BULGARIAN DRUG AGENCY'S

ANNUAL REPORT

2018

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

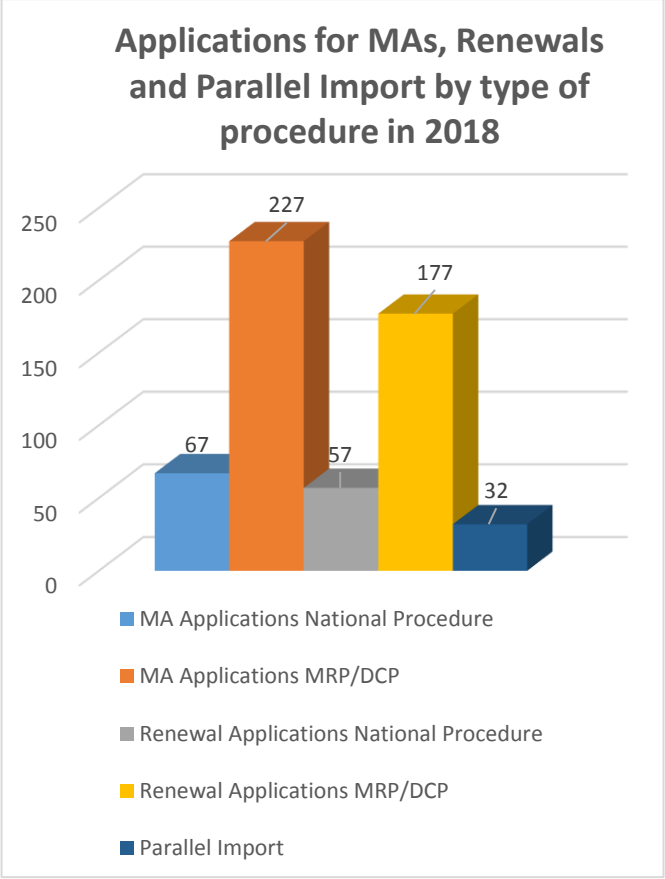
2.1.MARKETING AUTHORISATIONS OF MEDICINAL PRODUCTS

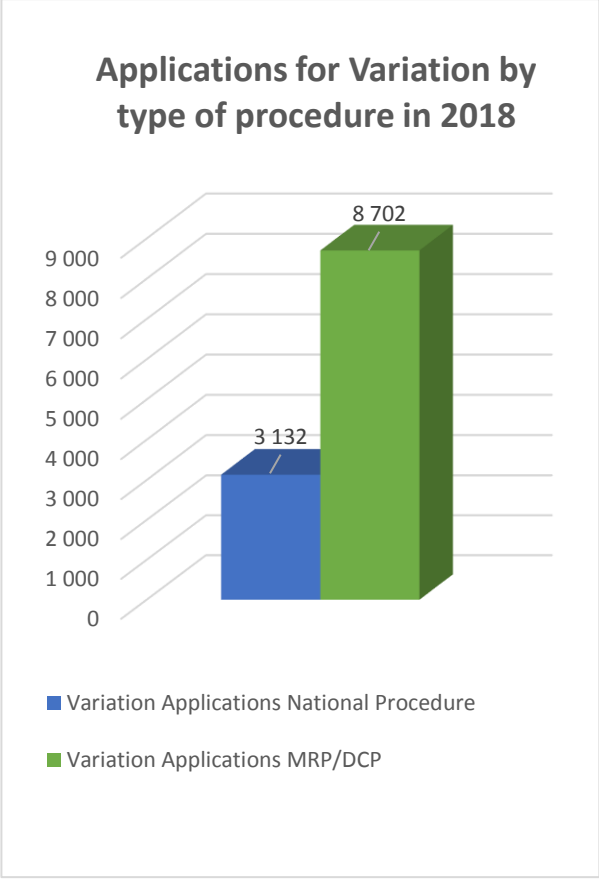
One of the BDA's main activities is the marketing authorisation (MA) of medicinal products in Bulgaria after expert assessment of their quality, safety and efficacy.

Received applications

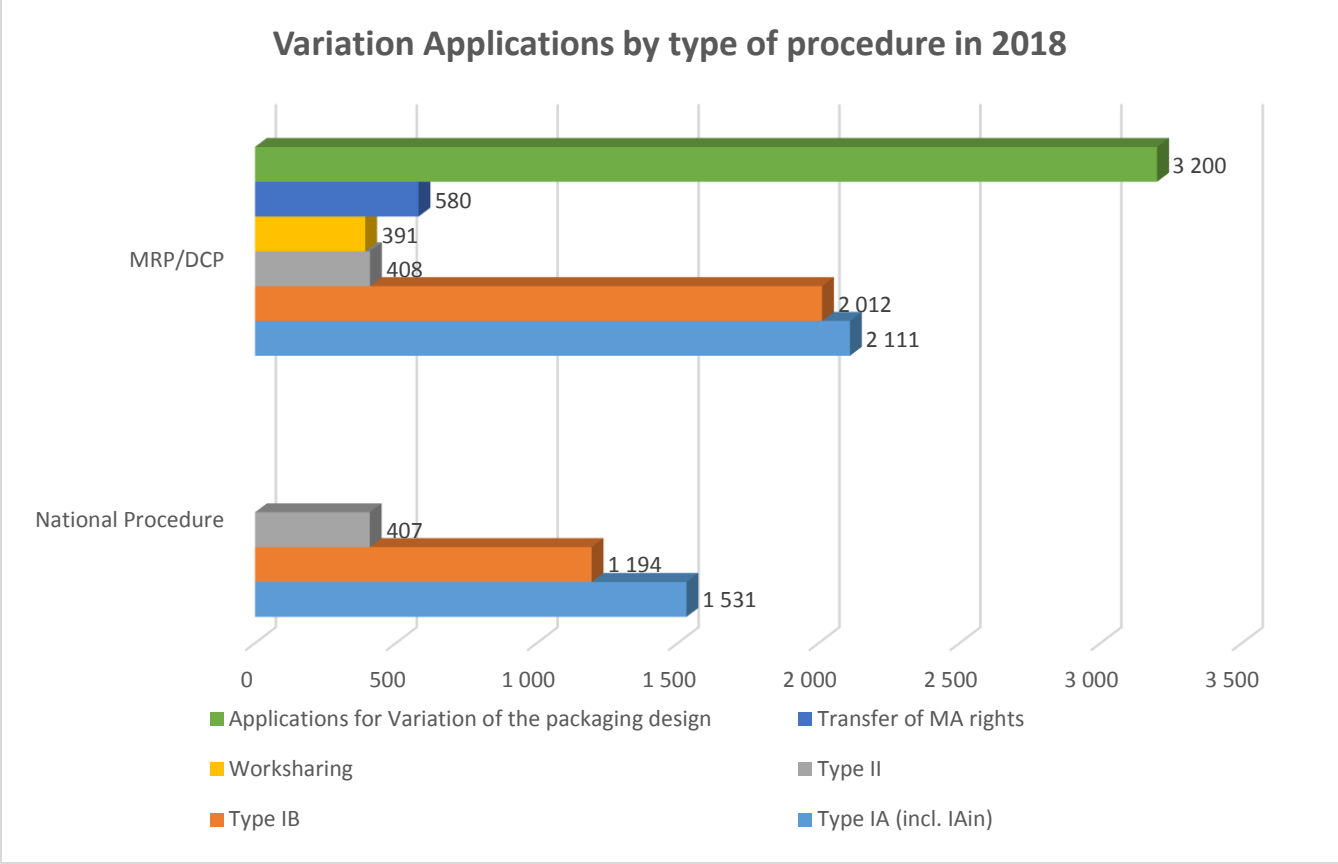
In 2018, there were received 12,394 applications for marketing authorisations, renewals, and variations under decentralized, mutual recognition and national procedures. A large number of the applications for variations include applying for group variations of marketing authorisations (in one application several changes are to be evaluated, regarding one authorisation; or one variation concerning several medicinal products). That is why the total number of procedures differs from the number of received applications.

In 2018, the BDA received 294 Marketing Authorisation Applications; 32 Applications for Parallel Import; 234 Renewals; and 11,834 Variations. They are distributed as follows:

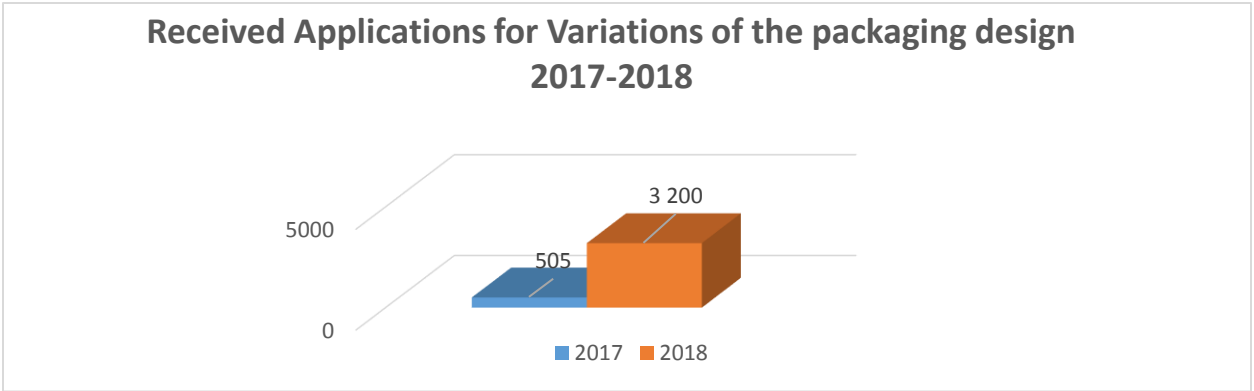


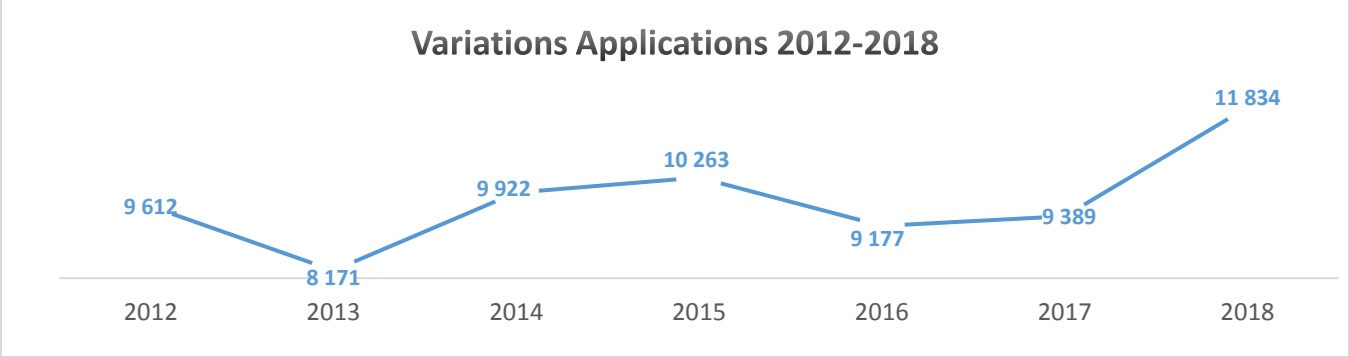


A significant part of the regulatory activity covers the assessment of variations in the marketing authorisations for medicinal products.

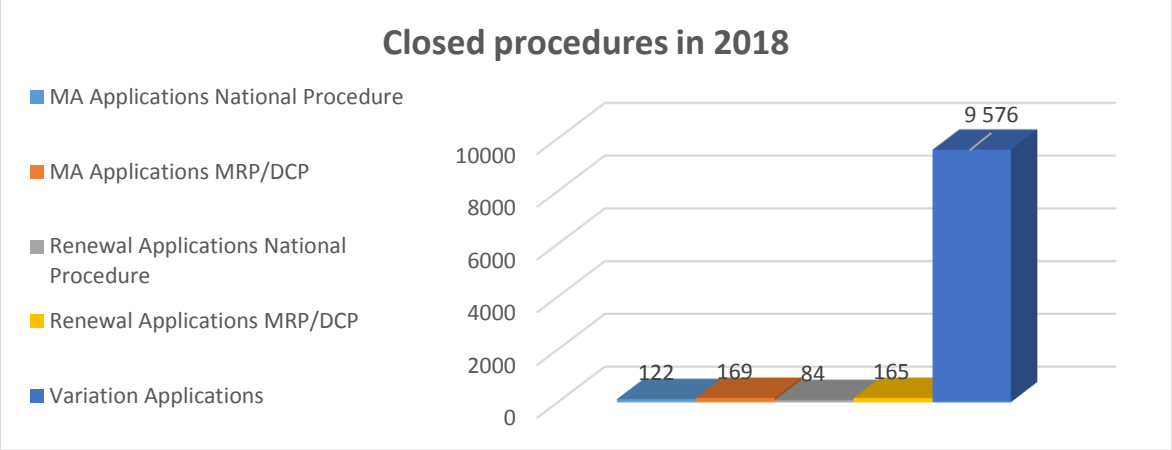


Over the past year, there was a significant increase in the number of the applications for transfer of marketing authorisations rights (580) due to the forthcoming Brexit and the legal requirement for the MAHs to be located within the EU. The forthcoming entry into force of the COMMISSION DELEGATED REGULATION 2016/161 (EU) laying down detailed rules on the safety features on the packaging of medicinal products for human use also imposed a campaign application for variation of the packaging design, resulting in 3,200 applications (Notifications according art. 61(3)).





Closed procedures



Additionally, the Agency issued 3 authorisations for line extension of a MA.

A total number of 9,576 Variations were completed for the year, including 366 procedures for MA transfer, as well as 2,291 changes to the package design and/or package leaflet.

In 2018, BDA, acting as an RMS, successfully completed two DCPs which began in 2017. Additionally, several DCPs, which Bulgaria had taken on as an RMS, based on the recommendation of the European Commission, were completed. At the same time, in connection with the anti-trust decision and recommendation of the European Commission, Bulgaria successfully finished as a RMS a number of procedures concerning a major pharmaceutical company.

In 2018, BDA undertook the commitments to be an RMS in 13 MRPs comprising 20 medicinal products, namely:

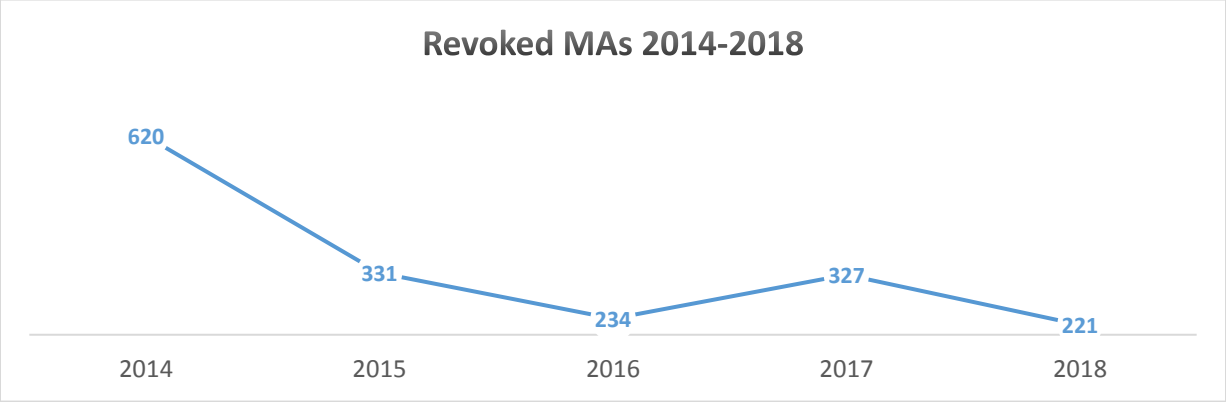
- 6 split procedures for 8 medicinal products;

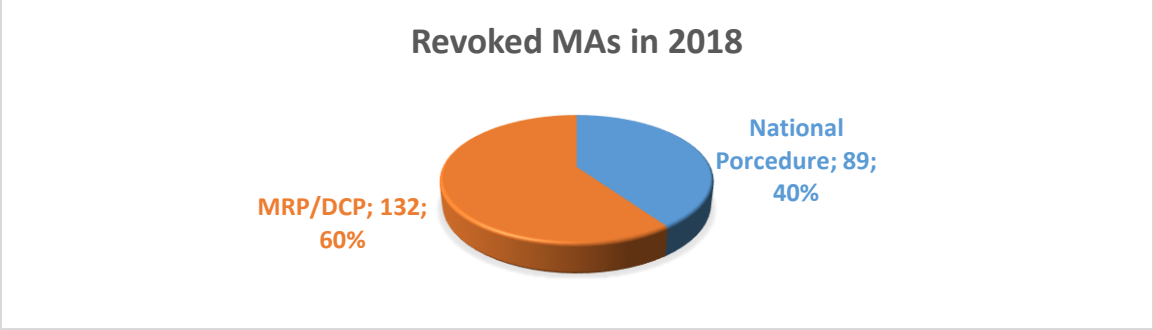
- 7 procedures resulting from the change of the reference Member State in relation to Brexit for 12 medicinal products.

Revoked Marketing Authorisations

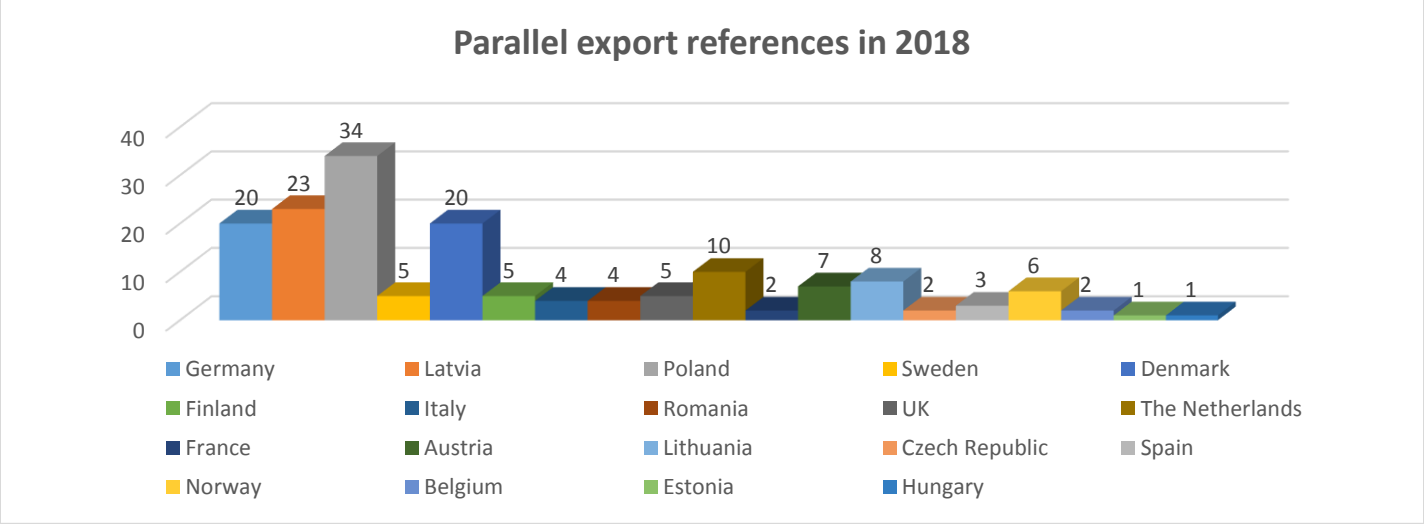
In 2018, 221 marketing authorisations of medicinal products were revoked as a result of the explicit request by the MAHs. None of them were associated with an identified serious risk to the public health or problems related to the quality of the products.

Following the European Commission's Implementation Decision C (2017) 7941 of 23.11.2017 concerning marketing authorisations of gadolinium-containing contrast agents for human use under Art. 31 of Directive 2001/83 / EC of the European Parliament and of the Council, BDA suspended the marketing authorisations of two medicinal products.





In connection with the requests received by BDA from the regulatory agencies of other EU Member States in 2018, 163 references for parallel exports were issued in 2018.



The biggest challenges for the Agency over the past year were:

• the forthcoming entry into force of Delegated Regulation 2016/161 which aims to prevent the entry of falsified medicinal products into the supply chain;

• the forthcoming Brexit.

Both of these factors contributed to a significant increase in the amount of workload the Agency was subject to which resulted in delays regarding certain procedures.

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.

The Bulgarian representatives at the EMA scientific Committees were nominated to prepare a number of reports on certain procedures. The following reports were delivered: Peer Reviews for SAWP, CHMP and COMP opinions, as well as PDCO, CAT and BWP.

Concerning the centralized procedures for marketing authorisation of the medicinal products, the Bulgarian representatives took part in multinational assessment teams together with Austria and Germany. An evaluation was made on the non-clinical part of the dossier (Non-clinical Modules 2.4 and 4).

2.2.MARKET SUPERVISION

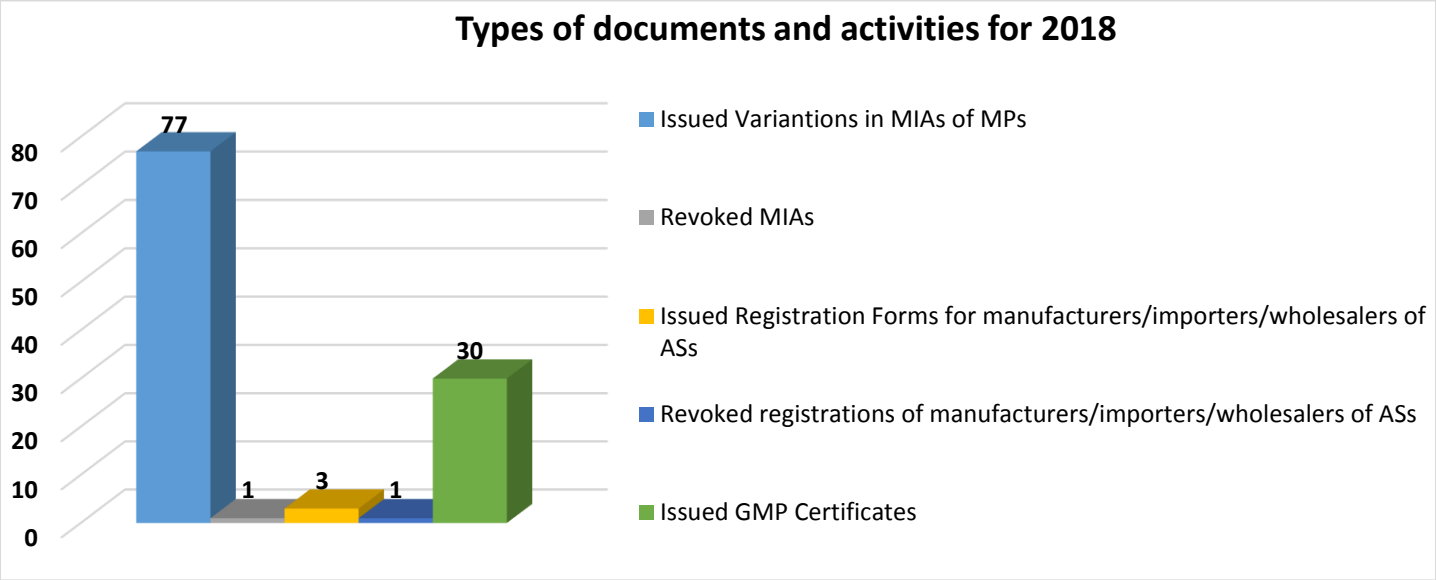
Another field of the BDA's activity is the issue of Manufacturing and Importation Authorisations (MIAs) of medicinal products (MP); registration of manufacturers, importers and wholesalers of active substances (AS); authorisation of retail trade of medicinal products in pharmacies; registration of medical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

Manufacturing authorisation and control

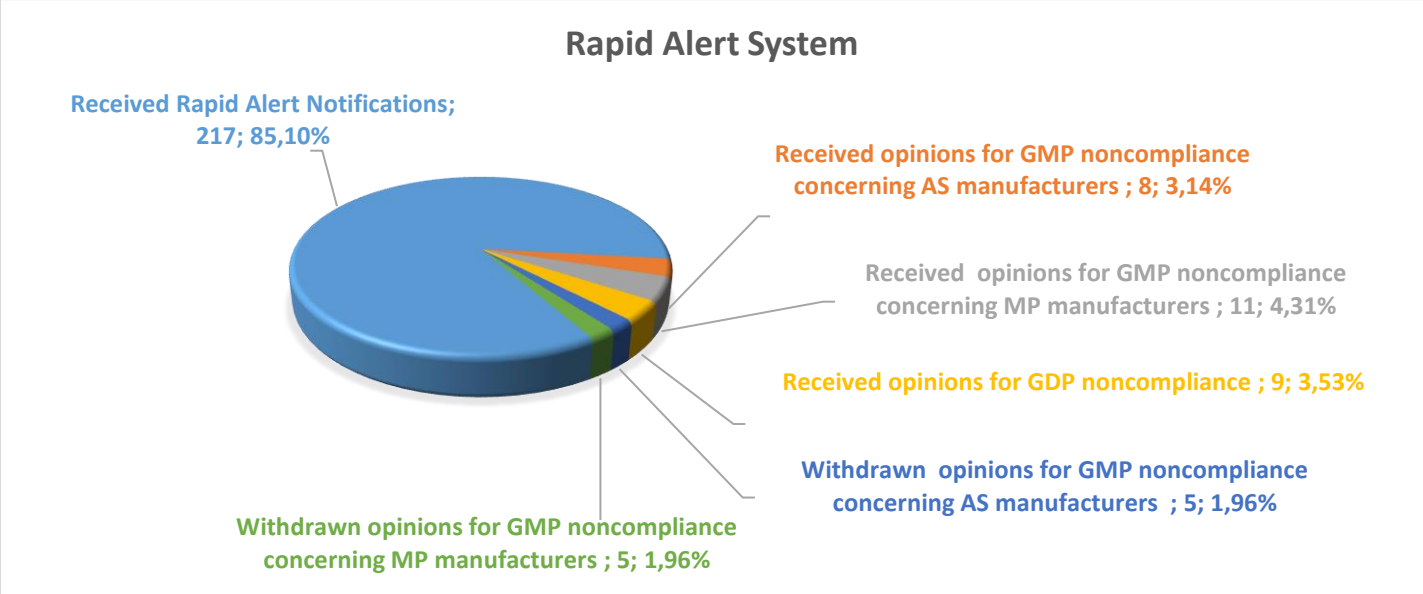
The Agency keeps an up-to-date electronic Register of Manufacturing/Importation Authorisations (MIAs) and Variations. The Eudra GMDP database is regularly updated regarding the issued MIAs and Wholesale Authorisations as well as the Good Manufacturing Practice (GMP) Certificates for medicinal products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

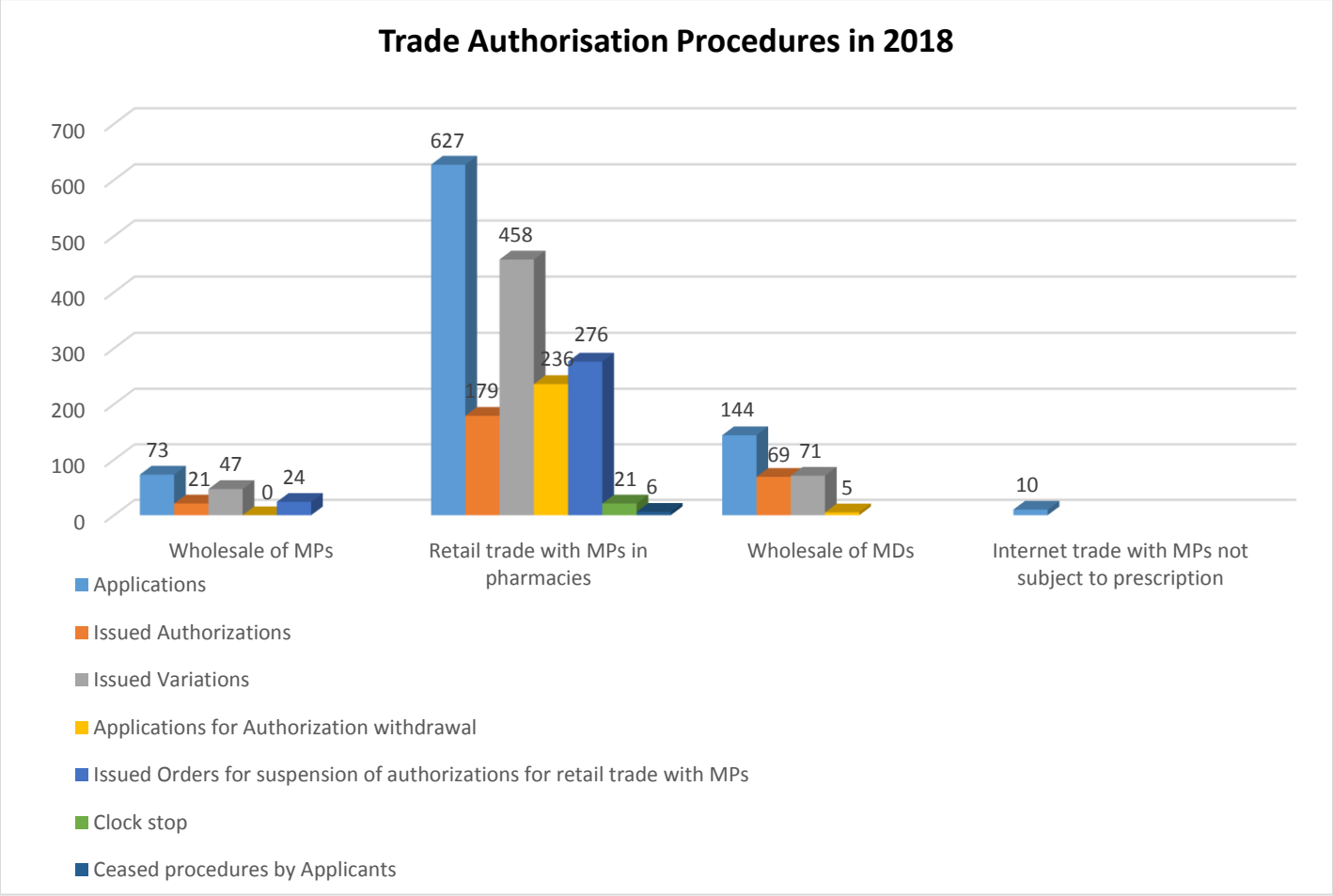


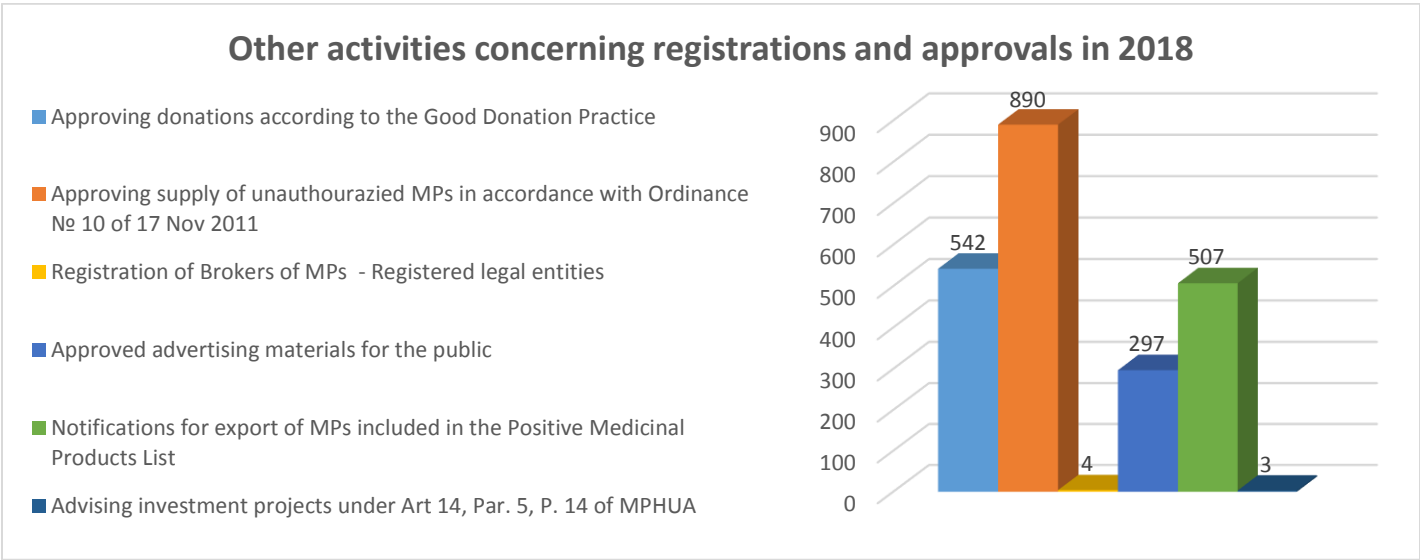
Inspections of manufacturers

In 2018, the BDA's inspectors carried out **47 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 2018 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.

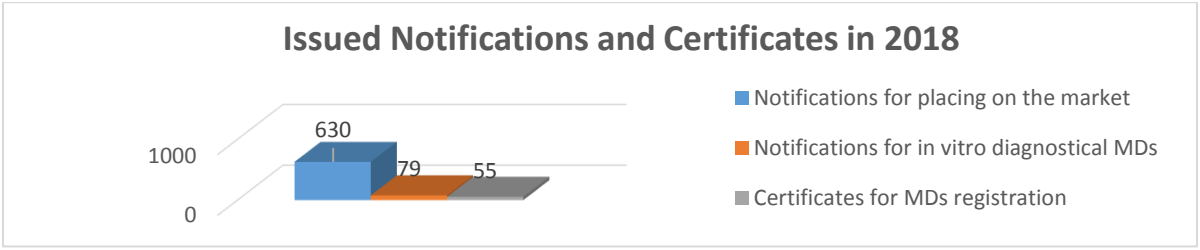
In 2018 inspectors from the agency performed a supervisory role in **a total of 4** GMP inspections on Bulgarian territory that were carried out by the regulatory authority of the Russian Federation – SID&GP, which led to the exchange of good practices and the improvement of their skills in the field of supervision and control over the manufacture of sterile and nonsterile medical products.

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



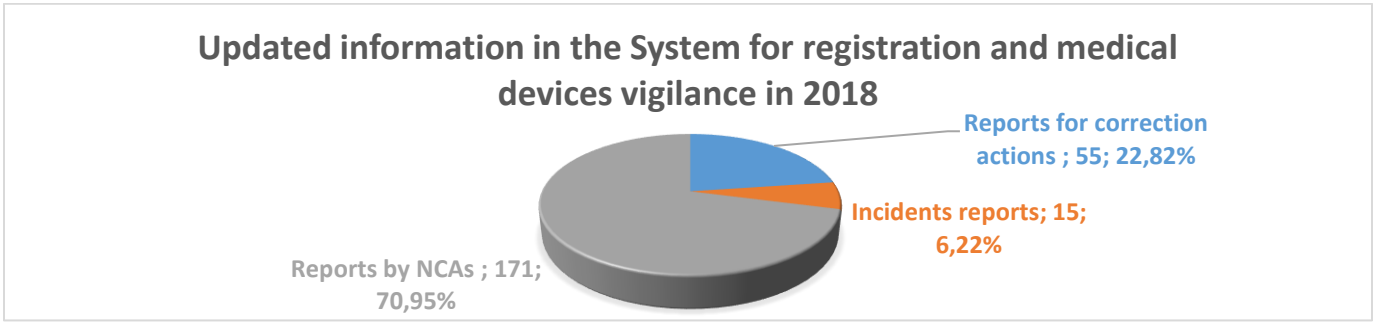


Medical Devices Registration



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 2018, validated records for **approximately 8000** medical devices were made.

Medical Devices Vigilance



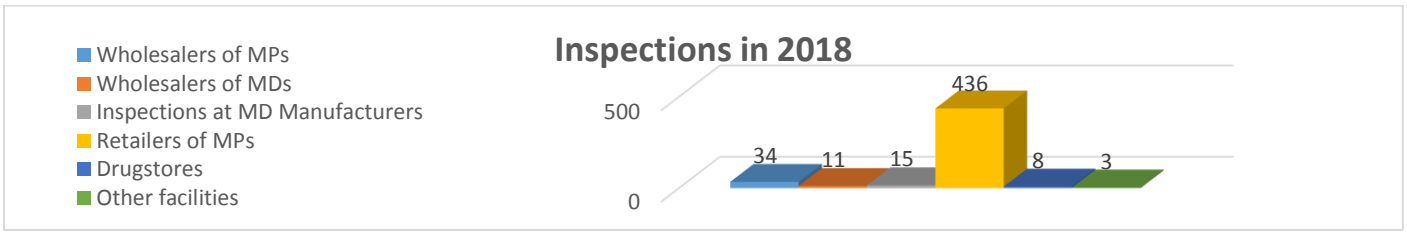
Clinical trials of medical devices

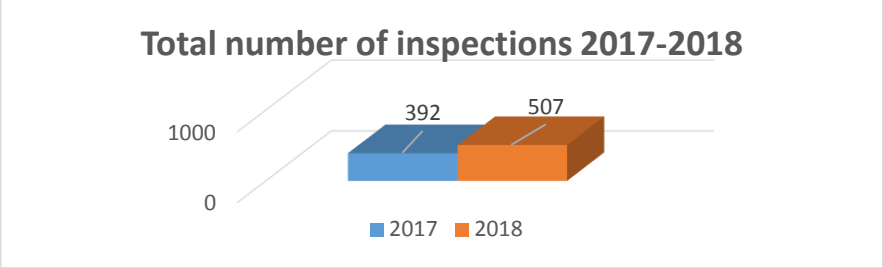
The received documentation was assessed and as a result **6 Clinical Trial Authorisations** and **2 Variations** were issued. In addition, further 3 notifications for clinical trials have been submitted.

2.3.CONTROL AND INSPECTIONS

In 2018, 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 Authorisation 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 507.





The most common violations in the retail trade with medicinal products

- Violation of the order of the chain of supply.
- Sale (dispensing) of medicinal product subject to medical prescription by pharmacists without being presented a prescription.
- Sale (dispensing) of medicinal product subject to medical prescription by assistant pharmacists.
- 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 of the MH.
- Improper storage of flammable medicinal products and medical products with an expired term of use.
- Sale (dispensing) of medicinal products by unauthorized personnel (lacking a pharmaceutical degree).

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), the *Combating Economic Crime* Sector at Regional Department of the Ministry of Interior and the Executive Agency *Medical Audit*, in the execution of Prosecutors' decrees following received signals for violations of the MPHUA and its secondary legislation.

During the market supervisory inspections, 23 samples of medicinal products were taken and were delivered for analyses in the BDA's laboratory.

Pharmacovigilance

The BDA's inspectors and experts participated in 7 inspections / re-inspections of marketing authorisation holders related to the pharmacovigilance system and risk management activities regarding the use of certain medicinal products.

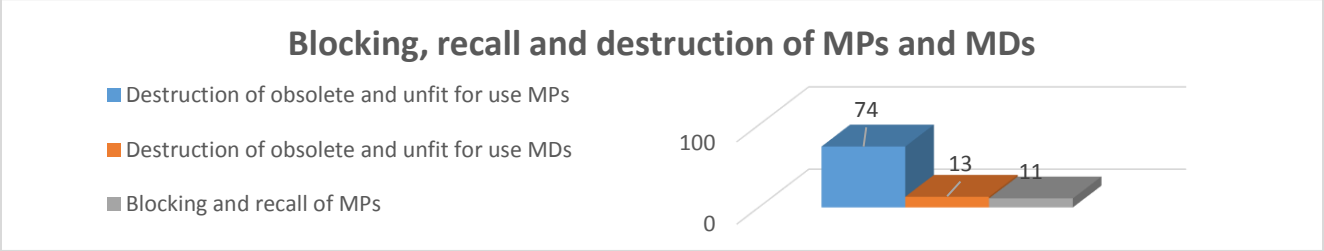
Control of clinical trials

The Agency's inspectors conducted 7 inspections at seven clinical trial centers on compliance with 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 **199** procedures for violations of the MPHUA**.**

Blocking, recall and destruction of medicinal products and medical devices

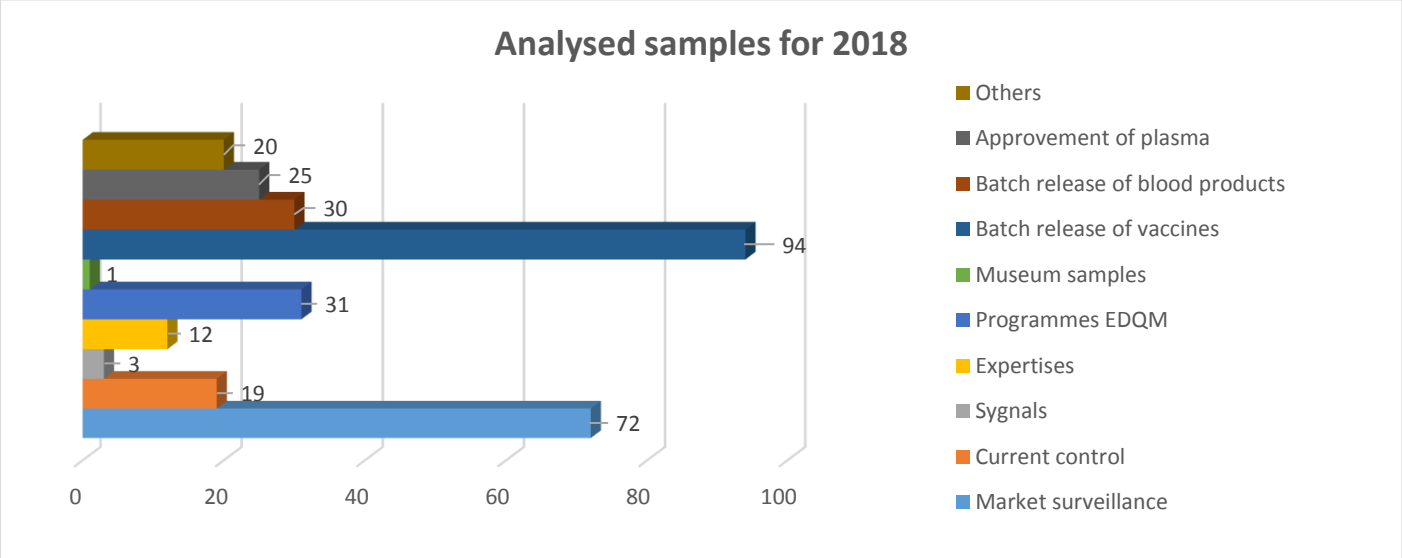


Received and processed complaints and signals from physical and legal entities concerning the trade with medicinal products and medical devices

The BDA took the necessary actions and conducted inspections with regards to **50** complaints and signals regarding violations of the MPHUA and its regulations for its implementation and **17** 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 Audit 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 authorisation in accordance with the MPHUA/MDA.

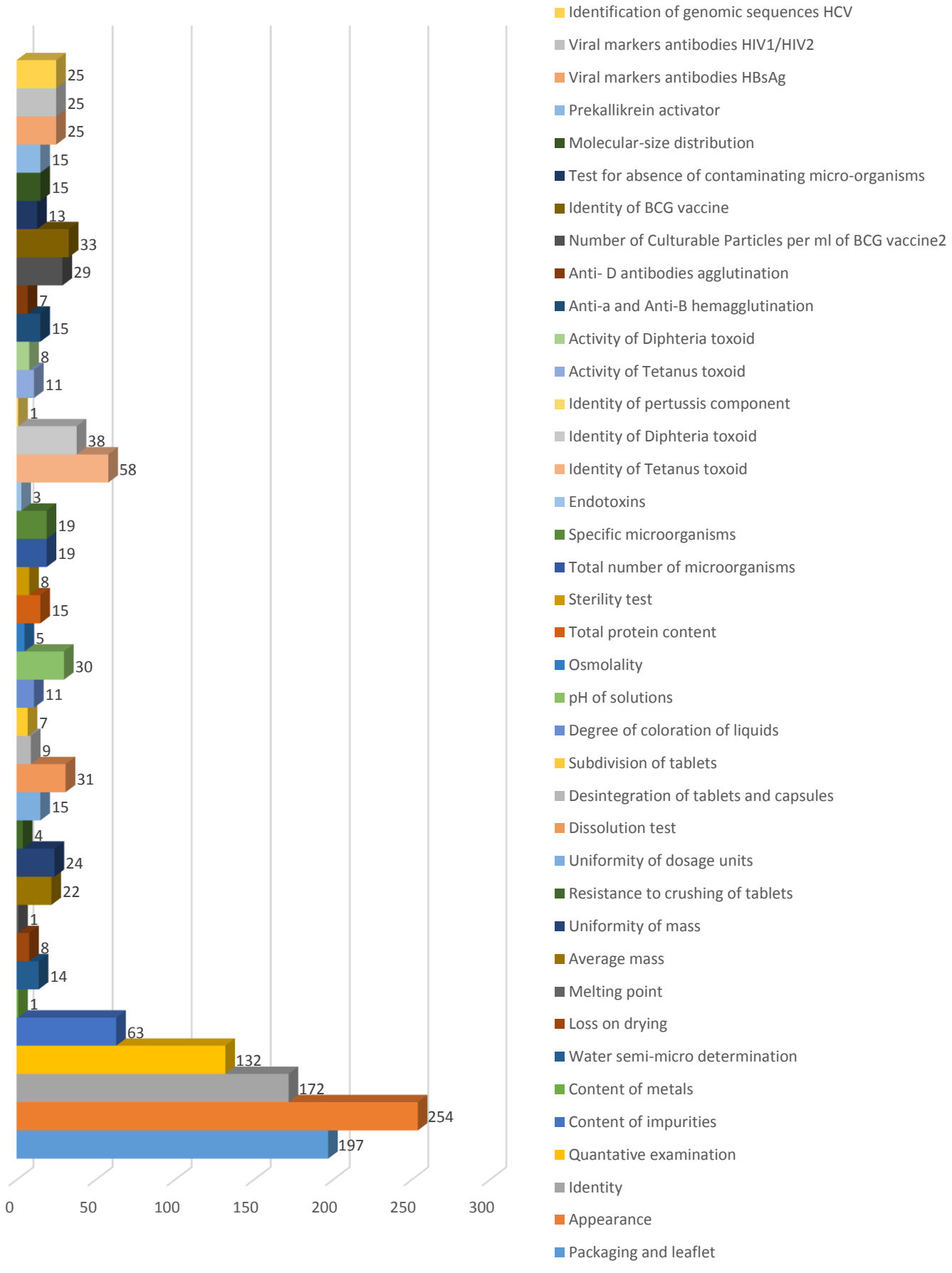
2.4.ANALYSES OF MEDICINAL PRODUCTS

In 2018, the BDA carried out analyses of **307** batches of samples submitted under different procedures. There was a **45.4%** increase in the number of the analysed samples by compared to all samples analysed in 2017.



In 2018, **1 382** tests were performed, which is **70.6%** more than in 2017. The results of all the tests correspond to the approved specifications of the medicinal products concerned. Data on the type of tests and their number are presented as follows:

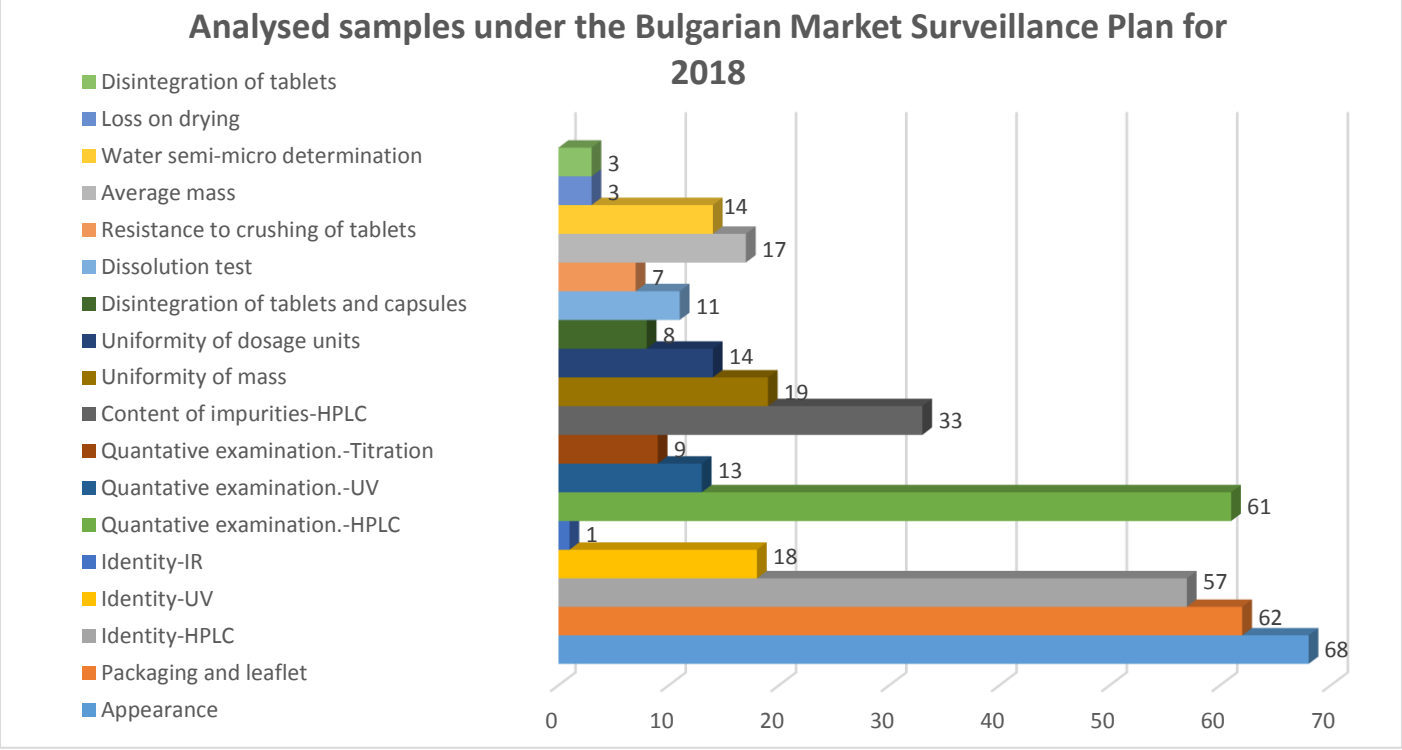
Performed analyses for 2018

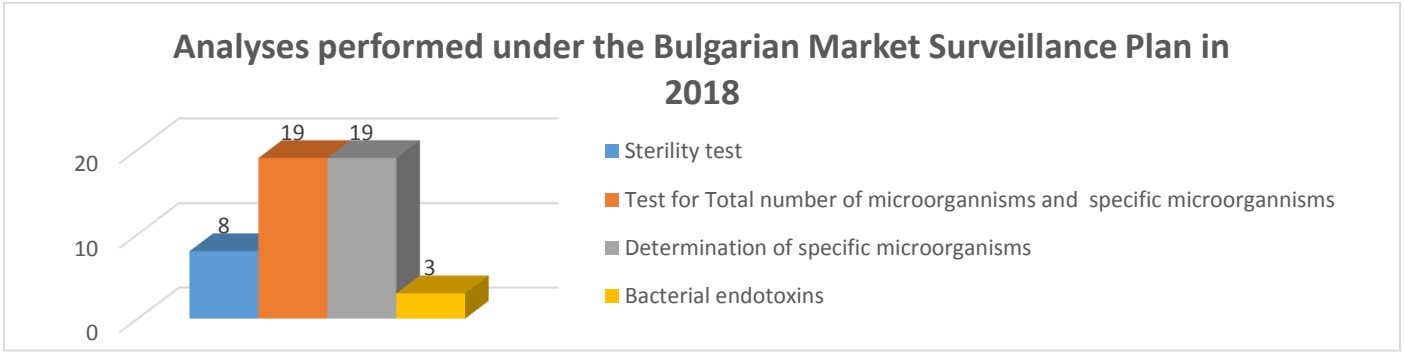


Analyses performed according to the Annual Plan for market surveillance

Under the **Annual Market Surveillance Plan for 2018, the Agency analysed 72 batches** of medicinal products with **13 different active substances** (Ambroxol hydrochloride, Cilostazol, Diltiazem hydrochloride, Flurbiprofen, Letrozole, Lidocaine hydrochloride, Metoclopramide hydrochloride, Metamizole sodium, Pregabalin, Rifampicin, Rosuvastatin, Troxerutin, Indometacine / Troxerutin, Paracetamol / Phenylephrin hydrochloride / Ascorbic acid). All analysed batches of medicinal products complied the requirements of the performed tests.

In relation to market surveillance testing, one of the 2018 goals was to monitor the content of impurities in cough syrups (Ambroxol hydrochloride) nearing the end of their shelf life after their packaging has been opened. Six medicinal products with a label shelf life of 1 month, 3 months and 6 months after the opening were tested. All products have met the specifications of the impurity content. All of the tested batches met the specifications for microbiological quality (Ph. Eur. 5.1.4.) traced near the end of their shelf life after the opening of the package.

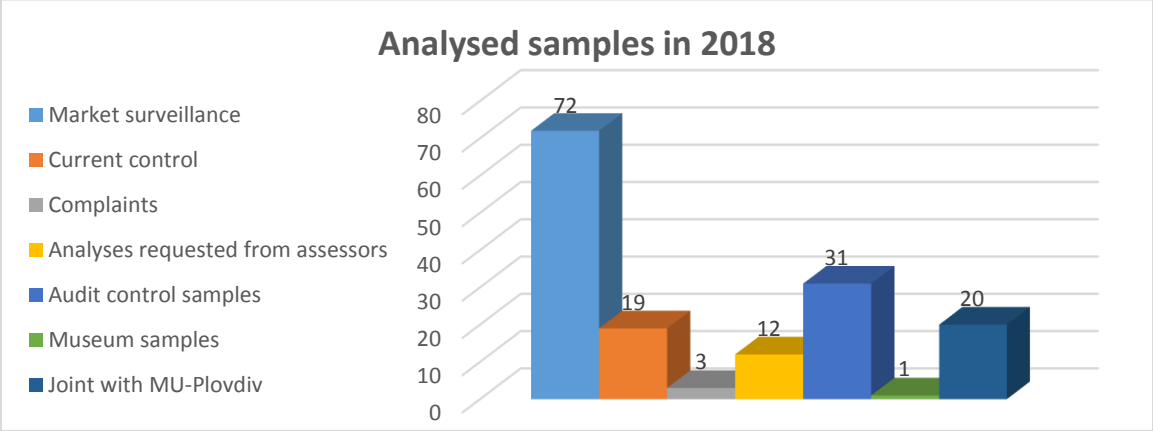




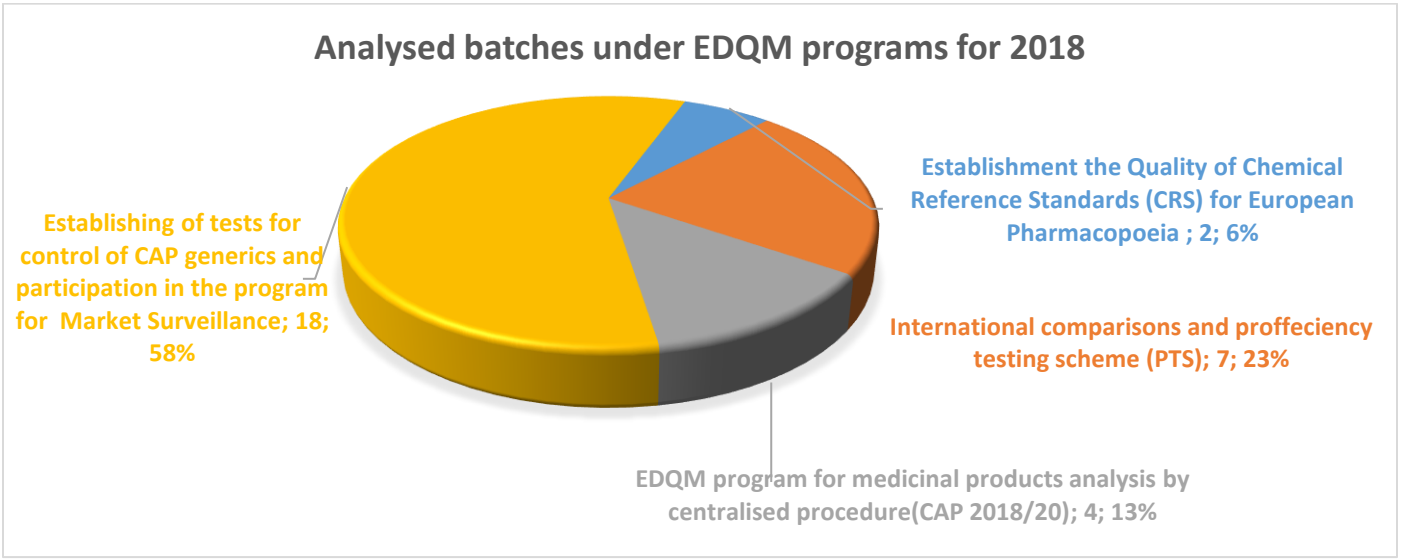
To assess their sterility (Ph. Eur. 2.6.1.), **8 samples** of medicinal products were tested. All complied with the sterility test. For bacterial endotoxin content (Ph. Eur. 2.6.14.), 3 samples of medicinal products for parenteral administration were tested and the results were in accordance with the specification. **Nineteen 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) and all complied with the approved test specification.

Physico-chemical and pharmaceutical analyses

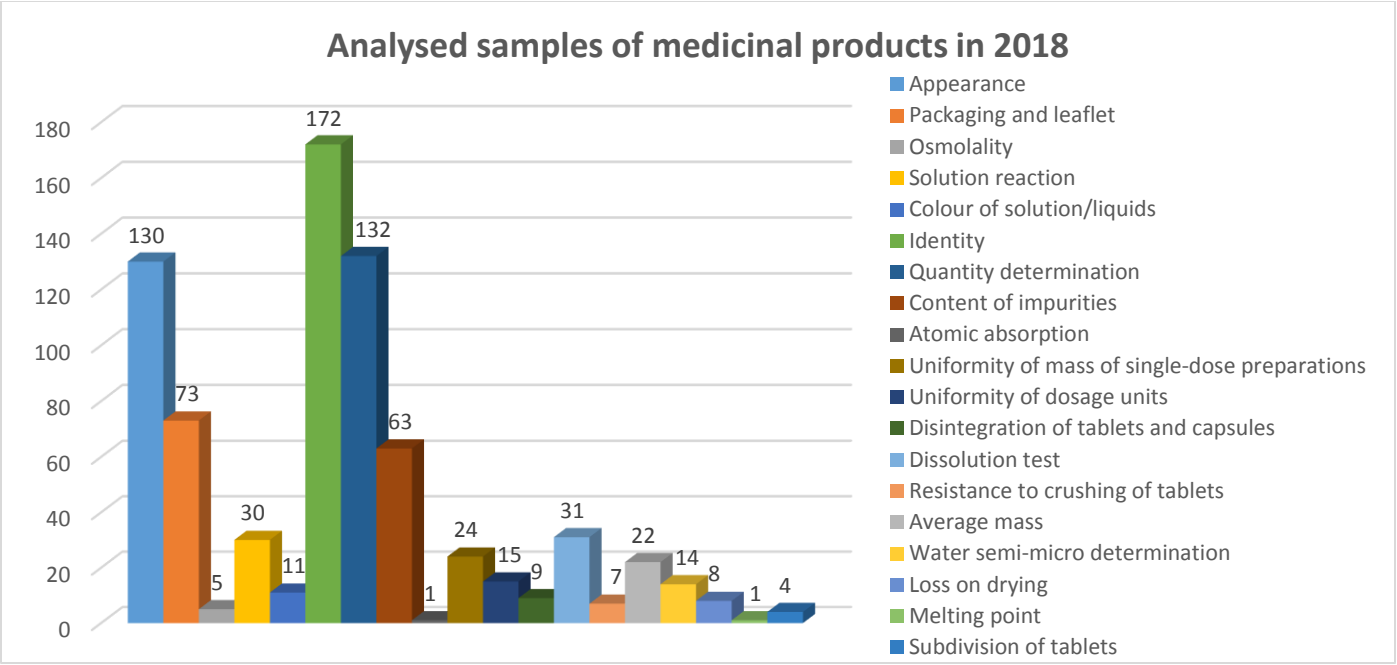
In 2018, 158 batches of medicinal products (35% more than in 2017) were analysed as follows:



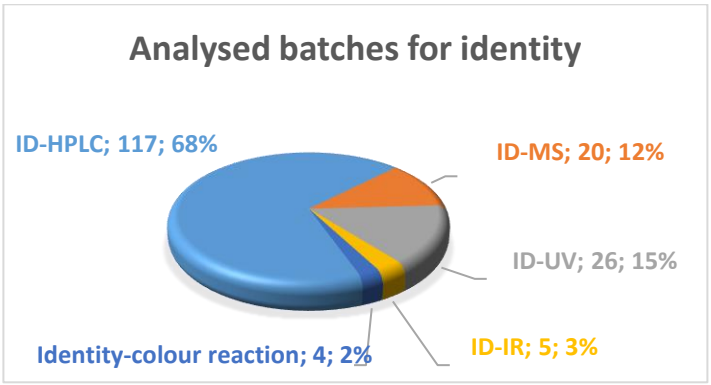
Three physico-chemical and pharmaceutical experiments were conducted on police or prosecutor's orders, during which 12 samples were analysed. A total of 31 samples were analysed in joint trials organised by the European Quality of Medicines and Healthcare Directorate (EDQM & Healthcare). Within the Proficiency Testing Studies the BDA participated in 4 PTS programs PTS187 (Volumetric Titration), PTS 188 (Quantitation Assay), PTS 189 (UV-Vis Spectrometry Assay), and PTS 190 (Melting point).

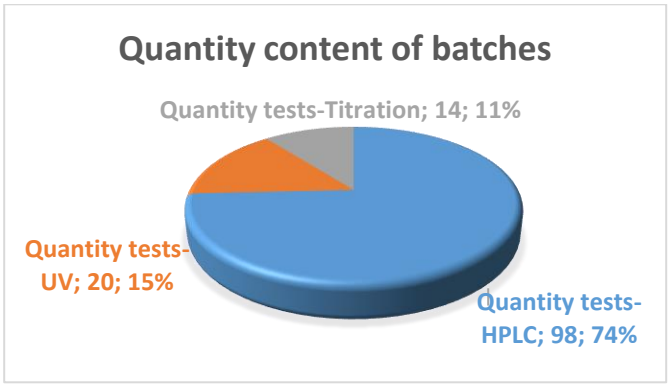


A total of 752 analyses of medicinal products were performed by physico-chemical and pharmaceutical methods (243% more than in 2017) as follows:



The following graphs show the distribution of analysis methods by analysed indicators:



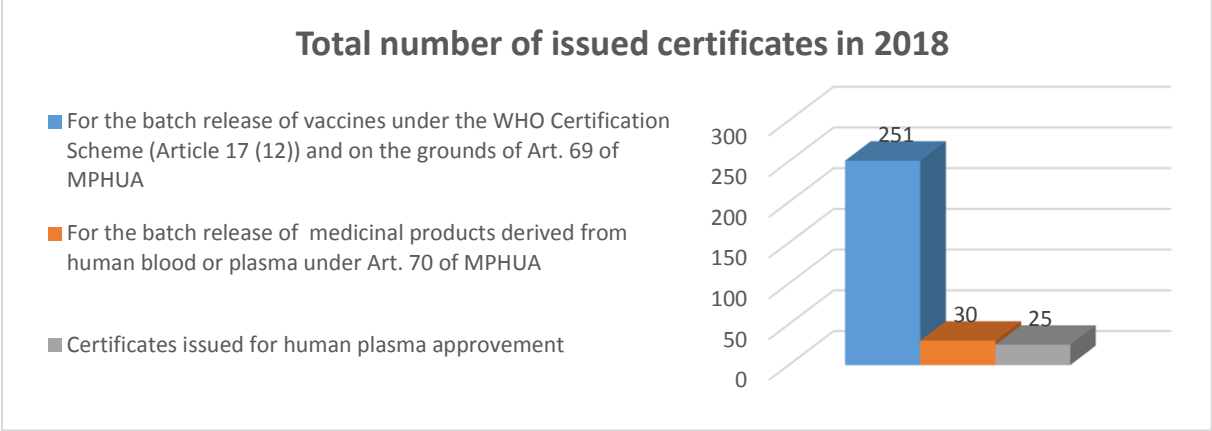


The trend in instrumentation methods used for sample analysis was retained. The largest share hold high-performance liquid chromatography (298 analyses or 39.6% of the studies), ultraviolet spectrophotometry (46 analyses or 6.1% of the studies) and dissolution test (31 assays or 4.1% of the tests).

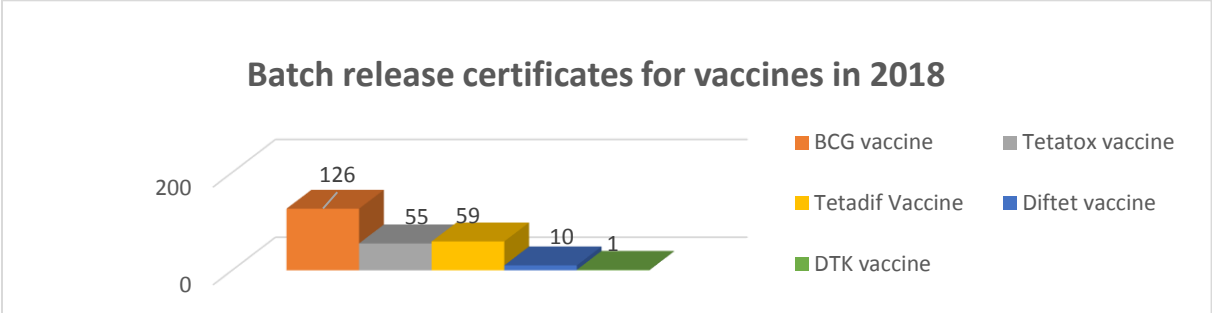
Biological analyses

The Agency officially releases batches of human blood or plasma vaccines and medicinal products under the Official Control Batch Release (OCABR) and the WHO TRS No. 978 Guideline on Batch Release Vaccines, 2013).

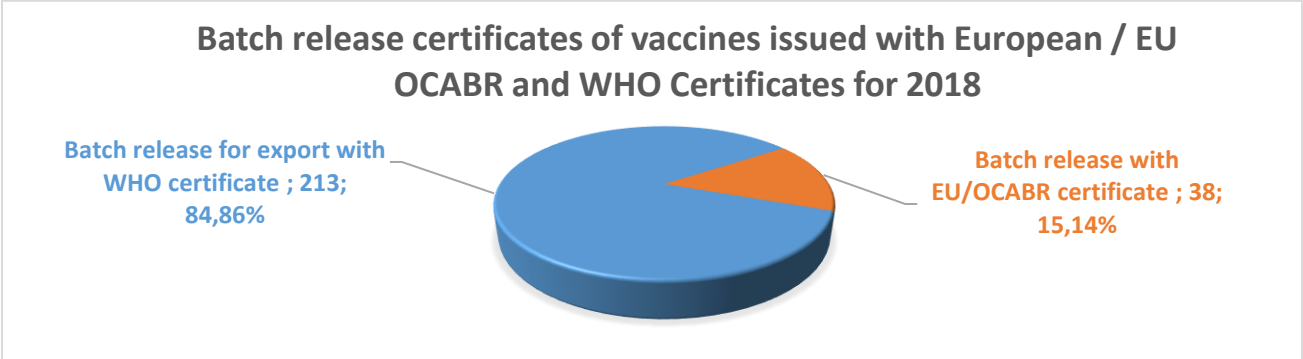
In 2018 the number of issued release certificates for batches of vaccines and medicinal products derived from human blood or plasma were 306, which is 30% more than in 2017. The distribution is as follows:



Issued certificates for vaccines:

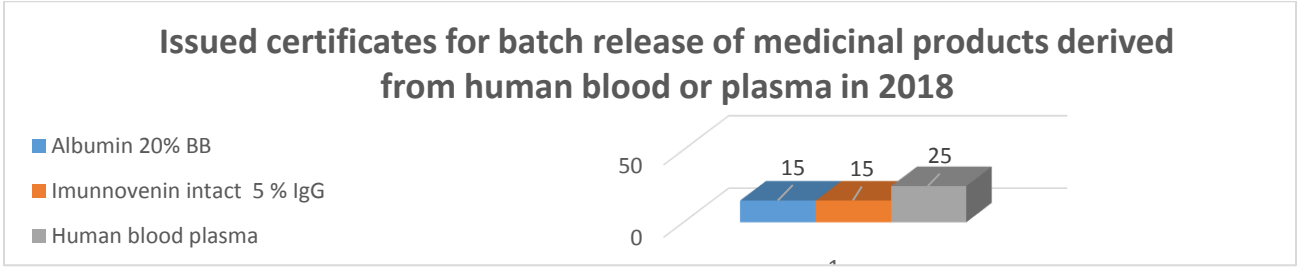


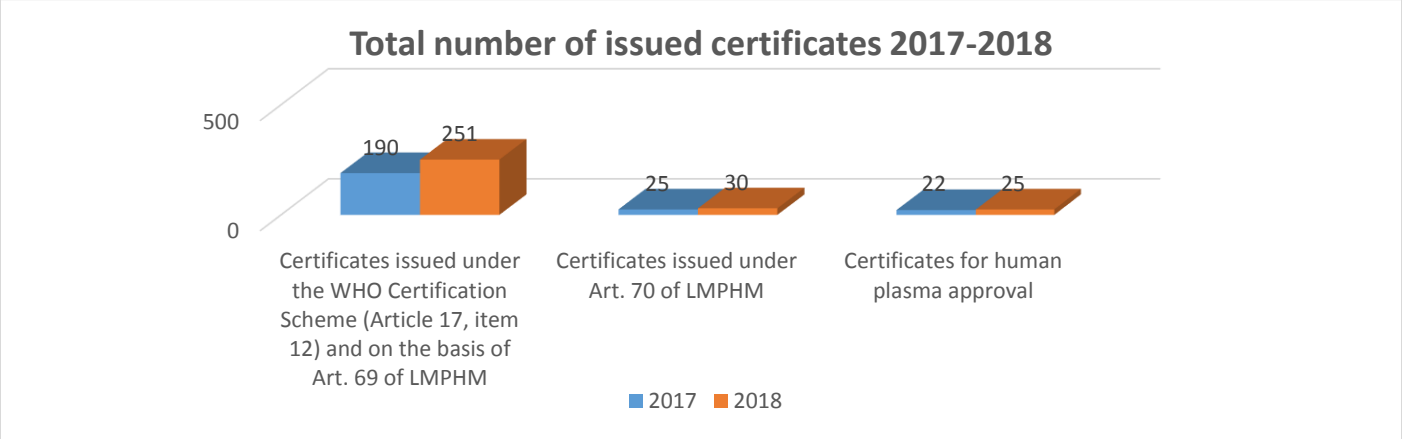
The European / EU OCABR certificates issued in 2018 were 38 which is 50% more than in 2017, and the number of issued WHO certificates was 213 which is 25% more than in 2017.



Medicinal products derived from human blood or plasma for release under Art. 70 of MPHUA

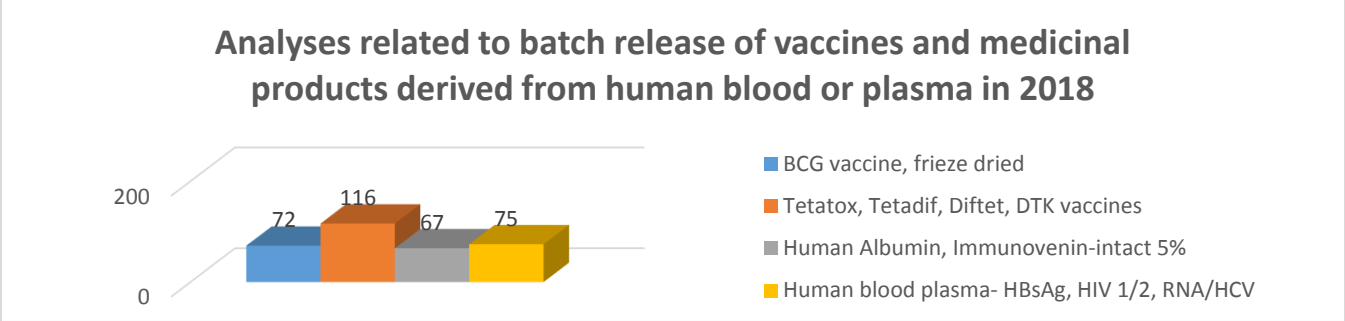
There is an increase of 30% in the number of certificates issued compared to the 2017 data.

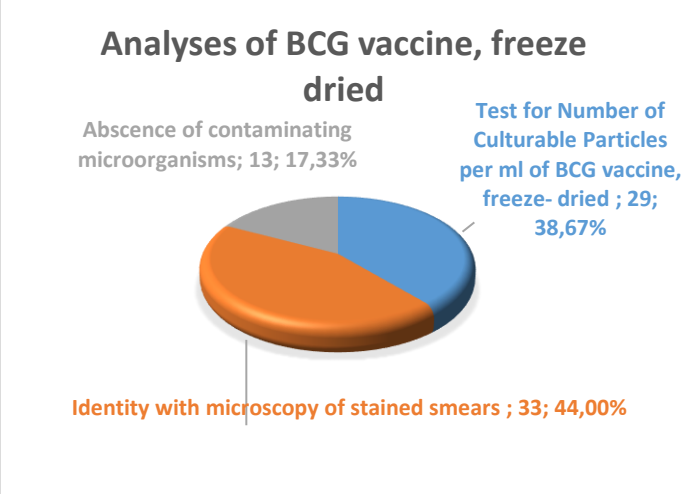


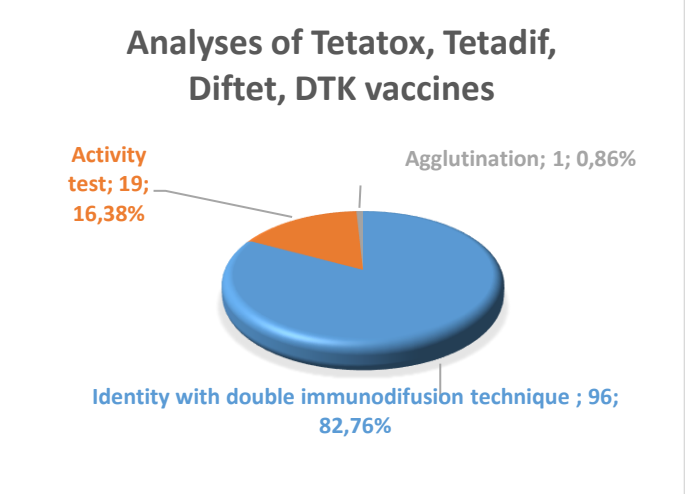


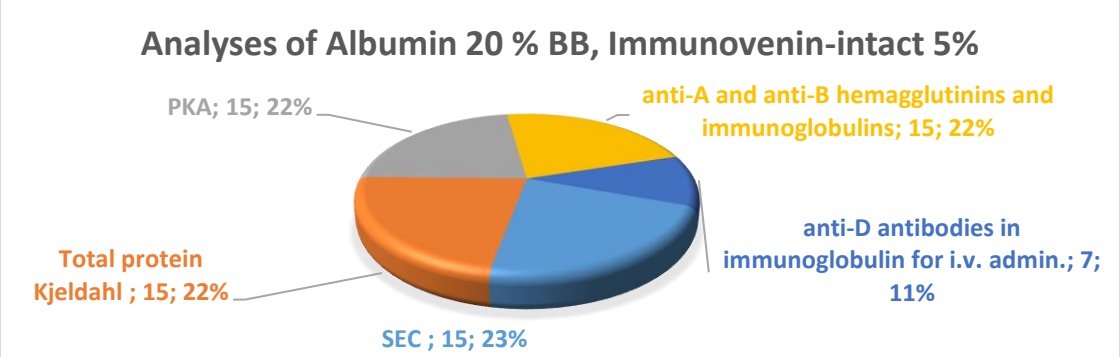
The total number of sample analyses performed during various procedures was 630 (25.3% more than in 2017). The results of all tests comply with the approved specifications of the medicinal products concerned.

The highest share is held by the analyses in relation to the batch release of vaccines and batches of medicinal products of human blood or plasma - a total of 578 analysed batches. For 248 batches the following tests were conducted: appearance, type of packaging (primary and secondary), labeling of primary and secondary packaging and leaflet. The analyses of the remaining 330 batches were distributed, as follows:







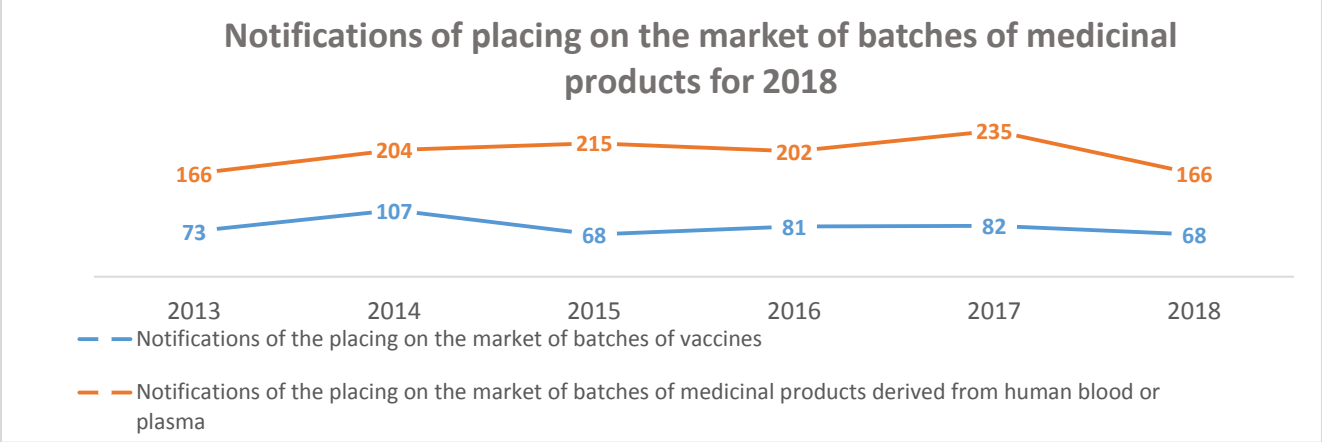


All forms of vaccine and human blood or plasma (306 batches) vaccine samples were evaluated for the appearance of the formulation, primary, secondary packaging and leaflet.

In 2018, the BDA experts participated in a collaborative WHO and EDQM study about the establishment of WHO International Standard (IS) for Prekallikrein Activator in albumin Biological Reference Preparation batch 7 (BRP7) to determine the hyperacid activator in blood products.

In 2018, a serological ELISA method was used to assess viral safety (determination of HbsAg and HIV1 / 2 antibodies) in human plasma samples in relation with the release of batches of human blood or plasma medicinal products under Art. 70 of MPHUA.

In 2018, 68 notifications of placing on the market of batches of vaccines and 166 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 relation with proposals from the European Pharmacopoeia Secretariat for the Expert group work program, experts from the Agency participated in the completion of 72 questionnaires which provided information on substances/monographs, national pharmacopoeia requirements and good pharmacopoeia practices. The BDA's experts processed 389 reports on comparator substances developed by expert groups of the European Pharmacopoeia.

In the past year, Appendices 9.7 and 9.8 of the 9th edition of the European Pharmacopoeia, as well as the amended *General Monograph Fermentation Products* (1468) were introduced. At the same time, the monographs *Phytomedion* (1036), *Emethylene hydrochloride pentahydrate* (0201), *Deoxycorporon acetate* (0322), *Chlorpropamide* (1087), *Opadrenolol hydrochloride* (0628) and *Highly purified water* (1927) pharmacopoeia were removed. Changes were published on the Agency's website.

In the Pharmacopoeia section of the BDA website, updated lists of translations of monograph titles were published for:

• Herbal substances and preparations included in the 9th edition of the European Pharmacopoeia to Appendix 9.7;

• Homeopathic preparations included in the 9th edition of the European Pharmacopoeia to Appendix 9.7;

• Radiopharmaceuticals included in the 9th edition of the European Pharmacopoeia to Appendix 9.6;

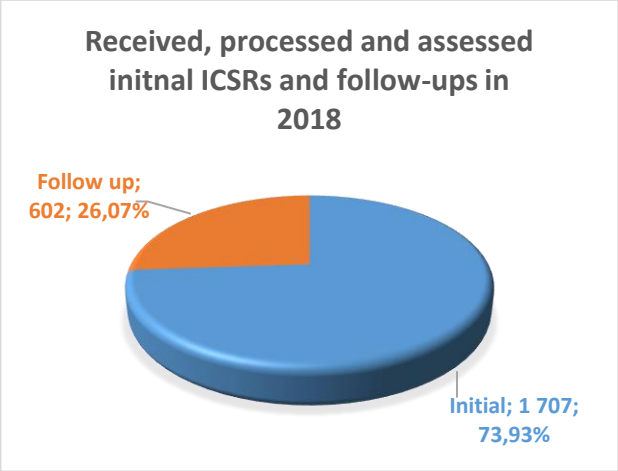
• Substances and preparations included in the 9th edition of the European Pharmacopoeia to Appendix 9.7.

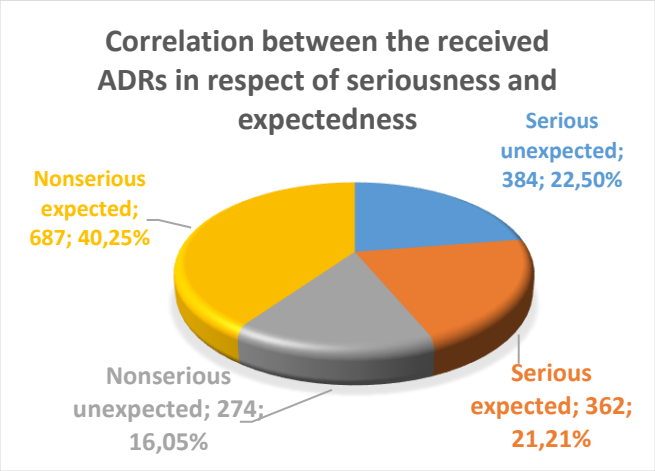
As a national pharmacopoeial secretariat, the BDA provides information on pharmacopoeial and terminological issues, lists of controlled terms. In 2018, new standard terms for formulations, packs, application devices, and pathways for the introduction of medicinal products and presentation units were translated into Bulgarian.

2.6.PHARMACOVIGILANCE

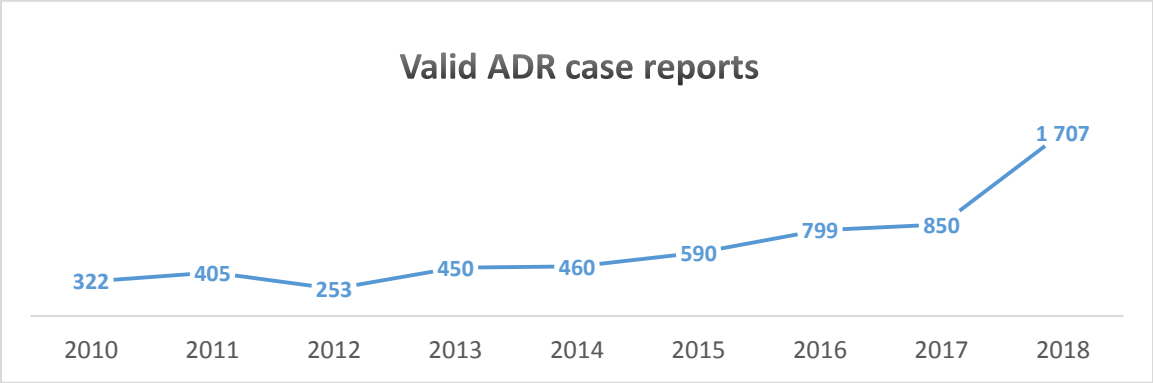
Adverse Drug Reactions Reports

The BDA's responsibilities include the assessment of received Individual Case Safety Reports (ICSRs). In 2017, the number of initial and follow-up reports that were received, managed and assessed increased in comparison to the previous year. The total number of ICSRs in 2018 was **2 354**. The valid ones were **2 309,** the initial reports being **1 707** and the follow-ups - **602**.

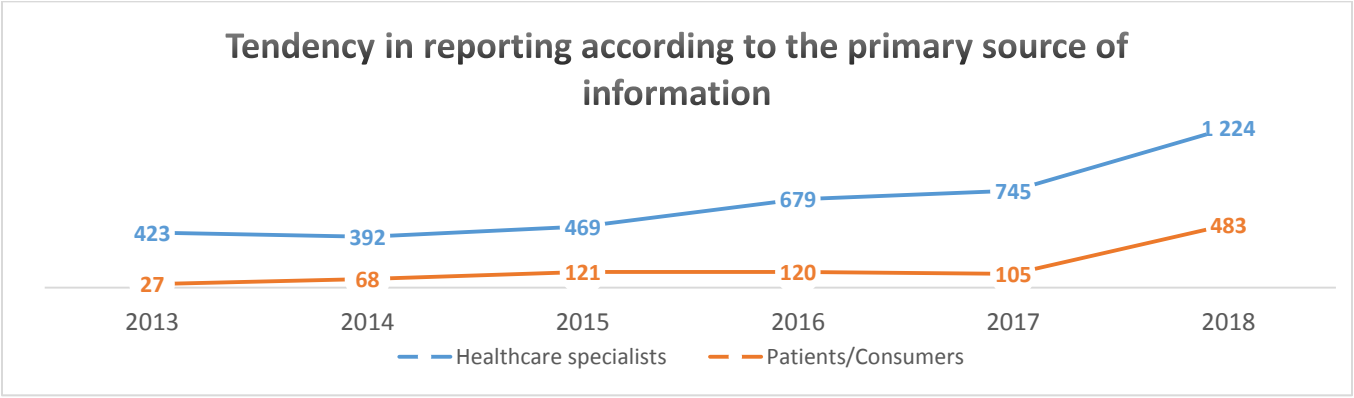




The tendency for increase in the reporting activity remains and the number of valid ICSRs from **850** in 2017 went to **1 707** in 2018 – a 201 percent increase.

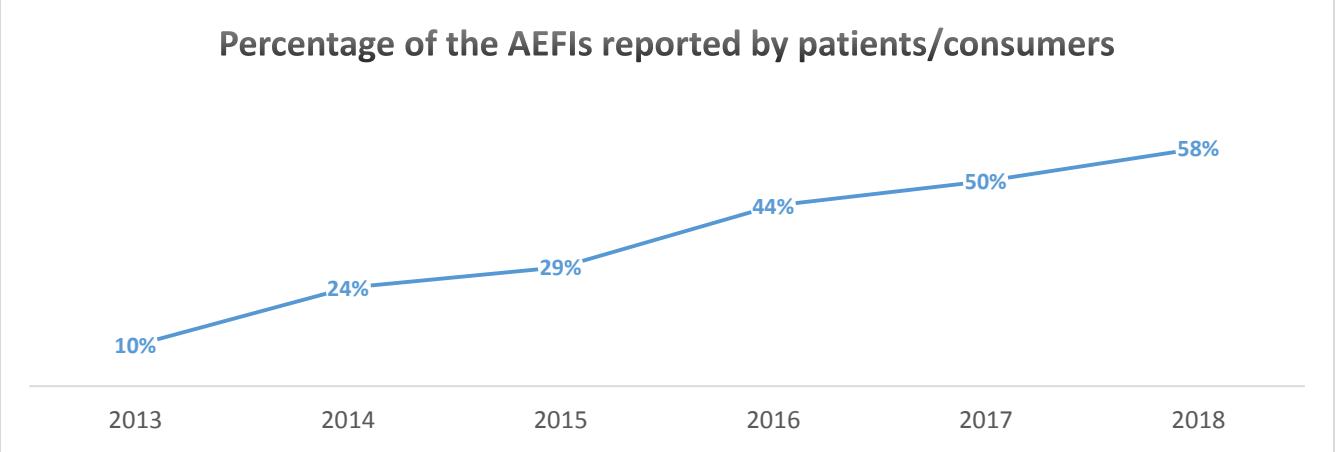


The reporting activity of healthcare professionals (HCPs) has been continuously increasing and reached **1 224** reports in 2018. The number of patient reports was 483, which is a 22 percent increase compared to 2017. The Marketing Authorisation Holders sent the biggest share of reports (1 450). Directly reported to the BDA were **151** reports by healthcare professionals and **106** reports by patients.



Adverse events following immunizations

The adverse events following immunizations (AEFIs) were 7% of the total number of reports. A total of 103 AEFIs were received, 51 of which were directly reported to the BDA (8 by healthcare professionals and 43 by patients or 84%) and 52 were received through the Marketing Authorisation Holders (35 by healthcare professionals and 17 by patients). The number of AEFIs reported by healthcare professionals was 43 (42%) and by patients - 60 (58%).



Information activities related to pharmacovigilance and risk communication

In 2017, BDA evaluated 59 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 2018, NPRAC held 11 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. Important support and scientific assessment was provided for several national ADRs cases. Together with the NPRAC was prepared the "Vaccine Safety and Patient Reporting" presentation at the PRAC Strategic Review and Learning Meeting within the Bulgarian Presidency of the Council of the European Union. The NPRAC provided recommendations on the evaluation of adverse drug reactions reported in Bulgaria during the past year.

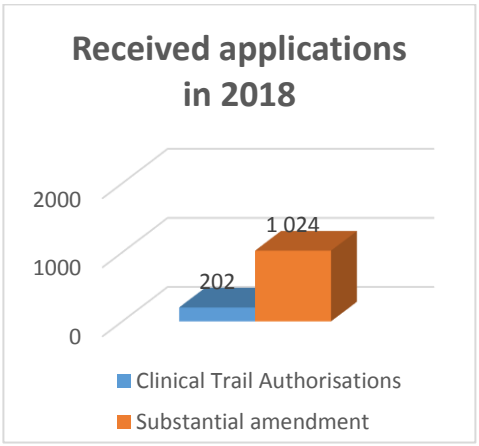
Training activity and participation in scientific fora

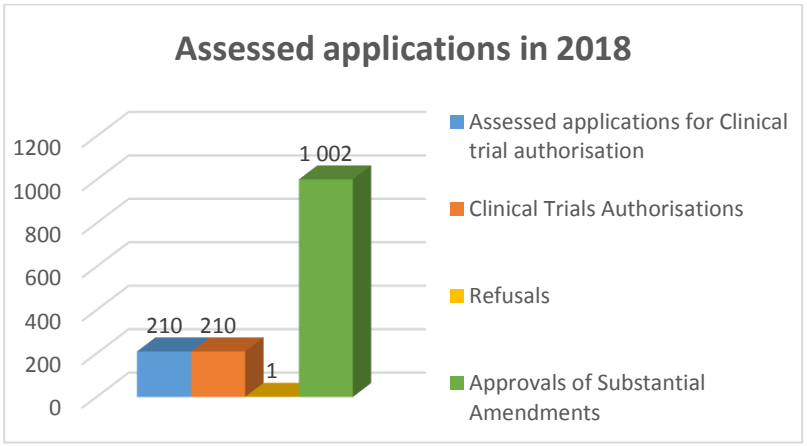
In 2018, the BDA held trainings on Pharmacovigilance for undergraduate students in Pharmaceutics, for postgraduates and for MAHs representatives.

2.7.CLINICAL TRIALS

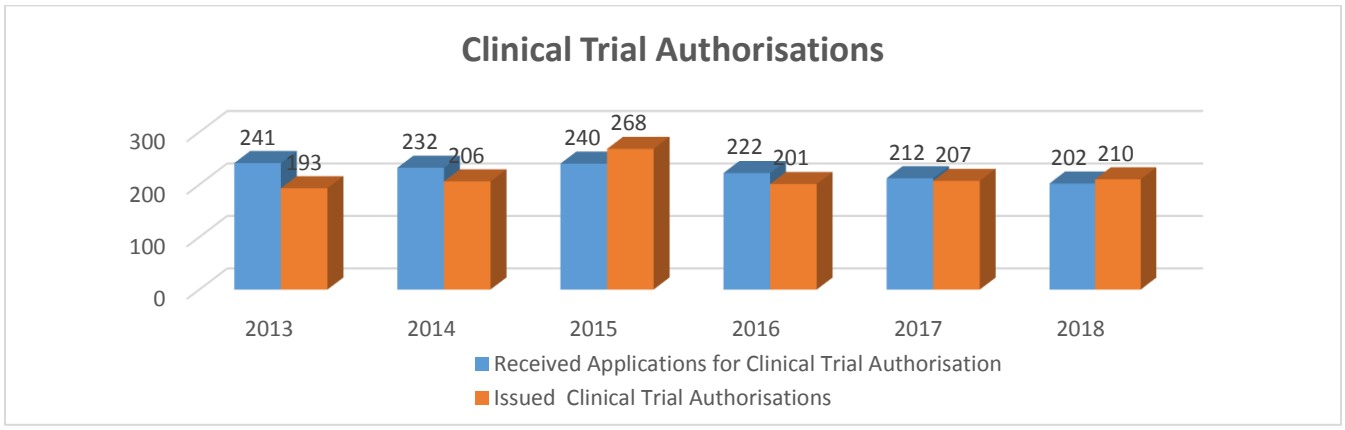
BDA has responsibility for authorisation and control of clinical trials conducted in Bulgaria. The activity includes assessment of the documentation for clinical trial authorisations, related substantial amendments and follow-up control on the implementation. BDA keeps and updates both a Register of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

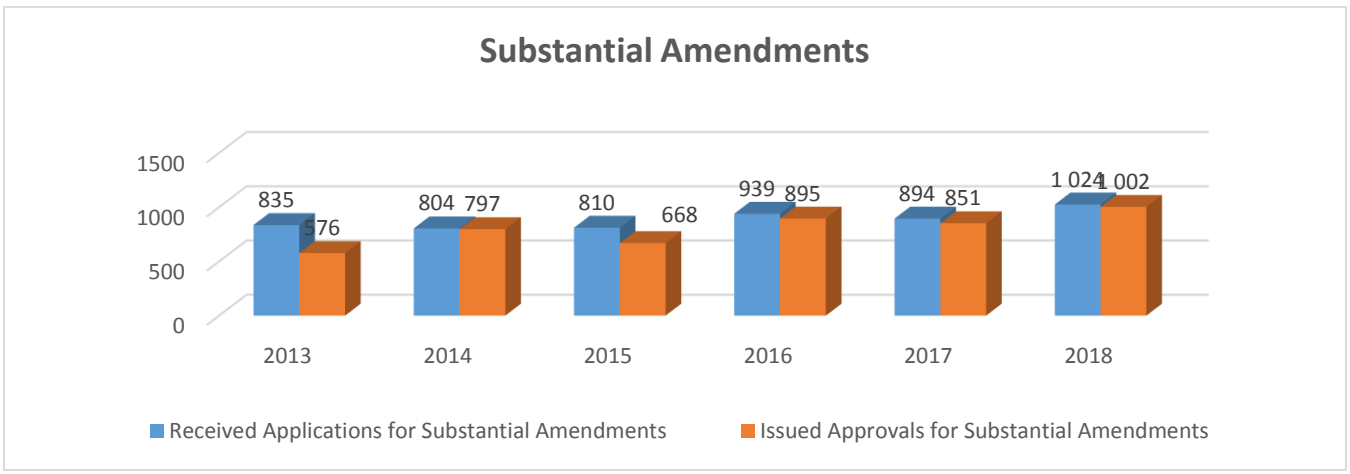
In 2018, the BDA received 202 Applications for Clinical trial authorisation and **1 024** Applications for Substantial amendment approval. The total number of applications was **1 226**.





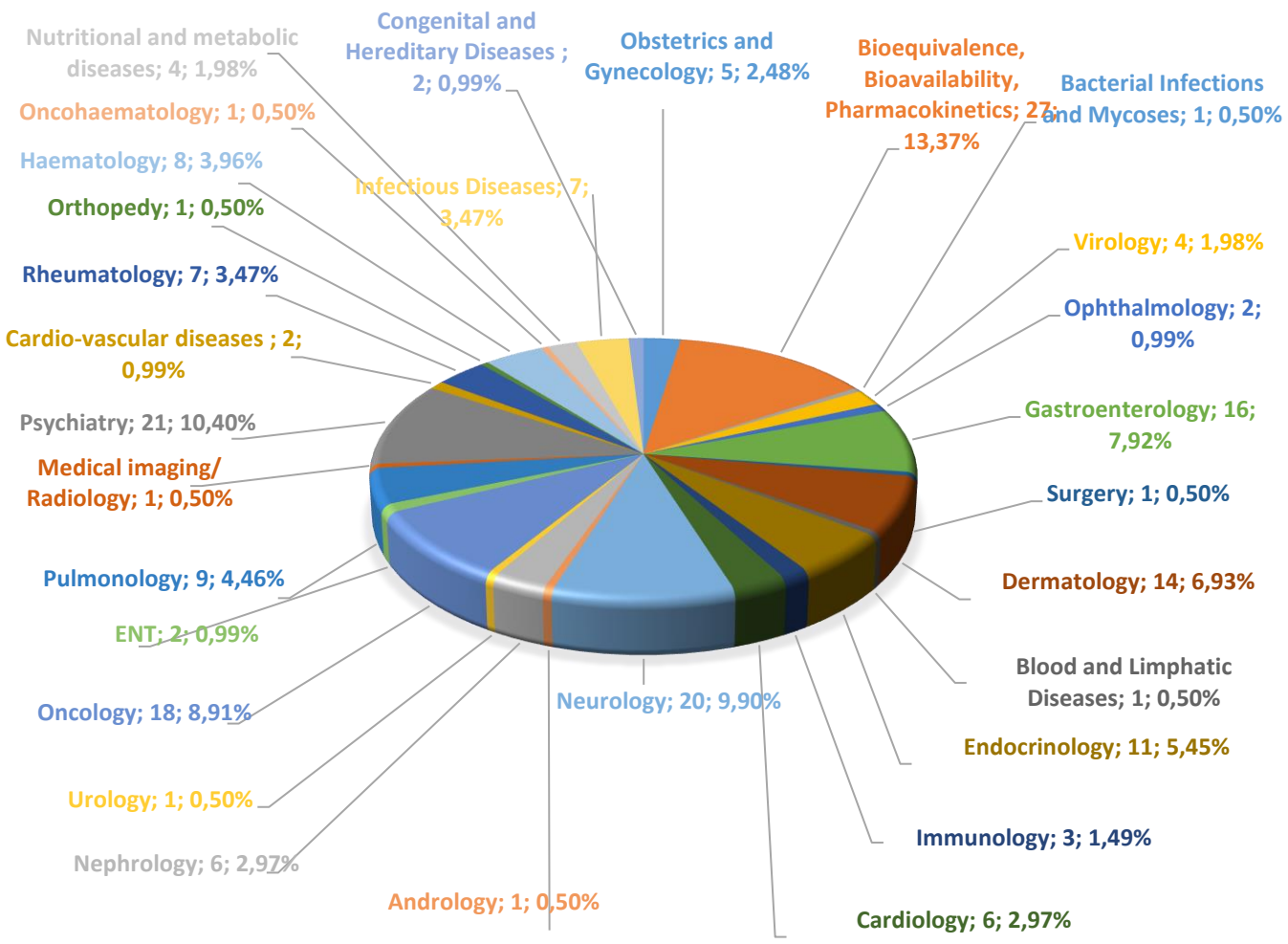
In 2018, the BDA issued **210** authorisations/notifications for agreement for Clinical trials and **1 002** authorisations for substantial amendments in Clinical trials. One application for clinical trial authorisation was refused.



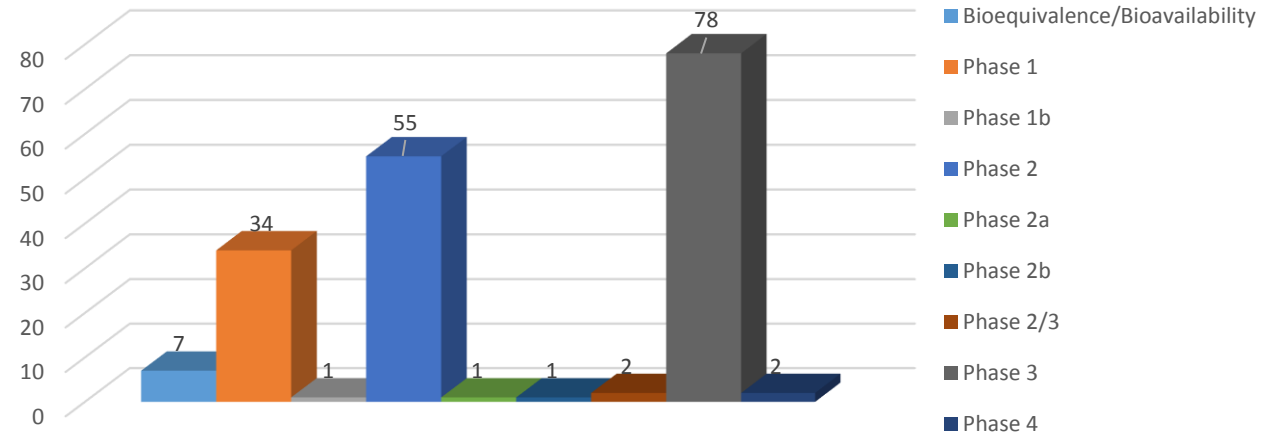


In 2018, the clinical trials sponsors were mostly interested in the areas of Neurology (9.9%), Psychiatry (10.4%) and Bioequivalence, Bioavailability, Pharmacokinetics (13.37%). A new area of interest is Andrology.

Clinical Trials by areas in 2018

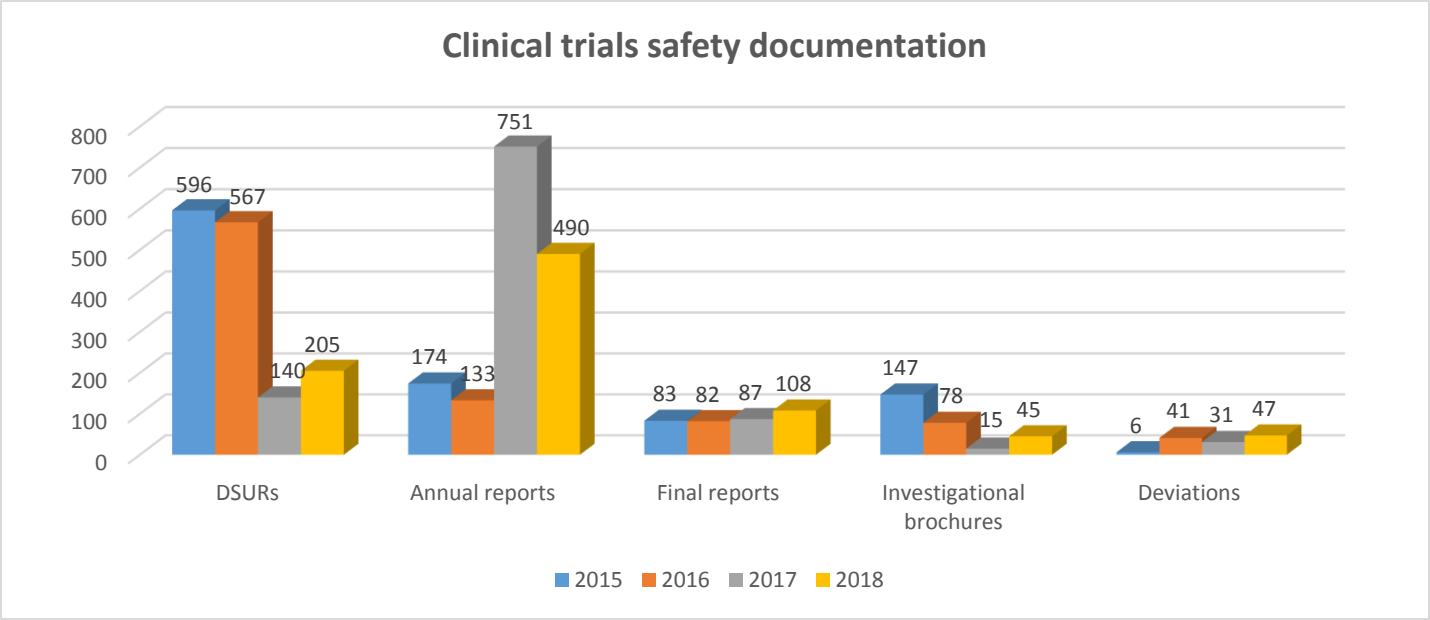


Clinical trials by phases in 2018



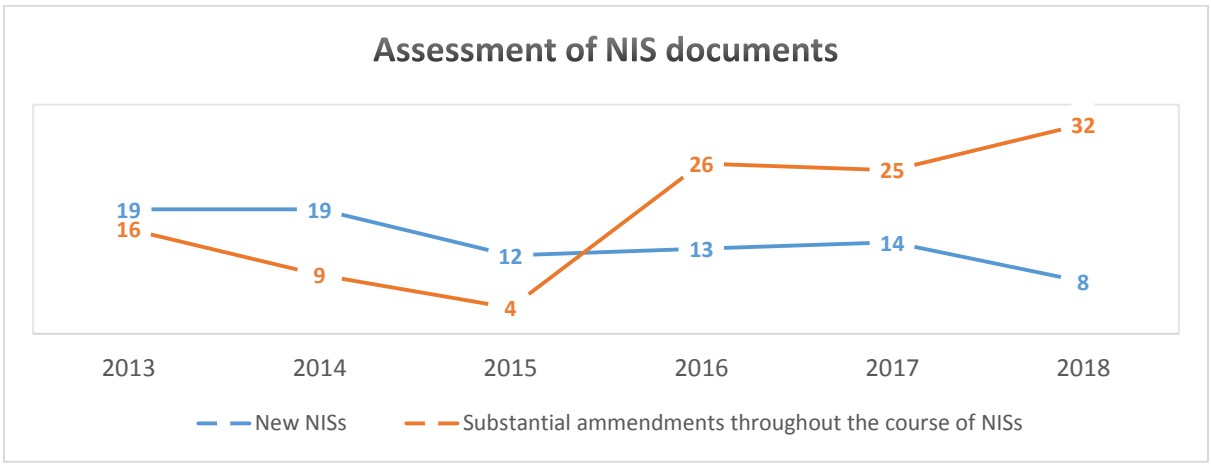
Clinical Trials Safety

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.

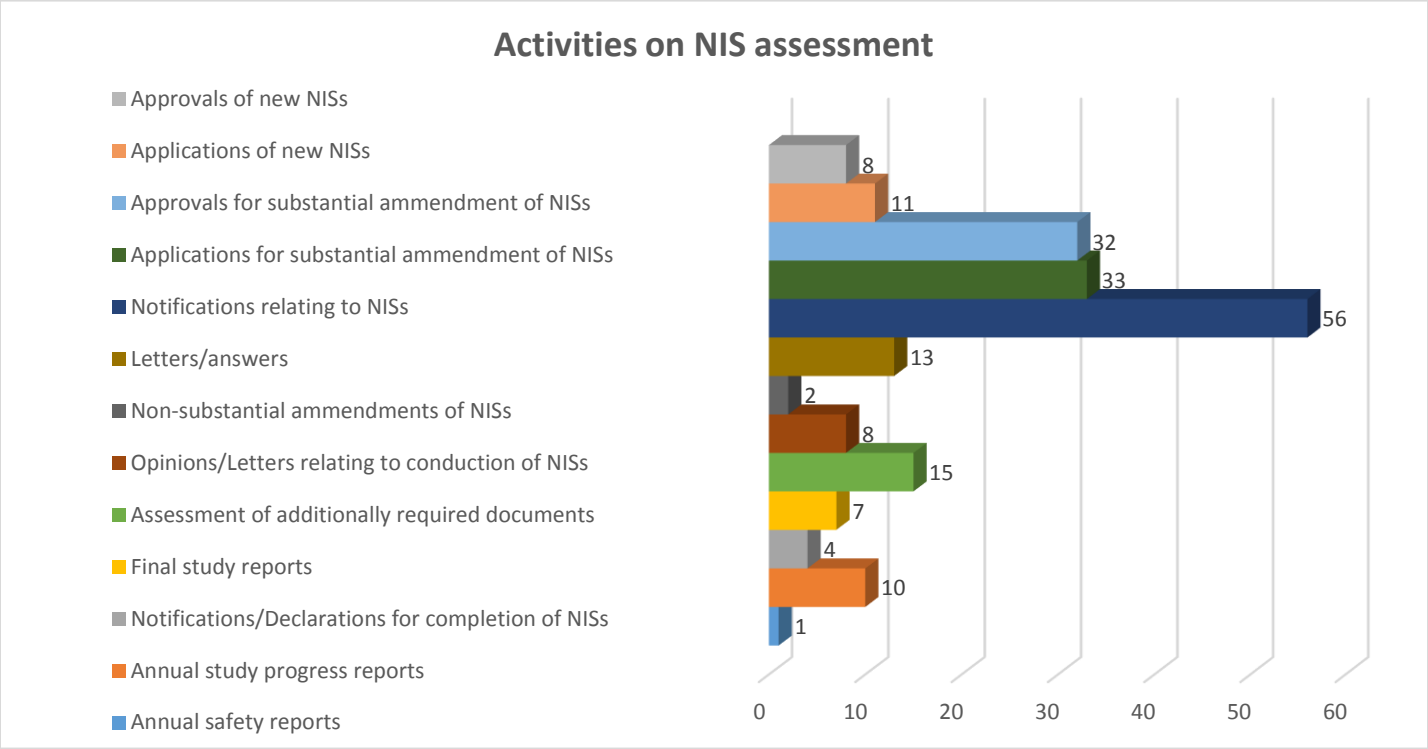


2.8.NON-INTERVENTIONAL STUDIES

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 2018, the Agency received and assessed documentation for 8 new non-interventional studies as well as documentation for 32 substantial amendments.



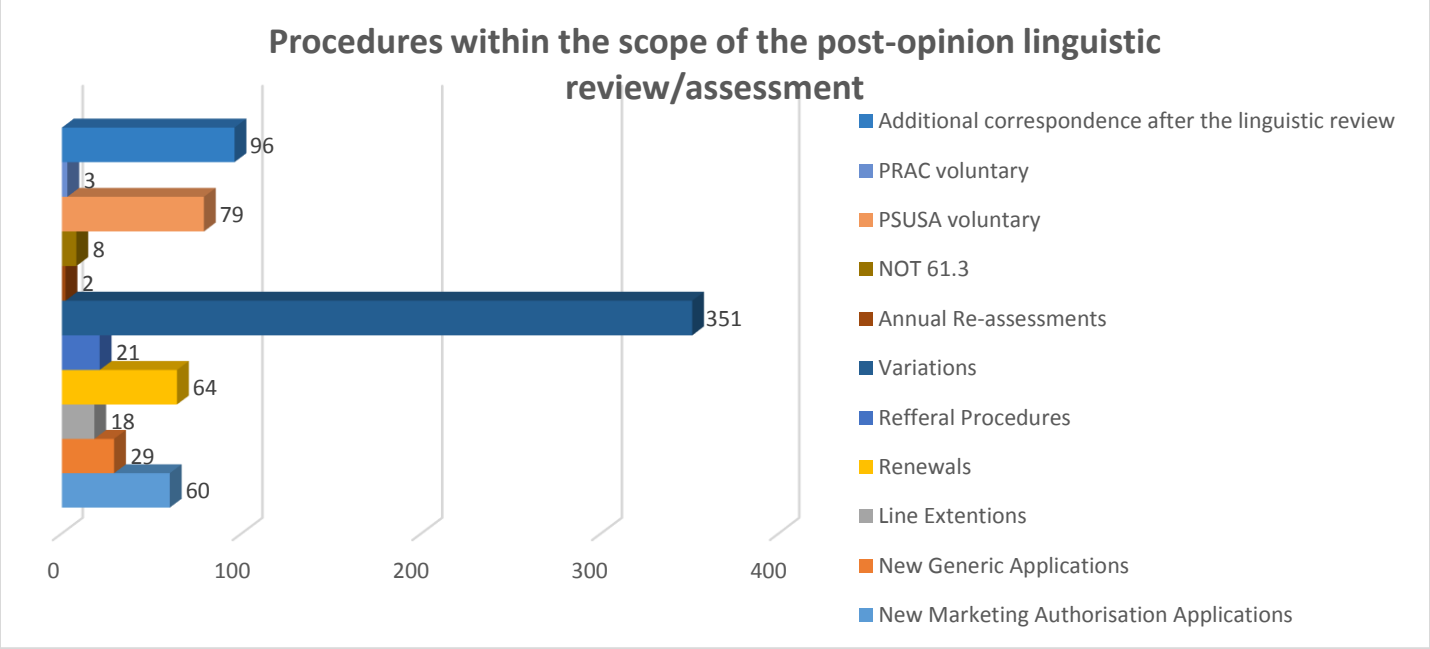
In addition, throughout the year there were 3 issued opinions on documentation regarding the conduction of non-interventional studies, which were found to be out of the scope of the non-interventional study definition under art 145 of MPHUA.

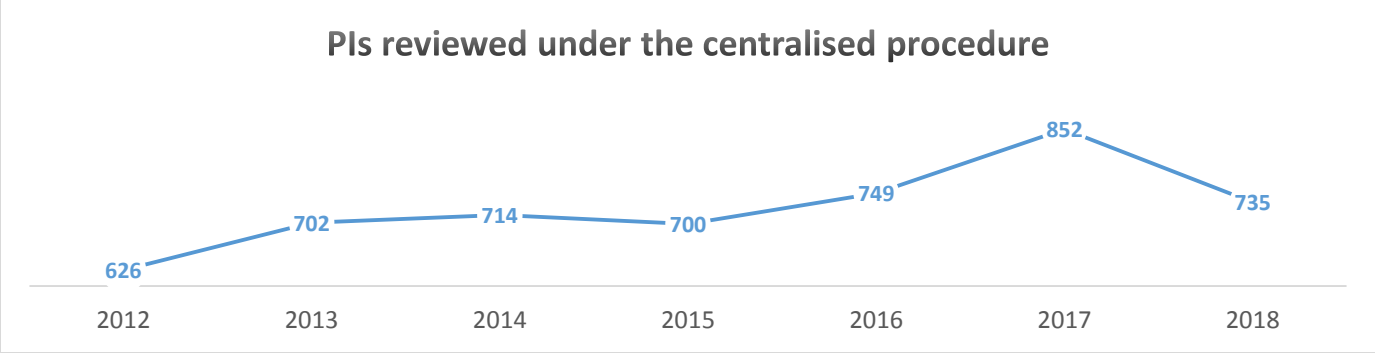


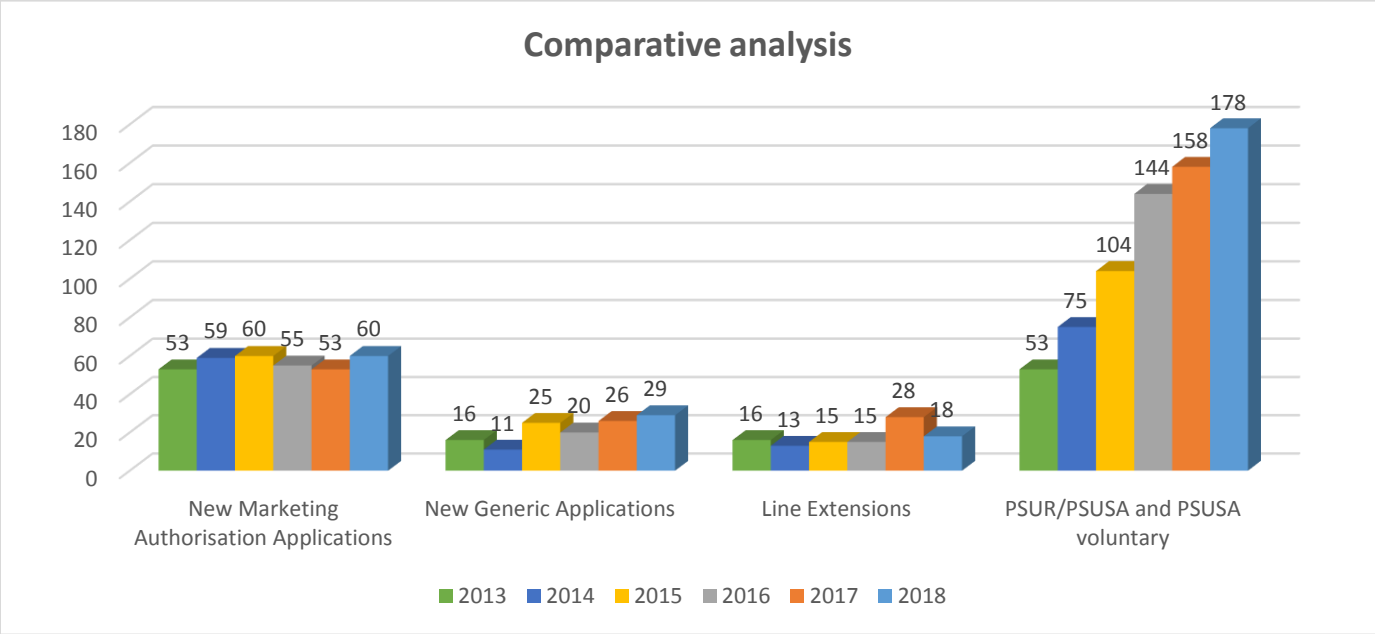
The BDA maintains an up-to-date non-interventional studies database.

2.9.MEDICINAL AND PRODUCT INFORMATION

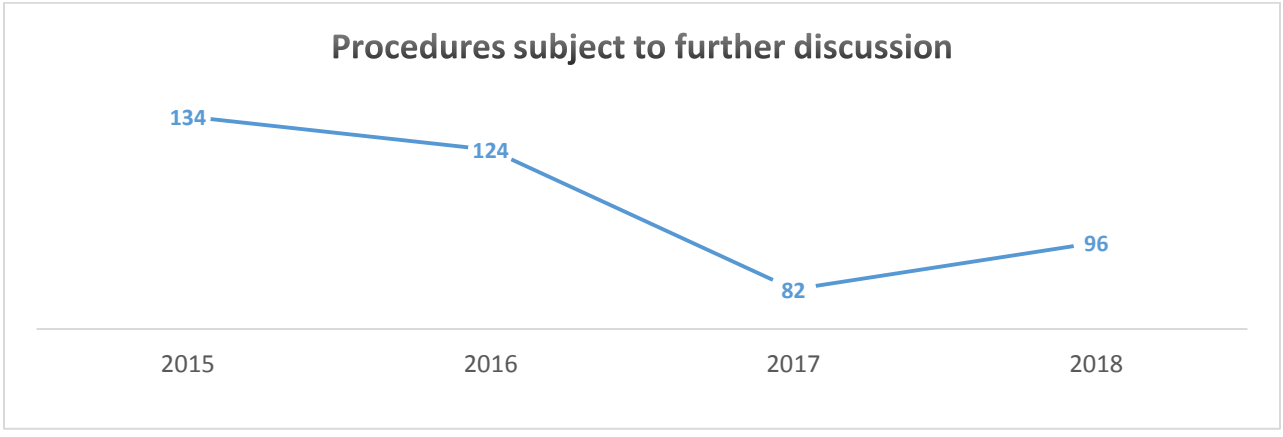
Assessment and expert activities concerning the linguistic review of the Product Information (PI) (Summary of Product Characteristics, Labelling and Package Leaflet) of medicinal products after CHMP opinion.





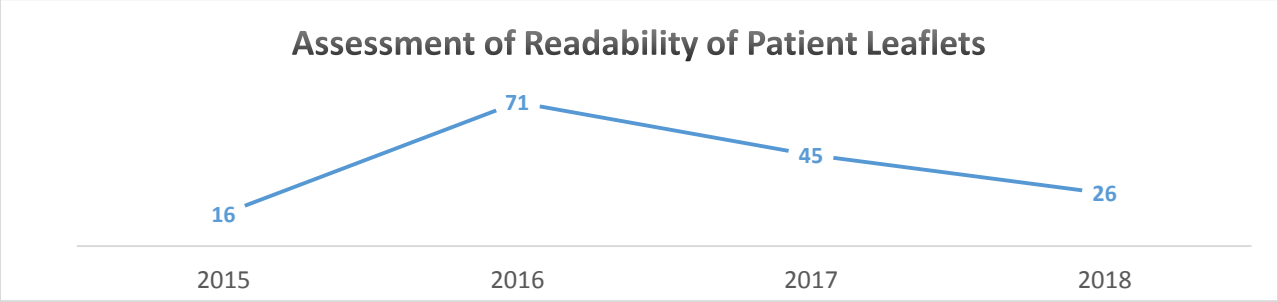


There is a trend of increase in the number of procedures of New Generic Applications, Line Extensions as well as PSUR/PSUSA including the voluntary PSUSA and PRAC recommendations and PASS.

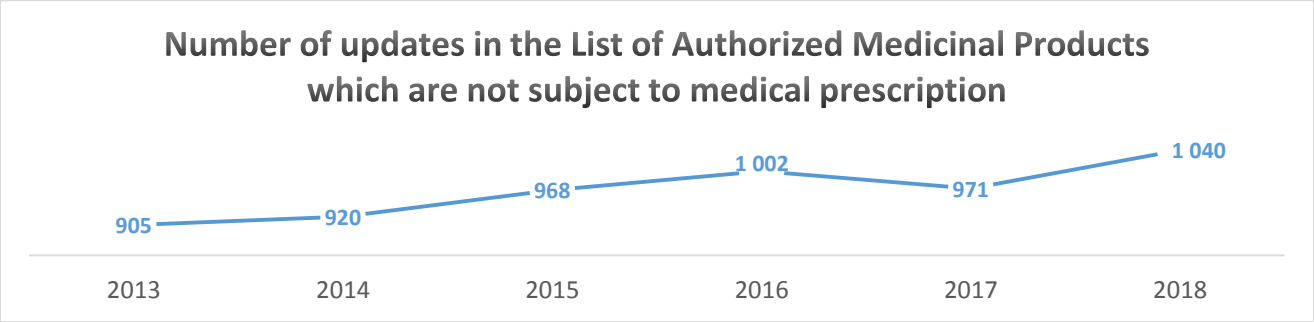


For the period 2015-2018, there is a trend of decrease in the number of procedures subject to additional co-ordination, which is one of the indicators for improving the quality of work.

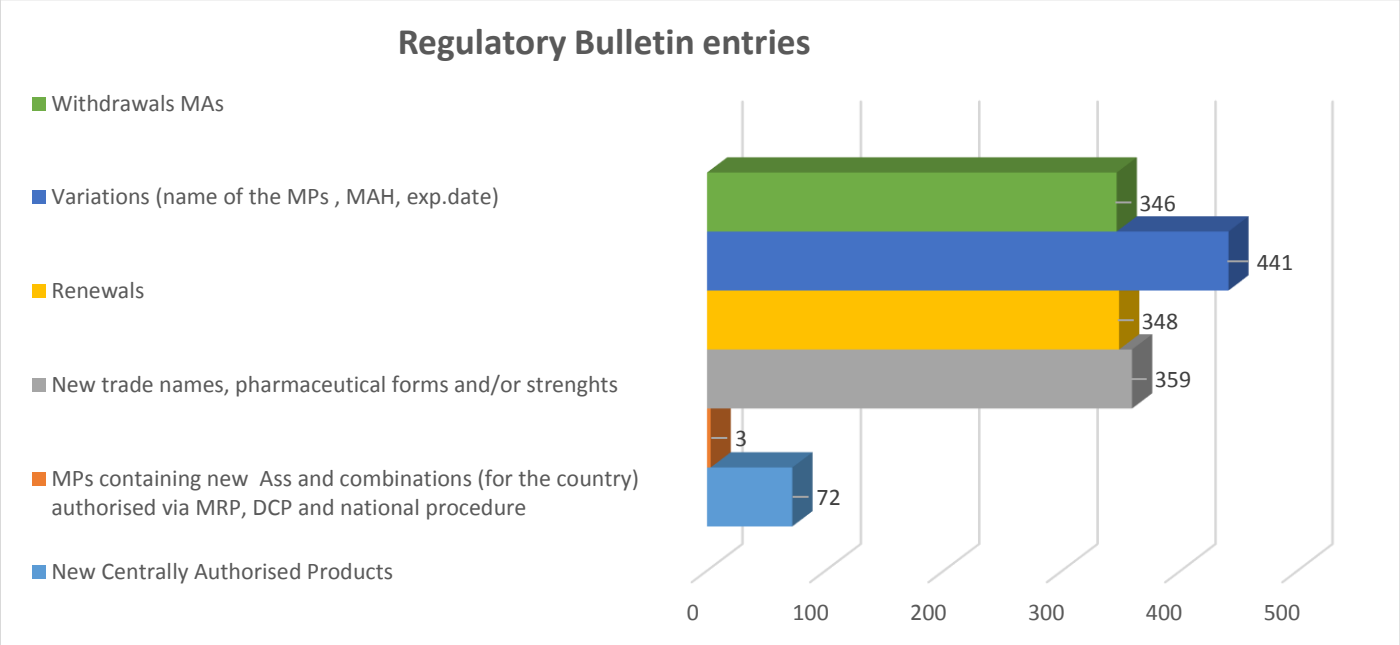
Part of the authorisation procedure is the assessment of the readability of the patient leaflets.



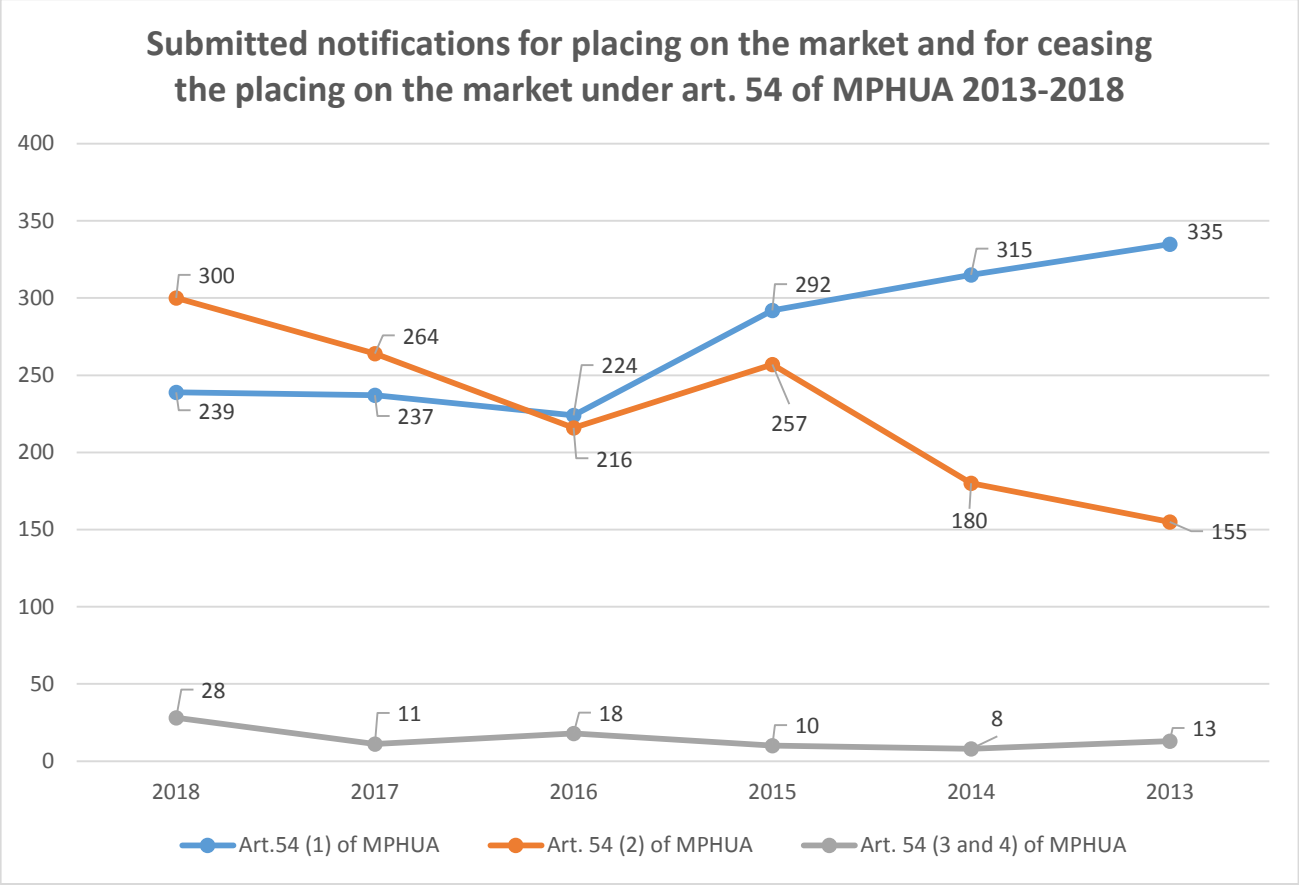
BDA monthly updates the List of Authorized Medicinal Products, which are not subject to medical prescription.



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.



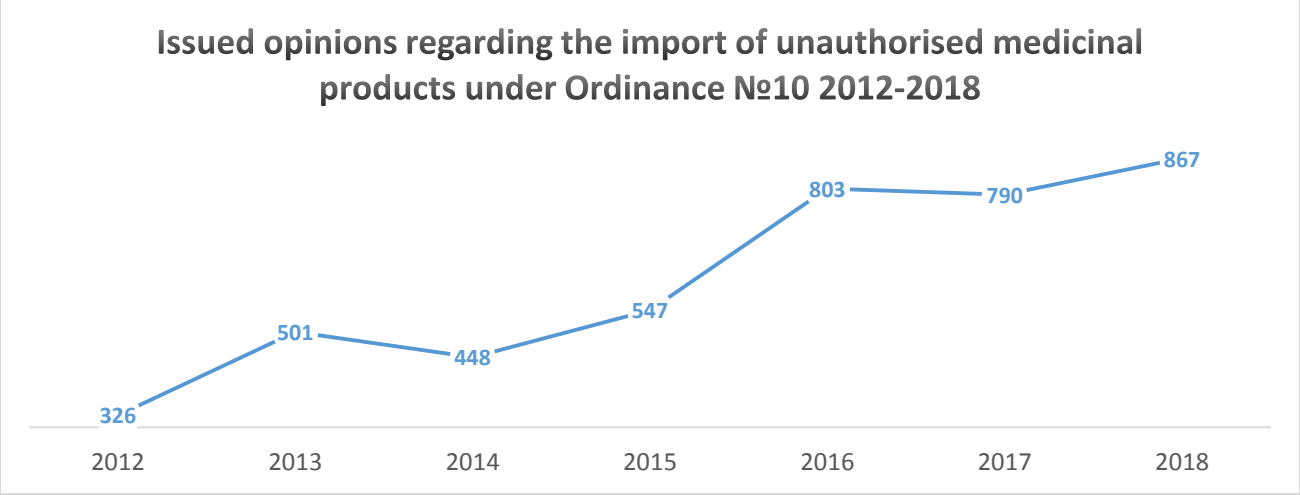
Notifications for placing on the market and for ceasing the placing on the market



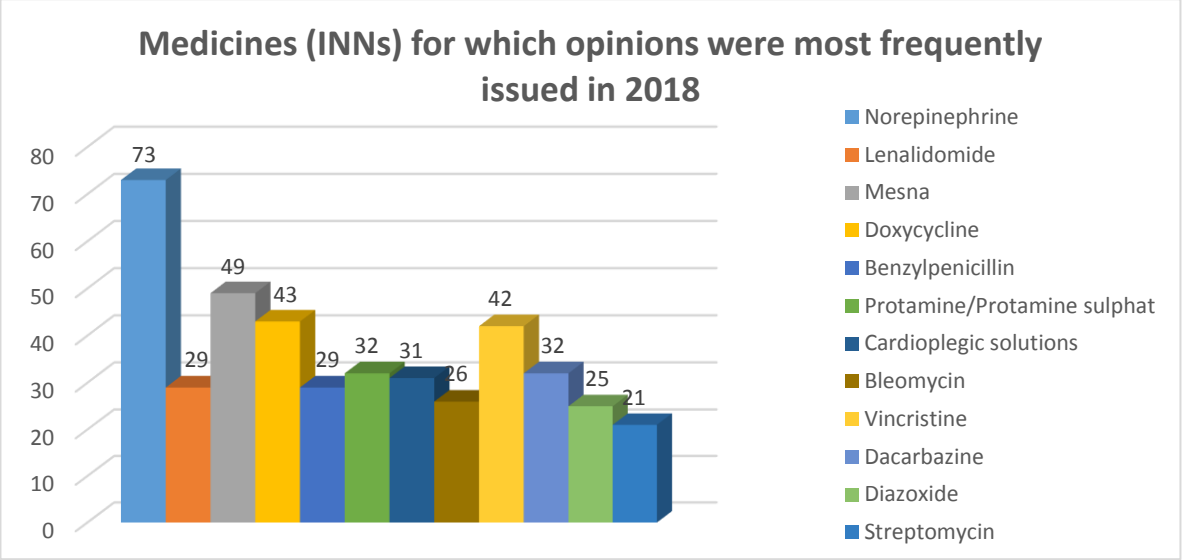
In 2018, 19 messages were published in connection with discontinuation of sales of non-alternative medicinal products in order to raise awareness among medical professionals and patients.

Opinions regarding the import of unauthorised in the country **medicinal products**

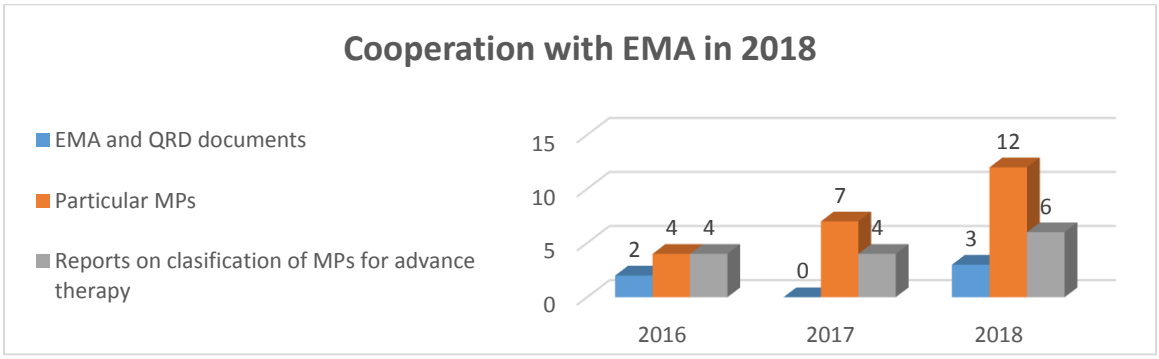
In 2018, 867 opinions regarding the import of unauthorised in the country medicinal products under the Ordinance № 10 were issued.



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, 8 expert opinions were issued. In addition, 2 expert reports were prepared for the Ministry of Interior.



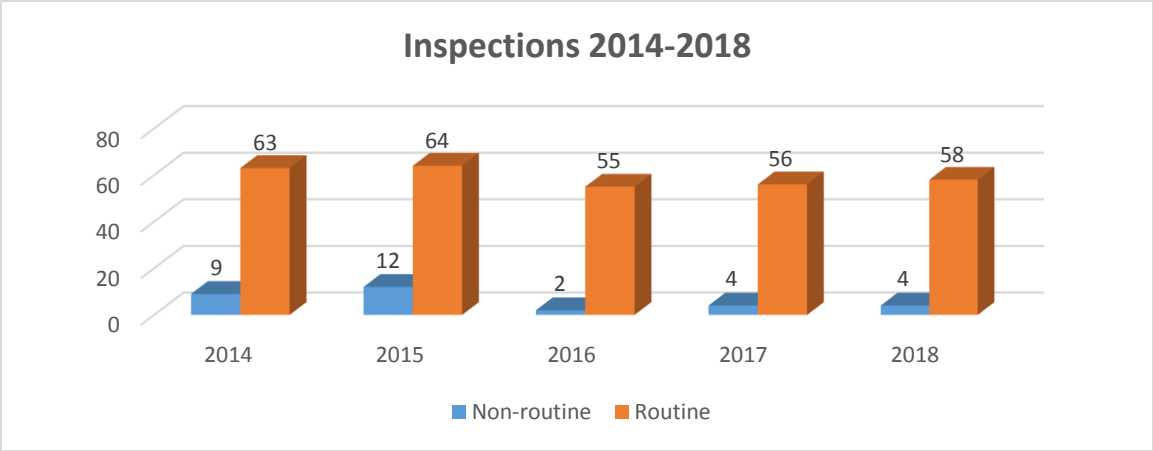
2.10. BLOOD TRANSFUSION SYSTEM SUPERVISION

The Agency's Executive Director acts as the competent authority for the operation of the blood establishments - Regional Centers of Haematology (RCH), the Haematology Wards (HW) and the Haemotology Laboratories (HL), collecting, testing, processing, storing, distributing, using, and ensuring the quality and safety of the blood and blood components and for the transfusion supervision for compliance with the BBDBTA, the Transfusion Haematology Standard and the Good Laboratory and the Good Manufacturing Practices.

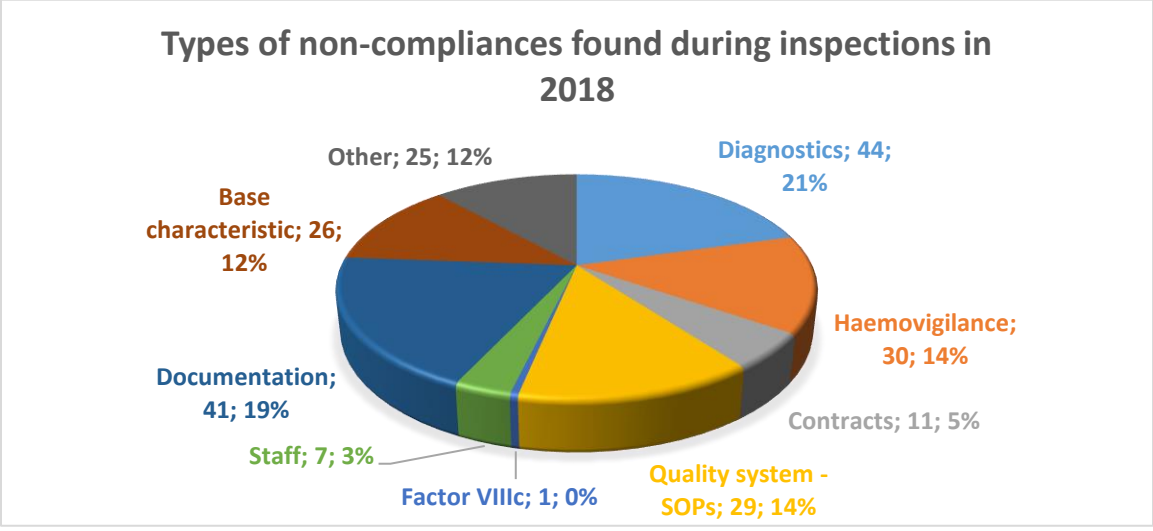
In 2018, national legislation transposed Directive 2016/1214 / EC. The change consists of introducing the Good Practice Guidelines developed by the Commission and the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe and published by the Council of Europe. This has led to significant changes in the Transfusion Haematology Standard mainly focused on the detailed description of each process.

Inspections

In compliance with the approved schedule for inspections in 2018, there were 58 routine inspections in healthcare facilities carried out, which included collecting, testing, storing, processing, distributing and using blood and blood components under Art. 15 of the BBDBTA. Four non-routine inspections were also carried out in accordance with the regulations in Ordinance № 26 of the Ministry of Healthcare.



The number of identified discrepancies varies between the years, as shown in the graph below. A comparison is possible because the medical establishments performing activities under art. 15 of the BBDBTA are subject to annual control according to art. 39, para. 2 of the BBDBTA.



In the period 2007-2010, the non-compliances were mainly related to the basic characteristics of the HWs, but the increased control on the quality systems showed non-compliances in the documentation of the processes during 2010-2016 - incomplete documents, omissions in the maintenance or provision of mandatory equipment, etc. In 2015 and 2016 there was a tendency for a relative decrease in the number and especially the criticality of the non-compliances. There was an increase of inconsistencies in 2018 due to the introduction of the Council of Europe's Good Practice Guidance.

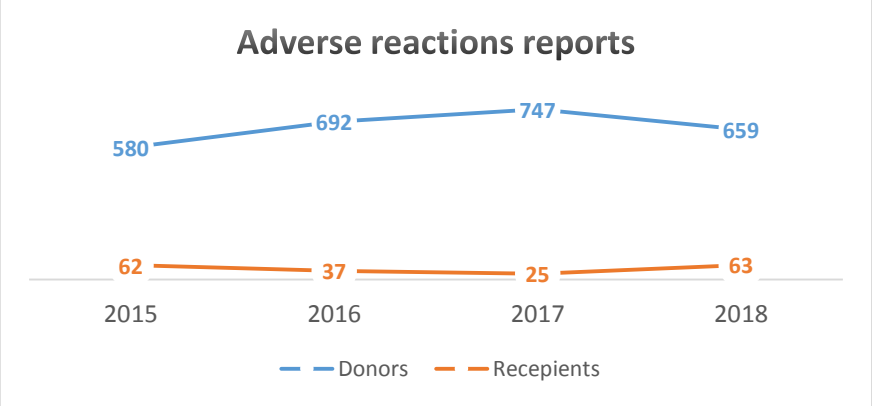
According to Art. 39, para. 4 BBDBTA, the Ministry of Health should be informed for the results of the inspections twice a year. The BDA has sent the summary reports as required. For the ascertained non-compliances the Agency issued instructions for corrective measures.

Haemovigilance

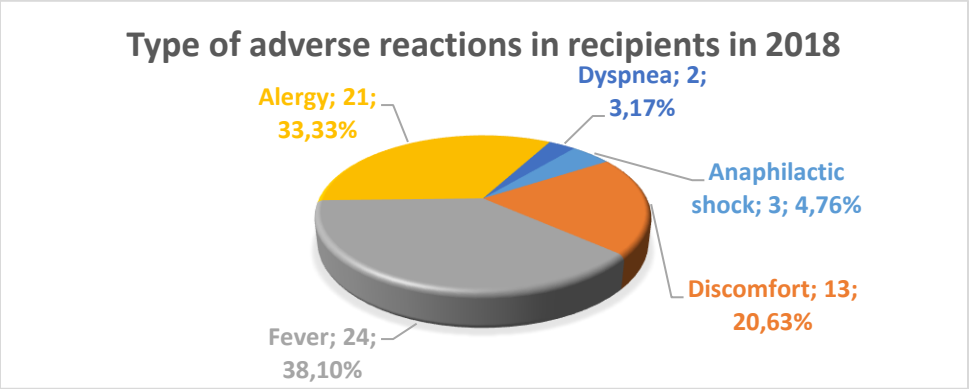
Haemovigilance is performed for the purpose of traceability of blood components, providing safe blood and blood components and preventing conditions for recurrence of adverse events and incidents in the transfusion process.

The supervision of the entire transfusion process, from the donation of blood to its clinical application, takes place thanks to the well-structured and functioning National Information System for Transfusion Haematology (NISTH) which acts as a three-layered register in addition to the register of the donors and recipients. The NISTH enables us to trace a unit of blood from the donor to the recipient, in case an adverse reaction arises. It has the capability to generate a 'dossier' of every unit of blood using only the software of the apparatus. The amendments to the Ordinance № 9 for the Establishment of Transfusion Haematology Standart from 2018 implemented **European criteria for the inspection of the information system** for transfusion haematology.

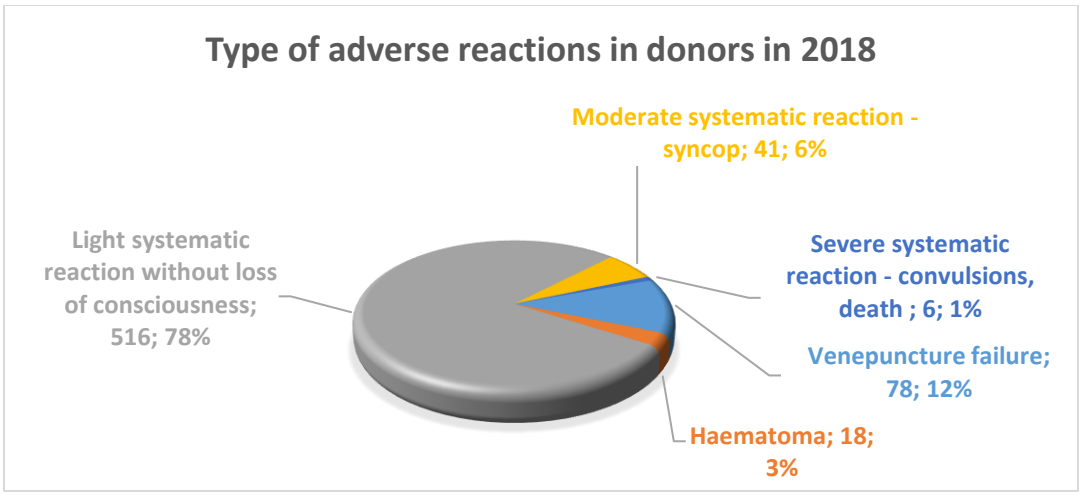
The BDA maintains a register for serious adverse reactions and events occurring during collection and use of blood and blood components. The persons, engaged in collecting, diagnosing, processing, transfusing and storing blood or blood components, are required to report immediately to the BDA serious adverse reactions and events or suspected serious adverse events/reactions. In 2018, the BDA received 722 reports for adverse reactions as follows:



In 2018, the BDA received 63 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 2017, the number of the reported adverse reactions increased.



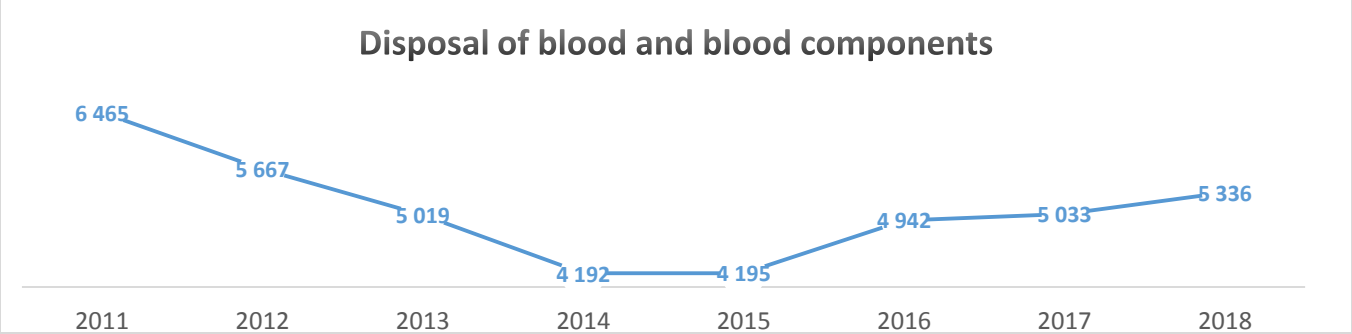
In 2018, the BDA received 659 reports for adverse reactions during blood donation. They were basically light systemic reactions without loss of consciousness or developing severe haematoma. The events of more severe systemic reactions were studied during the routine inspections. For all donors, the staff have adequately responded and there were no consequences for the blood donor's health. No procedural violations were found.



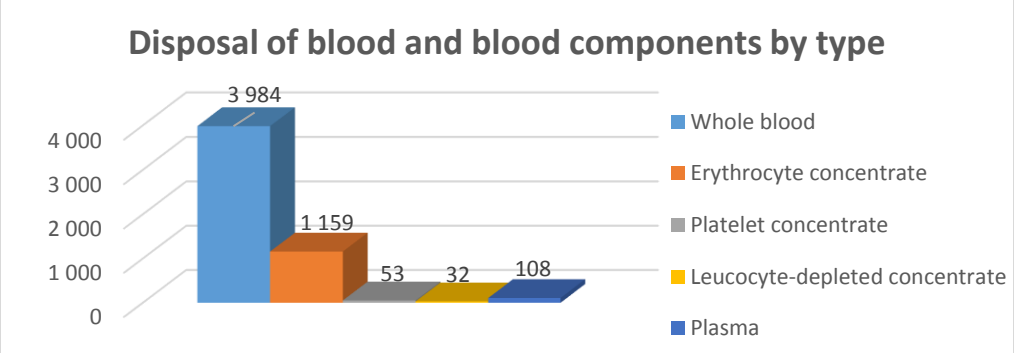
Disposal of blood and blood components and the reasons for the disposal

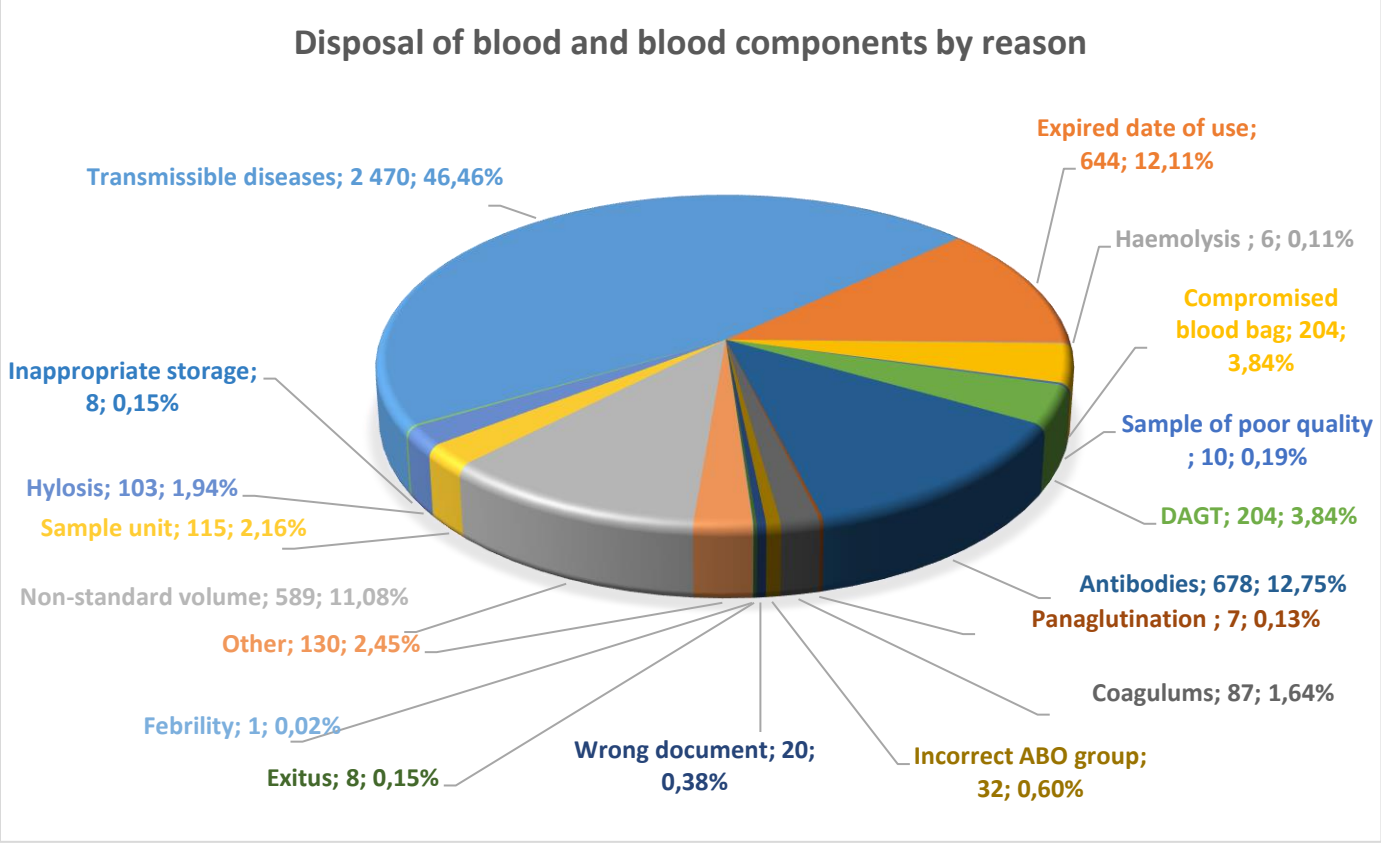
Based on the information received by the healthcare institutions, the BDA maintains a database on the disposed of blood and blood components and the reasons for the disposal.

In 2018, the transfusion system disposed of or transmitted for scientific use 5 336 units of whole blood or blood components (incl. erythrocyte concentrate, fresh-frozen plasma or platelet concentrate). The comparison to 2017 shows an increase of the disposed of or handed over for scientific purposes units with 303.



In 2018, the main part of the reasons for disposal of almost 75% of the units are factors found in the early stages of processing and examination of the blood in the blood establishments.





Measures to increase the efficiency of the inspection process

In connection with the trend of increase in the cases of West Nile-Fever disease in the neighboring countries, the BDA proposed measures to be implemented in the haemotransfusion system for the period June - November 2018, aimed at reducing the possibility of donating blood infected with West Nile Fever (WNV), and to maintain the safety of the blood and the blood components. The information was published on the BDA website in a timely manner and sent to the blood establishments, directly informing the healthcare professionals. In this regard, the Expert Council on Transfusion Hematology to the Minister of Health was being informed in due time about the occurrence of cases of transmissible diseases in other member states of the European Union through the Rapid Alert for Blood, as well as the guidelines for the measures taken by the haematransfusion system of each of the affected countries. In 2018, the Expert Council on Transfusion Hematology adopted an Action Plan on the occurrence of West Nile Fever in Bulgaria. At European Union (EU) level, such a plan was adopted in 2011 by the European Union. A proposal for an action plan for outbreak of a transmissible disease was sent to the Ministry of Health. This document presents an algorithm in such cases and the measures to be taken, respectively at national level (general measures) and in the affected areas (local measures).

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.

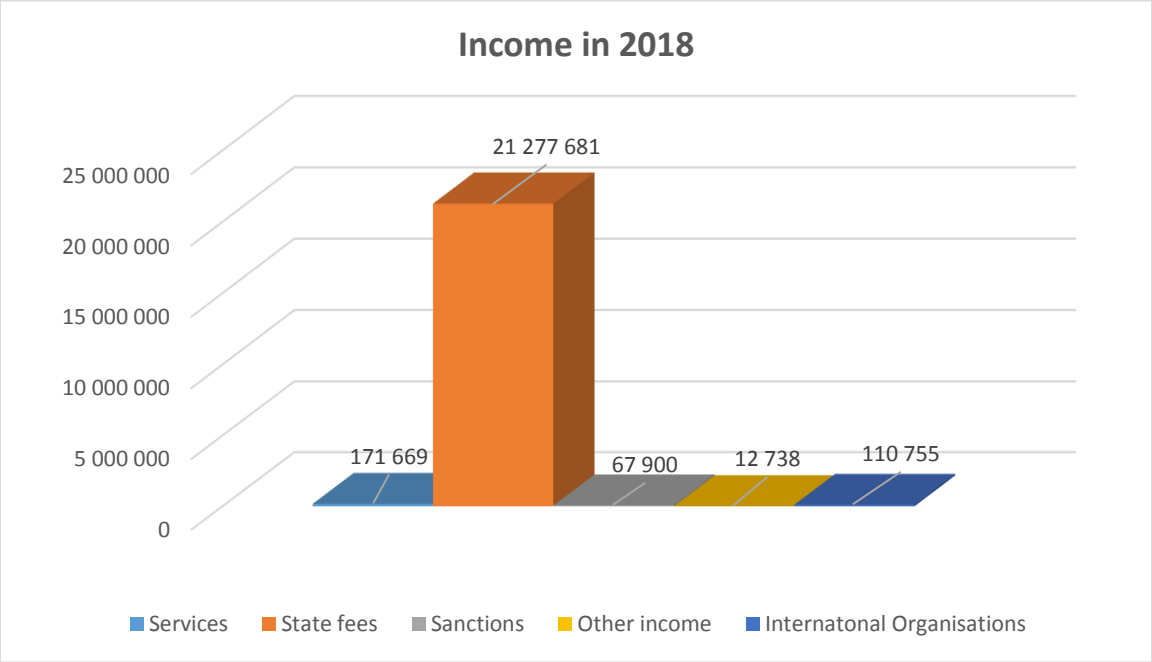
3. FINANCIAL RESULTS

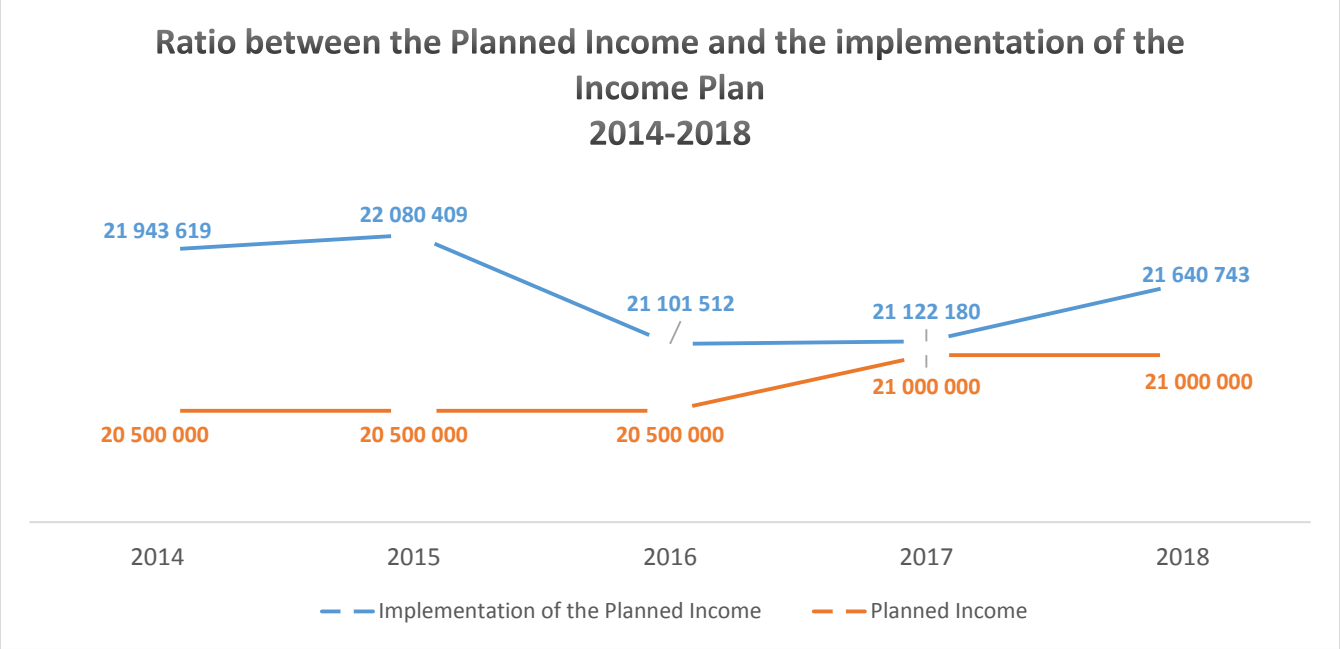
Income

The income part of the BDA's budget consists of its ensured income from the state budget in accordance with the MPHUA and the MDA as well as funds gained through its own activity (sanctions, services and other sources). The total income in 2018 was 21 640 743 BGN as the approved budget was 21 000 000 BGN and its implementation was 103%. This is an overfulfilment of 3% with the overfulfilment of states fees alone being

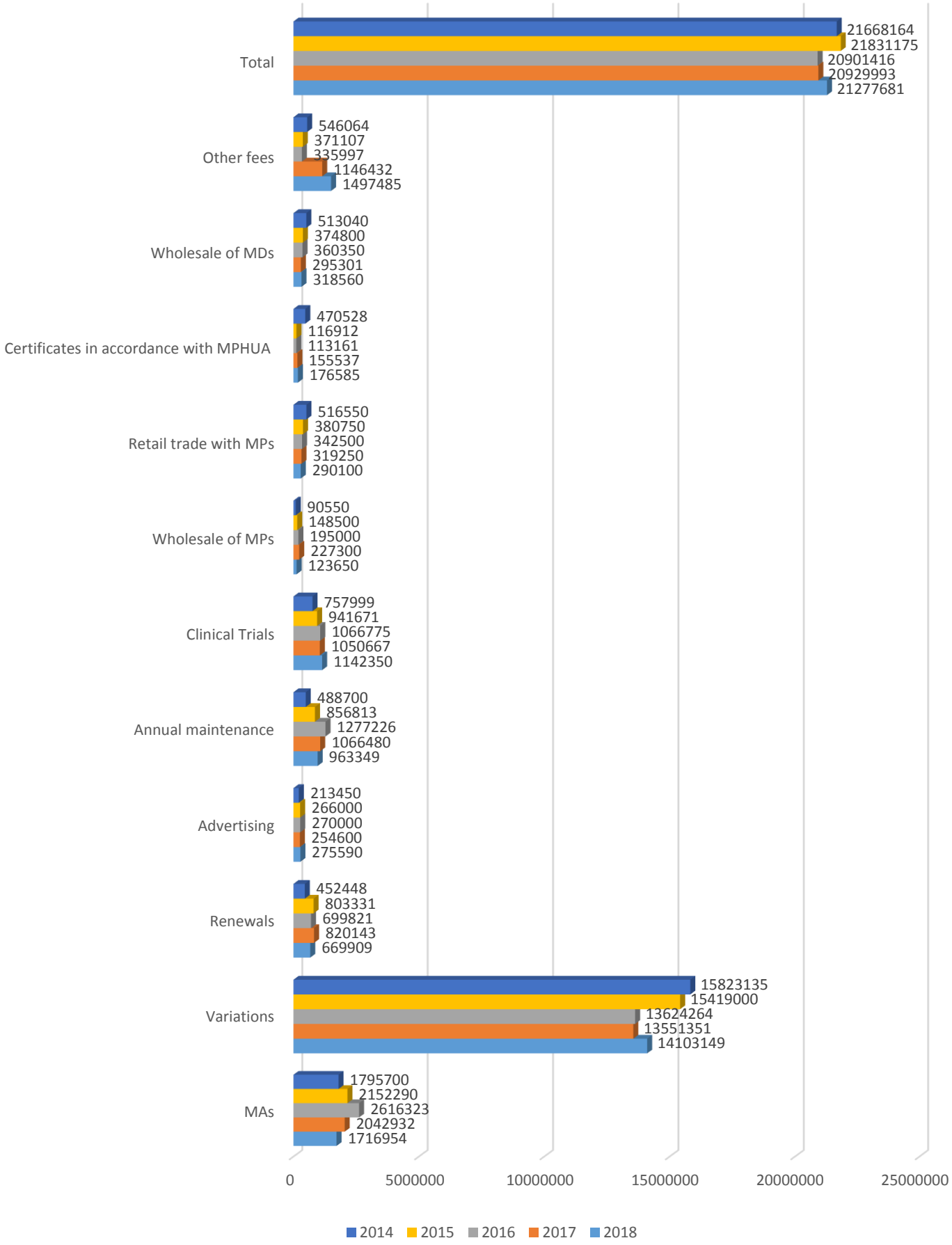
1.3%. The income from state fees was 98.3% of the whole income and is the main pillar of the BDA's income.

The graph below shows the allocation:

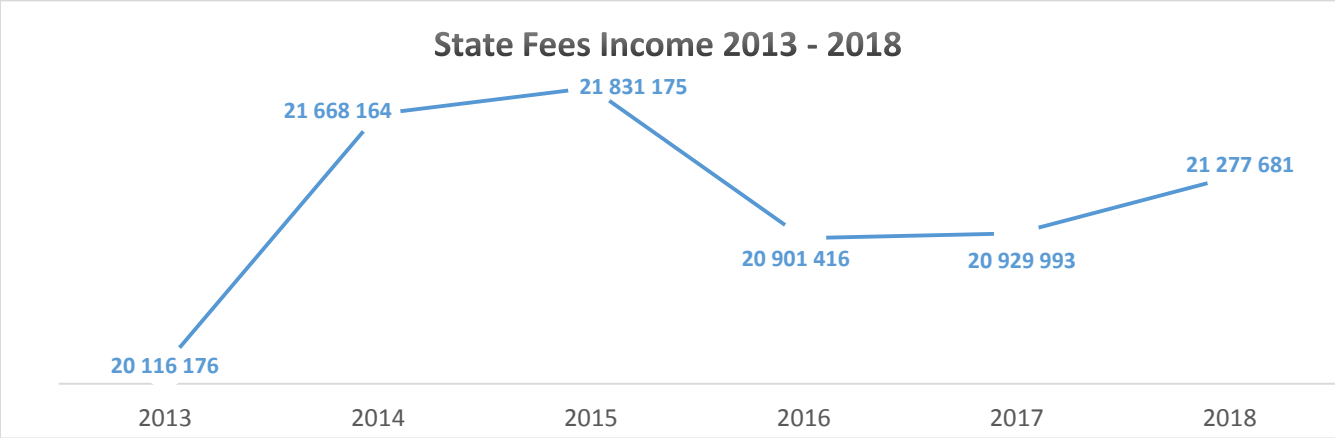




Structure of the state fees income by administrative service



As evident from the figures above, the income from fees for Variations is 66.3% of the whole income from state fees.



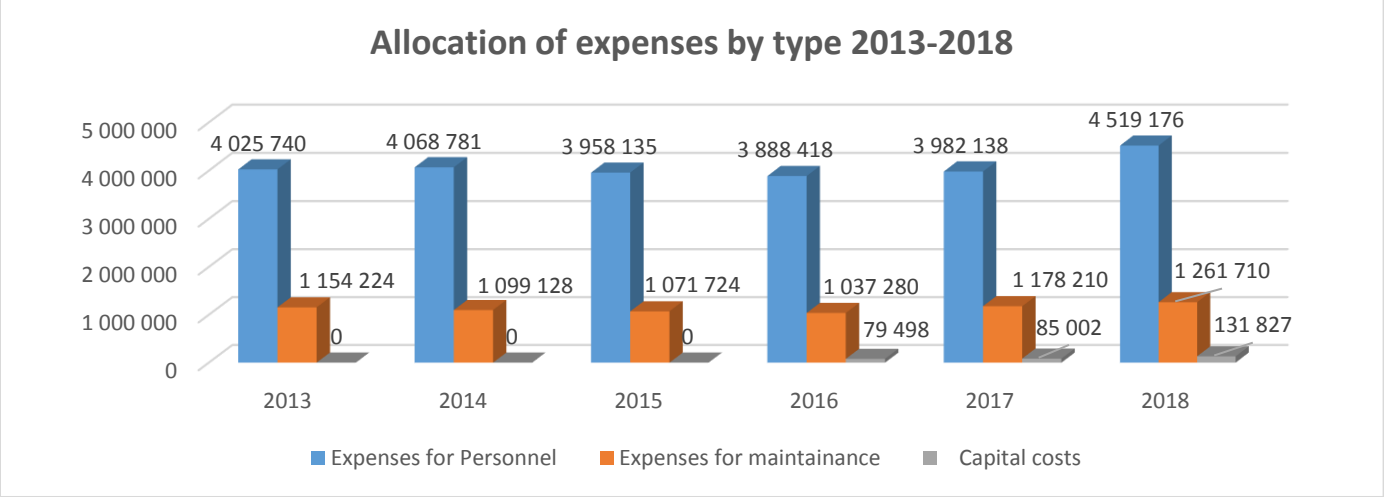
Although the state fees income in 2018 is higher than in 2017, the general trend of income decrease compared to 2014 and 2015 is maintained. The "distortion" of the real picture of the income is a result of the higher number of Variations applications in 2018. The reasons are two exceptional circumstances in the past year:

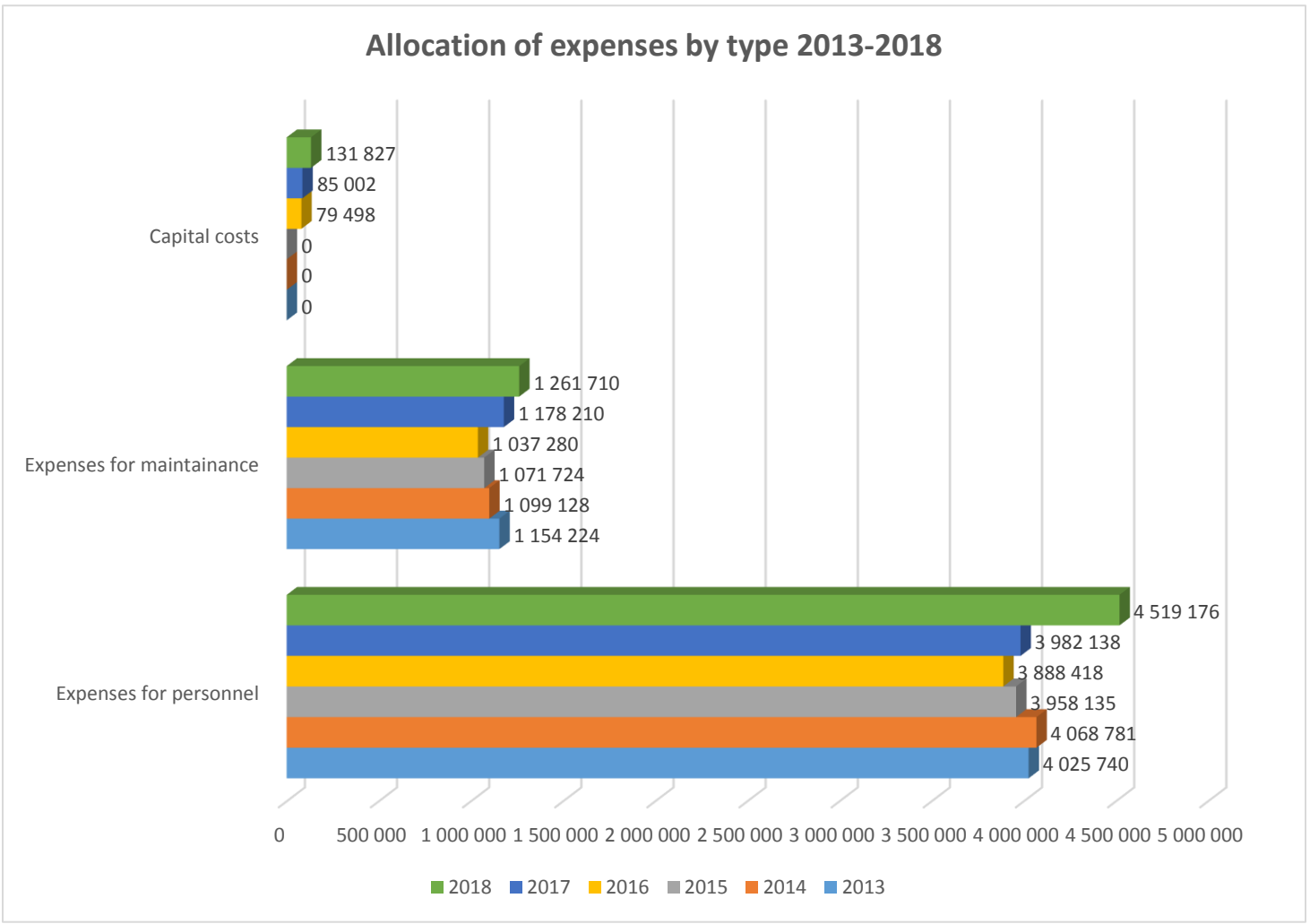
- The BREXIT and the requirement marketing authorisation holders to be located within the EU. In this regard, the marketing authorisation holders had to submit applications for transfer of the marketing authorisation rights for each medicinal product;
- The forthcoming entry into force of the Delegated Regulation 2016/161 demanded filing Variation Application for the packaging of each medicinal product.

The two circumstances imposed a campaign of filing Applications in 2018, and in 2019 a drastic drop in their numbers and income is expected.

Expenses

The total amount of expenses for 2018 is BGN 5 912 713 as the approved budget was BGN 6 087 000. The implementation is 97%. The savings are BGN 174 287 or 3%.

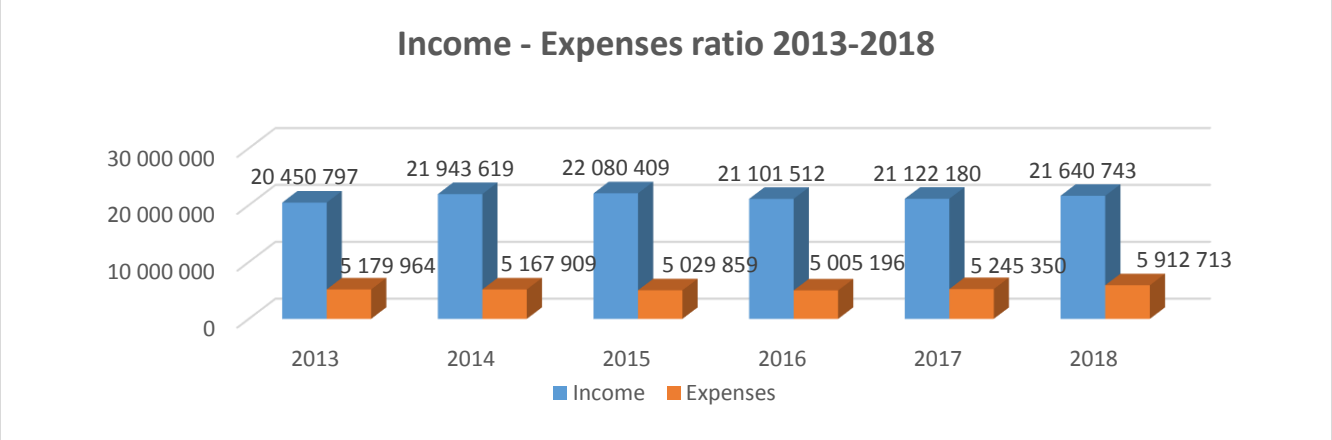




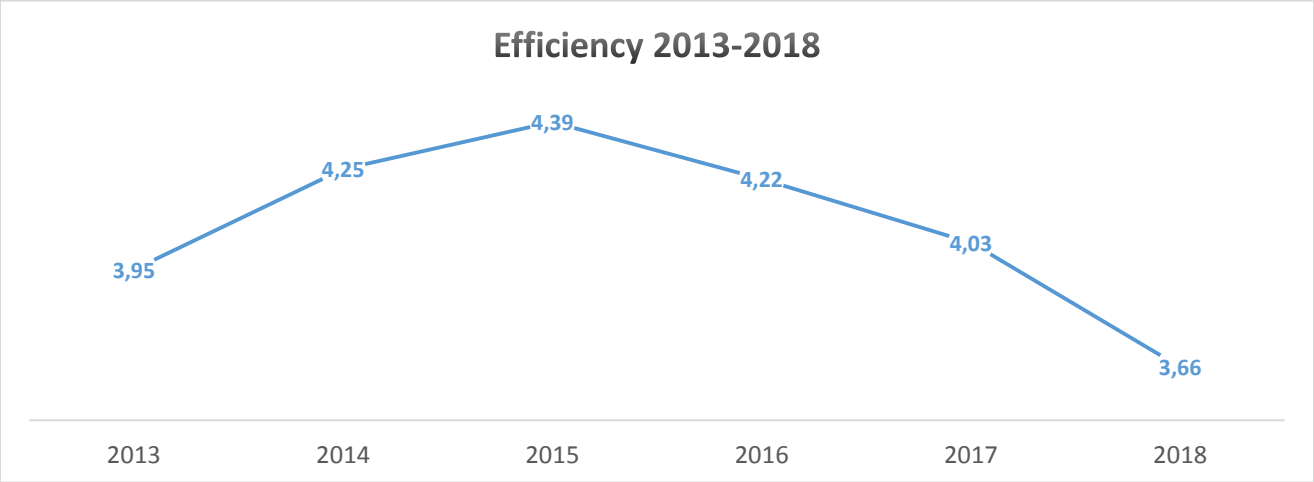
In executing the budget plan for 2018, the BDA spent BGN 131,827 for capital costs.

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 high positive amplitude of the efficiency values for 2014-2015 after the sharp downturn in 2013 is a consequence of an increase in the total value of income and the optimised level of expenses. In the following 2016 and 2017 there was a decrease because of the expected downward trend in the area of the highest income – the Variations; along with the increase in the expenses because of the increased minimal salary and respectively the insurance weight.

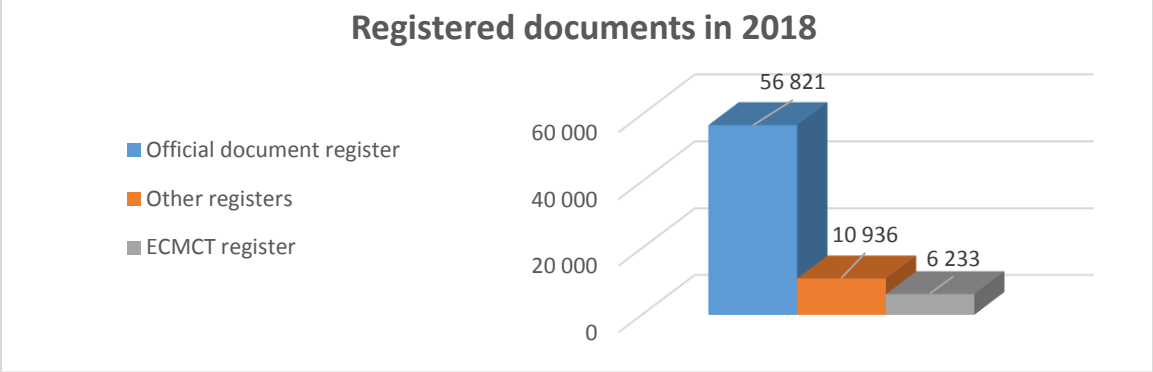
The efficiency of expenditure for 2018 is 3.66 and the efficiency planned by the budget was 3.45. Each 1 BGN of expenses "brought" 0.21 BGN additional income. The additional effect is 6%. There is a decrease in efficiency from 4.03 in 2017 to 3.66 in 2018 is justified by objective factors, namely the increase in the expenses due to the 1% increase in the amount of the payment to the Pensions Fund and the raise of the Minimal Salary in 2018 as well as spending part of the economy savings for purchasing long-term assets.

Additionally, a factor influencing the expenses level in 2018 was the Bulgarian Presidency of the Council of the EU. The BDA hosted three international meetings with more than 200 foreign delegates. The events were organized and partly funded by the Bulgarian Drugs Agency's budget, and in the other 13 meetings of the Regulatory Network and the NCAs for Medical Devices the BDA was represented in the hosting countries.

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 2018 are as follows:



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.

The AIS DOCMAN document flow system was linked to the Electronic Communications Interchange System (EMS), supported by the State Agency "Electronic Governance", which made the Bulgarian Drugs Agency "active" participant in the electronic communications exchange between the state administrations. New types of documents were created for workflow optimising and enhancing the control capabilities, including their processing by registration in electronic registers, whose maintenance in the information system is regulated. The technology for preventive, ongoing and joint control of the implementation of services and procedures was optimised as well.

5. PROCEDURES FOR AWARDING PROCUREMENTS

In 2018 the Agency carried out the following procedures for awarding procurements:

1. 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'.

2. A gathering of offers procedure for tender 'Delivery, installation, tuning, entry into service and after-sales service for an infrared spectrometer for the needs of the laboratory of the Bulgarian Drug Agency'.

3. A gathering of offers procedure for tender 'Delivery of net active electrical energy and choice of coordinator of the balancing group for the needs of the Bulgarian Drug Agency.

In regards to the entry into force of the amendments of the MPHUA on the 12.10.2018 which envisions the BDA to establish a Specialized computer system for tracking and analysis of the medical products contained within the Positive list, a market consultation was held in preparation of awarding the public procurement for its establishment.

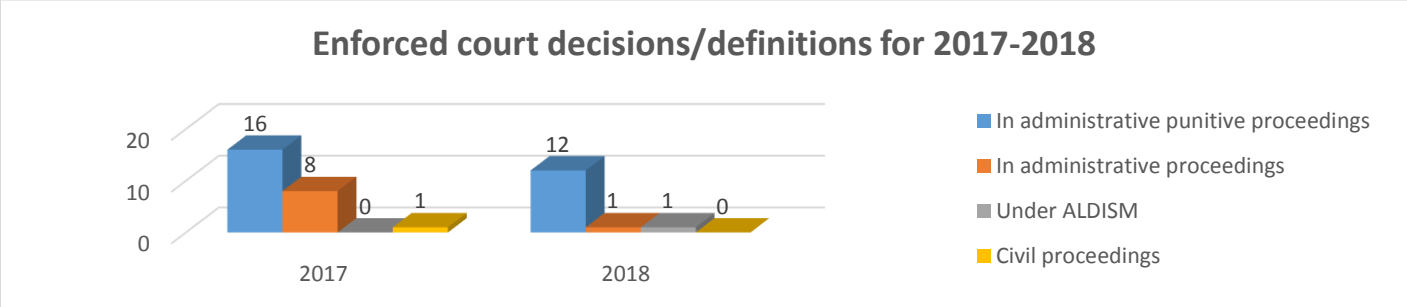
6. LEGAL PROVISION

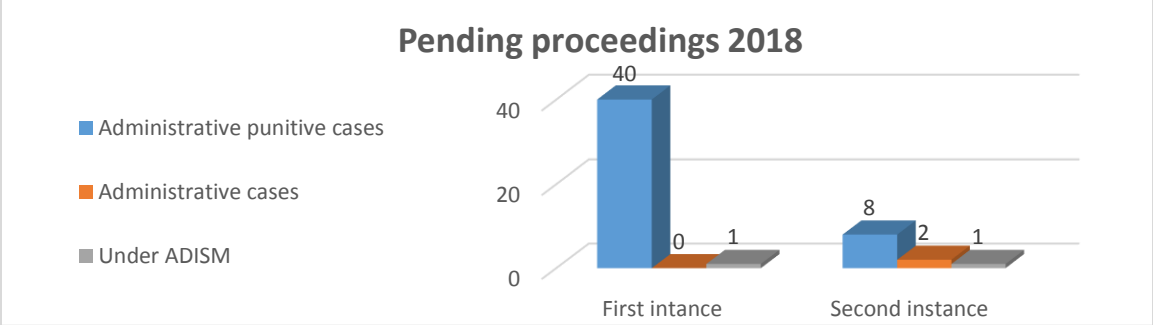
The main priority for the BDA is providing and ensuring the lawfulness of all administrative activities and of the issued administrative acts. In pursuit of their duties according to the BDA Structural Regulation and their

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 67 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:

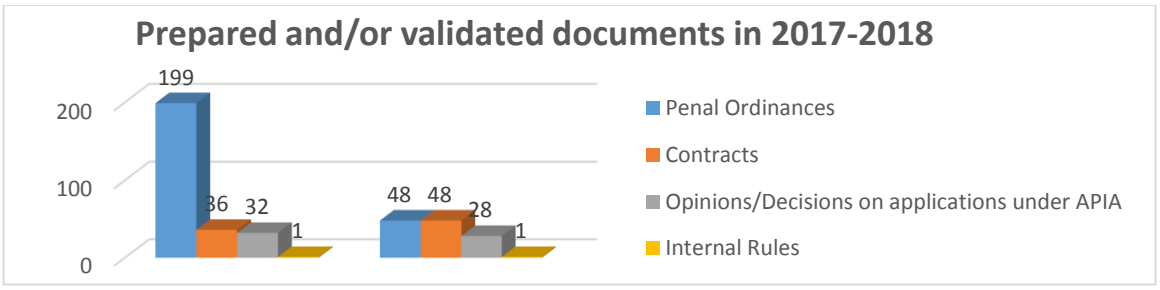




In 2018, there were no repealed penal ordinances. Regarding all appealed penal ordinances that entered into force, the respective actions for collecting the imposed fines and sanctions according to the procedure of Tax-Insurance Procedure Code were carried out.

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

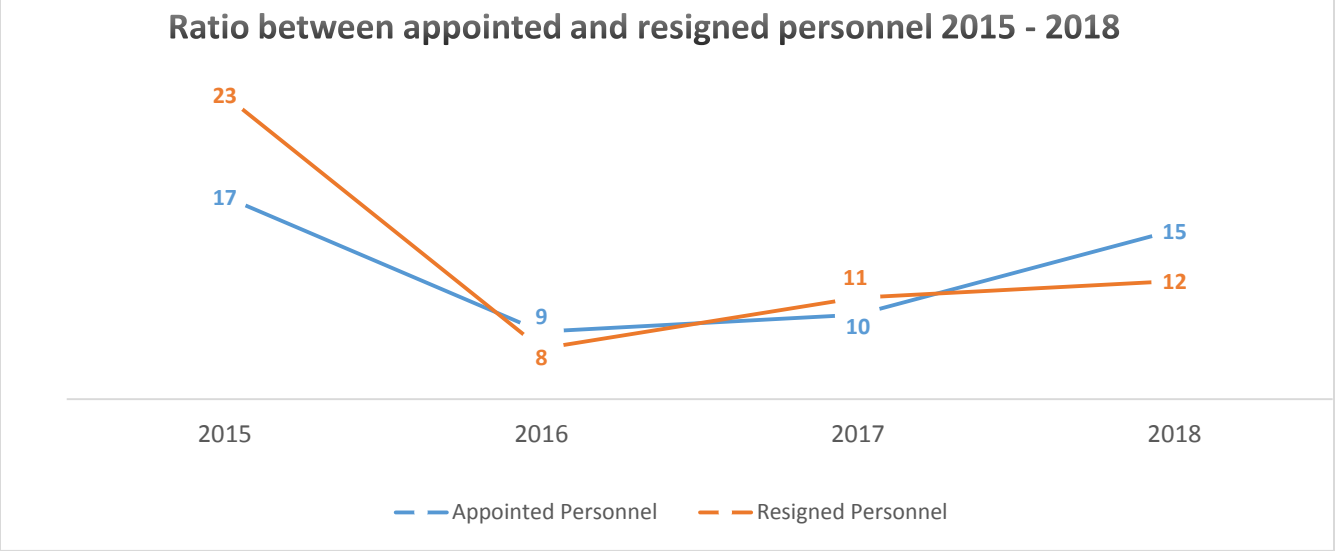
In 2018, "Internal rules for the organization and order for check-up of declarations and ascertaining conflict of interests in the BDA" was developed and approved. Questionnaires to examine drug regulatory issues among EU Member States were developed. Opinions have been issued on amendments and supplements to MPHUA and its secondary legislation.

Pursuant to a Council of Ministers Decree approving a report of the Interdepartmental Group on Problem Area "Independence of the Judiciary and Corruption", the legal advisors carried out an analysis of the administrative and penal provisions of MPHUA and MDA. The analysis identified weaknesses in legislation, including some related to contradictory court practice. As a result, particular proposals for changes in the legal framework are being prepared.

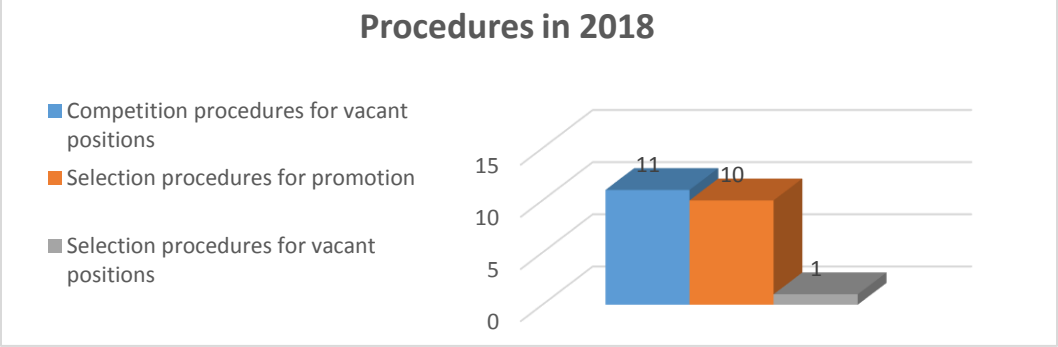
7. HUMAN RESOURCES MANAGEMENT

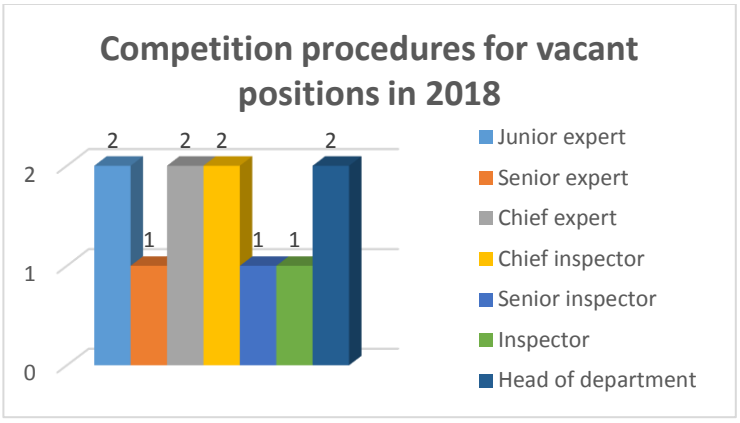
Personnel

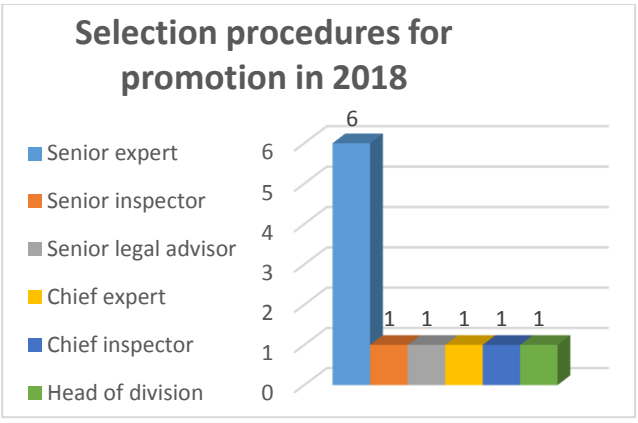
In 2018, the BDA appointed 15 new employees. There were 12 employees who resigned, including those who retired.



In 2018, the Agency held 11 **competition procedures for vacant positions** and 10 **selection procedures for promotion**, and **1 selection procedure for vacant positons** as follows:







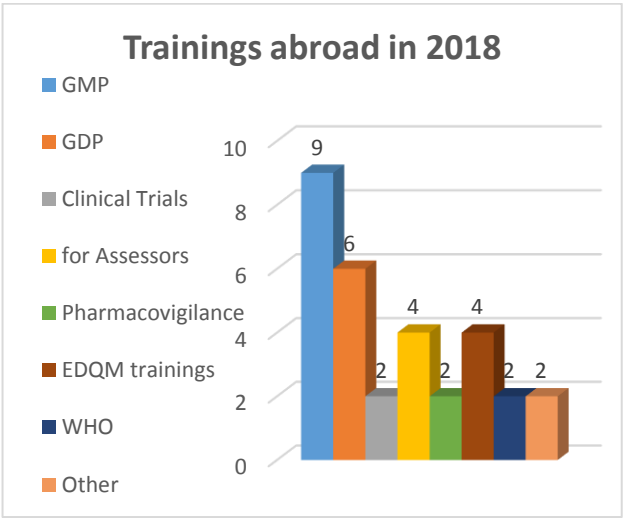
Qualification and training

The HR experts organized the mandatory and 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 auditing 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 2018, 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 with a 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.

Internal and external audits

According to the *Annual Program for conducting Internal Audits for 2018* 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 2018, 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.

After an internal audit for compliance with the membership requirements of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), the BDA applied for the launch of a procedure for membership of the Republic of Bulgaria in PIC/S. In October 2018, the BDA was informed that a documentation assessment team was designated.

In connection 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) that entered into force on 25th May 2018, a GAP analysis was performed after an overall internal audit to assess compliance with the requirements of the Regulation. In accordance with to the audit results, documents and mechanisms have been developed to meet the requirements

No inconsistencies were identified during the audits, but measures to improve the processes were considered and actions were undertaken to implement them.

BDA's laboratories are accredited for compliance with BSS ISO/IEC 17025:2006 by Executive Agency *Bulgarian Accreditation Service* (EABAS) and are attested by the European Directorate for the Quality of Medicines & HealthCare (EDQM & Healthcare).

At the end of May 2018, an external audit was conducted by EDQM under the Mutual Joint Audit (MJA) scheme. The audit passed successfully, all planned activities on the identified discrepancies were met and the EDQM attestation is due to be received.

As of July 23, 2018, the Quality Management System of the *Medicinal Products Analyses* Department passed to the new version of ISO / IEC 17025:2017 and an internal compliance audit was conducted in early September 2018. A package of documents was prepared in October-November 2018 in connection with the forthcoming re-accreditation in 2019 by EABAS.

IMS training

The quality management experts organize and coordinate the training of the BDA staff on quality management, information security and risk. During the year, training of all newly recruited employees of the agency was carried out.

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.

The Bulgarian Presidency of the Council of the European Union

Within the Bulgarian Presidency of the Council of the European Union, the BDA hosted three regular meeting of the regulatory network in Europe:

• Heads of Medicines Agencies (HMA II) 20-21 June 2018;

• Meeting of the European Medicines Agencies Co-operation on Legal and Legislative Issues (EMACOLEX) 29 - 30 May 2018;

• Working Group of Communication Professionals (WGCP) 10-11 May 2018.

More than 200 delegates took part in the three meetings who discussed topics within the Bulgarian Presidency's priorities in the field of the medicinal regulation, namely:

- Availability of appropriately authorised medicines
- Innovation and access to new medicines.

The topics are part of the EU Medicines Agencies Network Strategy to 2020.

The Heads of the medicines agencies discussed the challenges that each regulatory authority must solve not only on its own, but also in a wider European and global context. The topics included the progress of each EU Member State in relation to the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, the resources needed to implement it, as well as the existing differences and specificities in the national systems. The challenges related to the Commission Delegated Regualtion (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use and the provision of the conditions for its timely implementation were also shared and discussed. Another topic of discussion were various initiatives on early access to innovative medicines as well as in the context of the European Commission's proposal on health technology assessment. The European Medicines Agency and the EU Member States presented a report on the experience gained with medicinal products subject to additional safety monitoring. The report was adopted and then sent to the European Commission and the European Parliament. A discussion was held on strategic issues related to the UK leaving the European Union. The BREXIT Task Force reported the positive results of the study on the preparedness of Member States to undertake mutual recognition procedures and decentralized procedures where the United Kingdom is the reference country. For the first time the BDA invited representatives of the Serbian and Moldovan medicines agencies, who took part in the EMACOLEX meeting as observers.

During the Bulgarian Presidency of the Council of the European Union the remaining thirteen regular meetings of the Working Groups and Scientific Committees within the EU Medicines Agencies Network, were held toghether with other EU Member States. Experts from the Agency actively participated in their preparation and successful conduct.

On March 6, 2018, BDA's representatives took part in a conference on opportunities for better access to medicines for European citizens. The event was part of the calendar in the Health Sector of the Bulgarian Presidency.

Agreements for Cooperation

In 2018, three Agreements for Cooperation were signed with the Centre for the State Control of Drugs and Medical Devices (CECMED), Cuba, Medicines Evaluation Board (MEB), the Netherlands and the State Institute of Drugs and Good Practices (SIDGP) at the Ministry of Industry and Trade of the Russian Federation.

The Memorandum with CECMED, Cuba, envisages exchange of information on medicinal products and medical devices, including requirements for marketing authorisations, quality control and adverse reactions, as well as work for convergence of practices and optimization of compliance with health requirements for medicinal products products intended for use in human medicine.

The Agreement with MEW, the Netherlands, focuses on the field of pharmaceutical policies and strengthening the capacity and quality of medicines regulation through the training of Bulgarian specialists, as well as providing support and expertise for the BDA in the areas of preclinical, clinical assessment and assessment of the quality of medicinal products. It also envisages exchange of experience and good practices for the assessment of biological and biosimilar medicines, the assessment of the quality of specific pharmaceutical forms and the assessment of non-clinical data.

Collaboration with the SIDGP, the Russian Federation, aims to establish a cooperation framework for conducting inspections of compliance with good manufacturing practices, thus strengthening mutual trust, improving safety and unifying the quality of inspections, including through the bilateral participation of observers in pharmaceutical inspections on the territories of the two countries, the organization of educational inspections and the development of joint educational programs, projects for additional training and improvement of the inspectors' skills. Information exchange and development of strategies to combat falsified medicines are also planned.

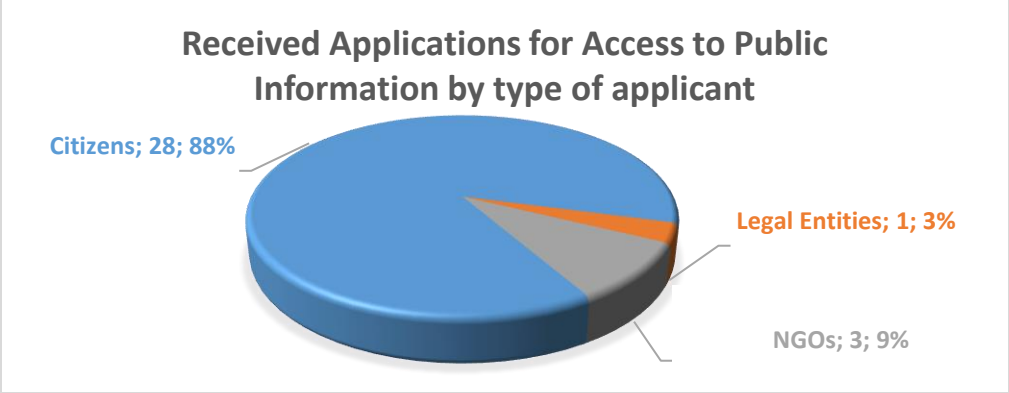
Agency's experts took part in meetings of the Expert group on the Delegated Act on Safety Features for medicinal products for human use and a Workshop hosted by the European Medicines Verification Organization; in a meeting of an expert group (national level) which drafted a Position on the Proposal for a Regulation of the European Parliament and of the Council amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products (COM (2018) 317) as well as in a discussion within a roundtable on the protection of healthcare professionals from exposure to hazardous medicines, especially from cytotoxic medicines, that took place at the European Parliament in Brussels, Belgium. The BDA was represented at the 14th Traditional annual symposium of Medicines and Medical Devices Agency of Serbia in Kragujevac.

In 2018, the European Commission's Blood Regulatory Committee, part of which is the Committee of Competent Bodies, set up Commission Expert Sub-Group on Inspections in the Blood and Tissues and Cells Sectors (IES). The established permanent subgroup will work in the field of European legislation on the blood, tissue and cell inspection process, the issues to be discussed will be related to the establishment of a regulation on the performance of quality system audits by the NCAs through the program CESIP of the VISTART project that finished in 2018. The agenda also includes the adoption of conditions for carrying out international, joint inspections of blood centers and tissue banks in the member states.

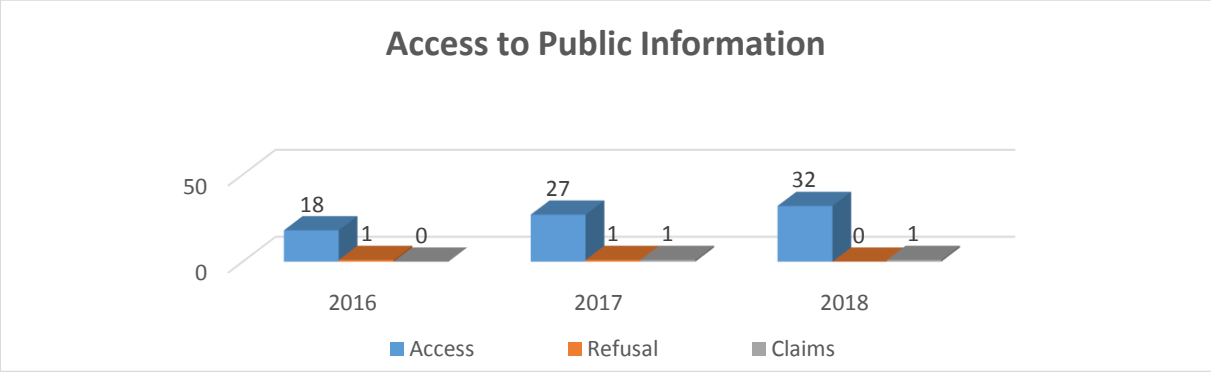
10. TRANSPARENCY AND COMMUNICATIONS

Access to Public Information

In 2018, the BDA received 32 Applications under the Access to Public Information Act (APIA) as 28 of them were submitted by citizens, 1 - by legal entities and 3 - by NGOs.



All the required accesses were granted in the set terms. There was one claim against a final act under APIA.



Communications

During the World Week for responsible use of antibiotics in 2018, the BDA published on its website promotional materials to support the campaign for reporting adverse drug reactions.