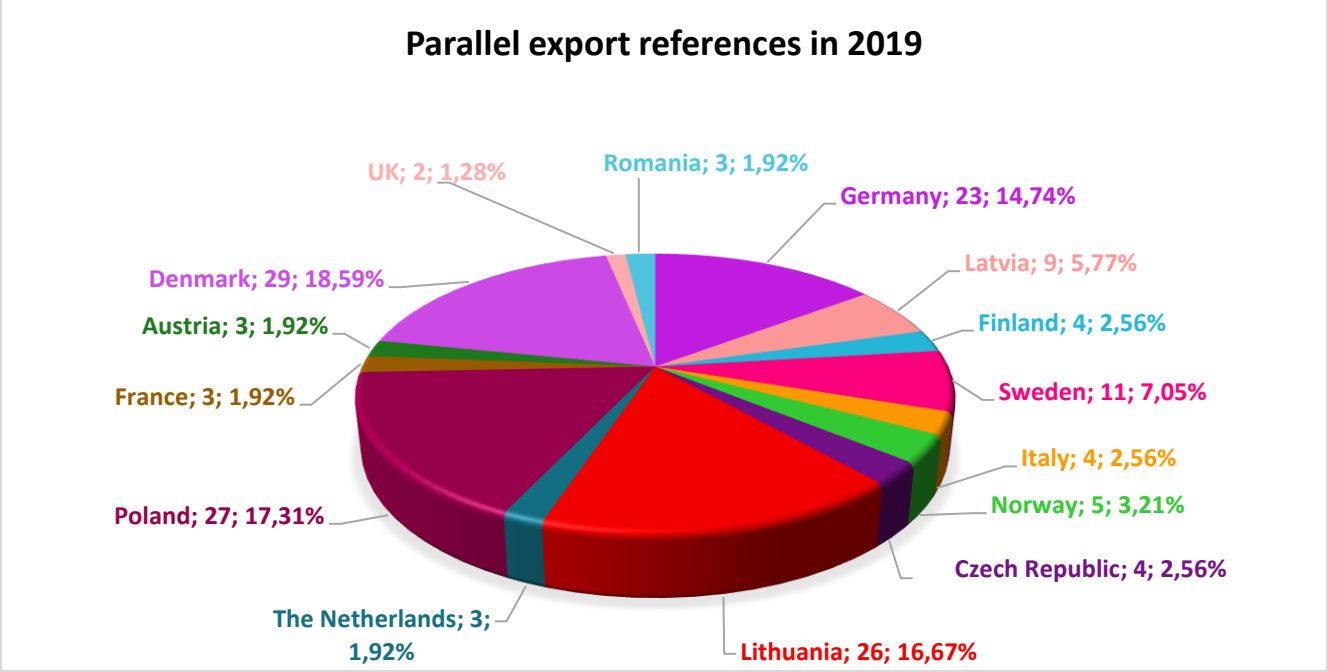
3.

The graphs below show the revoked Marketing Authorisations by type of medicinal product and by area.





In connection with the requests received by BDA from the regulatory agencies of other EU Member States in 2019, 156 references for parallel exports were issued.



As part of the European Regulatory Network, the BDA continued to fill in the EUDRA TRACK/CTS database and to exchange information on Mutual Recognition and Decentralized Procedures. EUDRA TRACK/CTS is a database for medicinal products during and after authorisation, renewal or variation of the Marketing Authorisation (MRP or DCP) procedures.

During the year, scientific consultations were held on the planned DCPs, of which Bulgaria will be the RMS.

In 2019, Bulgaria was appointed to prepare Peer Reviews for medicinal products for scientific advice before launching the relevant marketing authorisation centralized procedures. BDA’s representatives in the various Scientific Committees and Working Groups of the European Medicines Agency have been actively involved in the preparation of guidelines and scientific opinions on applications for marketing authorization, orphan designation and various case studies on the quality of documentation of biological medicinal products.

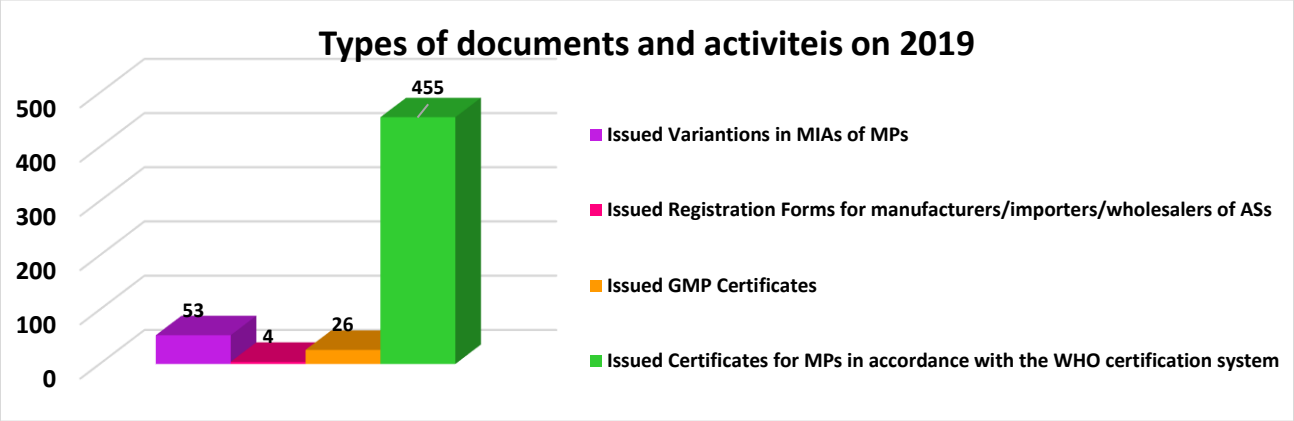
2.2. MARKET SUPERVISION

Another field of the BDA's activity is the issuing of Manufacturing and Importation Authorizations (MIAs) of medicinal products (MP); registration of manufacturers, importers and wholesalers of active substances (AS); authorization of retail trade of medicinal products in pharmacies; registration of medical devices (MD); wholesale authorization of medical devices; medicinal products advertising, as well as carrying out inspections of the entire distribution chain of medicinal products and medical devices.

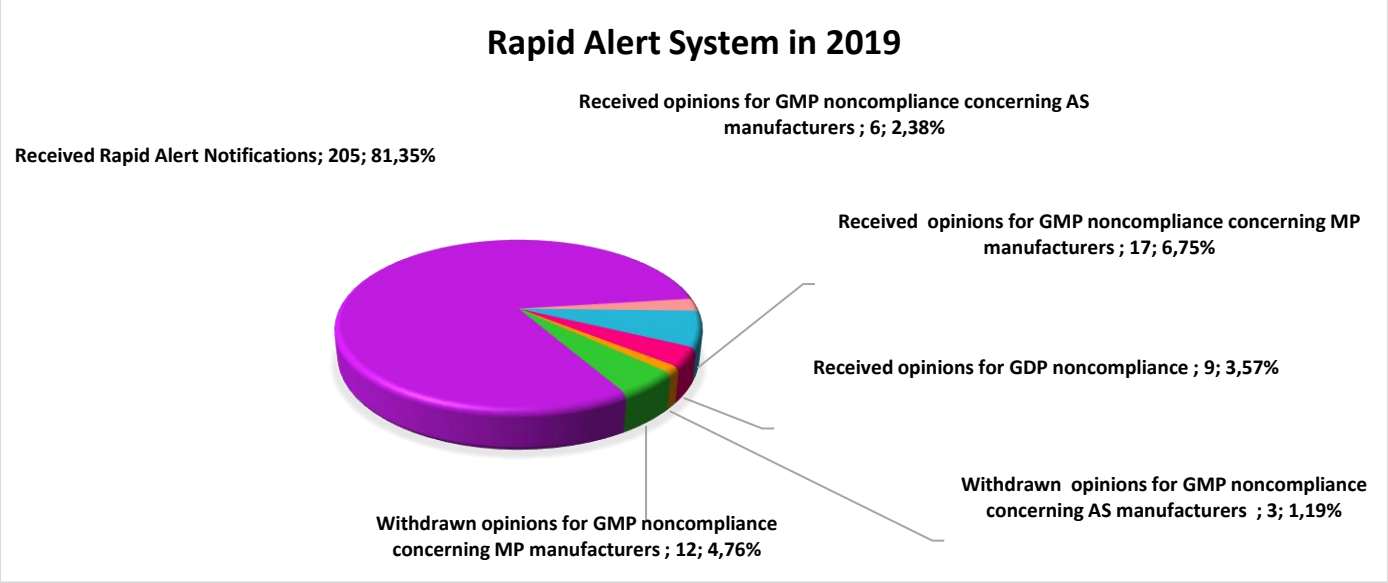
Manufacturing authorization and control

The Agency keeps an up-to-date electronic Register of Manufacturing/Importation Authorizations (MIAs) and Variations. The Eudra GMDP database is regularly updated regarding the issued MIAs and Wholesale Authorizations as well as the Good Manufacturing Practice (GMP) Certificates for medicinal products and active substances.

The BDA also keeps an up-to-date electronic Register of manufacturers/importers/wholesalers of active substances as well as of Brokers of medicinal products in Bulgaria. The Eudra GMDP is regularly updated regarding the registered manufacturers/importers/wholesalers of active substances.



Rapid Alert System Activities



Regarding the received notifications received, depending on the availability on the Bulgarian market, were issued orders for appropriate measures.

Inspections of manufacturers

In 2019, the BDA's inspectors carried out **34 inspections** of manufacturers/importers of medicinal products, active substances and investigational medicinal products (IMP) for compliance of the manufacturing, import, control and storage with the MPHUA, secondary legislation and acts and guidelines adopted by the European Commission. The inspections were carried out pursuant to the approved Annual Inspections Plan for 2019 in connection with applications for MIAs and Variations, applications for GMP Certification and applications for Registration of manufacturers, importers and wholesalers of active substances under Art. 167d of MPHUA.

During the reporting period, 8 inspections of manufacturers of medicinal products established in the territory of a third country (Turkey, Bosnia and Herzegovina, the Russian Federation, and Vietnam) were carried out to determine the compliance of the conditions for production, control and storage of medicinal products with the requirements of the Good manufacturing practice referred to in Directive 2003/94/EU/.

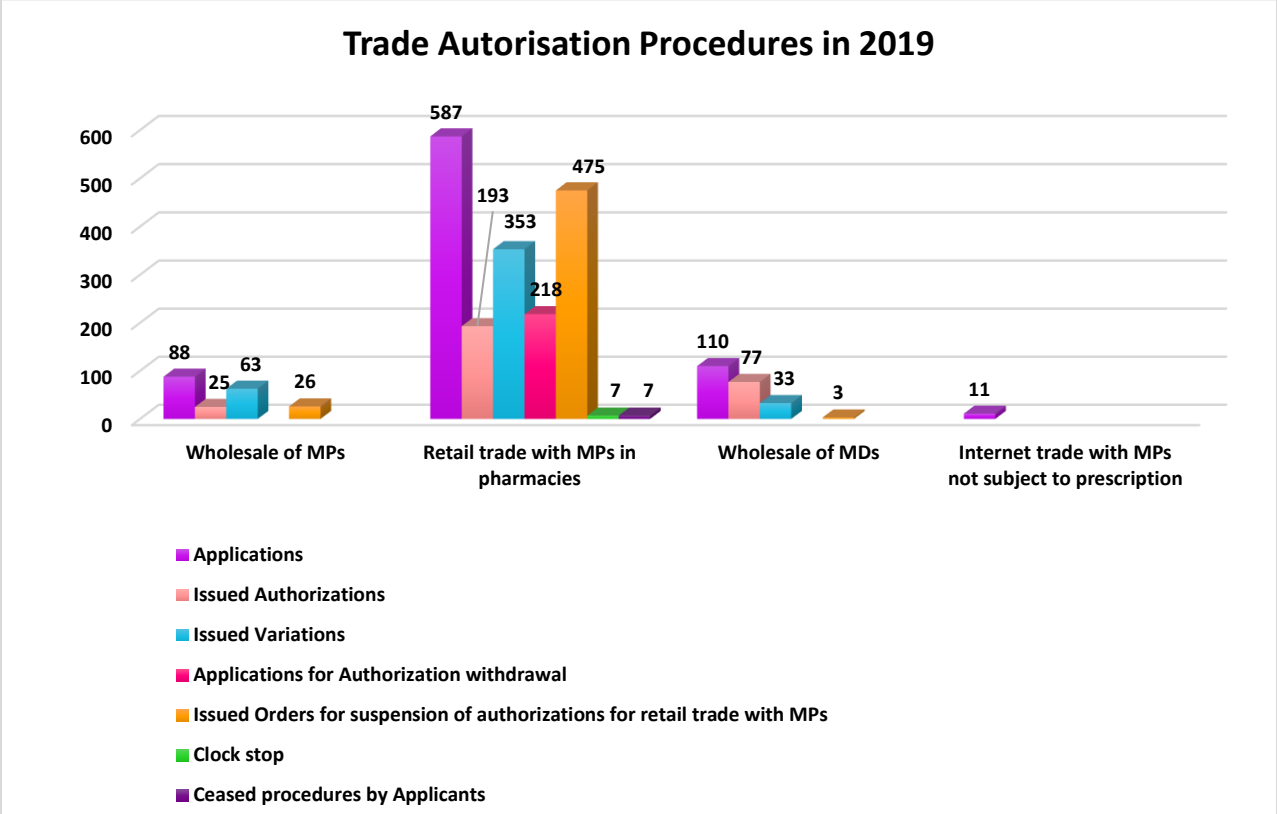
In 2019, an Agency inspector together with a representative of the Denmark's regulatory authority participated in a joint inspection to ascertain the compliance with the principles and requirements of the Good Manufacturing Practice of a manufacturer established in the territory of a third country.

On April 29, 2019, the US Food and Drug Agency (FDA) confirmed that the BDA has the capacity to carry out Good Manufacturing Practice (GMP) inspections. The FDA has confirmed the BDA's capability, capacity and procedures to be equivalent to the requirements of good manufacturing practice inspections, based on the performed audit assessment, which also included conflict of interest rules.

This conclusion is the result of the successful completion of the BDA's audit of the EU-FDA Regulatory Mutual Audit Program in connection with the concluded sectoral agreement between the European Commission and the US on the mutual recognition of the results of good manufacturing practice inspections in the pharmaceutical sector. According to the Sectoral Agreement, the results of inspections of manufacturing sites for medicinal products for human use in different territories will be mutually recognized. The Sectoral Agreement currently covers human medicinal products, with the exception of vaccines, blood plasma products and medicinal products for clinical trials.

An important objective for the Agency is the successful completion of the joint audit, scheduled for 2020, to be carried out by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and by the Canadian regulatory authority following the filed in 2018 application for PIC/S membership, as well as regarding the inclusion of the BDA in the scope of EU-Canada MRA (CETA) - Agreement between the European Union and Canada on mutual recognition in the field of Good Manufacturing Practice.

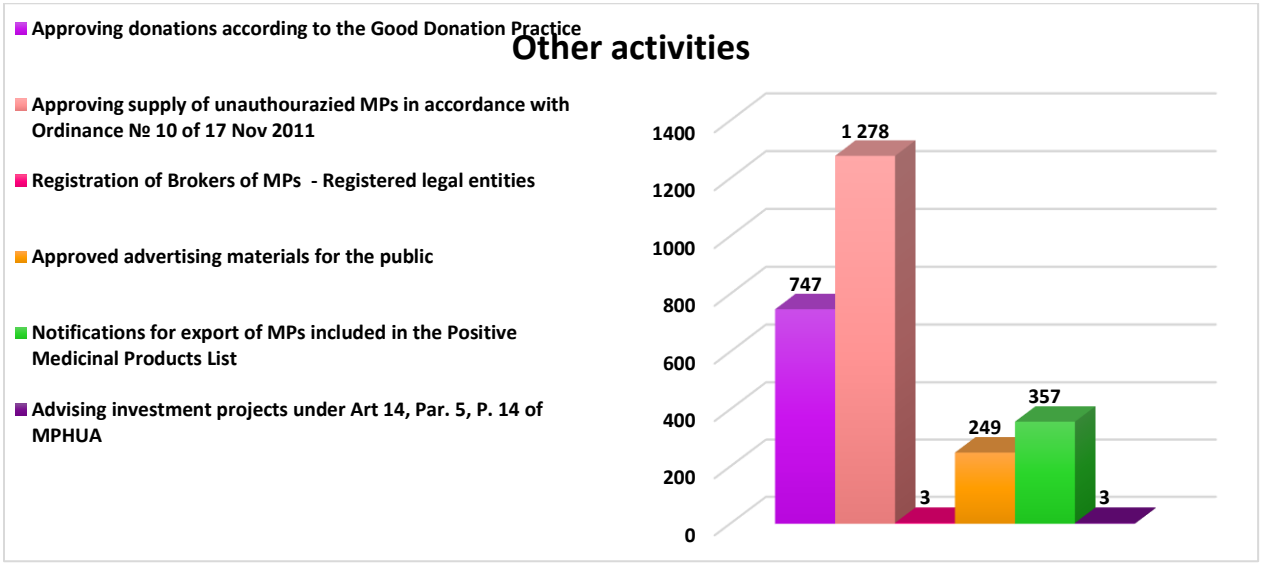
Authorization of wholesale and retail trade with medicinal products and medical devices



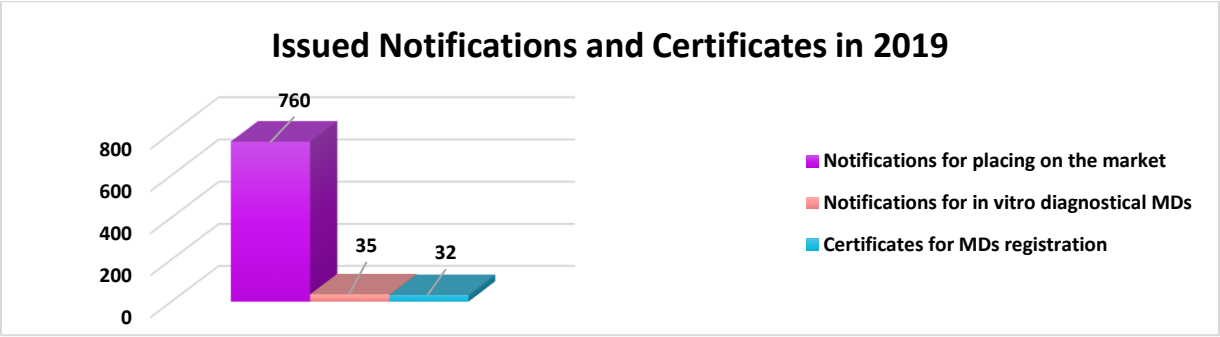
The register of wholesalers in medical devices maintained by the BDA was updated with 60 changes.

The withdrawals of wholesale with medical devices authorisations are due to the request of the authorization holders.

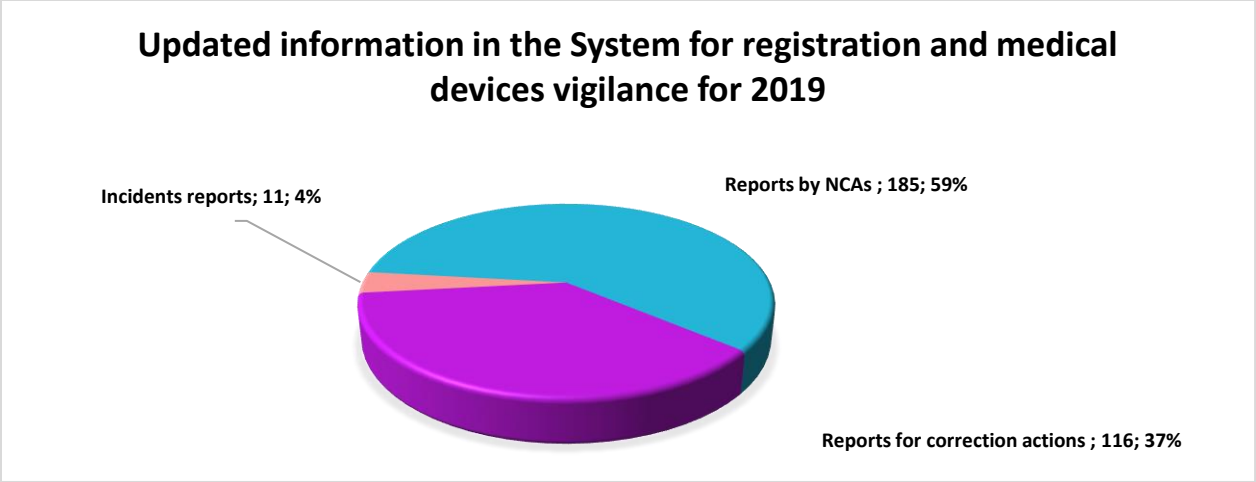
Other activities concerning registrations and approvals



Medical Devices Registration



Medical Devices Vigilance



The BDA maintains an electronic database containing data about medical devices manufacturers, importers and distributors, the competent authorities and institutions that cover completely or partly the cost of medical devices (National Health Insurance Fund, the Agency for Social Assistance, the Ministry of Health, and Health Insurance Funds). In 2019, validated records for **approximately 10 000** medical devices were made.

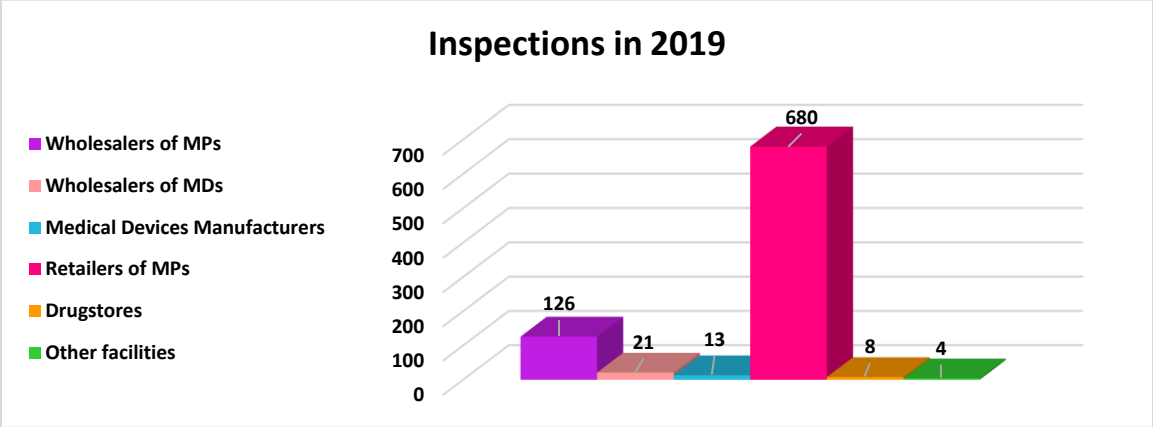
Clinical trials of medical devices

The received documentation was assessed and as a result **4 Clinical Trial Authorizations** and **6 Post Approval Changes of Clinical Trial Authorizations** were issued. In addition, further 5 CTA Applications have been submitted.

2.3. CONTROL AND INSPECTIONS

In 2019, for the purposes of state control and supervision of medicinal products under Art. 267 of MPHUA and the market supervision of medical devices under Art. 86 of MDA, the BDA exercised control on the activities of storage and sale of medicinal products and medical devices carried out by Wholesale and Retail Authorization holders for medicinal products and medical devices, in order to ascertain the compliance with the Good Distribution Practice (GDP) requirements, MPHUA, MDA and the regulations for their implementation.

The total number of inspections carried out on Bulgarian territory is 852.



The most common violations in the retail trade with medicinal products

- The sale (dispensing) of medicinal product subject to medical prescription by pharmacists without being presented a prescription.
- The sale (dispensing) of medicinal product subject to medical prescription by assistant pharmacists.
- The sale (dispensing) of medicinal products by unauthorized personnel (lacking a pharmaceutical degree)
- Improper storage of heat-sensitive medicinal products, as well as the storage of medical products covered by Annex 9 of Ordinance №28 from the 9th December 2008 by the MH.
- Improper storage of flammable medicinal products and medical products with an expired term of use.

Throughout the year, the BDA inspectors conducted joint inspections together with officials from the National Revenue Agency, the *Combating Organized Crime* Specialized Department at the *State Agency for National Security* (SANS) and the *Combating Economic Crime* Sector at Regional Department of the Ministry of Interior in the execution of Prosecutors' decrees following received signals for violations of the MPHUA and its secondary legislation.

During the market supervisory inspections, 743 samples of medicinal products were taken and were delivered for analyses in the BDA's laboratory.

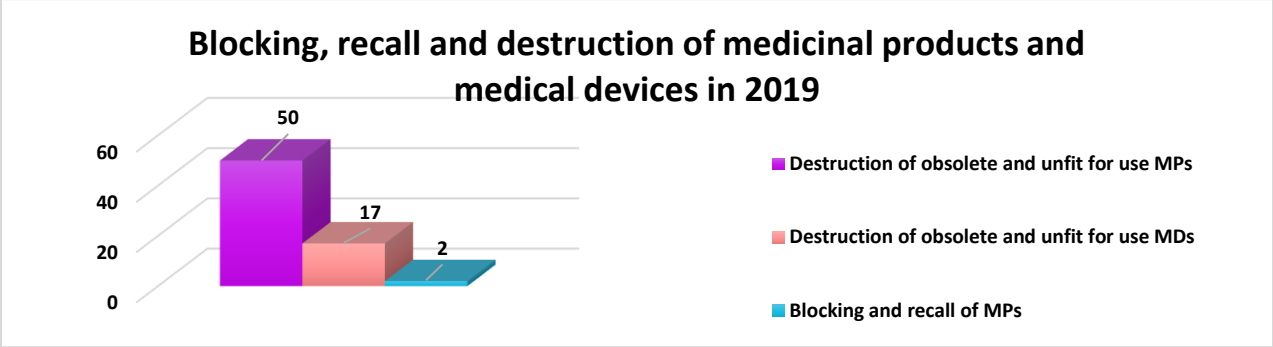
Pharmacovigilance inspections and Control of clinical trials

The BDA's inspectors conducted 9 inspections / re-inspections of marketing authorization holders related to the pharmacovigilance system or to risk minimization activities regarding the use of certain medicinal products and respectively for compliance with the Good Clinical Practice

Administrative-penal procedures

Given the ascertained violations, the adequate lawful measures of a preventive and punitive nature were taken. Penal Ordinances have been issued following the closure of **53** procedures for violations of the MPHUA and the imposed fines and financial sanctions were a total of **142 000 BGN,** with **70 000 BGN being natural person fines and 72 000 BGN being legal person financial sanctions.**

Blocking, recall and destruction of medicinal products and medical devices



The Agency received 32 notifications for disposal of medicinal products outside the country.

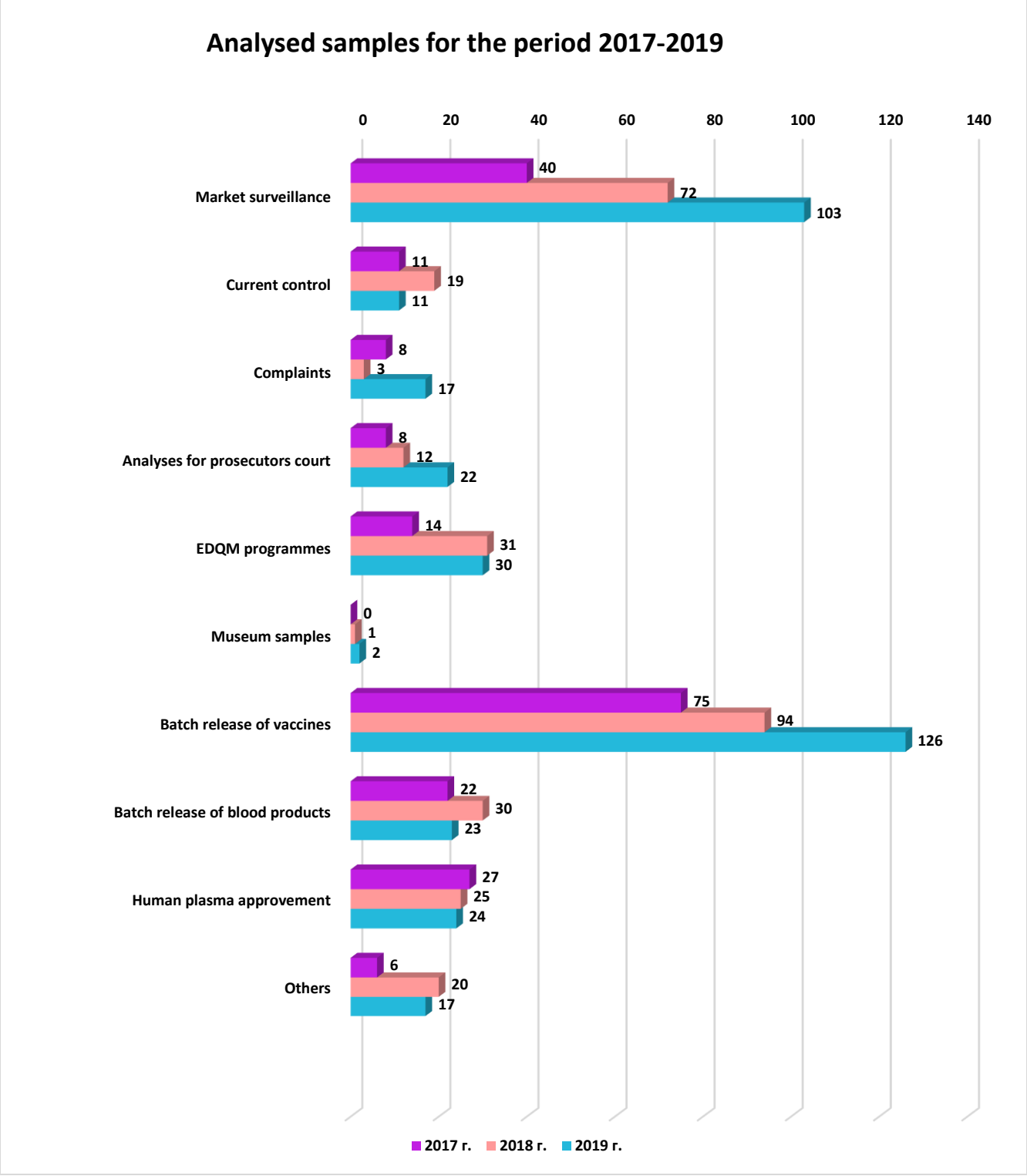
Received and processed complaints and signals from physical and legal entities concerning the trade with medicinal products and medical devices

The BDA took the necessary actions and conducted inspections with regards to **30** complaints and signals regarding violations of the MPHUA and its regulations for its implementation and **12** complaints and signals regarding violations of the MDA sent by citizens and organizations, including those forwarded by the Ministry of Health, the Commission for Consumer Protection (CCP) and the *Medical Supervision* Executive Agency. The complaints and signals contained allegations about the status, procedures and the organization of the work in pharmacies / drugstores, as well as allegations regarding the quality of medicinal products / medical devices or concerning the dispensing of medicinal products by unauthorized persons and the operation of facilities lacking a wholesale and retail trade authorization in accordance with the MPHUA/MDA.

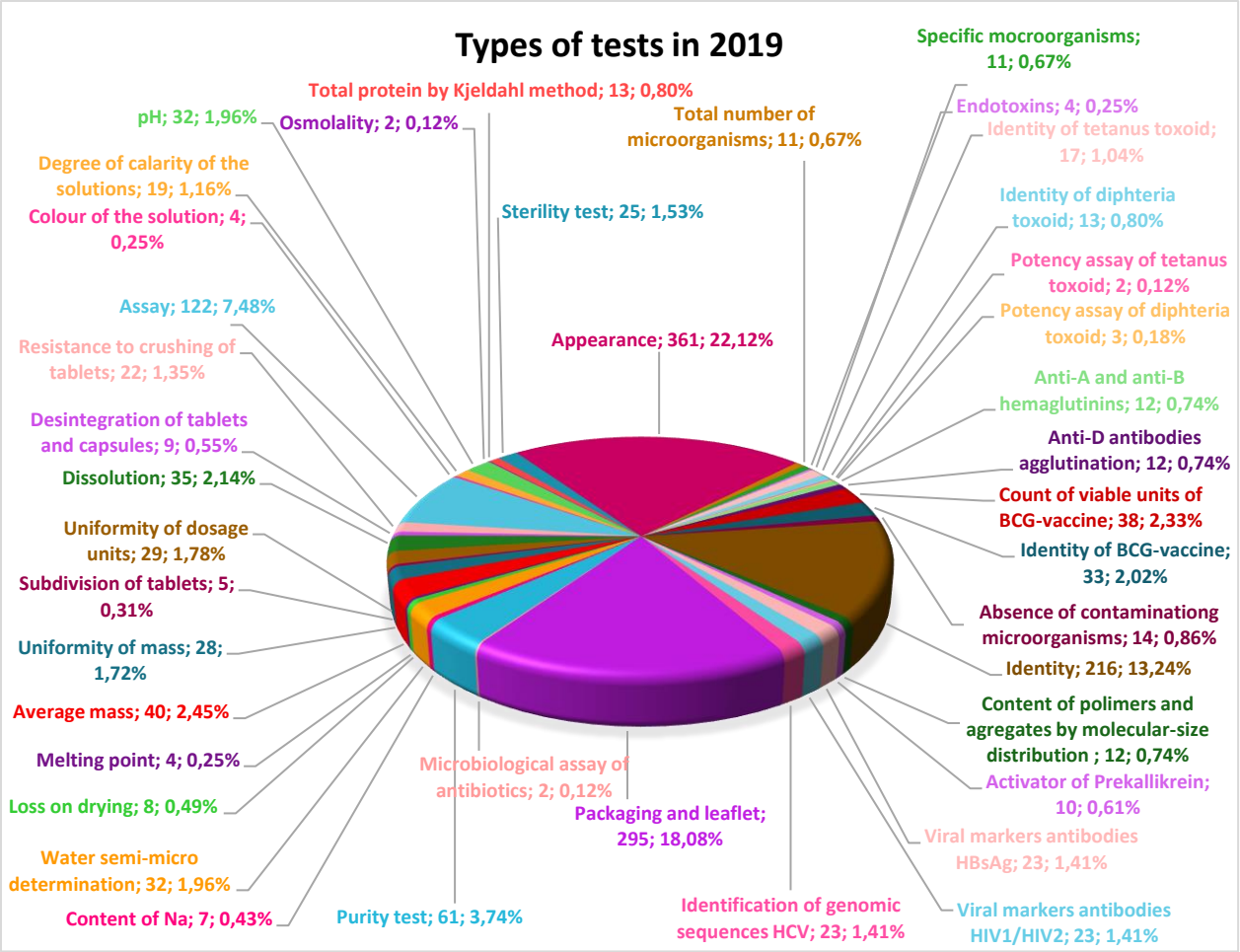
2.4. ANALYSES OF MEDICINAL PRODUCTS

Analytical activity

During 2019 BDA carried out analyses of a total of **375** batches of samples submitted under different procedures. There is an increase in the number of analysed samples by **22%** compared to those in 2018.

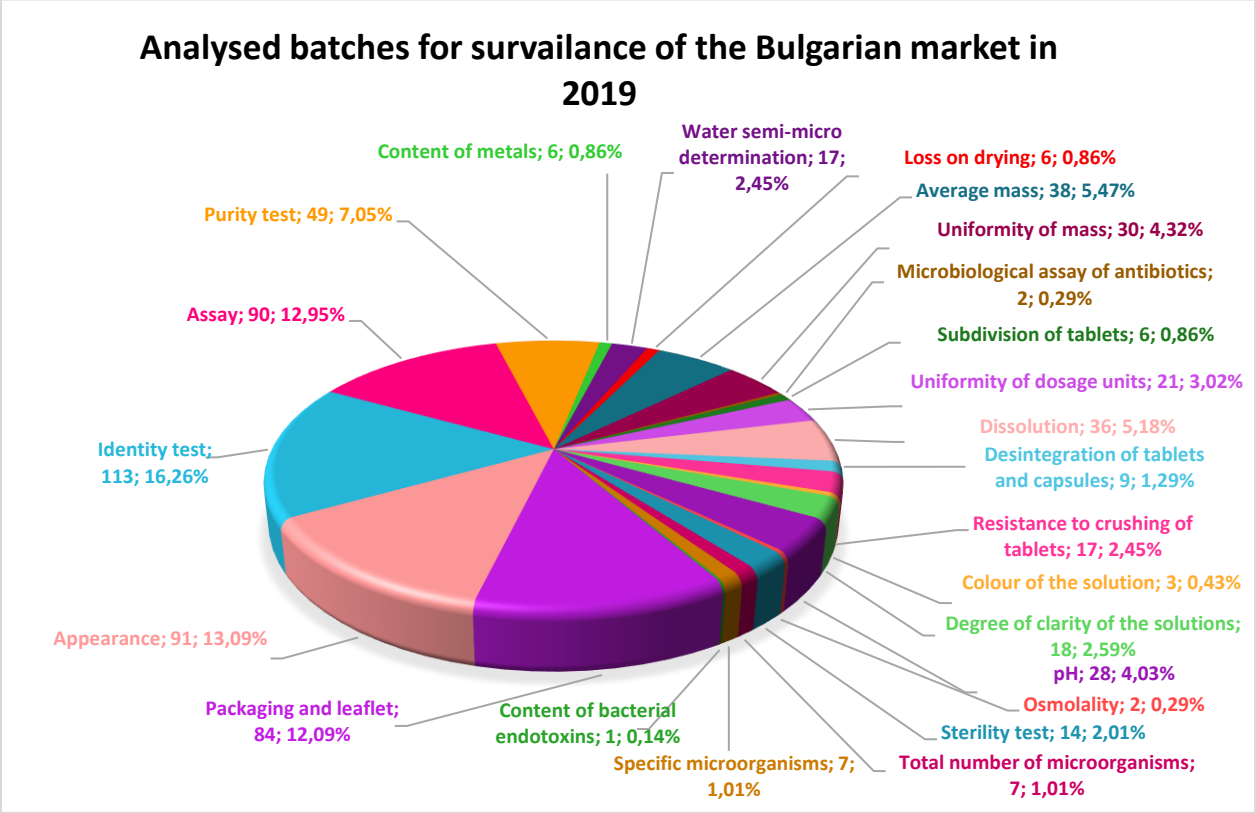


A total of **1 632** tests were performed in 2019, which is **18.2%** more than test performed in 2018. The results of all the tests performed comply with the approved specifications of the medicinal products concerned. Data on the type of tests and their number are presented as follows:



Bulgarian market surveillance

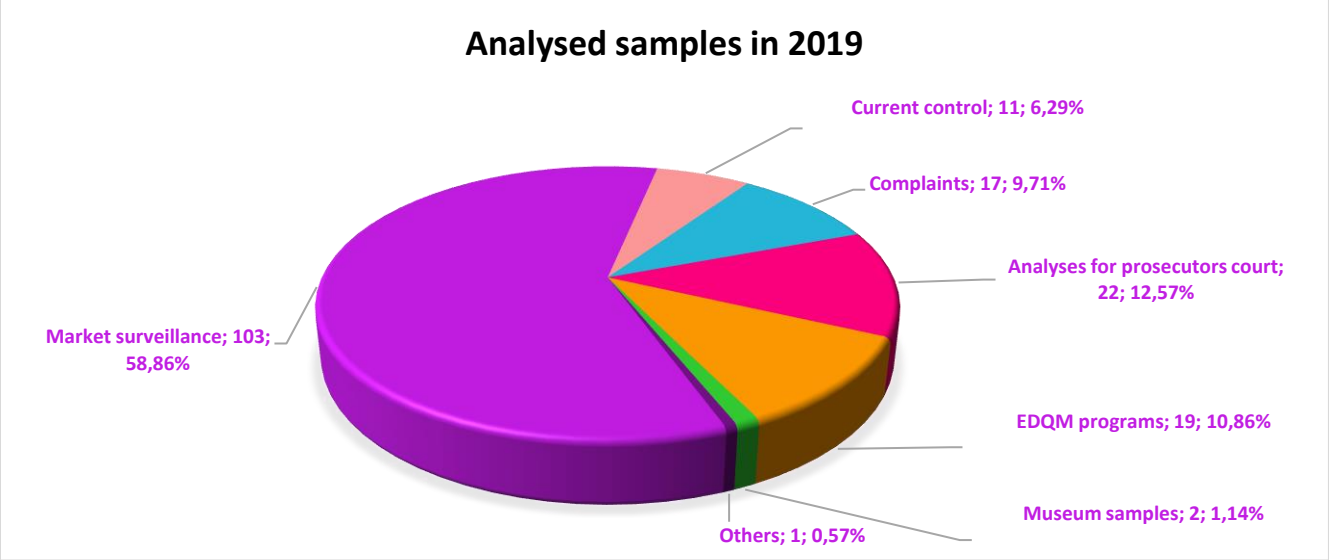
According to the **Bulgarian market surveillance plan in 2019 were analysed 103 batches** of medicinal products with **different active substances**: Gentamycin, Atorvastatine, Piracetam, Duloxetin, Ceftriaxone, Glimepeiride, Atenolol, Azelastine hydrochloride, Bethametasone/Gentamycin, Ivabradine, Pramipexol, Enalapril/Hydrochlorothiazide, Cefotaxime, Dexketoprofen trometamol, Magnesium sulfate, Benzoyl peroxide, Tamsulosin, Metildigoxin, Heparin sodium, Mometasone, Esomeprazole, Aripiprazole, Tadalafil, Sildenafil, solutions for infusion, containing different salts, herbal medicinal products. All analysed batches of medicinal products complied with the requirements for the tests done corresponding to the data below:



In connection with **market surveillance testing on batches** to assess their sterility a total of 25 samples of medicinal products were tested – solutions for infusion and solutions for injection. All complied with the sterility test requirements. For bacterial endotoxin content Ph. Eur. 2.6.14., 4 samples of medicinal products for parenteral administration have been tested and the results are in accordance with the specification. 12 samples were tested for microbiological quality assessment (total microorganisms, Ph. Eur 2.6.12., as well as specific microorganisms, Ph. Eur., 2.6.13., 2.6.31). For three samples of herbal medicinal products, a suitability test has been carried out. All results complied with the approved test specifications.

Physico-chemical and pharmaceutical analyses

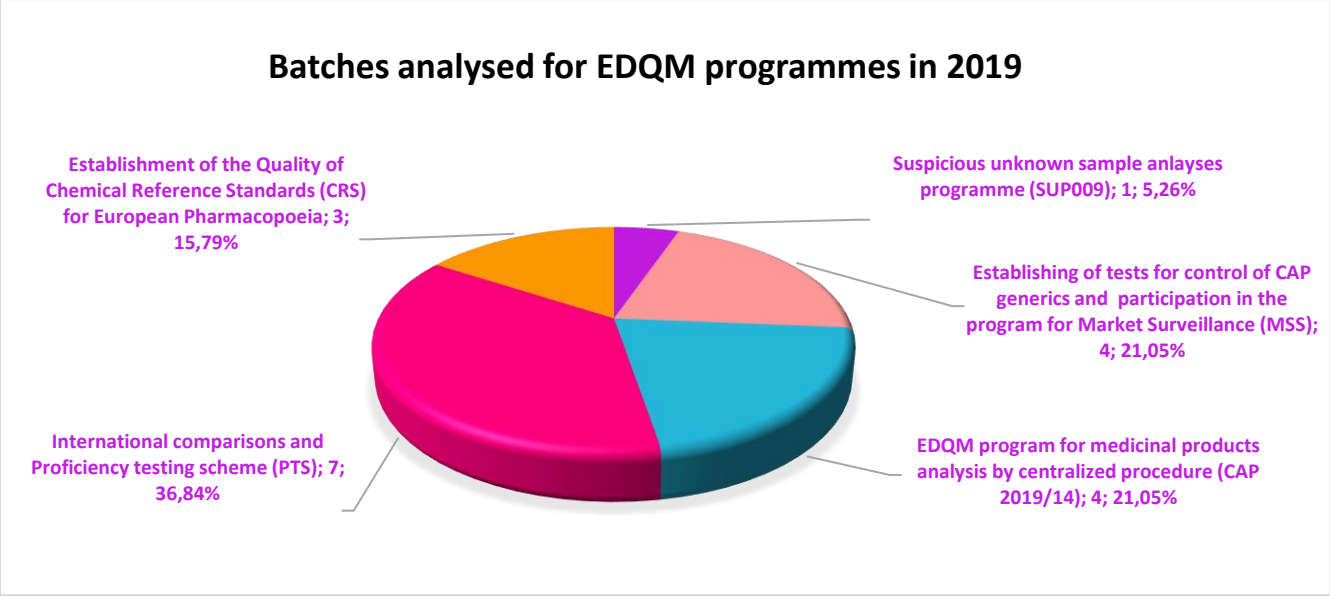
For the year 2019, 175 batches of medicinal products (15% more than 2018) were analysed as follows:



Eight physicochemical and pharmaceutical expert reports were prepared on police/prosecutor's order, on which 22 samples were analyzed.

Joint work with the European Directorate for the Control of Medicinal Products (EDQM)

A total of 19 samples were analysed in joint programs organized by the **European Quality of Medicines and Healthcare Directorate (EDQM & Healthcare).**



The agency participates in Proficiency testing studies (inter-laboratory comparisons and suitability tests). Within the Proficiency Testing Studies BDA participated with 7 batches in 5 PTS programs PTS 190 (Melting point), PTS194 (Optical rotation); PTS 195 (Assessment with infrared spectrometry for identity), PTS 196 (Assessment for Dissolution test). All results are very good and certificates of participation are obtained. The last for 2019, PTS 197 (HPLC test for quantification) will be recorded in 2020.

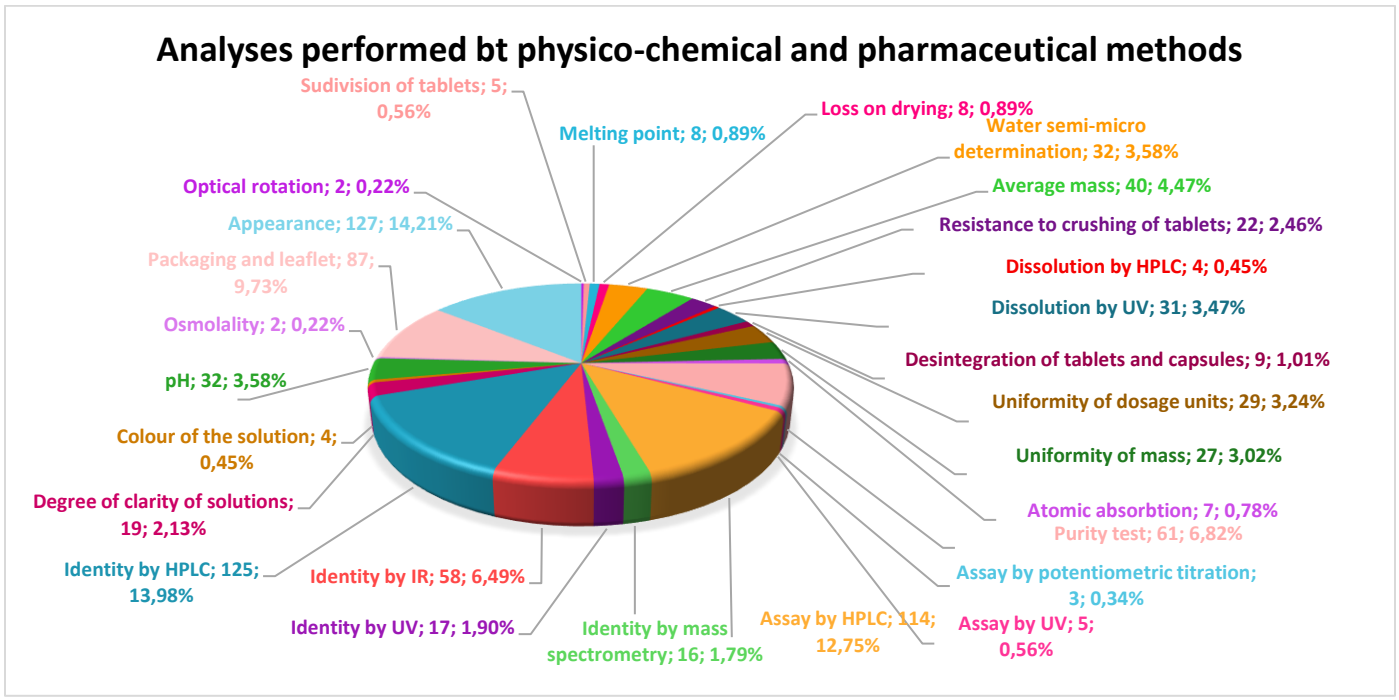
Under the European market surveillance programmes, the BDA took part in CAP 2019/14 (Project quality control of medicinal products approved by centralised procedure), analysing 4 batches, and 4 more batches of medicinal products were analysed in connection with the participation in a project for control of CAP-products in parallel distribution.

To establish the quality of chemical reference substances (CRS) for a European pharmacopoeia 3 batches of medicinal substances were analysed.

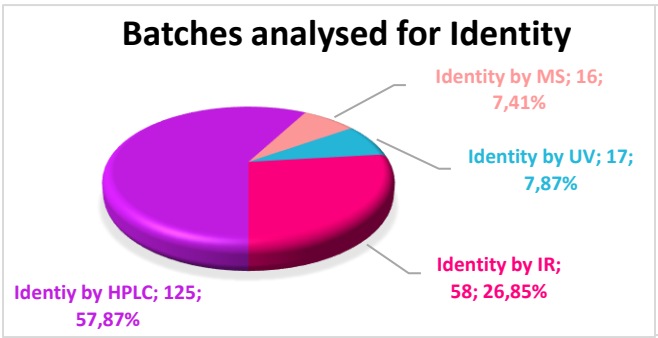
Within the Suspicious Unknown Sample Analysis Programme (SUP009) 1 sample was analysed

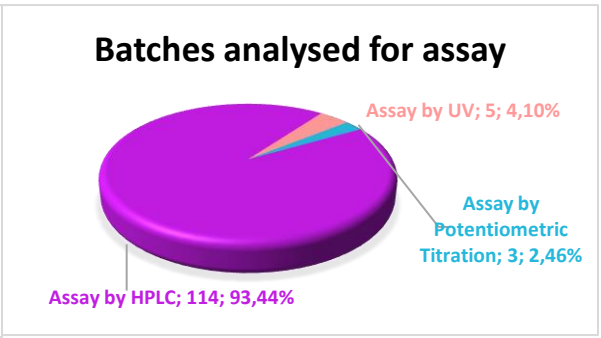
At the end of 2019 the project for analytical control of medicinal products on the European market with active substance Sildenafil (MSS058) was launched, and it will be completed in March 2020.

A total of 890 analyses of medicinal products were performed by physico-chemical and pharmaceutical methods with 18% more than 2018 (752 analyses for 2018), as follows:



The following graphs show the distribution of methods of analysis of tested indicators:





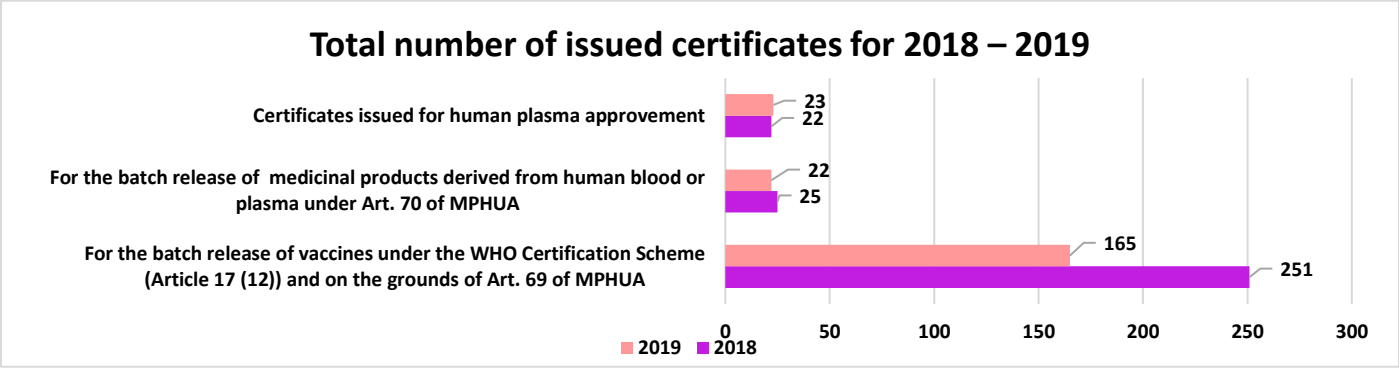
The trend in instrumental methods used for sample analysis remains the same. The largest share is High-performance liquid chromatography-HPLC (243 analyses or 27.3% of the total number of studies), ultraviolet spectrophotometry-UV-Vis (53 analyses or 6.0% of the total number of studies) and the dissolution test (35 analyses or 4.0% total number of tests). In 2019, the number of tests for the uniformity of dosage units of low-dossage preparations was increased, including the uniformity of the delivered dose of a group of medicinal products containing the active substance Mometasone, which are the pharmaceutical form nasal spray.

Biological analyses

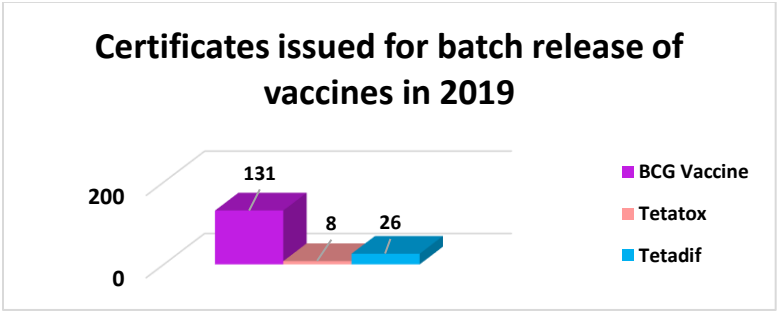
Experts from the BDA officially release batches of human blood or plasma, vaccines and medicinal products under the procedure for Official Control Batch Release (OCABR) and in compliance with the WHO TRS No. 978 Guideline on Batch Release Vaccines, 2013). On samples of the Market surveillance plan, tests were performed to determine the microbiological quality-sterility, total number of microorganisms, specific microorganisms and bacterial endotoxins.

Released certificates for batches of vaccines and medicinal products derived from human blood or plasma are issued in 2019 are total number of 213. In 2019, there is a slightly decrease in the number of certificates issued for batches of vaccines compared to the data from 2018 (251).

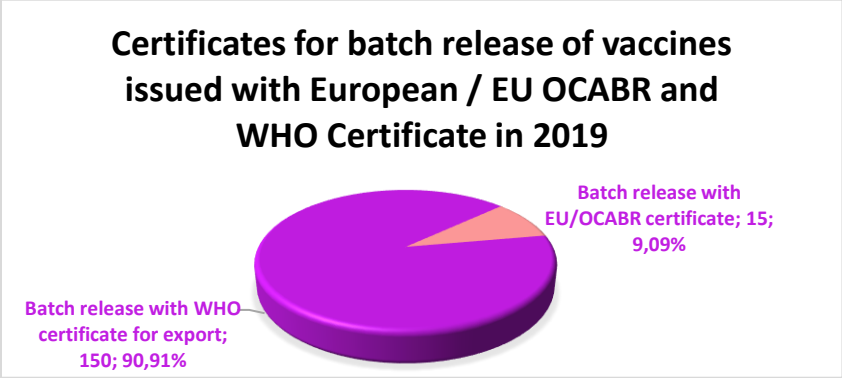
All submitted samples shall be carried out at least an assessment of batch documentation, appearance test, packaging and leaflet. All batches are released within the legal timeframe under the MPHUA. The distribution is as follows:



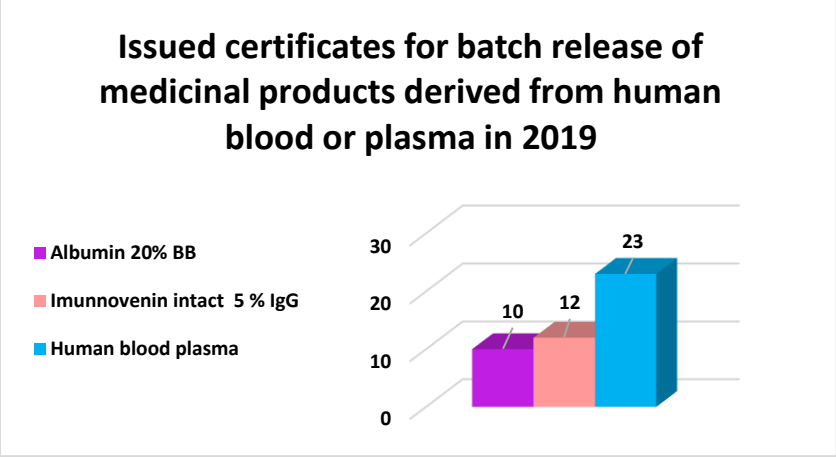
Certificates issued by type of vaccines are distributed according to the graph below:



The number of the European/EU OCABR certificates for batch release of vaccines issued in 2019 were 15 and the number of WHO certificates issued in 2019 were 150.



Medicinal products derived from human blood or plasma for release under Art. 70 of LMPHM are distributed according to the graph below:



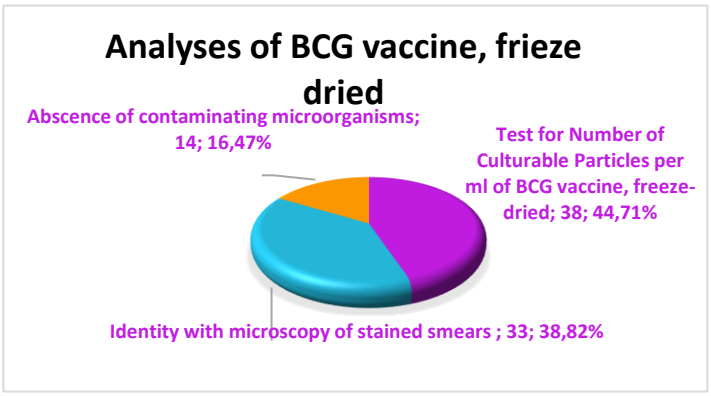
The total number of sample analyses performed on different procedures is 743 (18.0% more than 2018 when they were 630). The results of all tests carried out comply with the approved specifications of the medicinal products concerned.

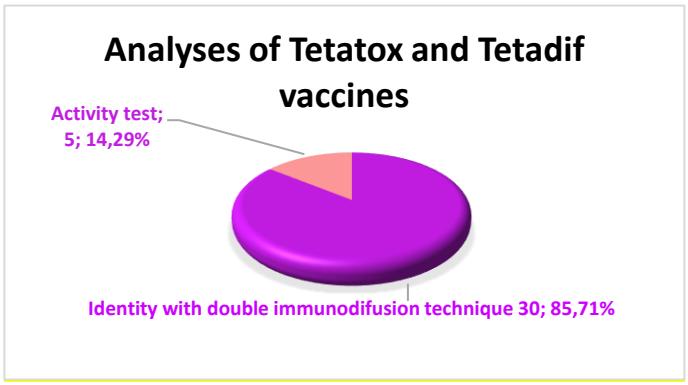
For all medicinal products derived from human blood or plasma and samples of vaccines including samples obtained in connection with repackaging due to termination of contractual relations with a supplier (total 234 units), an assessment of the appearance of the primary and secondary packaging and patient leaflet are carried out.

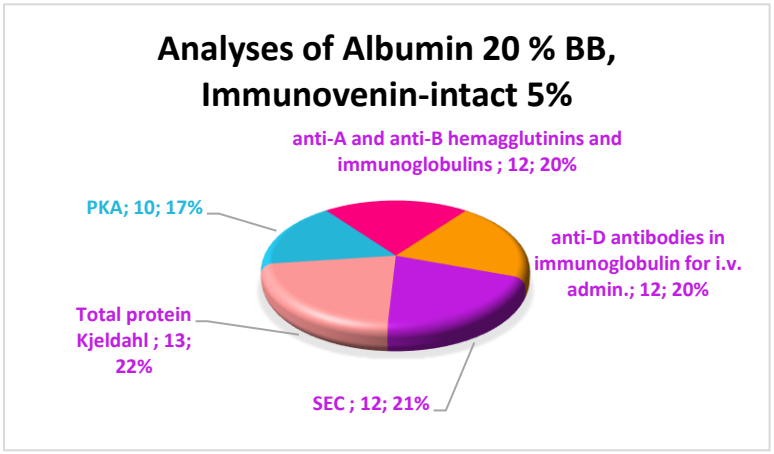
Three batches of the Immunovenin Intact, released in the end of 2018 and in the beginning of 2019, were analysed for "Content of an activator of prekallikrein". All results complied with the approved test specifications.

The activity test is carried out for post-marketing control of 5 batches of BCG vaccine. For one batch, released with WHO certificate, non-compliant result is obtained at the 29th month of the shelf-life. The marketing authorisation holder, the “Market Surveillance and Inspection Directorate” and the division of WHO Prequalified

Vaccines are notified of the test results.





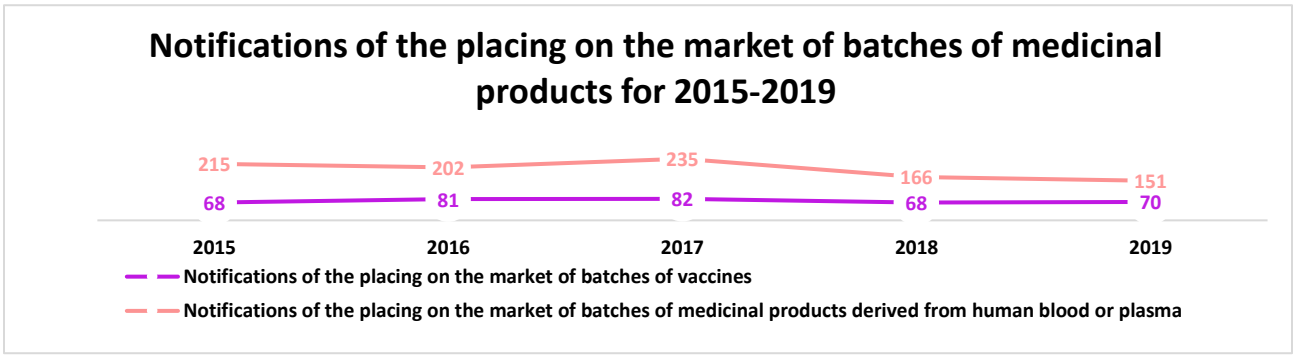


In 2019, BDA experts participated in the

•Inter-laboratory evaluation for sutability test- PTS for sterility, organized by LGS Standards PT-PH-05 (PH068) for a total of 5 test samples. The results obtained are very good.

•PTS 202 Immunoglobulin Molecular-size distribution for a total of 5 samples, organized by EDQM. A report will be sent by the organizer after processing of the results.

In 2019, 70 notifications of the placing on the market of batches of vaccines and 151 notifications of the placing on the market of batches of medicinal products derived from human blood or plasma were issued.



2.5. PHARMACOPOEIAL ACTIVITIES

In connection with proposals of the Secretariat of the European Pharmacopoeia for the work program of expert groups, BDA answered 44 surveys and sent information on substances/monographs, national pharmacopoeia requirements and good practice. The Agency processed 376 reports on chemical reference standards (CRS) developed by expert groups of the European Pharmacopoeia.

In the past year, the 10th edition of the *European Pharmacopoeia* and supplements 10.1 to 10.3 was introduced. The *narrow leaved cassia, fruit (0208)* and *insulin, bovine (1637)* monographs dropped out from *European Pharmacopoeia*. The changes were published on the Agency's website.

On the BDA's website were published:

• Herbal substances and preparations included in the 9th edition of the European Pharmacopoeia to supplement 9.8;

• Homeopathic preparations included in the 9th edition of the European Pharmacopoeia to supplement 9.8;

• Substances and preparations included in the 9th edition of the European Pharmacopoeia to supplement 9.8.

As of the beginning of public consultations on the texts of the *European pediatric formulation* an announcement was published on the BDA website in the *Pharmacopoeia section*. The Bulgarian Pharmaceutical Union was notified.

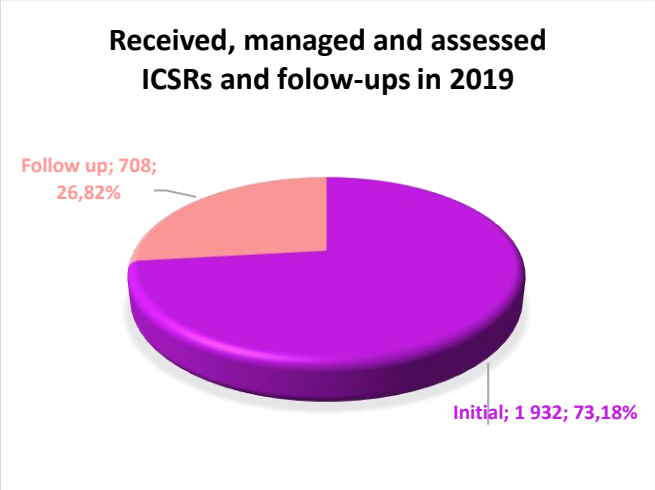
In the next 2020-2022mandate of expert groups to the European Pharmacopoeia, Bulgaria will be represented by 8 experts in 9 groups.

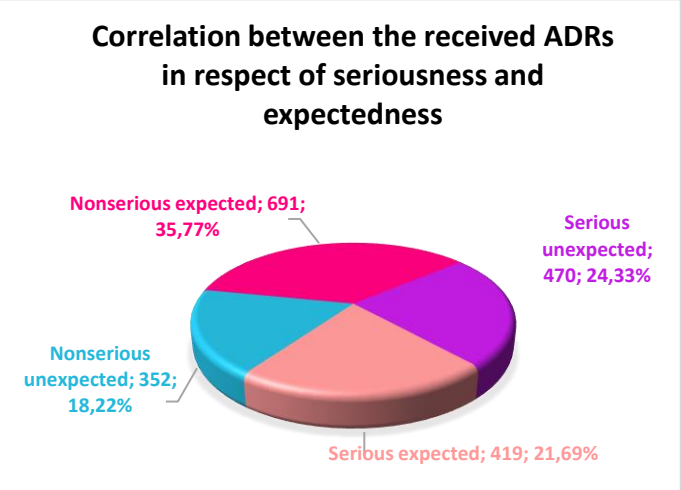
BDA as the National Pharmacopoeia Secretariat provided consultations on pharmacopoeia and terminological issues, updated and regularly reviewed translations of monographs, lists of controlled terms, etc. New standard terms of dosage forms, packaging, routes and methods of administration were translated into Bulgarian and were introduced into the EDQM database.

2.6.PHARMACOVIGILANCE

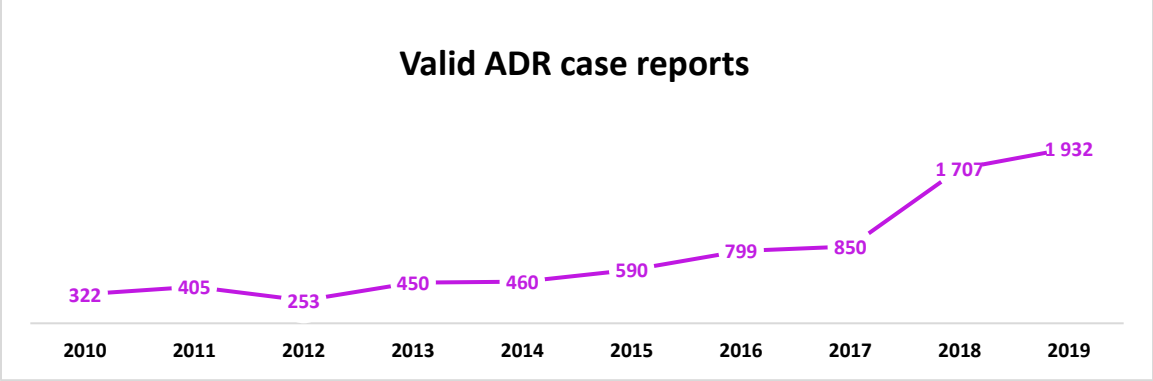
Adverse Drug Reactions Reports

A part of the BDA responsibilities includes assessment of the received Individual Case Safety Reports (ICSRs). In 2019, the number of the initial as well as the follow up reports that were received, managed and assessed increased in comparison to the previous year. The total number of ICSRs in 2019 was **2 669**. The valid ones were **2 640** as the initials being **1 932** and the follow ups - **708**.

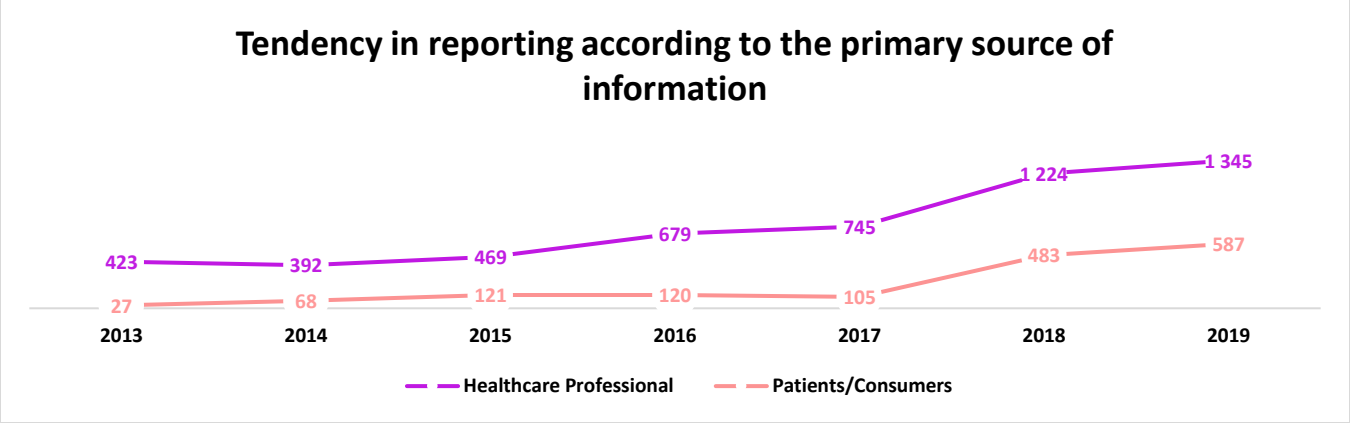




The tendency for increase of the reporting activity is kept and the number of valid ICSRs from **1 707** in 2018 went to **1 932** in 2019 – the increase is 13,18 per cent.

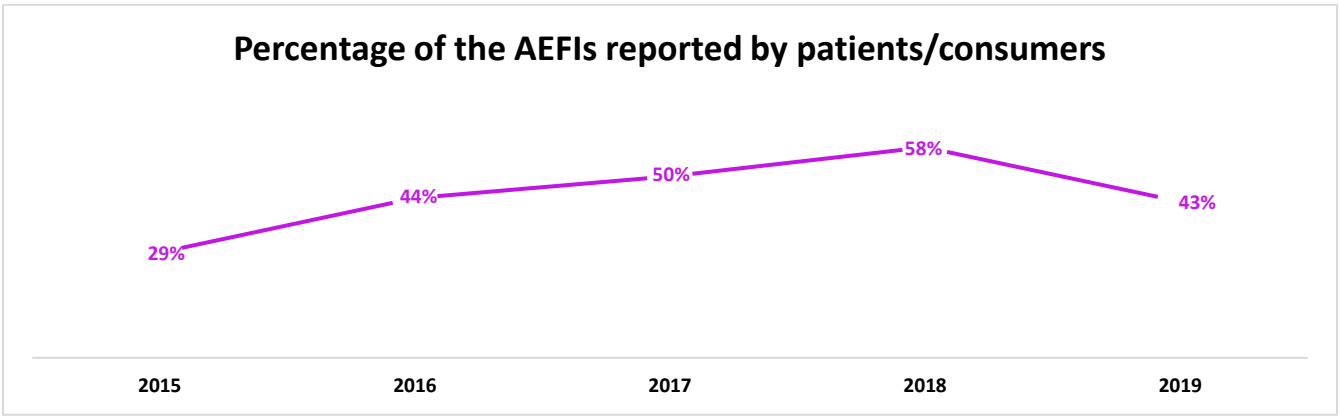


The reporting activity of healthcare professionals (HCPs) was continuously increasing and reached **1 345** reports in 2019. The number of patient's reports was 587, which is an increase compared to 2018. The Marketing Authorization Holders sent the biggest share of reports (1 670). Directly reported to the BDA were **126** reports by healthcare professionals and **136** reports by patients.



Adverse events following immunizations

The adverse events following immunizations (AEFIs) were 6% of the total number of reports. Of the total of 117 AEFIs directly reported to the BDA were 32% (8 by healthcare professionals and 30 by patients), received through the Marketing Authorisation Holders were 79 (59 by healthcare professionals and 20 by patients). The number of AEFIs reported by healthcare professionals were 67 (57%) and by patients were 50 (43%).



Information activities related to pharmacovigilance and risk communication

In 2019, BDA evaluated 53 Educational Materials and additionally agreed on 35 Direct Healthcare Professionals Communication letters.

Activities related to the National Pharmacovigilance Risk Assessment Commission (Local PRAC, NPRAC)

In 2019, NPRAC held 10 meetings prepared and chaired by the BDA. NPRAC provided recommendations for the Bulgarian position within the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC). The

Commission also provided its recommendations for the national implementation of the adopted EU regulatory decisions.

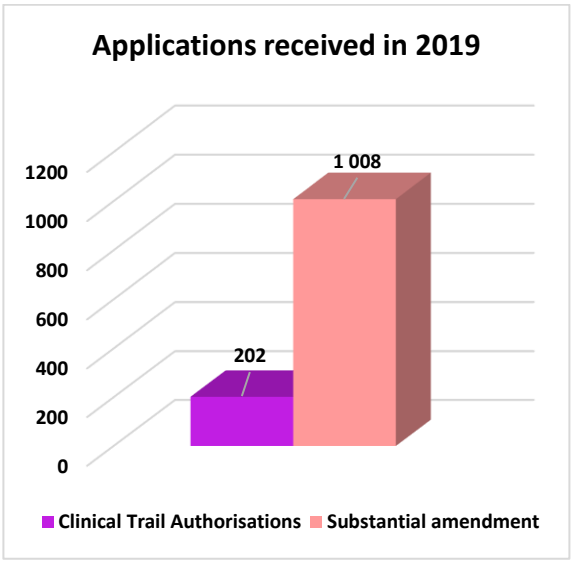
Training activity and participation in scientific fora

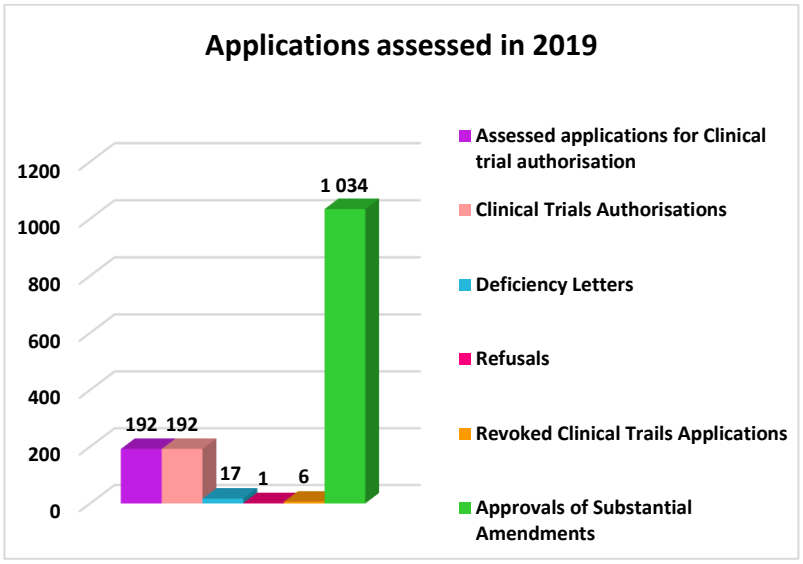
In 2019, the BDA held trainings on Pharmacovigilance for students in Pharmaceutics.

2.7.CLINICAL TRIALS

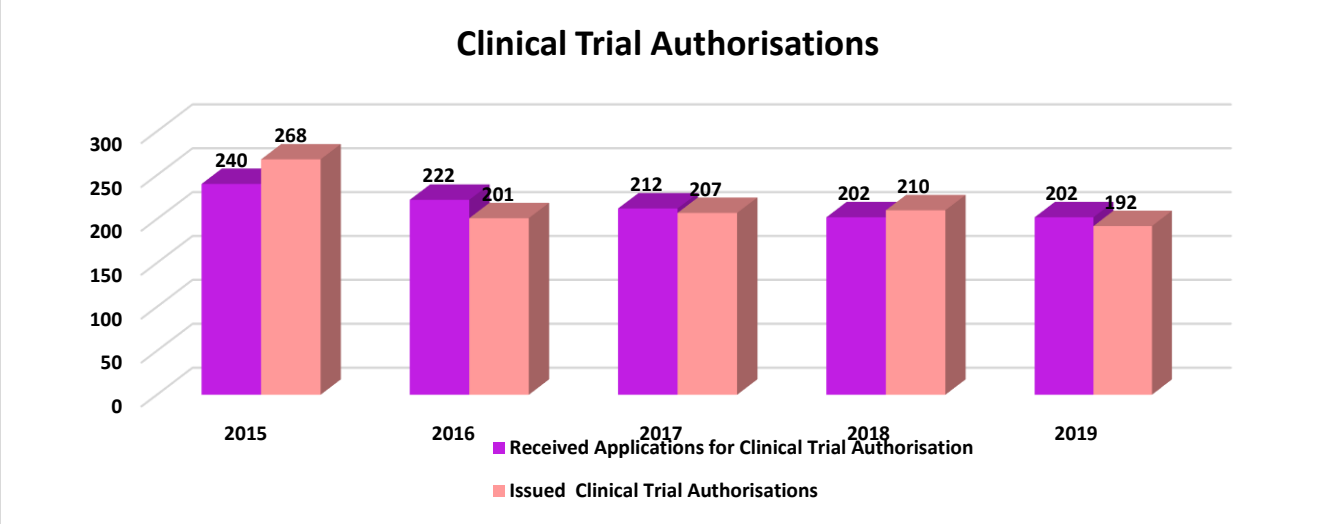
BDA has responsibility for authorisation and control of clinical trials conducted in Bulgaria. The activity includes assessment of the documentation for clinical trial authorizations, related substantial amendments and follow-up control on the implementation. BDA keeps and updates a Register of the authorized clinical trials and electronically submits data for clinical trials in the Eudra CT database.

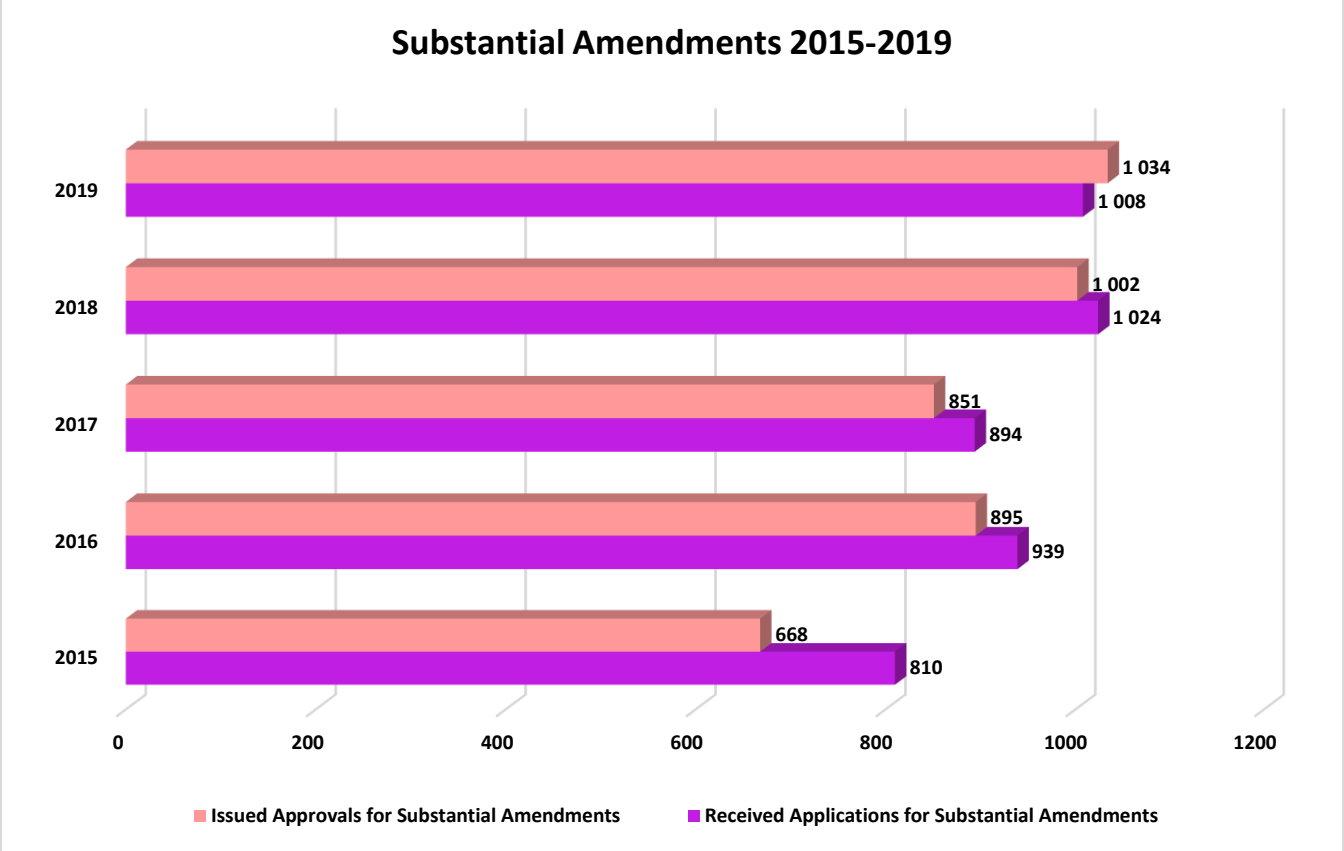
In 2019, the BDA received **202** Applications for Clinical trial authorization and **1 008** Applications for Substantial amendment approval. The total number of applications was **1 210**.



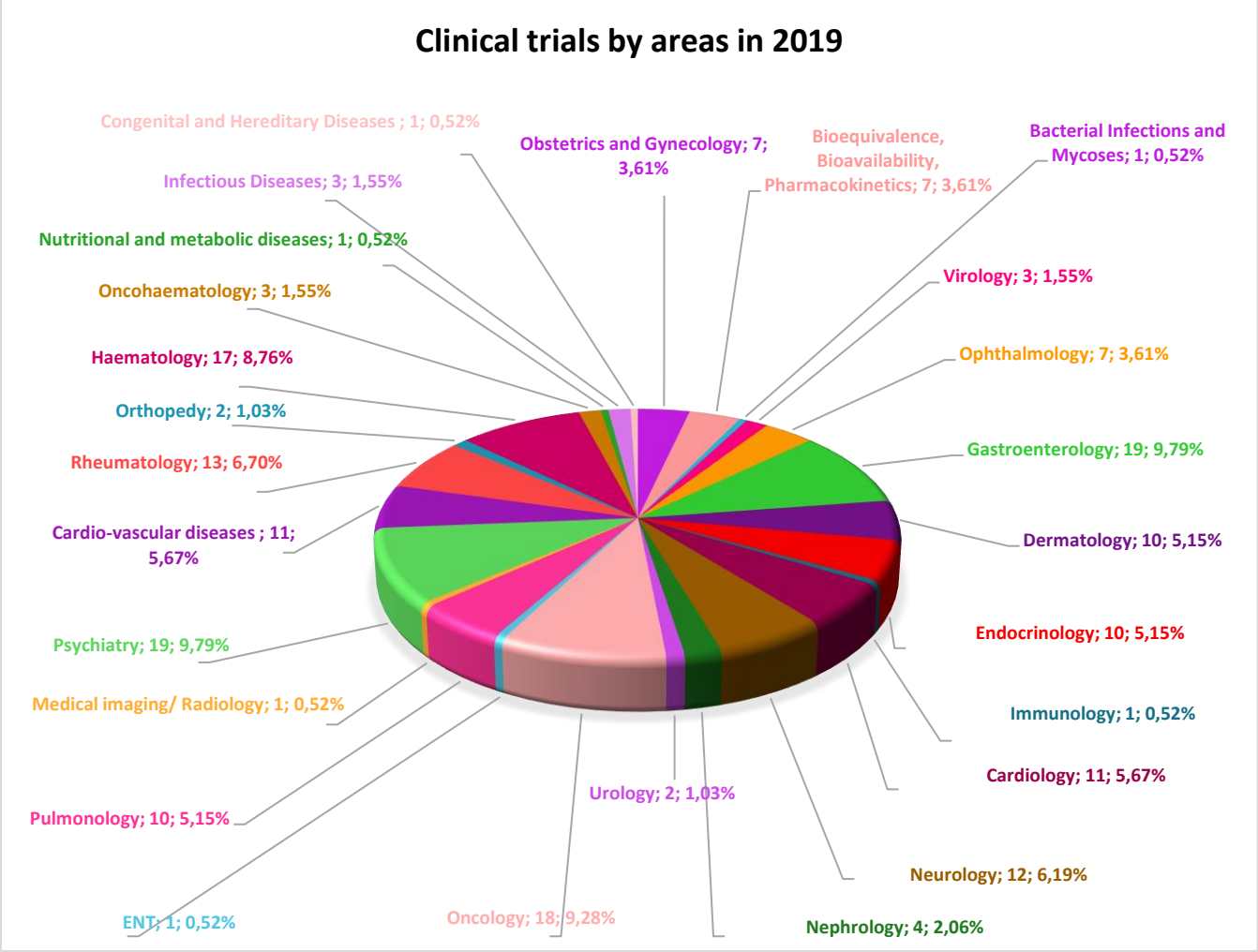


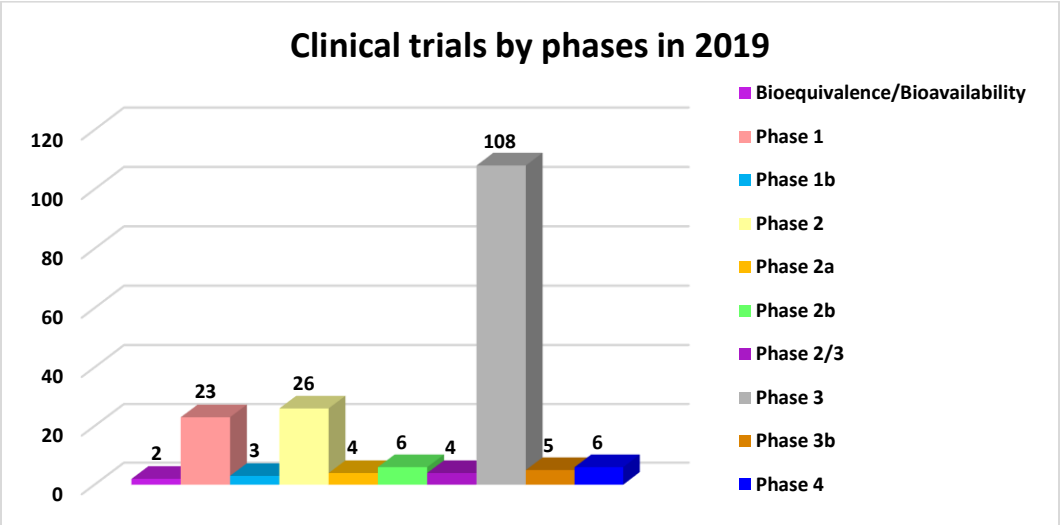
In 2018, the BDA issued **192** authorizations/notifications for agreement for Clinical trials and **1 034** authorizations for substantial amendments in Clinical trials. One application for clinical trial authorization was refused.





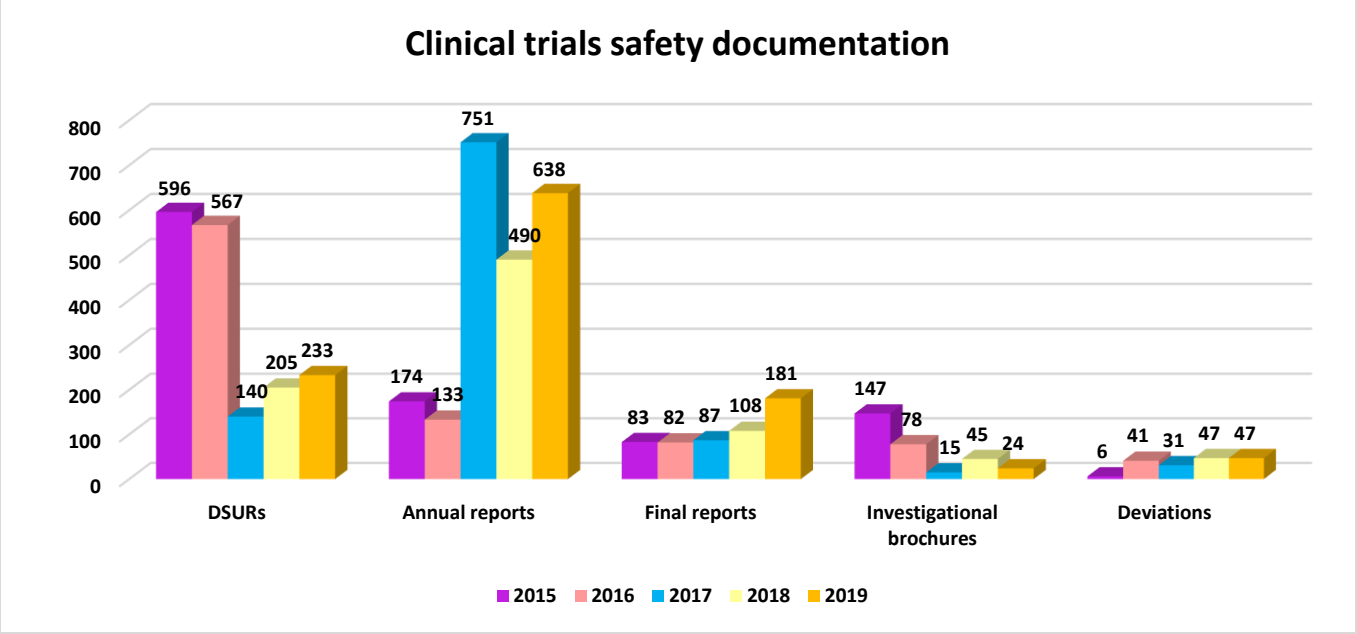
In 2019, the clinical trials sponsors were mostly interested in the areas of Psychiatry and Gastroenterology (9.79 % each), Oncology (9.28%) and Haemotology (8.76%).





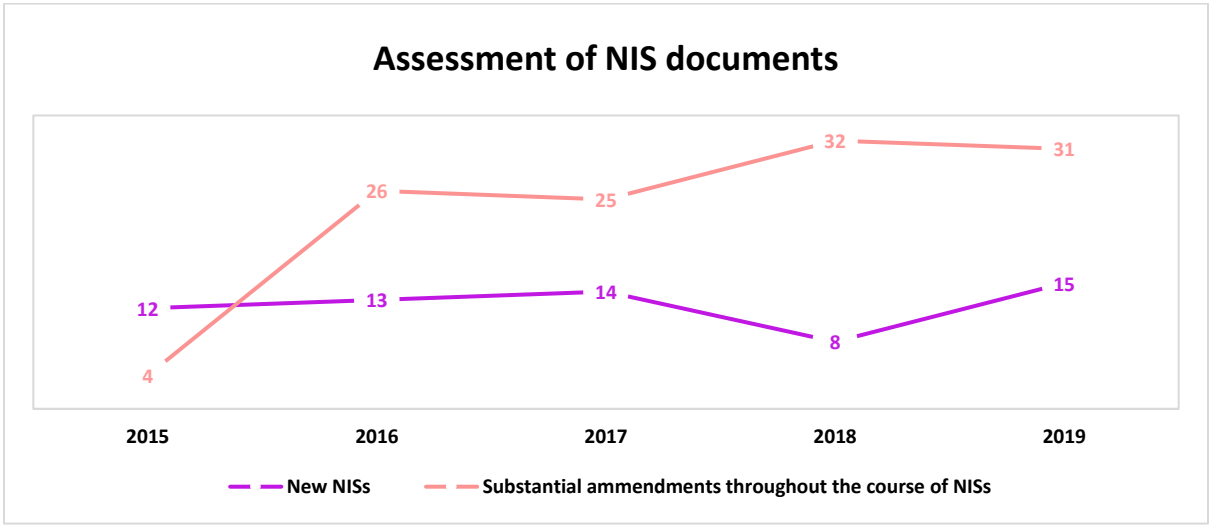
Clinical Trials Safety

The BDA supervises the safety data for medicinal products in the authorized Clinical trials by assessment of the submitted to the BDA safety reports. The clinical trials supervision also includes assessment of final study reports, documents submitted for information, etc.

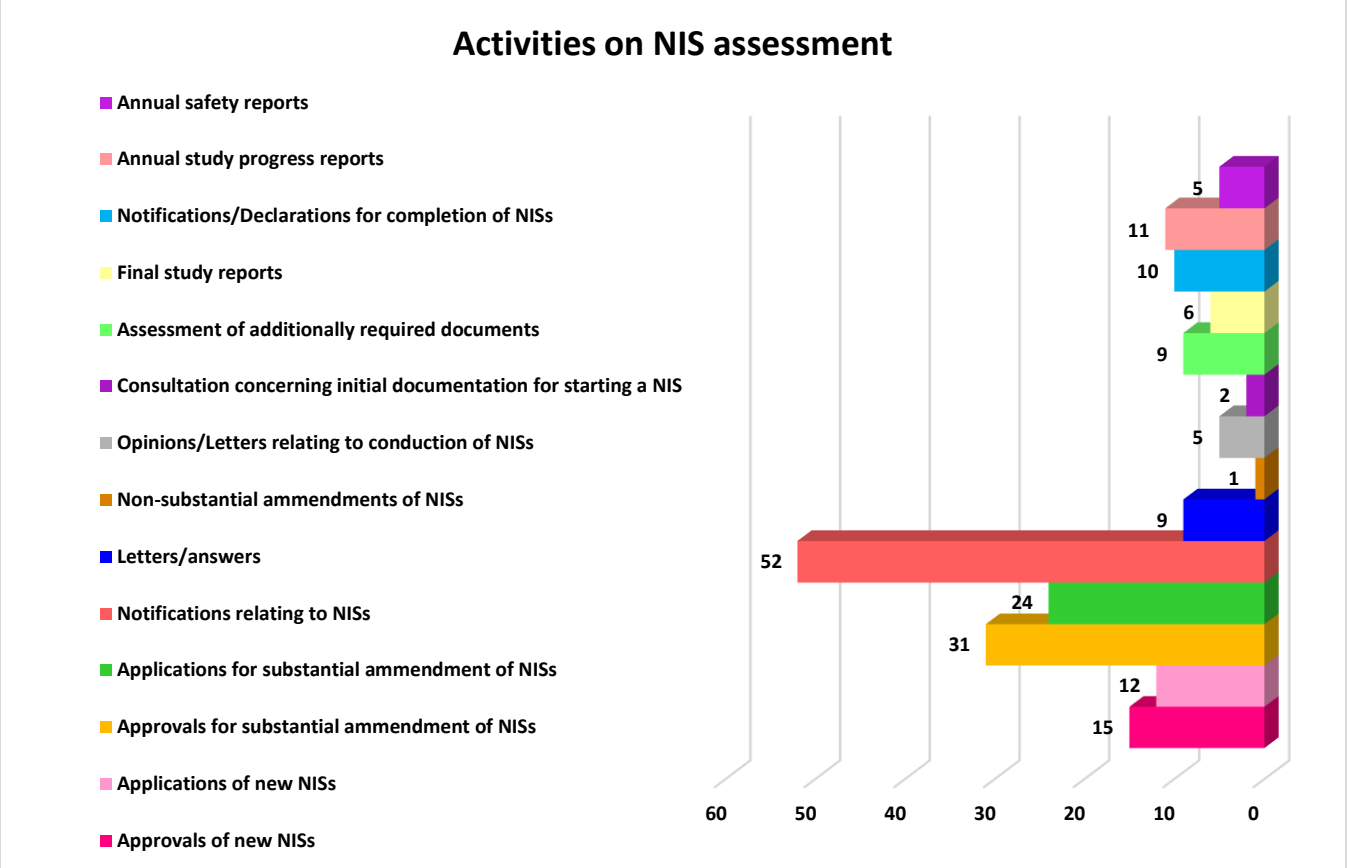


2.8. NON-INTERVENTIONAL STUDIES

Assessment and approval of submitted documents for conduction of non-interventional studies (NISs) with medicinal products falls within the scope of the BDA's responsibilities. In 2019, the Agency received ad assessed documentation for 15 new non-interventional studies as well as documentation for 31 substantial amendments.



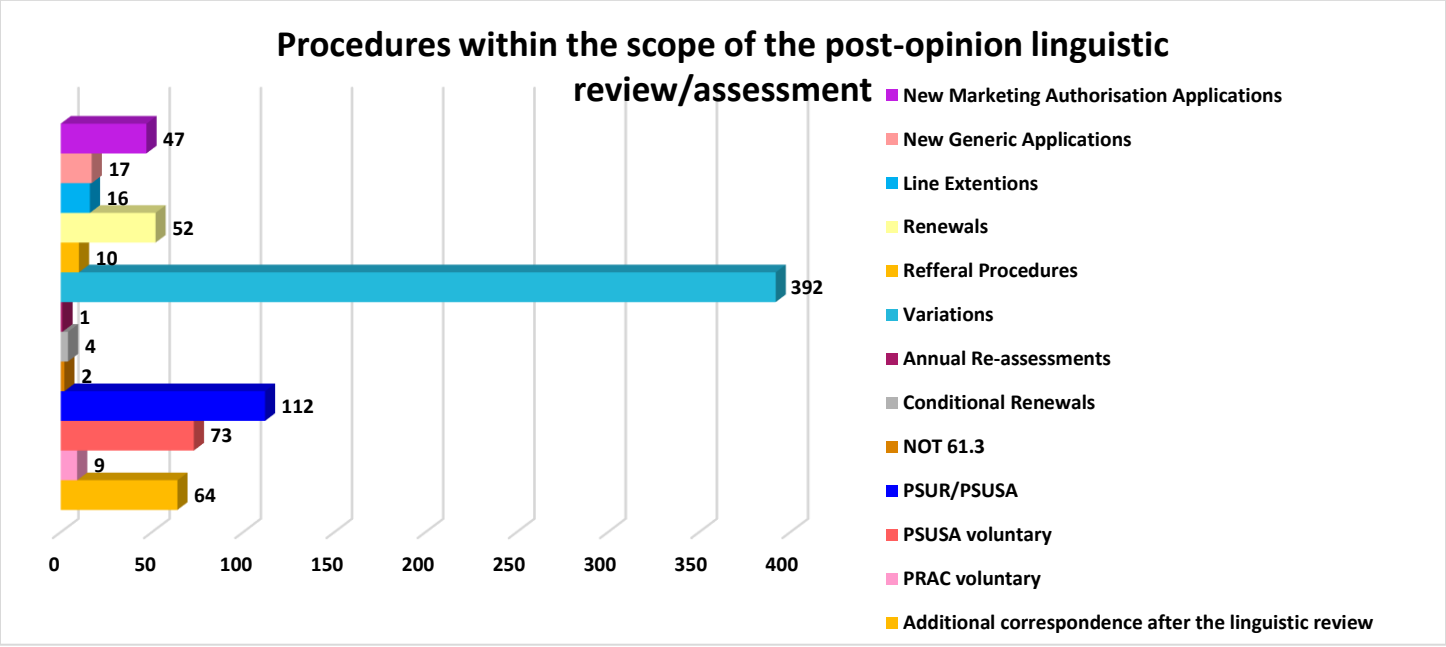
In addition, throughout the year there were issued 3 opinions on documentation regarding conduction of non-interventional studies, which were found to be out of the scope of the non-interventional study definition under art 145 of MPHUA.

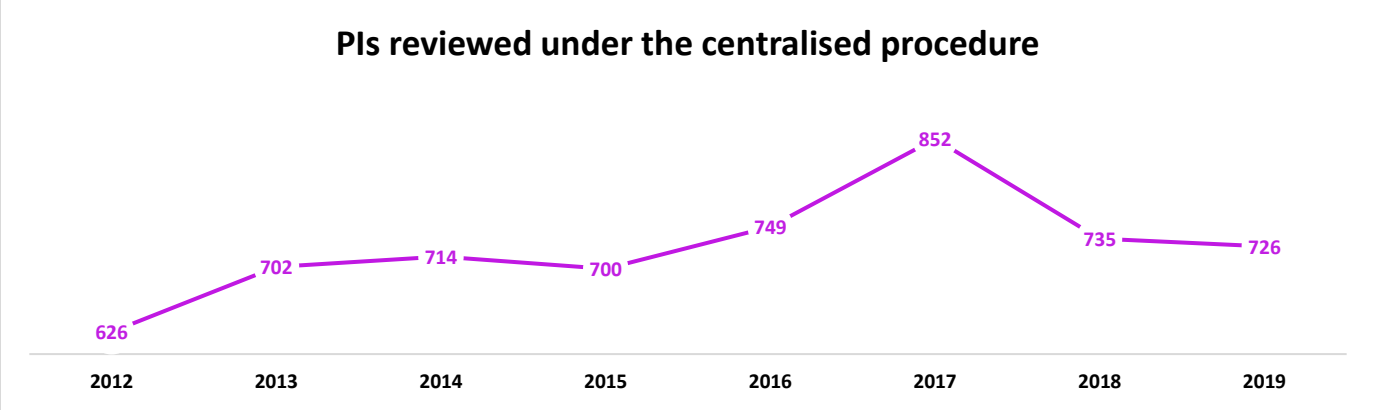


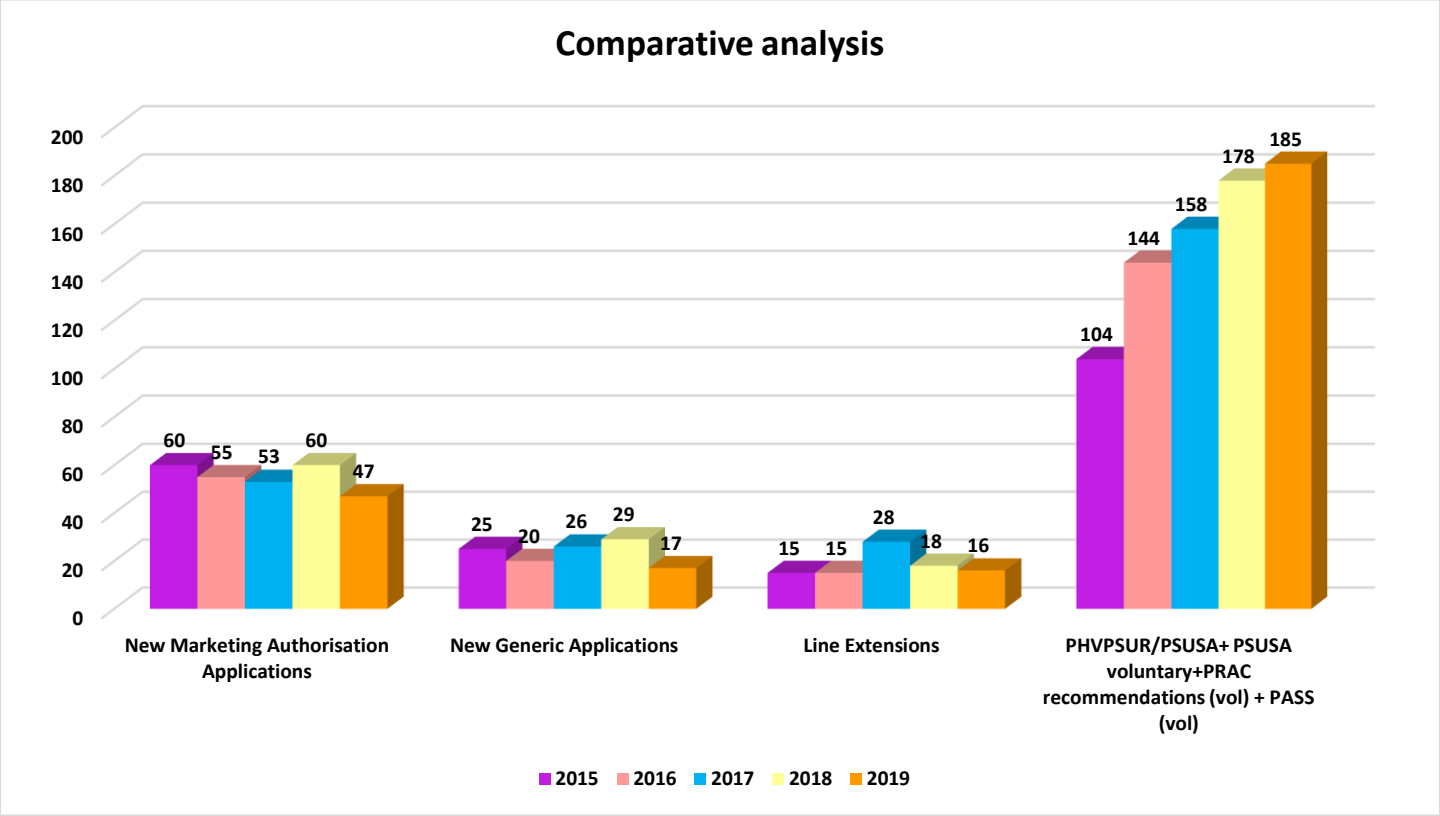
The BDA maintains an up-to-date non-interventional studies database.

2.9. MEDICINAL AND PRODUCT INFORMATION

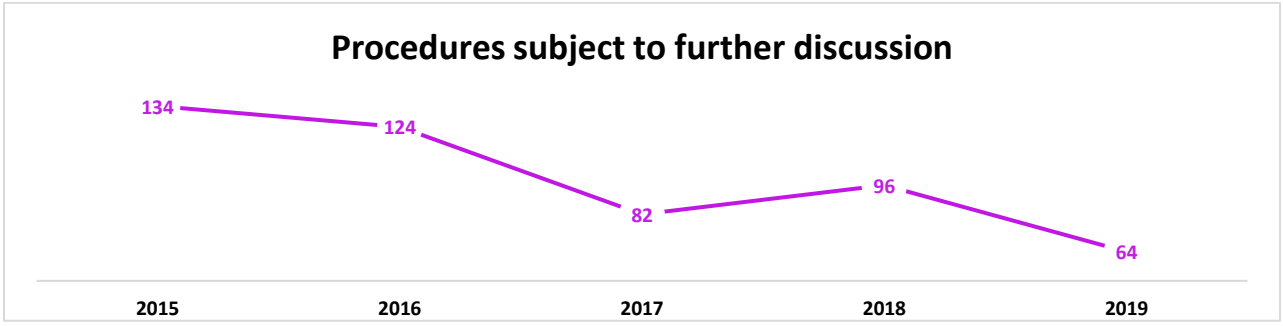
Assessment and expert activities concerning the linguistic review of the Product Information (PI) (Summary of Product Characteristics, Labelling and Package Leaflet) of medicinal products after CHMP opinion.





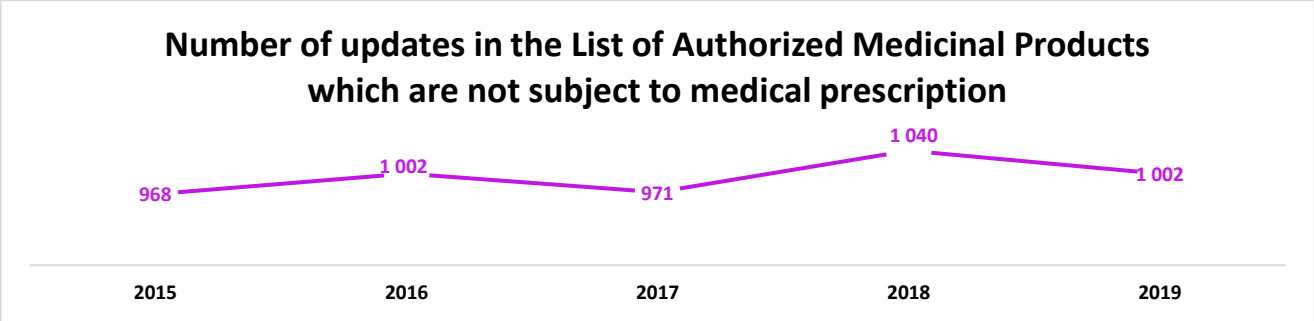


There is a downward trend in the number of procedures of New Marketing Authosrisation Applications, New Generic Applications and Line Extension of the marketing authorization, and an upward trend in PSUR / PSUSA, including voluntary PSUSA voluntary procedures + PRAC recommendations (vol) + PASS (vol).

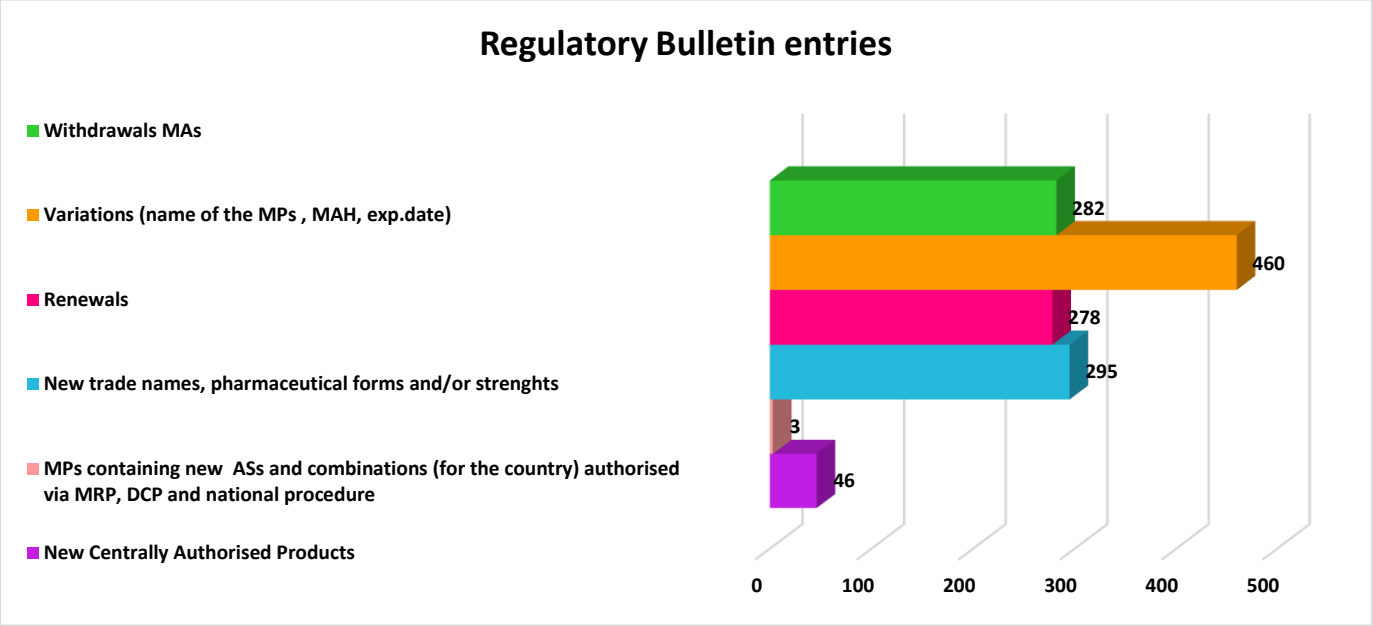


For the period 2015-2019, there is a trend of decrease in the number of procedures subject to additional co-ordination, which is one of the indicators for improving the quality of work.

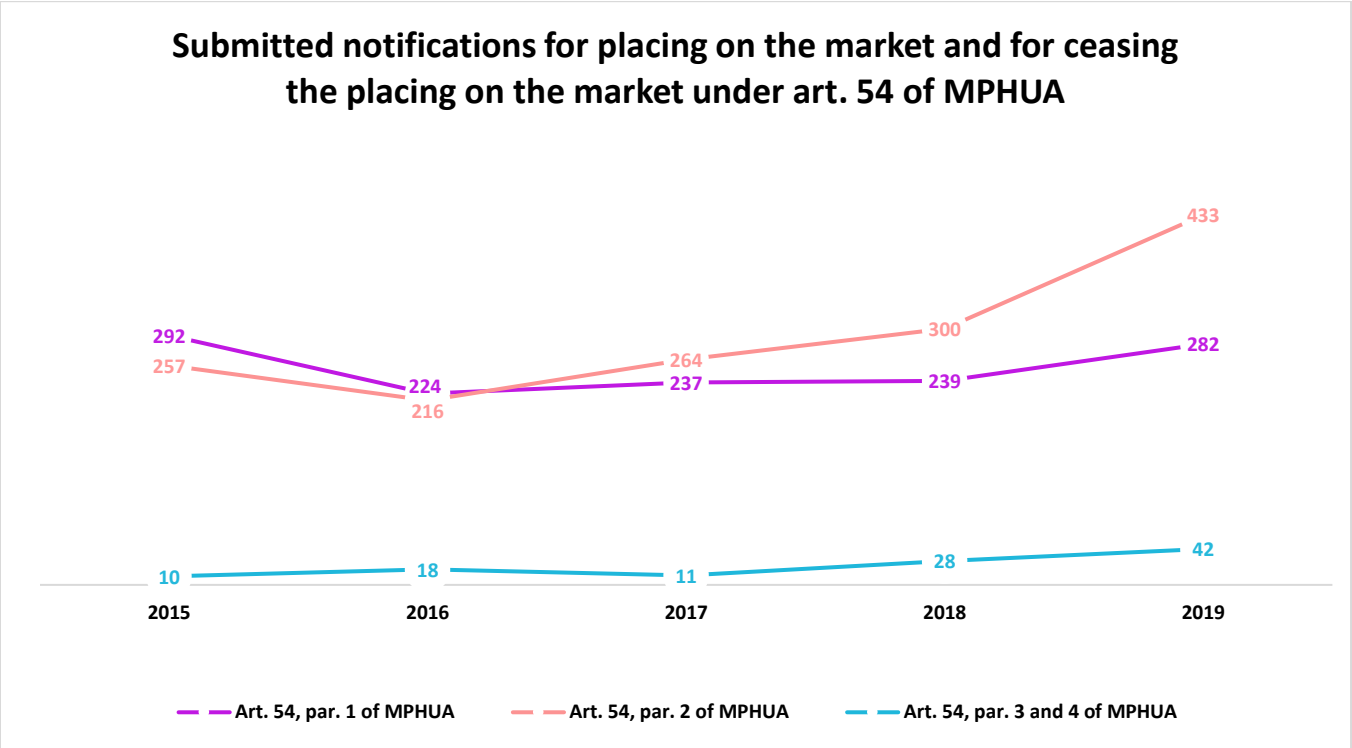
Monthly, the BDA updates the List of Authorized Medicinal Products, which are not subject to medical prescription.



A Regulatory Bulletin providing information on newly authorised medicinal products (new molecules and combinations, new trade names, new pharmaceutical forms and/or strengths), renewals and variations in MA, as well as withdrawals, is published on the BDA's website monthly.



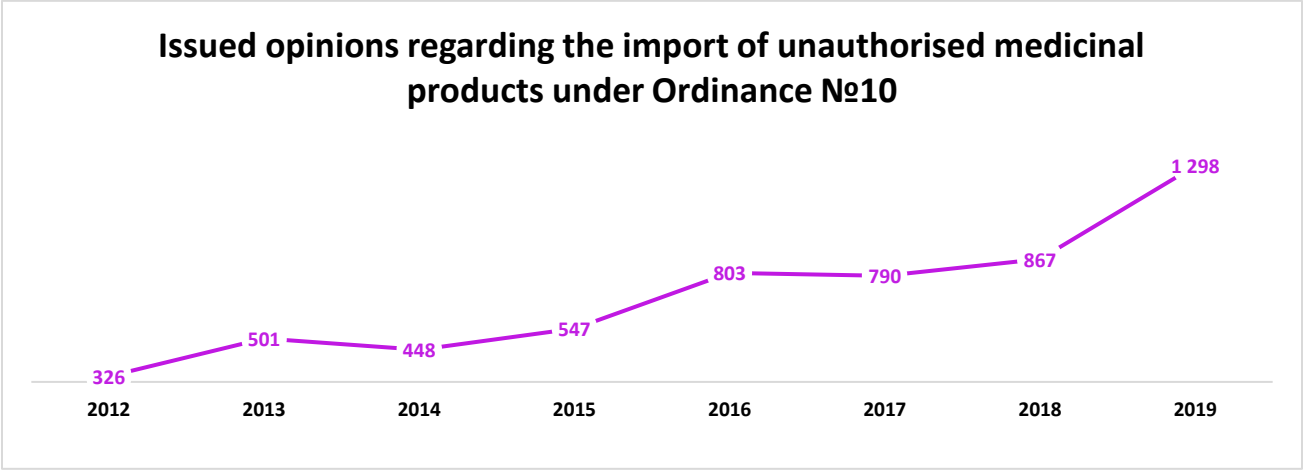
Notifications for placing on the market and for ceasing the placing on the market



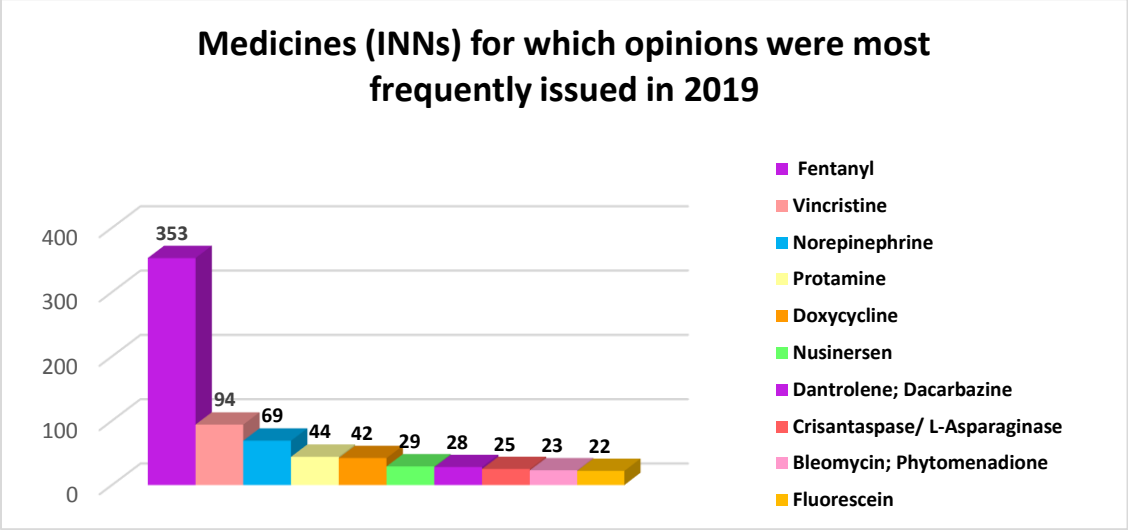
In 2019, discontinuation of sales, temporarily or permanently, is due mostly to marketing/commercial or manufacturing reasons (including discontinuation, inventory depletion and inability to resume production in the short term, optimization of the company's portfolio, changes in packaging).

Opinions regarding the import of unauthorised in the country medicinal products

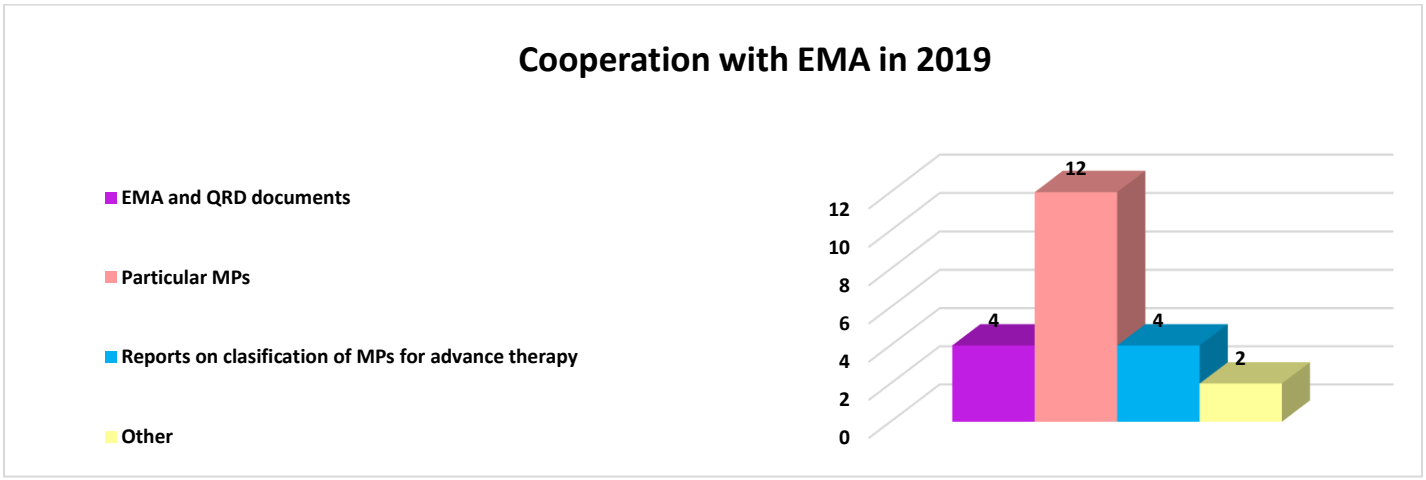
In 2019, 1 298 opinions regarding the import of unauthorised in the country medicinal products under the Ordinance № 10 were issued.



The analysis shows medicines for which opinions were most frequently issued:



With regard to exemption from the obligation, the data on the packaging and / or the package leaflet of the medicinal product shall be in the national language according to Art. 63/3 / of Directive 2001/83, 6 expert opinions were issued. In addition, 3 expert reports were prepared for the Ministry of Interior.



2.10. BLOOD TRANSFUSION SYSTEM SUPERVISION

The Agency's Executive Director shall act as the competent authority for the operation of the blood establishments - Regional Centers of Haematology (RCH), the Haematology Wards (HW) and the Haematology Laboratories (HL) according to the BBDBTA. European legislation seriously regulates the transfusion process (from the vein of the blood donor to the vein of the recipient) in order to provide blood and blood components with the required quality and safety, as well as to protect the health and safety of blood donors and patients in need of blood transfusion.

At the end of 2019, the European Commission published a report on the compliance of the EU legislation in the transfusion Haemotology field with the current scientific developments, as well as with the public frame of mind in the Member States. The European legislation is expected to be updated.

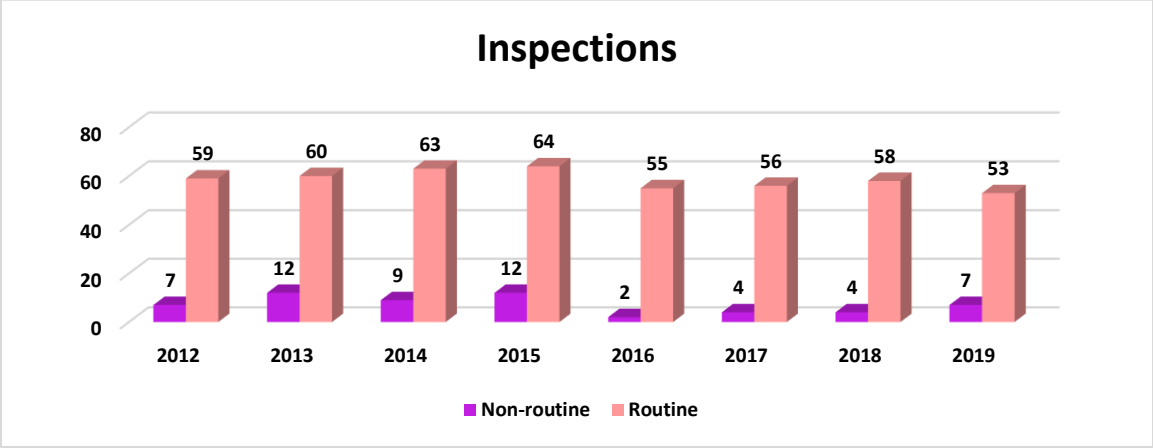
The main activities performed by the RCHs, HWs and HLs in transfusion hematology, as well as by the healthcare facilities transfusing blood and blood components as part of the treatment of patients are regulated under the BBDBTA, the Regulations on the Structure and Activity of the Centers of Transfusion Haematology (CTH) and the Medical Standard for Transfusion Haematology (MS on TH), approved by Ordinance No. 9 / 25.04.2006 of the Ministry of Health.

In 2019, the Nucleic Acid Amplification Test (NAT) was introduced, and the necessary equipment was installed in all CTHs throughout the country. The method is without alternative for increasing the safety of blood and blood components for transfusion and of the plasma for the production of medicinal products, as it examines the donated blood for transmissible infections markers.

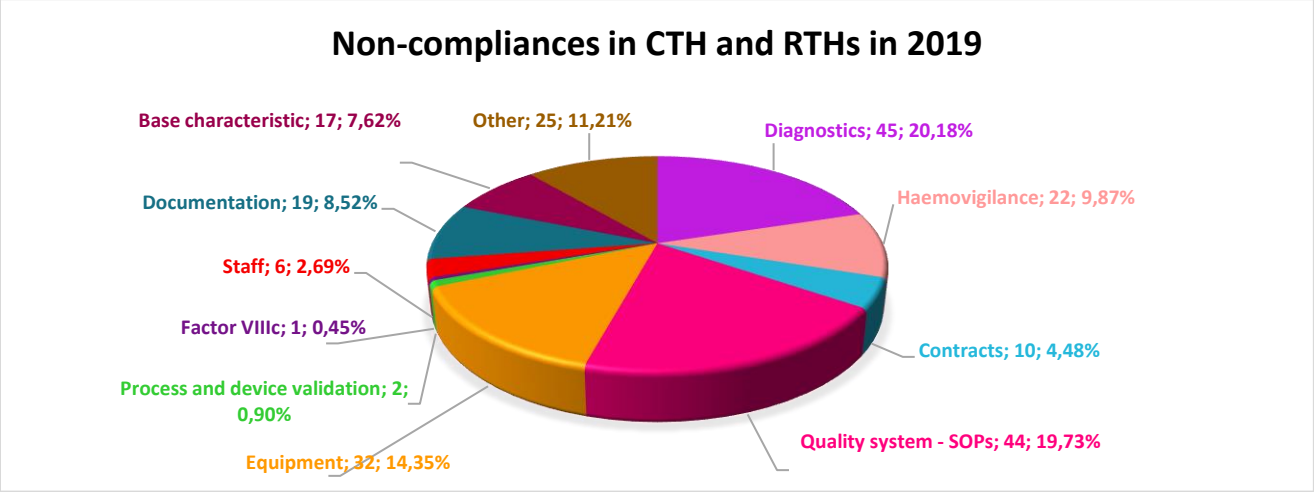
In 2019, preparations began for the introduction of a new, up-to-date blood donation test thorugh the Nucleic Acid Amplification (NAT) Test, by the necessary devices installed in all CTHs throughout the country. The test is an additional one, building on the tests currently being carried out for markers of transmissible infections. It has no alternative to improving the safety of blood and blood components for transfusion and plasma for the production of medicinal products, as it examines the donated blood for markers of transmissible infections by a new method - looking for donor RNA or DNA for the particular causer.

Inspections

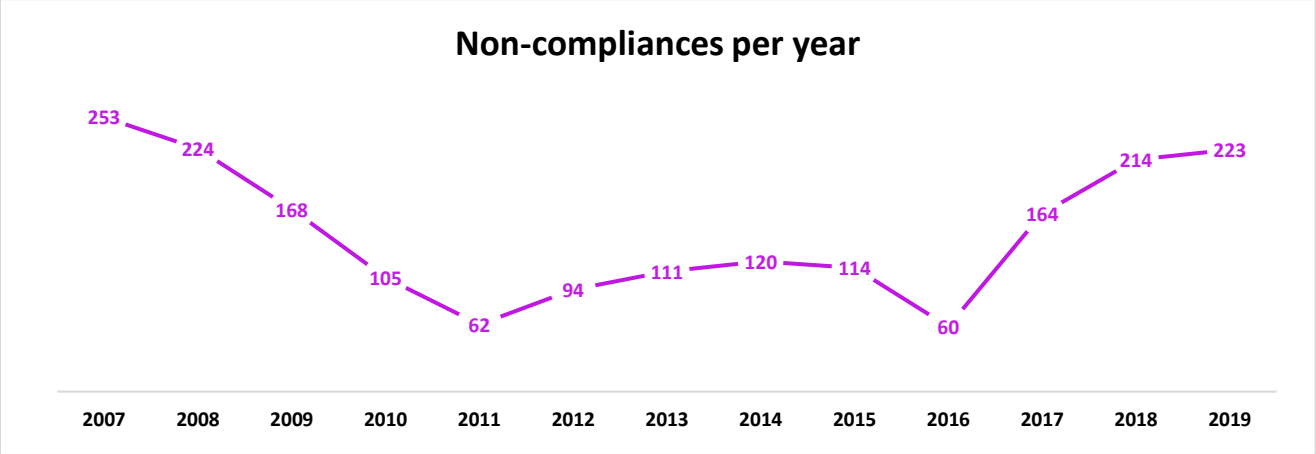
In compliance with the approved schedule for inspections in 2019, there were carried out 53 routine inspections in healthcare facilities collecting, testing, storing, processing, distributing and using blood and blood components under Art. 15 of the BBDBTA. Seven non-routine inspections were also carried out in accordance with the regulations in Ordinance № 26 of the Ministry of Healthcare.



In 2019, 172 blood establishments were inspected as well as 40 healthcare facilities and a total of 223 non-compliances were found.



There were found no critical non-compliances requiring the suspension of the blood establishments' activity.



The changes to the Transfusion Hematology Standard, which came into force in 2018, and in particular the introduction of good practice guidelines by the Council of Europe, led to increased number non-compliances in 2018 and 2019. NAT test technology will also increase the requirements towards the blood establishments' quality systems and may lead to an increase non-compliances in the coming years.

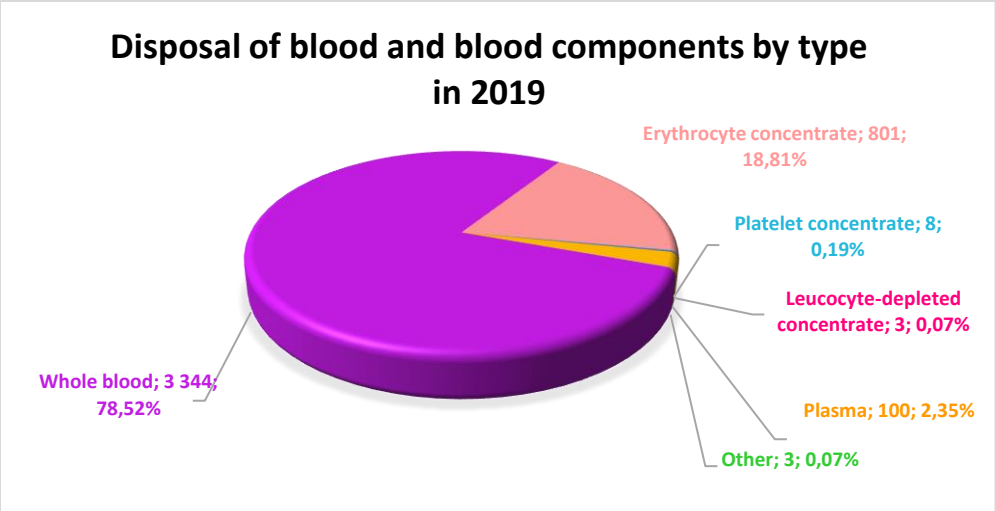
According to Art. 39, para. 4 BBDBTA, the Ministry of Health should be informed for the results of the inspections twice a year. The BDA has sent the summary reports as required. For the ascertained non-compliances the Agency issued instructions for corrective measures. In 2019, were not issued any Acts for Ascertainment of Committed Administrative Violation (AACAV). The reasons for this are most often related to the adequate corrective actions taken within the specified deadline.

Disposal of blood and blood components

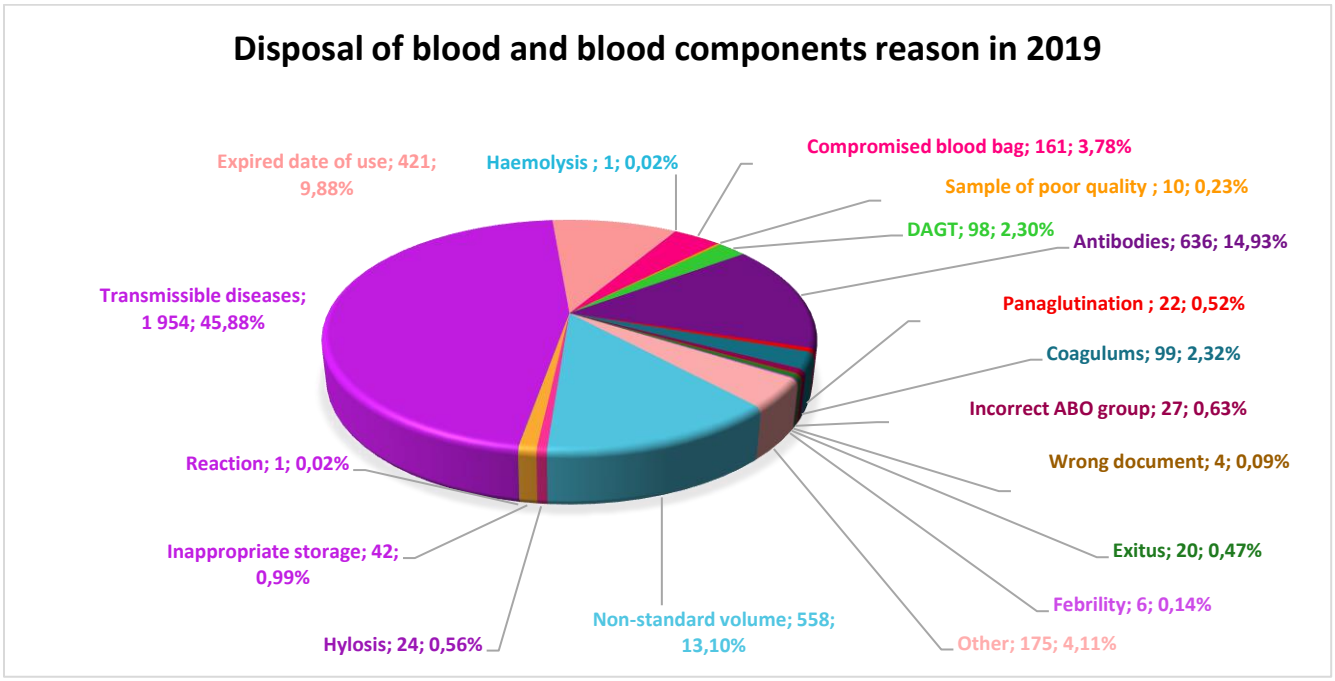
Based on the information received by the healthcare institutions, the BDA maintains a database on the

disposed of blood and blood components and the reasons for the disposal.

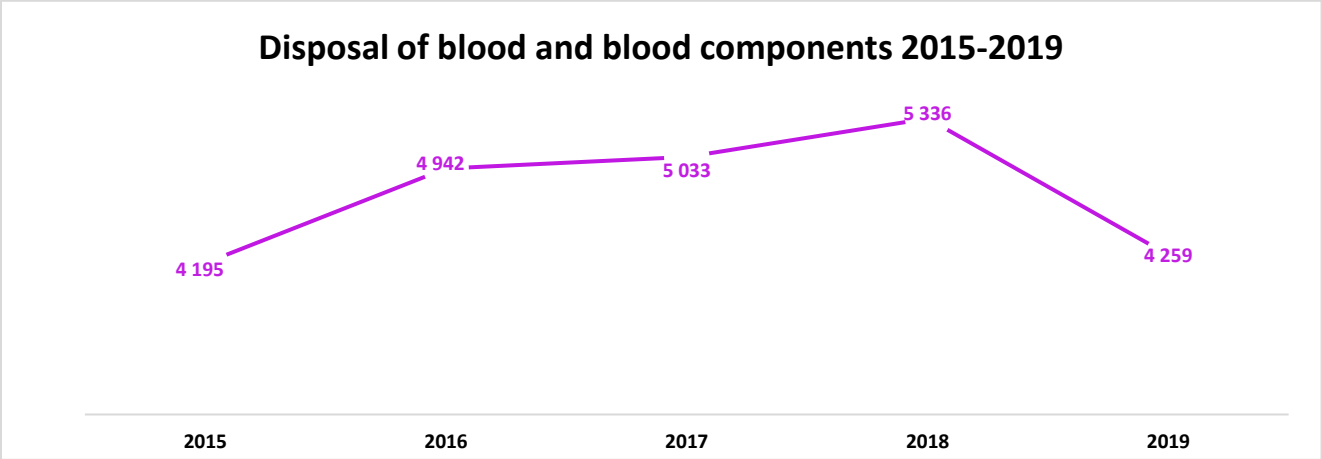
In 2019, the transfusion system disposed of or transmitted for scientific use 4 259 units of whole blood or blood components (incl. erythrocyte concentrate, fresh-frozen plasma or platelet concentrate). The comparison to 2018 shows a decrease of the disposed of or handed over for scientific purposes units with 1 077.



In 2019, the main part of the reasons for disposal of almost 78.52% of the units are factors found in the early stages of processing and examination of the blood in the blood establishments. The largest percentage of disposed of blood components is for erythrocyte concentrate which is most commonly used in the healthcare facilities. Despite the varying number of the reports to the BDA concerning destroyed blood components, a decrease in the number of destroyed components was observed in 2019.



In 2019, the most common causes for the disposal of a large number of units of blood and blood components are the transmissible infections markers, expiration date, antibodies, mismatch in the volume of blood taken. Other cases include units with hemolysis, chylosis, positive direct antiglobulin test (Direct Coombs), non-compliance with the original blood group, etc.

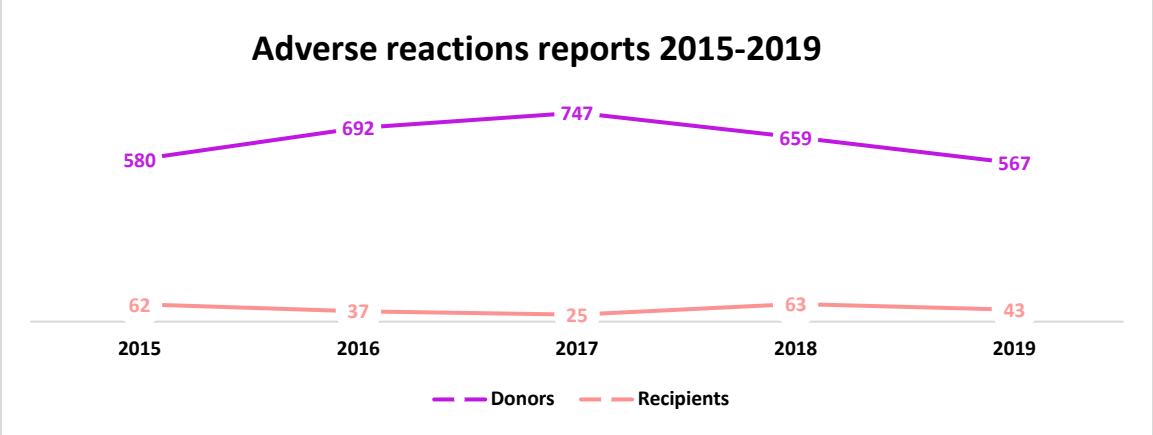


Haemovigilance

Haemovigilance is performed for the purpose of traceability of blood components, providing safe blood and blood components and preventing conditions for recurrence of adverse events and incidents in the transfusion process.

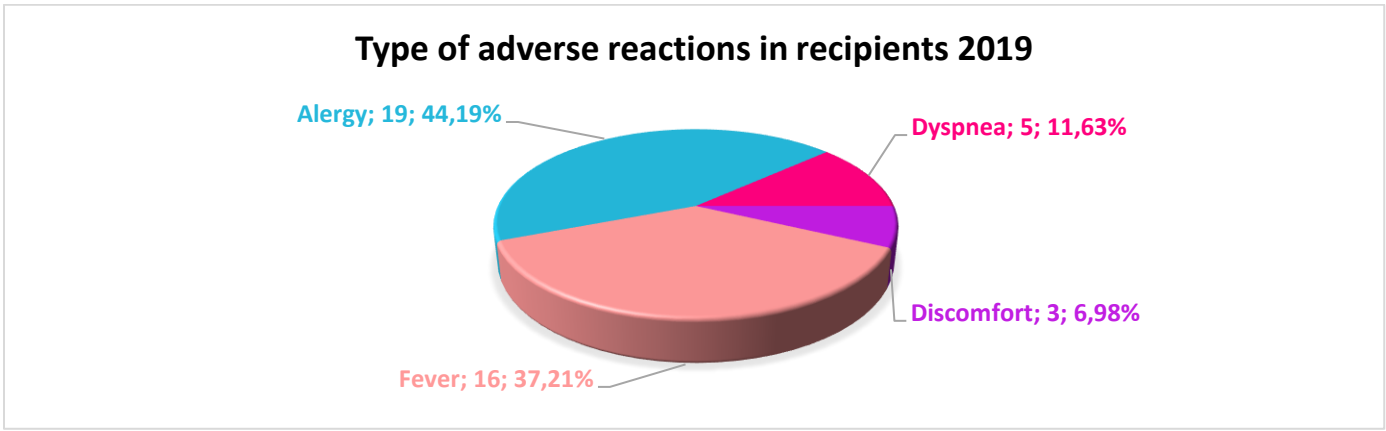
The amendments to Ordinance No. 9 for the approval of the Medical Standard for Transfusion Hematology of 2018 introduced the European criteria for inspection of an information system for transfusion hematology. At the end of 2018, National Information System for Transfusion Haematology (NISTH) was started operating in the all blood centers‘ work. The full implementation of the system will enable the NAT test to be included in it and thus will guarantee the functioning of the future sustainability of the NAT testing and will provide the tools for creating a "dossier" of each blood component.

The BDA maintains a register for serious adverse reactions and events occurring during collection and use of blood and blood components. The persons, engaged in collecting, diagnosing, processing, transfusing and storing blood or blood components, are required to report immediately to the BDA serious adverse reactions and events or suspected serious adverse events/reactions. In 2019, the BDA received 610 reports for adverse reactions as follows:

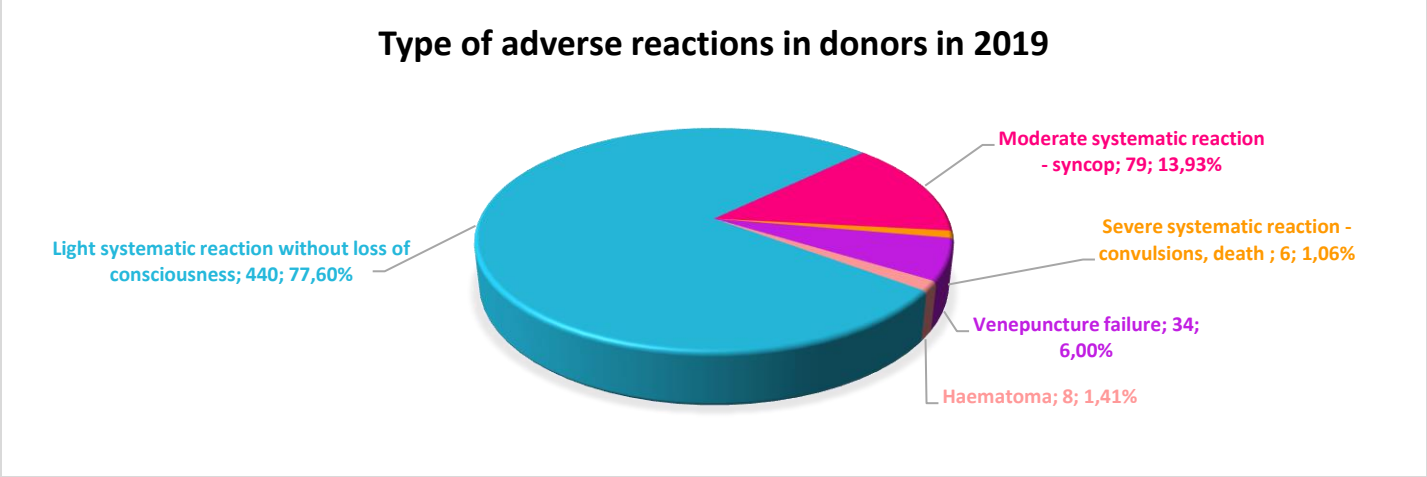


In 2019, the BDA received 43 reports for adverse reactions after transfusion of blood or blood components. The reactions were classified as light and moderate and the patients recovered completely after the transfusion. Most of the reactions were allergic reactions and fevers. Compared to 2018, the number of the reported adverse reactions decreased.

There are no reports to the BDA regarding concerning a serious adverse reaction related to the quality of blood or blood component shipped from the centers for transfusion hematology.



In 2018, the BDA received 567 reports for adverse reactions during blood donation. They were basically light systemic reactions without loss of consciousness or developing severe haematoma. The events of more severe systemic reactions were studied during the routine inspections. For all donors, the staff have adequately responded and there were no consequences for the blood donor's health. This year, the number of unsuccessful venipunctions is lower than the number during the previous one. No procedural violations were found.



Measures to increase the efficiency of the inspection process

In accordance with the requirements of the European directives, in case of outbreak of a dangerous transmissible infection somewhere in the EU, it is necessary to inform all workers in the system about the case and the measures taken. To reduce the possibility of donating blood contaminated with the West Nile Fever (WNV) and to preserve the safety of blood and blood components on the BDA website, has been published Information and circulated to the CTHs in the country. The Expert Council on Transfusion Hematology under the Minister of Health was promptly informed about the notifications for transmissible diseases in other EU Member States received by the BDA through the Rapid Alert System for Blood and Blood Components (RAB).

In 2019, the first confirmed case of West Nile Fever (WNV) in Bulgaria was registered. The WNV affected the nervous system and the patient developed meningoencephalitis. The case was identified as autochthonous or local as no records of travel abroad and out of the area patient's residence. The causative agent was confirmed by PCR at NCIPD - Sofia, and there was a corresponding increase in IgM evident in the blood tests. The clinical and laboratory criteria for issuing Rapid Alert were present. Following clarification, a notification was sent to the competent authorities of other EU Member States via the RAB.

In 2018, the Expert Council on Transfusion Hematology adopted an Action Plan for the occurrence of West Nile fever in the country. The document sets out an algorithm for actions and measures to be taken, at national level (general measures) and in the affected areas (local measures). The respective measures have been undertaken to strengthen donor control and clinical judgment, as well as postponing all donations of supposedly infected donors for 28 days after their flu-like symptoms have passed.

2.11. SPECIALIZED COMMITTEES TO THE AGENCY'S EXECUTIVE DIRECTOR

According to Art. 47 of the MPHUA to the Agency's Executive Director operate the following Specialized Committees: Committee for medicinal products; Committee for immunological medicinal products; Committee for homeopathic medicinal products; Committee for herbal medicinal products; Committee for radiopharmaceuticals; Commission for medicinal products with application in pediatrics; Commission for Advanced Therapies; Pharmacovigilance Risk Assessment Commission. Under BDA's supervision work Commission for determining product affiliation, Expert Council on Advertising, Expert Council on Retail Trade with Medicinal Products.

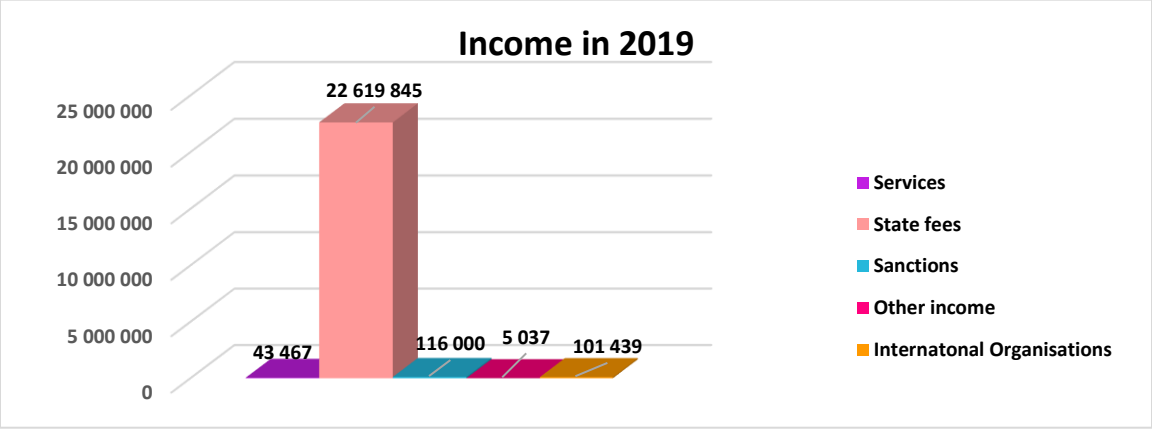
BDA's officials participate in the national commissions and expert councils such as National Commission for evaluation of Adverse Events Following Immunisation, Transparency Commission, Health Technology Assessment Commission, Interdepartmental Commission on the composition, characteristics and names of infant formulas and follow-on formulas, Higher Pharmacy Council and Expert Council on Haemotransfusion at the Ministry of Health.

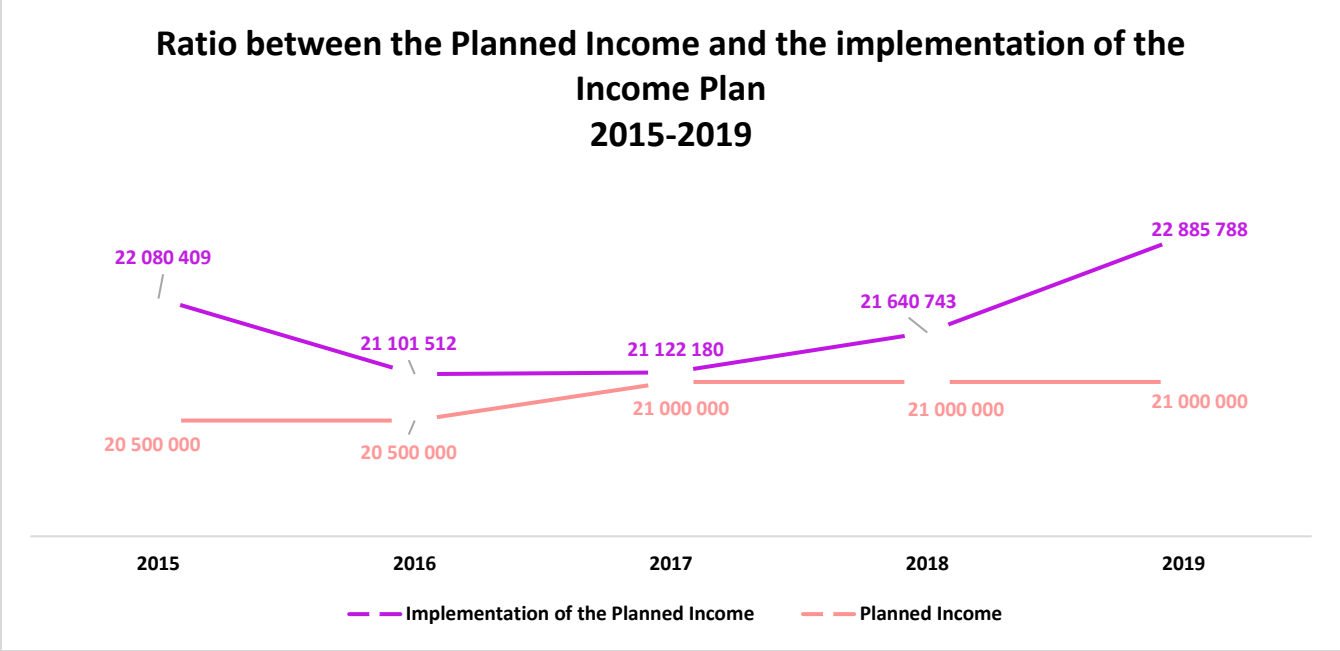
3. FINANCIAL RESULTS

Income

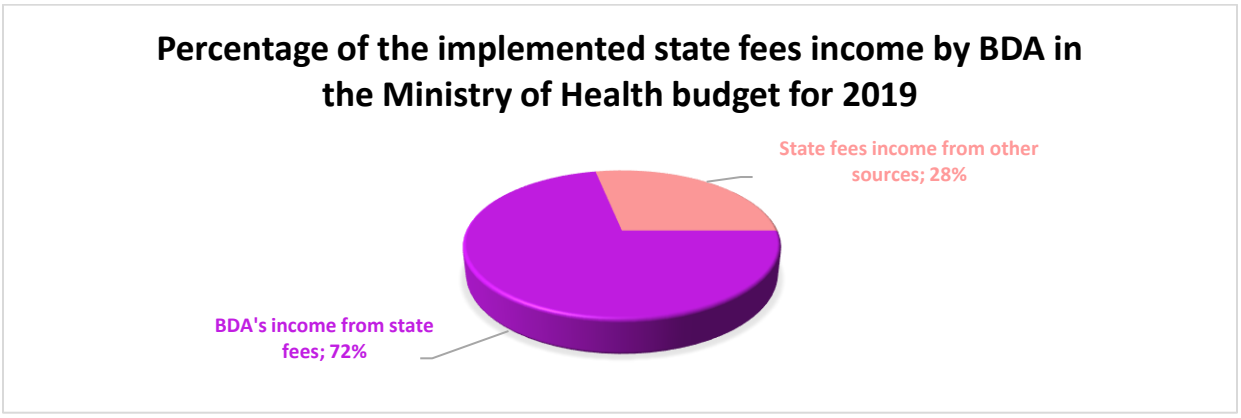
The income part of the BDA's budget is consistent of own income from state fees in accordance with the MPHUA and the MDA as well as sanctions (fines) and other sources. The total income in 2019 was 22 885 788 BGN as the approved budget was 21 000 000 BGN so the implementation is 108.98%. There is an overfulfilment of 8.98% as the overfulfilment of states fees alone was 7.7%. The income of state fees was 98.84% of the whole income and is the main pillar of the BDA's income.

The graph below shows the allocation:

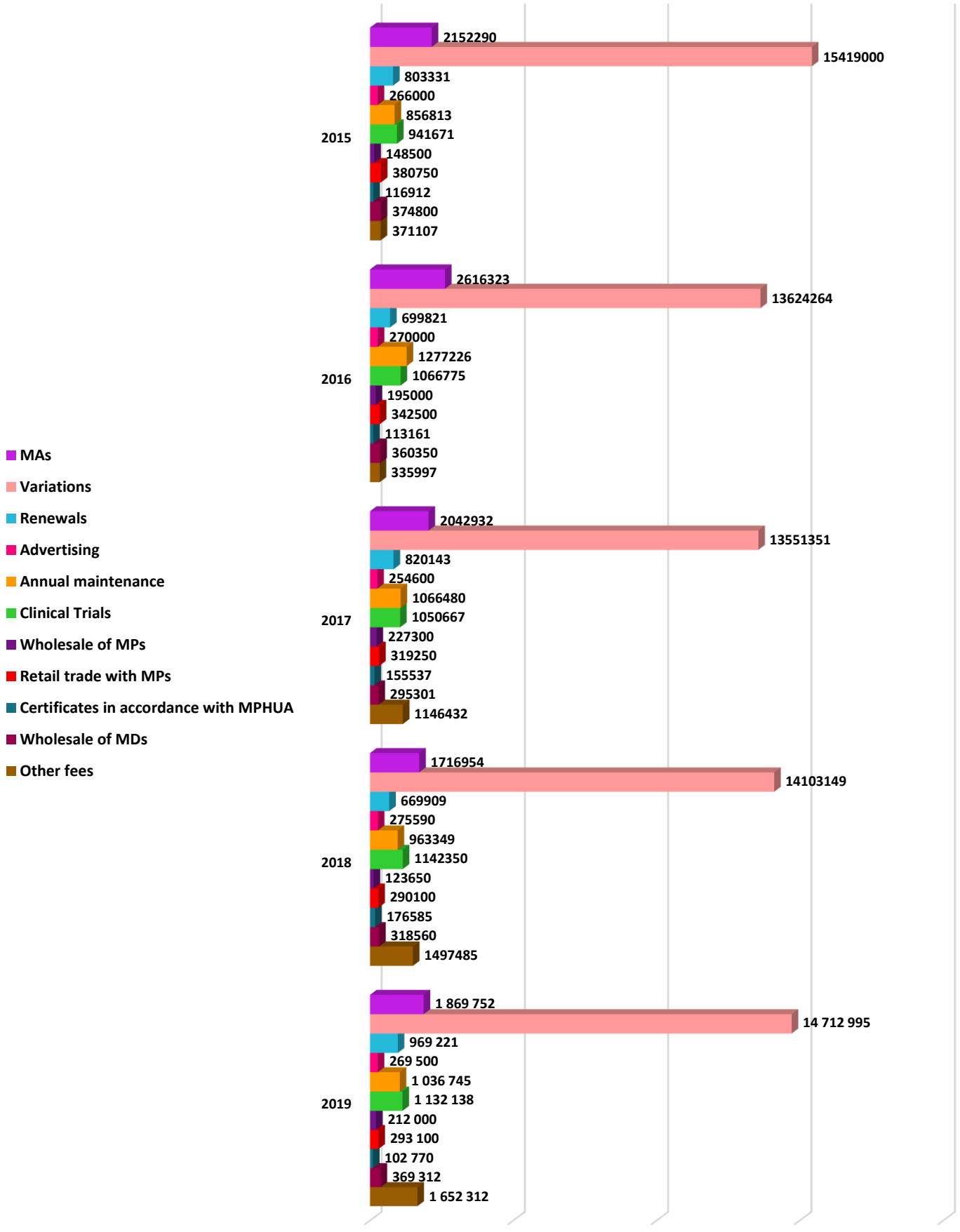




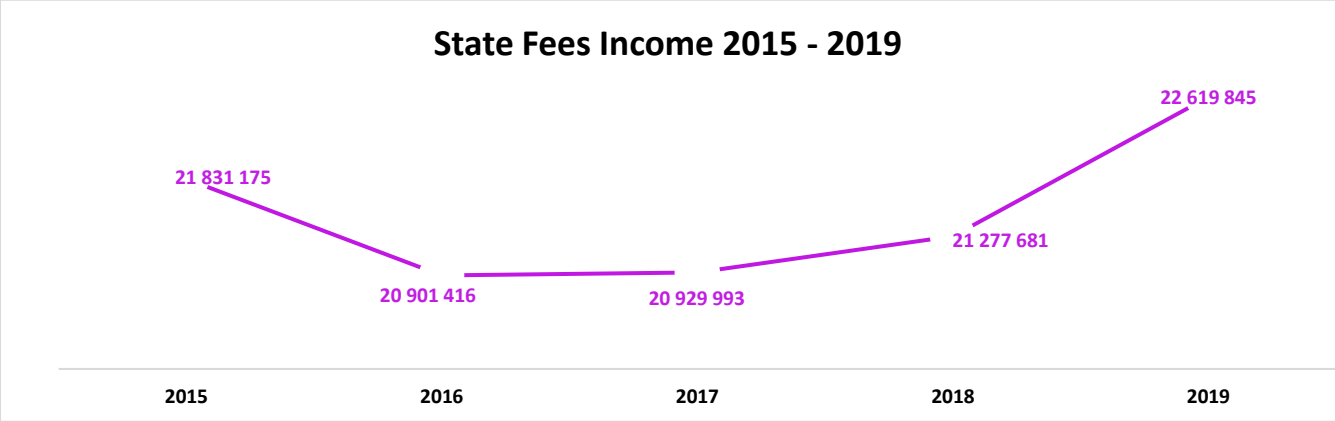
In 2019, the BDA generated BGN 22 619 845 income from state fees as the planned income was BGN 21 000 000. The expected income from state fees by the Ministry of Health were BGN 29 260 000. The BDA's income from state fees is 72% of the income budget of the Ministry of Health for 2019.



Structure of the state fees income by administrative service

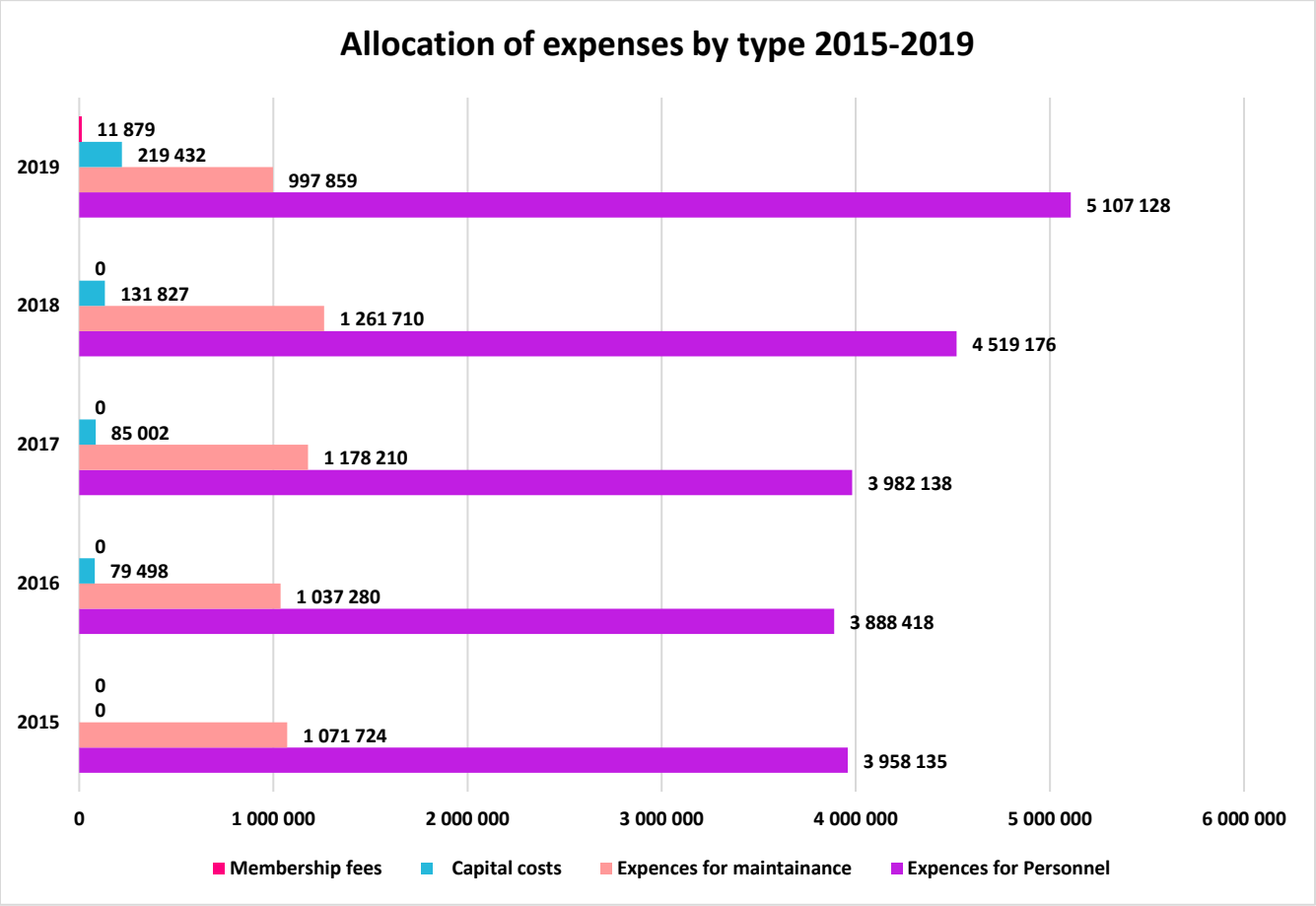


As evident from the figures above, the income from fees for Variations is 65% of the whole income from state fees.



Expenses

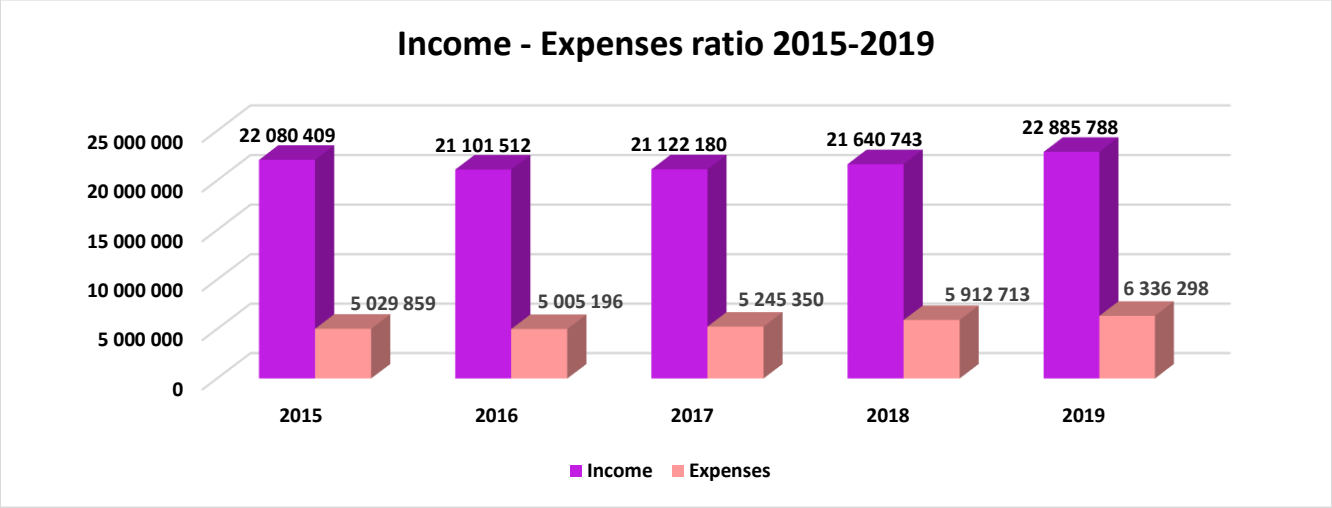
The total amount of expenses for 2019 is BGN 6 336 298 as the approved budget was BGN 6 793 138. The implementation is 93.27%. The saving are BGN 456 840 or 6.73%



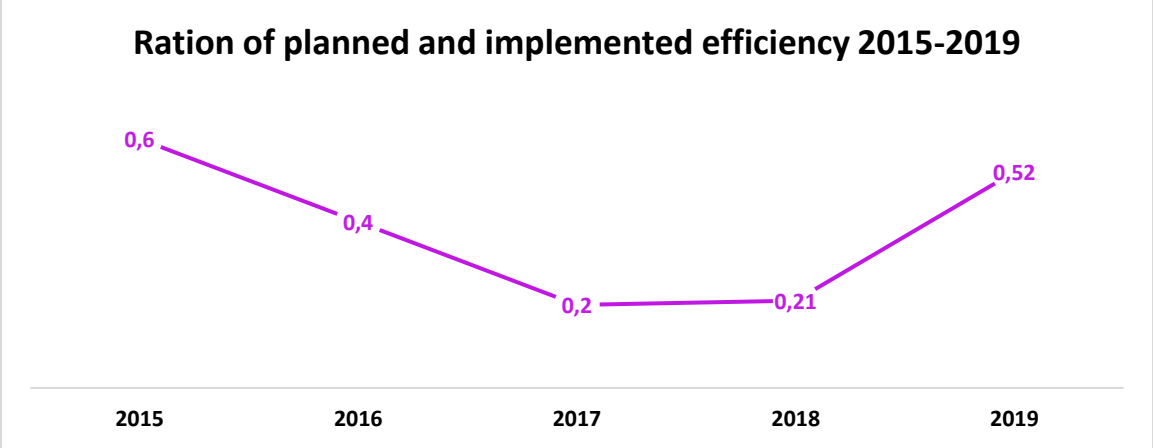
Executing the budget plan for 2019, the BDA spent BGN 219 432 for capital costs.

Effectiveness

Efficiency indicators are quantitative characteristics of the income-expense ratio.



The effectiveness indicator shows how much income each unit earns or how many leva income were received for each spent lev.

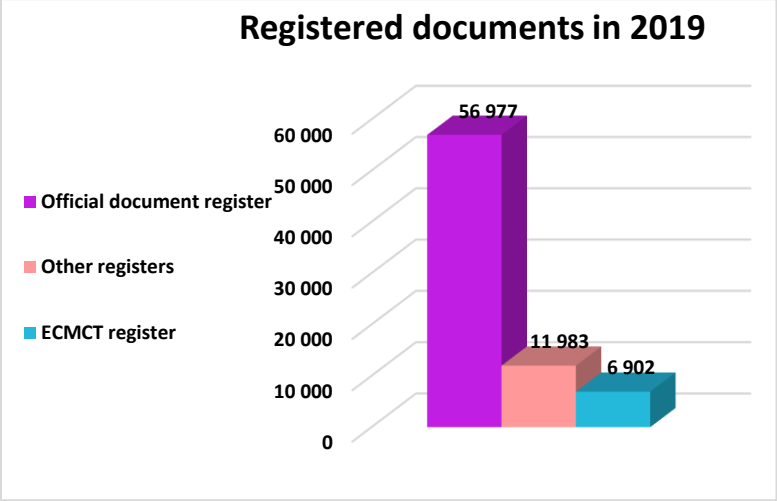


The Cost Effectiveness Ratio for 2019 is 3.61 and the planned was 3.09, meaning that each BGN 1 expense has 'brought' an additional effect of BGN 0.52 above planned, which represents two and a half times increased additional effect compared to the previous two years.

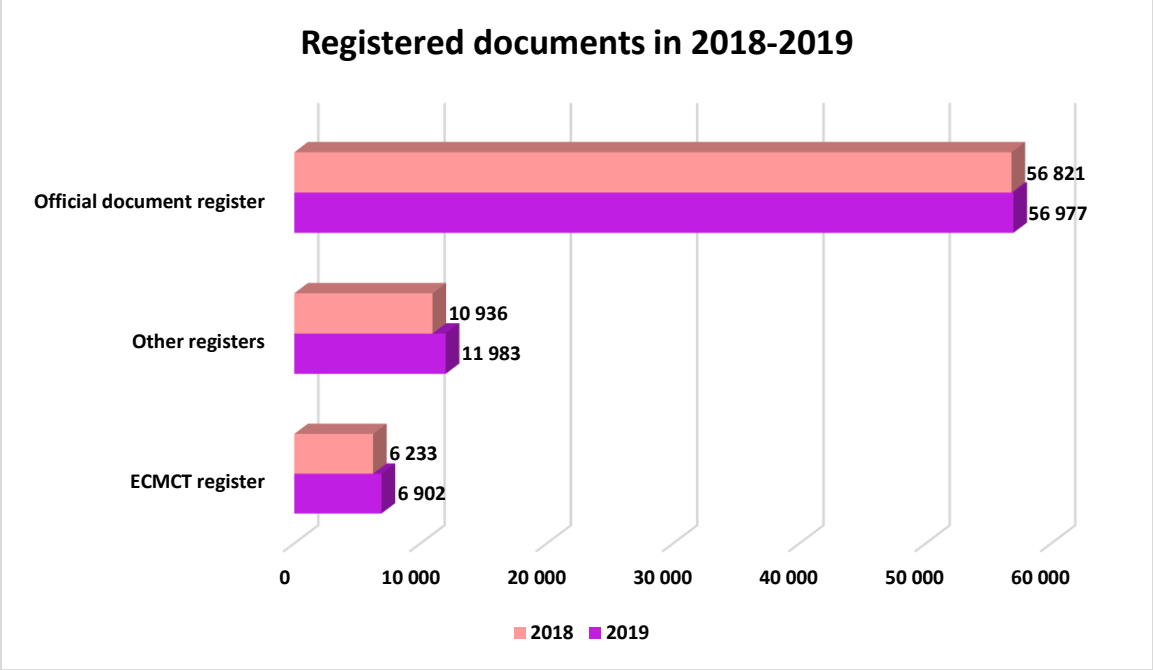
4. ADMINISTRATIVE SERVICES

In compliance with the requirements of the Administrative Services Ordinance, the users of the administrative services contact the BDA through the administrative service unit.

The documents registered in the Automated Information System (AIS) DOCMAN©2 in 2019 are as follows:



A mild increase in the document flow is evident when comparing the data for 2018 and 2019.



In compliance with the requirements of the Administrative Services Ordinance, the list of unified names of the administrative services provided by BDA, which is included in the IISD, has been updated.

5. PROCEDURES FOR AWARDING PROCUREMENTS

In 2019, the Agency carried out the following procedures for awarding procurements:

1. A gathering of offers procedure for tender „Delivery, installation, tuning, entry into service and aftersales service for gas chromatography system with flame ionization detector and autosampler for the needs of the laboratory of the Bulgarian Drug Agency“;

2. A gathering of offers procedure for tender „Delivery of 20 computer configurations for the needs of the laboratory of the Bulgarian Drug Agency ”;

3. A gathering of offers procedure for tender „Delivery, installation, configuring and entry into service of 19 discs 1,2TB 10K SAS 25X2,5 DRIVE UPG for upgrading the disc array DELL EMC UNITY 300 and 1 expansion box for the needs of the laboratory of the Bulgarian Drug Agency“.

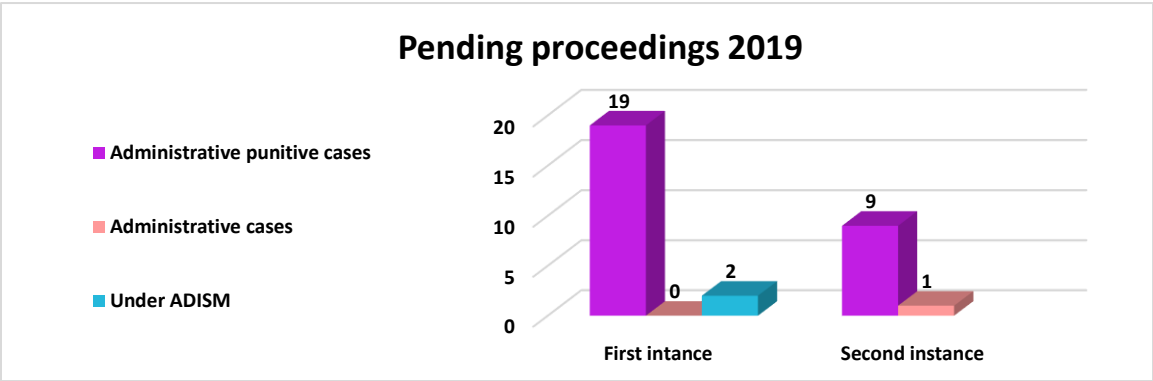
4. A public competition procedure ‘Procurement of airplane tickets for the transport of passengers and luggage, hotel reservations and accommodation during business travel abroad for the needs of the Bulgarian Drug Agency’.

6. LEGAL PROVISION

The main priority for the BDA is providing and ensuring the lawfulness of all administrative activities and of the issued administrative acts. In pursuance of their duties according to the BDA Structural Regulation and their job descriptions, the legal advisors provided day-to-day legal assistance in respect of the lawful execution of the administrative activities in the field of medicinal products, medical devices and transfusion supervision.

Litigation

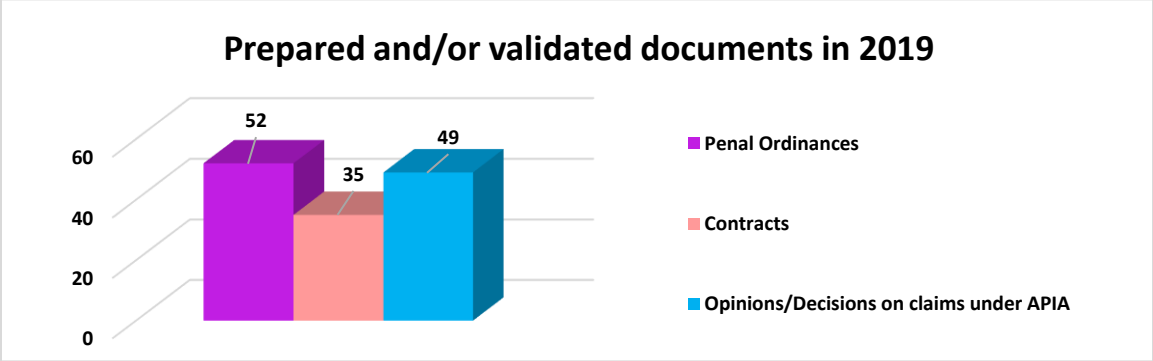
The BDA’s legal advisors carried out litigation in 72 legal proceedings on administrative punitive, administrative and civil cases and cases under the Act on Liability for Damages Incurred by the State and the Municipalities (ALDISM). The information for the development of the proceedings is shown in the diagrams below:



In 2019, there were no repealed penal ordinances. Regarding all appealed penal ordinances that entered into force, the respective actions for collecting the imposed fines and sanctions according to the procedure of Tax-Insurance Procedure Code were carried out.

Cassation appeals were drafted in cases of unfavorable court decisions.

Validation of the lawfulness of acts of the Executive Director



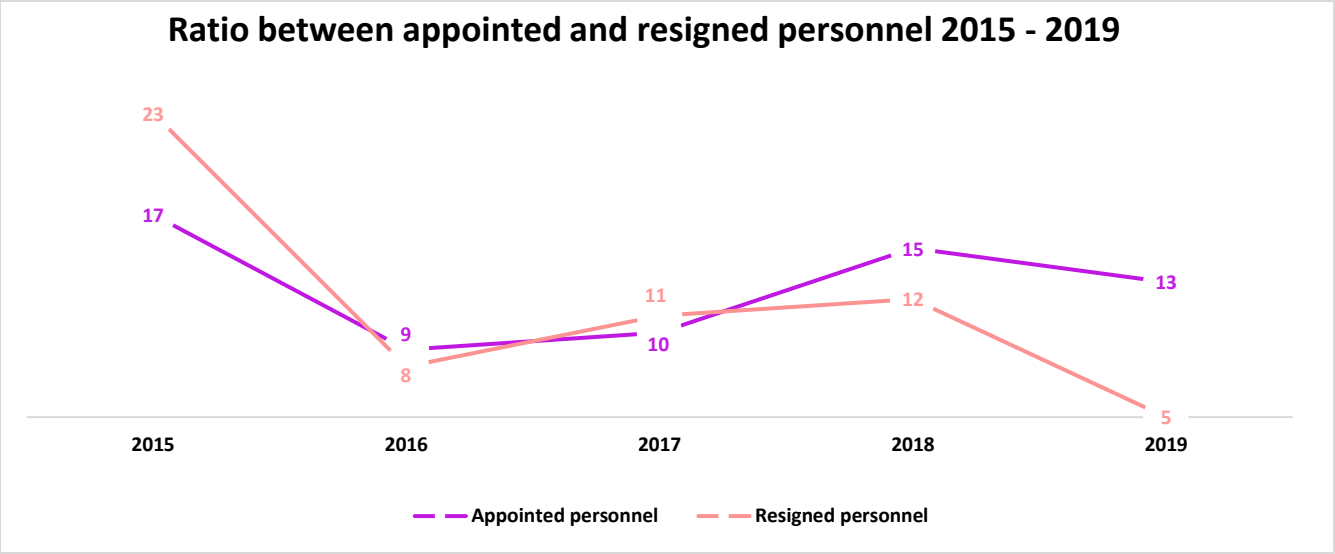
Participation in the development of internal rules, draft legislation and opinions on draft legislation

In 2019, opinions on draft laws for amending and supplementing the MPHUA and its subordinate legislation were prepared. The legal advisors participated in an interagency work group assigned to draft amendments to the Medical Devices Act in connection with the entry into force of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC and Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

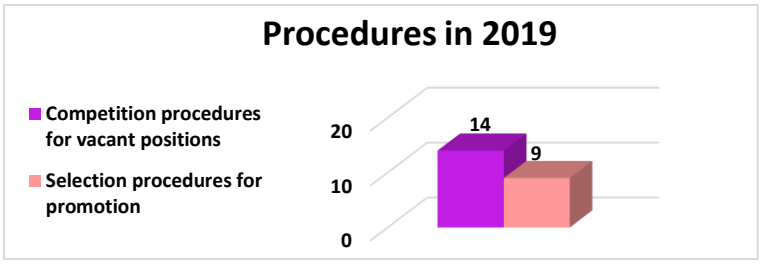
7. HUMAN RESOURCES MANAGEMENT

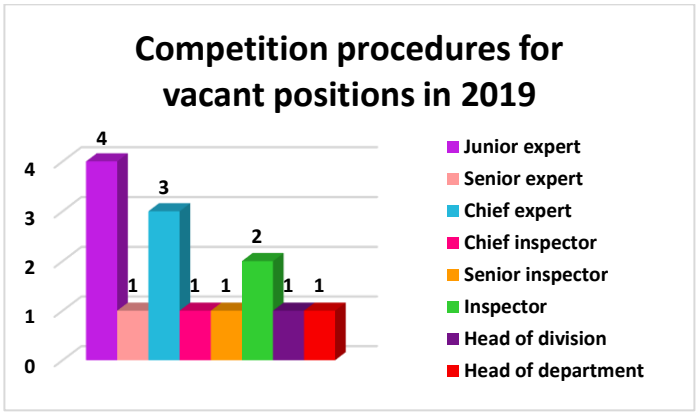
Personnel

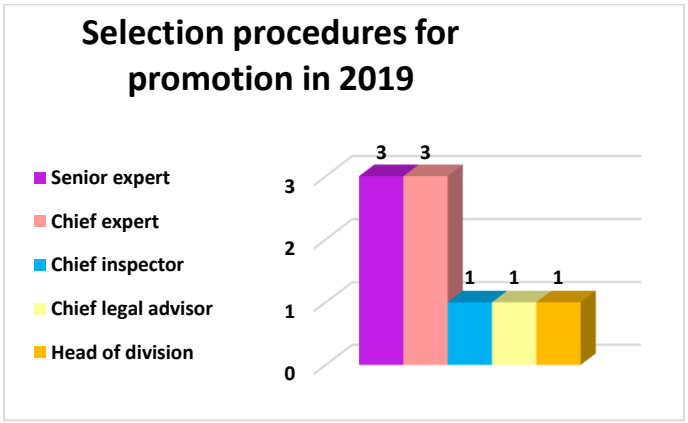
In 2019, the BDA appointed 13 new employees. There were 5 employees who resigned, including those who retired.



In 2019, the Agency held 14 **competition procedures for vacant positions** and 9 **selection procedures for promotion** as follows:







Following the completion of the annual evaluation for 2019, on the basis of the received assessments and in accordance with the provisions of the Ordinance on the conditions and procedure for evaluating the performance of the employees in the state administration, an increase in the rank of the eligible employees was made.

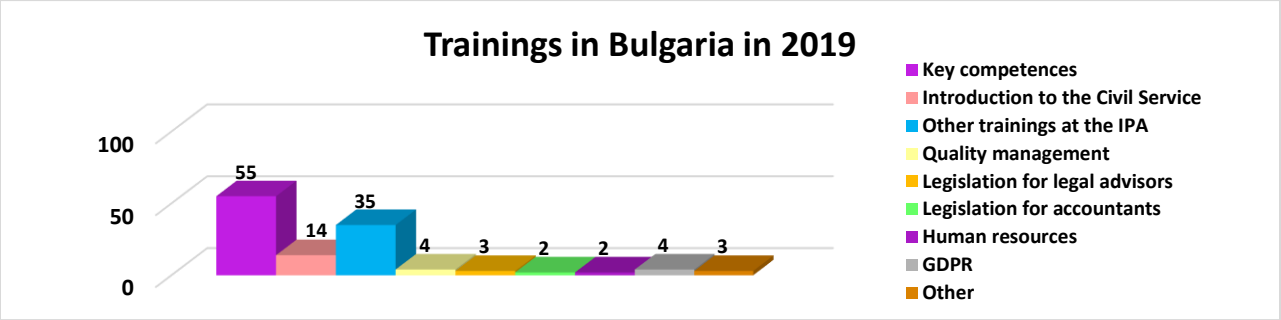
Qualification and training

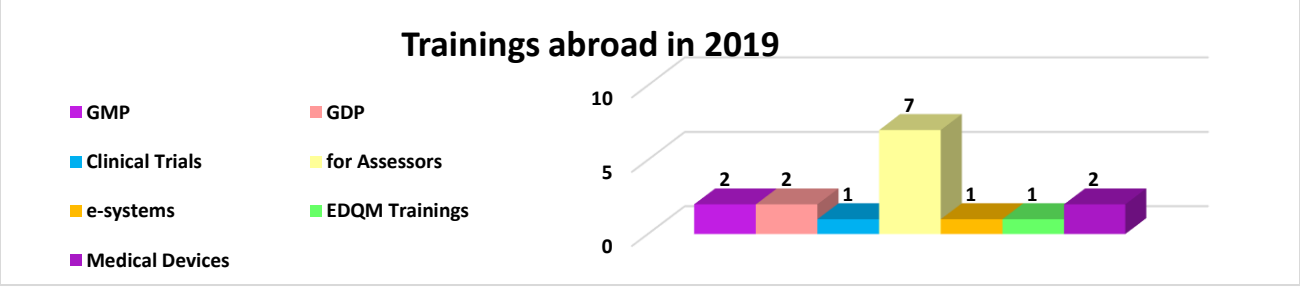
The HR experts organized the mandatory and the specialized trainings for qualification improvement of the Agency's employees. They monitored the implementation and included the successfully passed trainings in the employees' dossiers. The BDA's experts actively use the online Learning Management System (LMS) of the EU regulatory network. The LMS is designed for employees from the national competent authorities (NCAs) and the EMA providing access to appropriate and high-quality opportunities for scientific and regulatory trainings thus ensuring its quality and promoting the harmonization of evaluation standards

BDA staff actively participates both in face-to-face trainings and in webinars. Except for the specialized trainings, the Agency's employees improve their communication and computer competences. The BDA experts take part in training projects in order to prepare themselves for working with different systems. Part of the trainings finish with certificate after successfully passing exams.

BDA staff participated in the following types of trainings:

1. scientific and regulatory trainings;
2. for auditors for quality management systems;
3. related to the implementation of the European and Bulgarian legislation on medicinal products, medical devices and the blood transfusion system.





8. INTEGRATED QUALITY MANAGEMENT, INFORMATION SECURITY AND RISK MANAGEMENT SYSTEM

Maintenance and Improvement of the Integrated Quality Management, Information Security and Risk Management System (IMS)

In 2019, the maintenance and the improvement of the Integrated Quality Management, Information Security and Risk Management System was successfully continued in accordance with ISO 9001 and ISO / IEC 27001 and scope of certification: Expert evaluation and supervision of quality, safety and efficacy of medicinal products. Pharmacovigilance. Expert evaluation of advertising of medicinal products. Control of manufacturing, wholesale and retail of medicinal products. Expert evaluation, registration and market surveillance of medical devices. Supervision of blood transfusion system.

With the entry into force of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and the introduction of new requirements for the protection of personal data with regard to their processing by automation or other means, were put in place processes, mechanisms and rules. By order of the Executive Director of the BDA, a personal data protection officer has been appointed.

Internal and external audits

According to the *Annual Program for conducting Internal Audits for 2019* and implemented IMS, the BDA's quality management experts conducted internal audits of the Agency's structural units, processes and activities. The results show that the BDA's employees are familiar with the IMS. They apply the system and work to optimize its processes.

In July 2019, a control audit of the IMS was held by the accrediting organization Intertek. There were no identified non-compliances and an improvement of the IMS was ascertained.

With regard to Regulation (EU) 2016/679 – GDPR which has been applicable since 25 May 2018, a comprehensive internal audit was carried out to assess compliance with the requirements of the Regulation. In line with the audit results, steps have been taken to improve the functioning of the system.

In May 2019, a comprehensive internal audit was conducted in order to "Establish the compliance of the processes in the Executive Agency for Medicines with the requirements of standards BDS EN ISO 9001: 2015, BDS ISO / IEC 27001: 2014 and the Integrated System Quality Management and Information Security. Identifing Measures for Improvement of the MIS. " It has been established that the implemented Integrated Quality, Risk and Information Security (MIS) Management System at the Agency is maintained and functioning in accordance

with the requirements of BDS EN ISO 9001: 2015 and BDS ISO / IEC 27001: 2014. The BDA's Management has provided visible management support and adequate organizational, financial and information and technological resources for the processes execution and for the maintenance of the MIS. The BDA staff is highly aware about the compliance with the MIS requirements.

In October 2019 was conducted an audit concerning the conformity of the pharmacovigilance system processes carried out in the Agency with the requirements of Directives 2010/84 / EU, 2012/26 / EU and 2001/83 / EU, Regulations (EC) No 520 / 2012, 726/2004, 1027/2012, 1235/2010, MPHMA, GVP and the implemented MIS. No inconsistencies were identified in accordance with national and international legislation and ewe identified opportunities for improvement of the pharmacovigilance processes.

In June 2019, a Management Review was conducted, reporting the following:

- Meeting the objectives set for the relevant period;
- Information on changes and expectations of the BDA's activities, including changes in internal and external circumstances that would affect the processes in the Agency;
- Information on the efficiency and effectiveness of the IMS and processes in the BDA.
- proposals for improving the processes and the services.

9. INTERNATIONAL COOPERATION

The BDA coordinates international activities and cooperation with regulatory and supervisory authorities of other countries and with organizations working in the field of medicinal products regulation and control, including the Agency's expert's participation in scientific committees and working groups at EMA, the European Commission, the EDQM, the European Pharmacopoeia and other bodies and institutions. BDA regularly attends meetings of the HMA and EMA, committees and working groups of the two organizations, as well as their joint initiatives.

Agency's experts took part in meetings of the Expert group on the Delegated Act on Safety Features for medicinal products for human use and a Workshop hosted by the European Medicines Verification Organization; in a discussion on 'Drug shortages: a requirement for tangible political commitment in the EU' with representatives of the European Commission in Brussels, Belgium. The BDA was represented at the 14th Traditional annual symposium of Medicines and Medical Devices Agency of Serbia in Kragujevac.

10. INFORMATION TECHNOLOGIES

In 2019 were taken measures to improve the reliability and speed of operation of information systems in the BDA. In this regard, a new disk array was installed and put into operation. BDA implements reliable software solutions to protect information security.

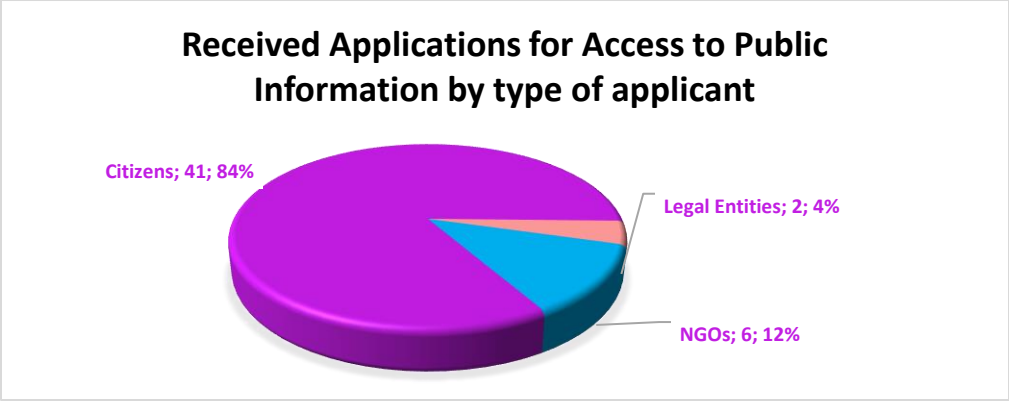
The BDA actively participates in the project of the Ministry of Health "Development, completion and integration of the necessary registers and administrative services for the implementation of the National Health Information System".

The Agency's IT experts organise and control the interaction between the BDA's and EMA's information systems.

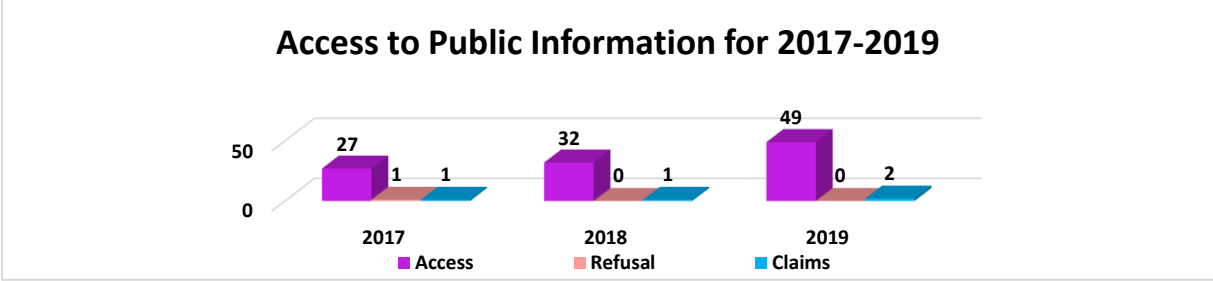
11. TRANSPARENCY AND COMMUNICATIONS

Access to Public Information

In 2019, the BDA received 49 Applications under the Access to Public Information Act (APIA) as 41 of them were submitted by citizens, 2 - by legal entities and 6 - by NGOs.



All the required accesses were granted in the set terms. There were 2 claims against a final act under APIA.



Communications

On the occasion of the European Antibiotic Awareness Day - 18 November, the "World Antibiotic Awareness Week" was launched. In this regard, the European Medicines Agency launched a social media campaign to promote accountability for antibiotic use and to raise public awareness on the growing problem of

antibiotic resistance posing a worldwide health threat. In support of the EMA campaign, a press release was published on the BDA‘s website.

From November 25-29, 2019, the Fourth International Annual Educational Campaign for Awareness on Adverse Drug Reactions and National Reporting Systems "Drug Safety Week" was held. BDA once again coordinated the Bulgarian participation in the campaign with the assistance of partners from universities, professional organizations, unions, patient associations, health portals and sites and the industry. Each year are distributed short animated videos on a specific topic, developed by the Uppsala Monitoring Center of WHO, Sweden. The theme of the 2019 campaign was "Multiple Medication Therapy: Reporting Adverse Drug Reactions Helps the Safe Use of Multiple Medicines at the Same Time".

12. ANEXES

12.1 HISTORY

Medicinal regulation is the contemporary internationally adopted term to denote the totality of activities carried out by the state in different spheres of the pharmaceutical sector so as to ensure society with medicines of high quality, efficiency and safety.

In compliance with the adopted terminology nowadays, established on the basis of long scientific and practical experience, a medicine is any finished product which is a substance or combination of substances intended for the treatment or prophylactics of diseases in people and is offered in a finished package, as well as a substance or combination of substances administered to people to diagnose or recover, correct or change human's physiological functions.

The beginning of the state control on medicines in Bulgaria is based on an indispensable prerequisite – the introduction of the official pharmacopoeia. This happened in 1879, only a year after Bulgaria was liberated from the Ottoman rule. The legal document is "Temporary rules on the structure of the medicinal management in Bulgaria". The date is 1 February 1879. This is the document that lays the basis of the state control on pharmacies.

The birth date of the medicinal regulation in Bulgaria is considered to be 31 October 1904, when together with the publication of Decree 44 of Royal prince Ferdinand by virtue of Art. 169 of the Public Healthcare Protection Act, the chemical laboratory at the Public Healthcare Protection Directorate was established and regulations for its worked were published. In 1908 the chemical laboratory was transformed into a Chemical Institute at the Public Healthcare Directorate. In 1935 this institute was set up as a department of the newly-founded Institute of Public healthcare, including a microbiological and hygiene department. The chemical department was presented by four control laboratories then – medicinal control, control of vitamins and food, control of poisonous substances and bacteriological control.

In 1945 a Central Institute on norms and control of biological substances was founded. In 1949 the institute was renamed in State Control bacteriological Institute. In 1954 the department on the control of medicines at the Central Pharmaceutical Institute (later Scientific-research Chemical-pharmaceutical Institute /SRCPI/) joins the State Control bacteriological Institute and the State Institute for the control of medicines (SICM) was founded.

After the demonopolization, the decentralization of the production, supply and distribution of medicines in 1991, SICM turned out to be the only State institution, competent in the medicinal sector. International experience was gained and the foundation of a different institute was prepared, an institute which gradually superseded SICM – doubtlessly prestigious in the sphere of the control of quality. This internal evolution was backed up by a state decision in 1992, when the council of ministers transformed the State Institute for Control of Medicines into a National Institute for Medicinal products (NIMP).

In 1999 the Pan-European Regulatory forum was launched and it gathered the intellectual potential of the whole European pharmaceutical regulation and a dialogue began, in which positions were harmonized, priorities were outlined and the policy for this sector was laid down. The participation of Bulgaria and the other associated countries was planned as a form of training and gaining experience, but as a partnership as well, in which the opinion of all countries was valuable. What is important for the institution is the participation in joint trials within

the framework of European Network of Official Medicines Control Laboratories (OMCL) and the European Directorate for the Quality of Medicines (EDQM) at the Council of Europe.

The legal framework of the necessity to amend and supplement legislation in Bulgaria was outlined when the Act for the amendment and supplementation of the Pharmaceuticals and Pharmacies Serving Human medicine Act was passed. The Act was renovating in the following aspects: new terms for "medicine", "medicinal product", "medicinal substance" were introduced; medical devices were included in the range of the Act; the texts, concerning clinical trials were up-dated. By virtue of the Act the Bulgarian Drug Agency at the Ministry of Healthcare was established, which was defined as a body for the supervision of the quality, efficiency and safety of medicines. It has extended rights and functions, including the ones on the issuance of manufacturing authorizations, marketing authorizations under art. 3, par. 3 and 5, (medical devices and in vitro diagnostic means), keeping different registers, registration of drugstores etc.

12.2 INFOGRAPHICS