ИЗПЪЛНИТЕЛНА АГЕНЦИЯ ПО ЛЕКАРСТВАТА

ГОДИШЕН ДОКЛАД 2016

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BULGARIAN DRUG AGENCY

BULGARIAN DRUG AGENCY'S ANNUAL REPORT 2016

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Executive Director of the Bulgarian Drug Agency

INSTEAD OF A FOREWORD

In the past year, the Bulgarian Drug Agency (BDA) continued to build Bulgaria's reputation as a reference country in Community procedures for Marketing Authorisations. The Agency successfully completed two procedures within the set deadlines. For the first time, Bulgaria was a reference country in a Decentralized Procedure as the Agency's experts assessed a fixed combination of active substances and six member states were concerned. Within the second procedure, Bulgaria was a reference country in a Mutual Recognition Procedure with Romania as a concerned member state. BDA experts have provided a number of scientific advices on forthcoming community procedures where Bulgaria is expected to be the reference country.

In 2016, we continued the efforts of increasing the communication activity for adverse drug reactions reporting as part of the policy of raising the medicines use public awareness. Over the past three years, there has been a steady upward trend in adverse drug reaction Reports, with an increase in 2016 by 73.69 per cent of the valid case reports compared to 2014. The training activities and the Agency's participation in scientific fora concerning the topic have increased and in the past year, Agency's staff presented six scientific reports to healthcare professionals, patients and professional organizations, some of which were published in scientific periodicals.

As a continuation of the policy for optimizing and unifying the business processes and for enhancing the administrative capacity in 2016, part of the specialized administration in the Agency was restructured. Within the Market Supervision and Inspections Department all inspection activities on the wholesale and retail of medicinal products and medical devices, on pharmacovigilance and on clinical trials were fused in one structural unit. The Agency was sought for partnership in inspections for ascertainment of compliance with the Good Manufacturing Practice in third countries and along with that the BDA's analytical potential was enhanced (in 2016, a last generation of High Performance Liquid Chromatography System was purchased and capital expenses for delivery and installation of PCR Device for amplification of nucleic acids and of Device for horizontal gel electrophoresis for separation and detection of nucleic acids were approved).

The total income of the Agency's activities in 2016 was 21 101 512 BGN as the approved budget was 20 500 000 BGN. The implementation of the income is nearly 602 000 BGN more than planned, i.e. there is 3% overfulfilment of the income part of the budget while the types and amounts of the state fees have not been changed. The Agency saved 351 447 BGN and the efficiency of expenditure coefficient was 4.21 while the planned by the budget coefficient was 3.81. In 2016, no

complaints and reports relating to the activities of the Agency's employees were received, which is an indicator for customers' satisfaction with the BDA's administrative services.

The success in 2016 would have been impossible without the coordinated efforts of the BDA's staff, the external experts, the regulatory bodies of the other EU Member States, the support of the Ministry of Health, and the leadership of the European Medicines Agency.

I would like to thank them all and to introduce you the summarized Agency's results in the main directions of activities in the form of this Annual Report.

Assoc. Prof. Assena Stoimenova,
PhD, MScPharm, MPH

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 regulated by three acts - the Medicinal Products for Human Use Act (MPHUA), the Medical Devices Act (MDA) and 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 Authorizations 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 AUTHORIZATIONS OF MEDICINAL PRODUCTS

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

The charts below show the data about the applications and documentation for various procedures as well as the closed procedures:

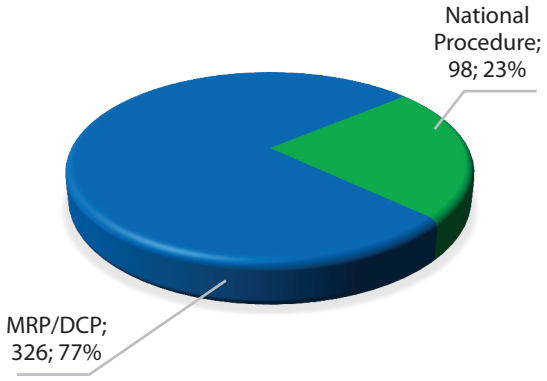


Fig. 1 **MA Applications for 2016**

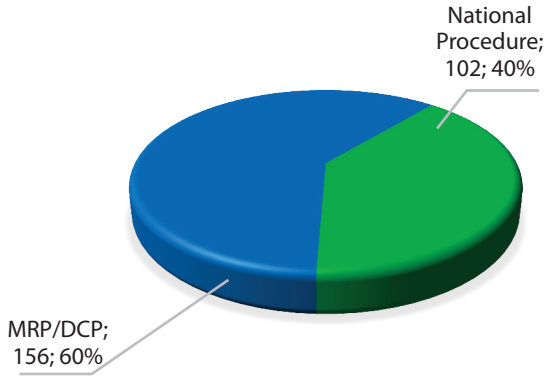


Fig. 2 **Renewal Applications for 2016**

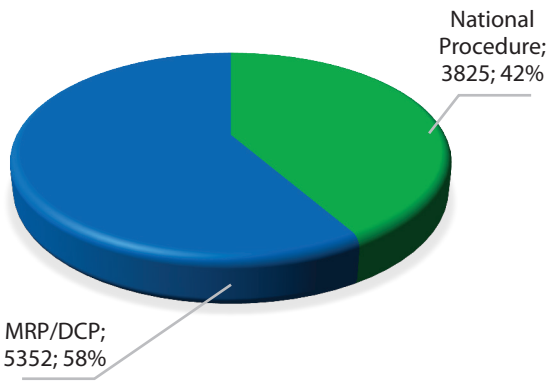


Fig. 3 **Variations Applications for 2016**

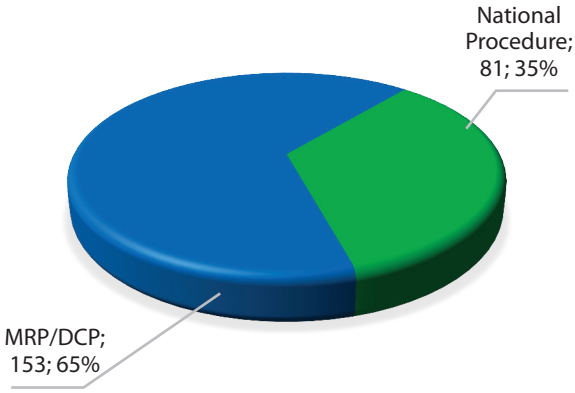


Fig. 4 **Revoked MAs for 2016**

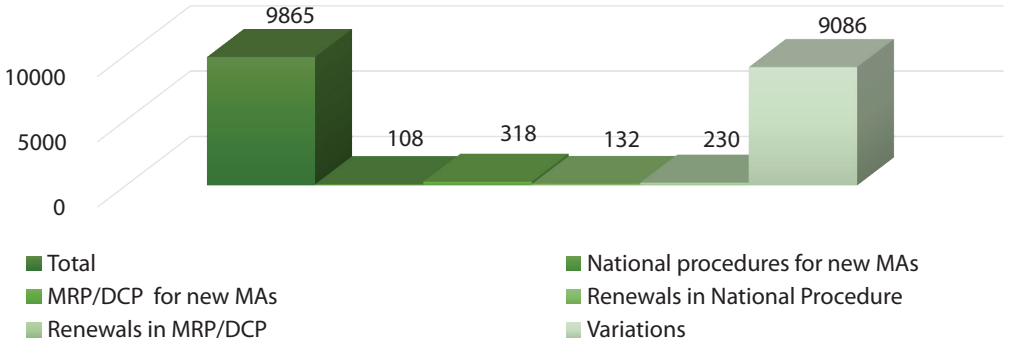


Fig. 5 **Number of closed procedures in 2016**

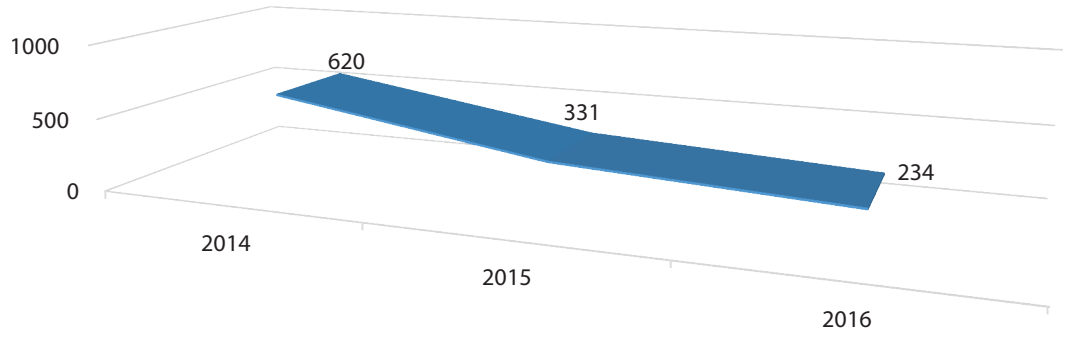


Fig. 6 **Number of revoked MAs in 2014-2016**

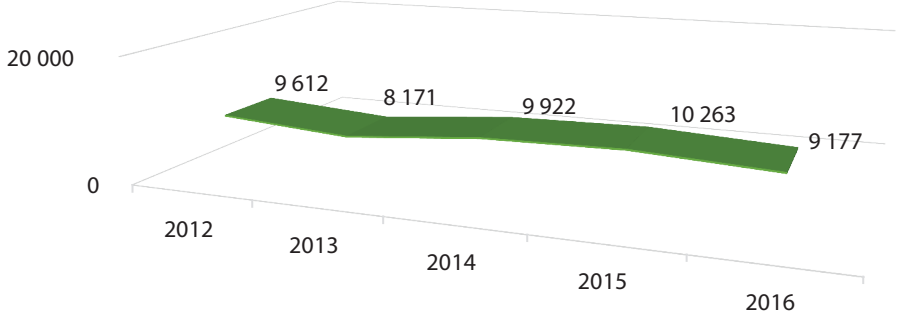


Fig. 7 **Number of received Variation Applications during 2014-2016**

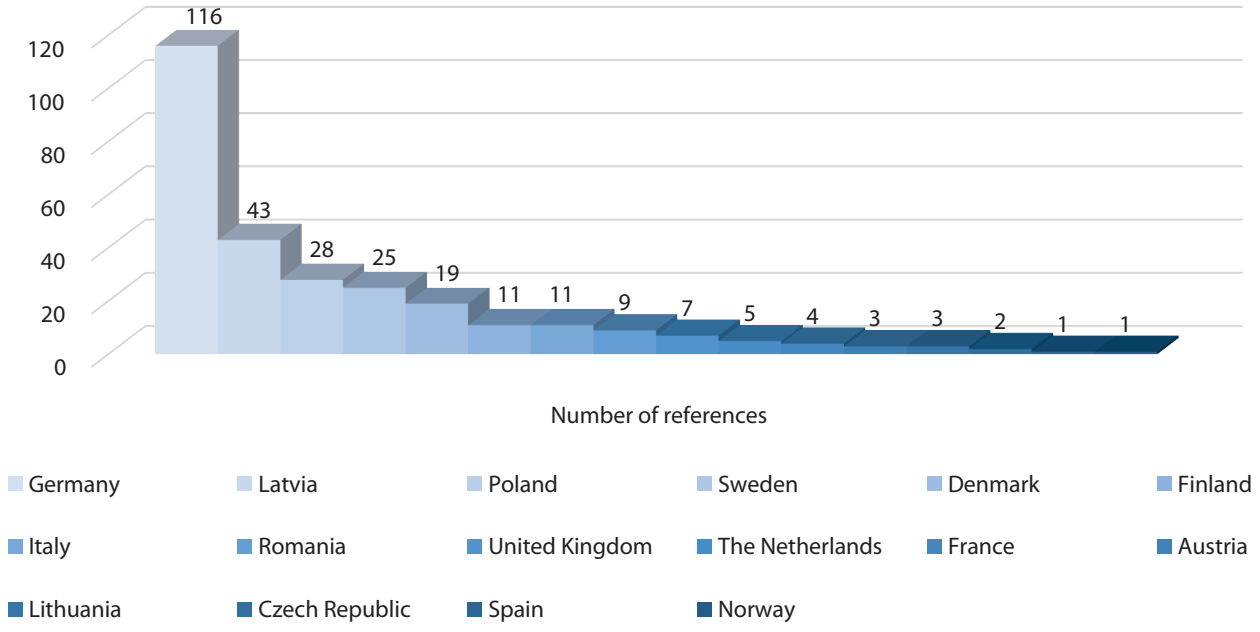


Fig. 8 **Parallel export references issued in 2016**

In 2016, BDA as a Reference Member State (RMS), successfully completed and closed in the defined deadlines two Community procedures. As RMS in the DCP procedure, BDA evaluated the documentation for marketing authorization of medicinal products (fixed combination) containing the active substances *ramipril* and *amlodipine*. The concerned Member States (CMS) were Austria, Greece, Portugal, Romania, Slovakia and the Czech Republic. In the second procedure *Zondaron solution for injection/infusion*, containing the active substance ondansetron, the CMS was Romania. The procedure started and was closed with the approval by the CMS within the prescribed period by issuing a Marketing Authorization.

BDA provided scientific advice for different purposes and questions concerning the forthcoming MRP/DCPs with RMS Bulgaria. BDA delivered a scientific opinion on a major change in the composition of medicines and the following new bioequivalence studies as well as scientific opinions about the prescription status of medicinal products.

2.2 MARKET SUPERVISION

Another field of BDA's activity is issuing 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 medicinal products and medical devices distribution chain.

Manufacturing authorization and control

BDA keeps an up-to-date electronic Register of 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.

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.

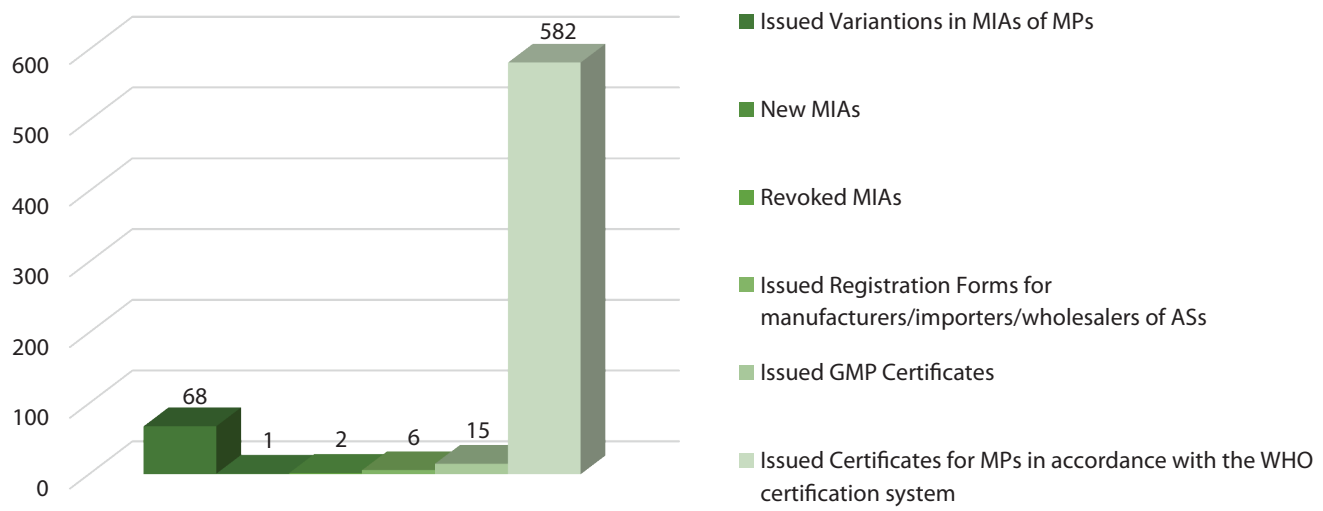


Fig. 9 **Types of documents and activities**

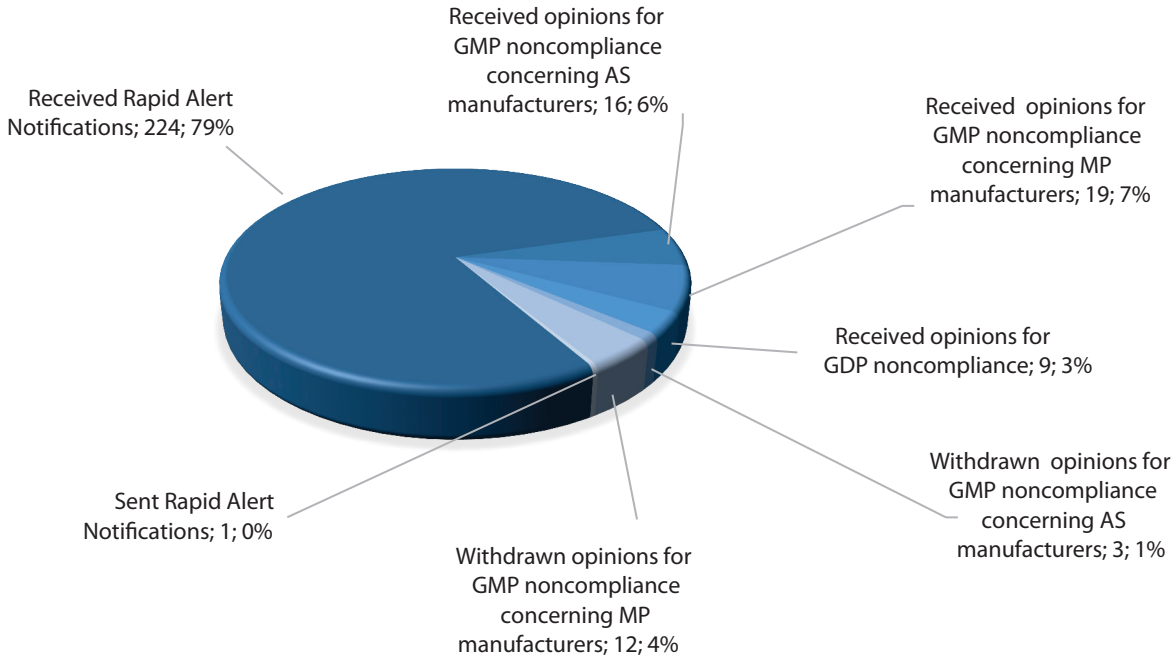


Fig. 10 **Rapid Alert System Activities**

Inspections at manufacturers

In 2016, BDA's inspectors carried out 28 inspections at manufacturers/importers of medicinal products, active substances and investigational medicinal products (IMP) for compliance with the MPHUA of the manufacturing, import, control and storage, secondary legislation and acts and guidelines adopted by the European Commission. The inspections were carried out pursuant to the approved Annual Inspections Plan for 2016 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.

One inspector took part as a supervising inspector in a joint inspection carried out by World Health Organization (WHO) representatives in the premises for manufacturing, control and storage of medicinal products owned by a Bulgarian manufacturer.

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

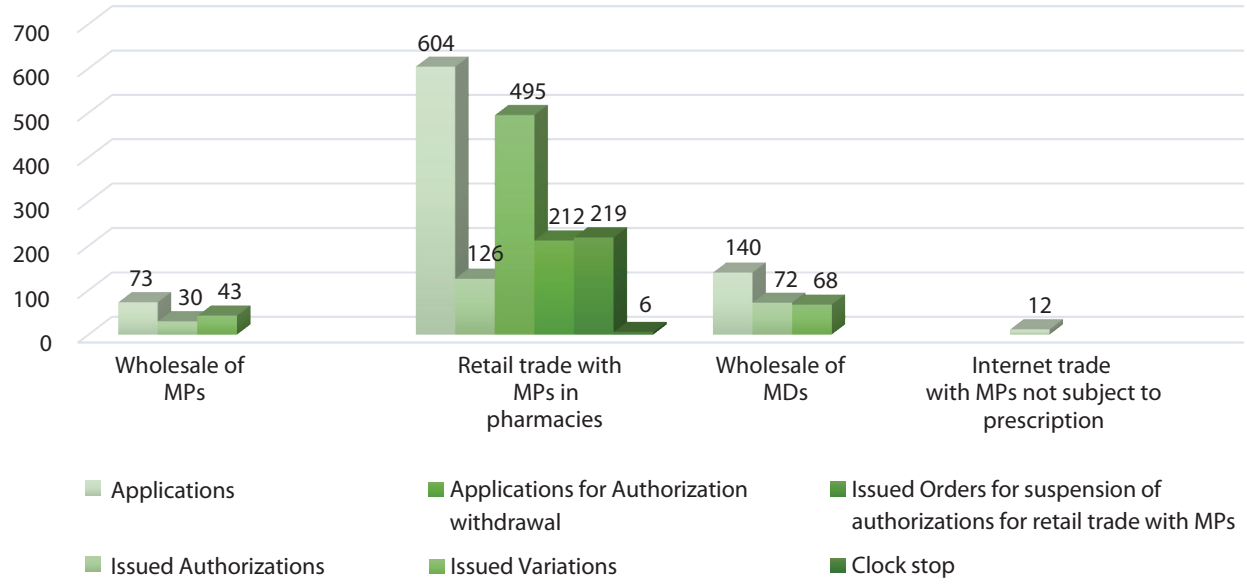


Fig. 11 **Trade Authorization Procedures**

Other activities concerning registrations and approvals

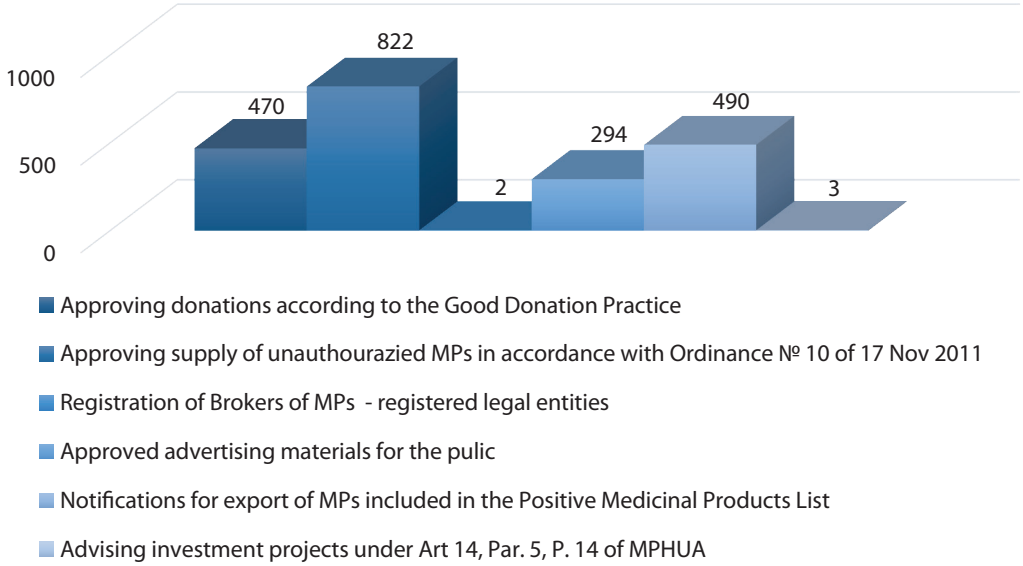


Fig. 12 **Other activities**

Medical Devices Registration

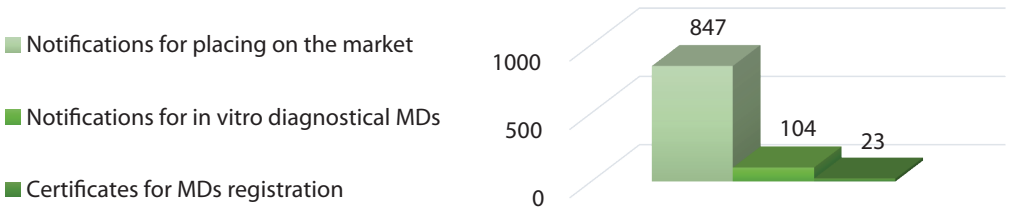


Fig. 13 **Issued Notifications and Certificates in 2016**

BDA maintains an electronic database containing data for the medical devices manufacturers, importers and distributors, for the competent authorities and institutions that cover all or part of the medical devices cost (National Health Insurance Fund, the Agency for Social Assistance, the Ministry of Health, and Health Insurance Funds). In 2016, were made validated records for **7 456** medical devices.

Medical Devices Vigilance

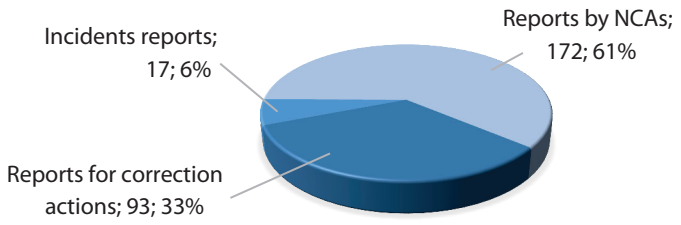


Fig. 14 **Updated information in the System for registration and medical devices vigilance**

Clinical trials of medical devices

The received documentation was assessed. As a result, 1 Clinical Trial Authorization and 3 Amendments for clinical trial of medical devices were issued.

2.3 CONTROL AND INSPECTIONS

In 2016 for the purposes of the state control of medicinal products under Art. 267 of MPHUA and the market supervision of medical devices under Art. 86 of MDA, BDA exercised control on the activities of storage and marketing of medicinal products and medical devices carried out by Wholesale and Retail Authorization holders for medicinal products and medical devices, to ascertain the compliance with the Good Distribution Practice (GDP) requirements, MPHUA, MDA and the regulations for their implementation.

There were carried out **582** inspections including:

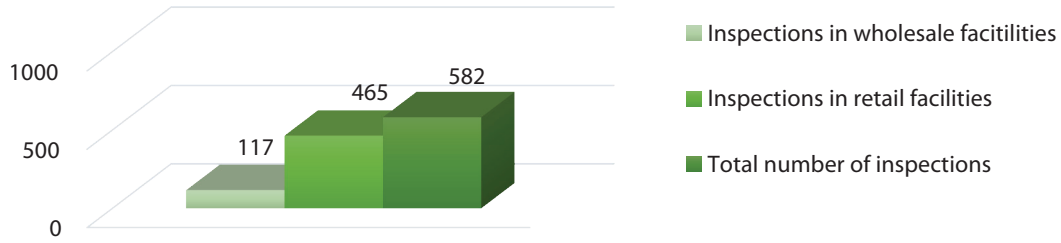


Fig. 15 **Inspections in 2016**

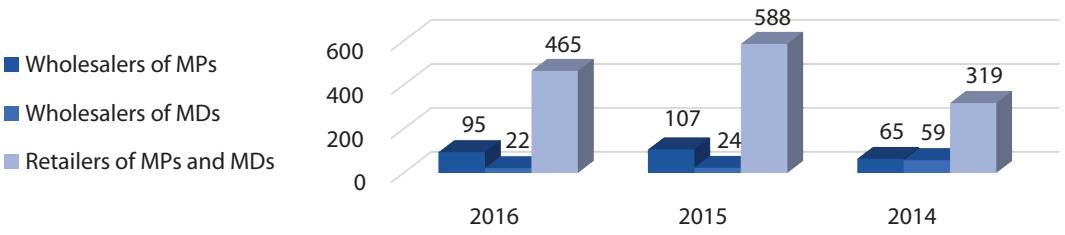


Fig. 16 **Inspections during 2014-2016**

Fig. 17 **Inspections in facilities for retail trade with medicinal products and medical devices in 2016**

The most common violations in the retail trade with medicinal products

- Selling (dispensing) medicinal product subject to medical prescription by assistant pharmacists.
- Selling (dispensing) medicinal product subject to medical prescription by pharmacists without being given a prescription.
- Head of pharmacy employed by another trader and working at another pharmacy.
- Improper storage of heat-sensitive medicinal products.
- Improper storage of medicinal products with expired term of use or with impaired primary and/or secondary package.

Violations with a greater danger degree

- Dispensing medicinal products by unauthorized persons (without pharmaceutical degree).
- Trading medicinal products/medical devices in facilities without authorization/certificate or facilities operating in violation of an issued authorization/certificate.

During 2016, the BDA inspectors performed joint inspections together with officers at 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, after receiving signals about storage and sales of unauthorized medicinal products, and in connection with signals from the Bulgarian Pharmaceutical Union, citizens and MAHs concerning illegal sale of medicinal products on the Internet.

In connection with the submitted in 2016 signals about shortage or lack of certain medicinal products on the Bulgarian market, inspections at wholesalers and retailers were carried out for identifying violations related to the supply chain and sales of medicinal products as well as availability on the market.

During the market supervising inspections, **56** samples of medicinal products were taken and were delivered for analyses in the BDA's laboratory.

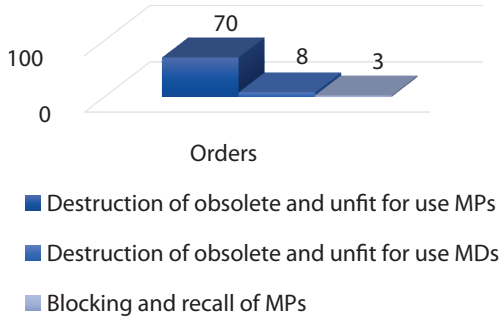
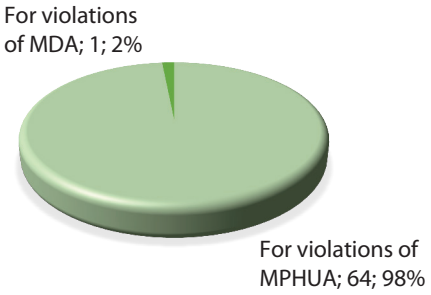


Fig. 18 **Blocking, recall and destruction of medicinal products and medical devices**

Administrative-penal procedures

Given the ascertained violations, the adequate lawful measures of preventive and punitive nature were taken.

By Penal Ordinances were closed **65** procedures - **64** for violations of MPHUA and **1** for violations of MDA. There were drawn up 65 Acts for Ascertainment of Committed Administrative Violation (AACAV). For ascertained minor administrative violations under Art. 28 of Administrative Violations and Penalties Act (AVPA), was issued **1** Instruction.



Фиг. 19 **Issued Penal Ordinances**

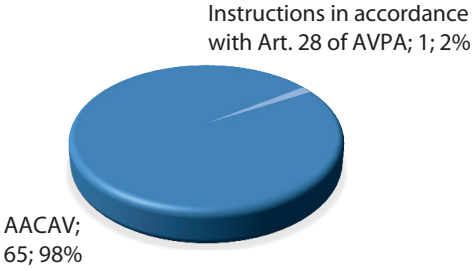


Fig. 20 **Drawn up Acts for Ascertainment of Committed Administrative Violation**

In 2016, the imposed with Penalty Ordinances fines and financial sanctions by the BDA Executive Director are **96 000 BGN** and BDA received **67 850 BGN**.

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

BDA processed 78 complaints and signals from citizens and organizations, including those forwarded by the Ministry of Health, the Commission for Consumer Protection (CCP), the Medical Audit Executive Agency, Bulgarian Pharmaceutical Union (BFU), etc., containing allegations about the status, the procedures and the organization of the work in pharmacies / drugstores, as well as allegations regarding the quality of medicinal products / medical devices or about dispensing medicinal products by unauthorized persons, as well as facilities not authorized for wholesale and retail trade in accordance with the MPHUA/MDA.

The largest number of signals was sent by individuals and legal entities, as well as by the CCP and the Ministry of Health. The predominant number of complaints was for violations of the MPHUA.

2.4 MEDICINAL PRODUCTS ANALYSES

Physico-chemical and pharmaceutical analyses

One of the Agency's activities is the performance of physico-chemical and pharmaceutical analyses. In 2016, 111 batches of medicinal products were received for analyses. The analysed batches were 107. The performed analyses were 227 in total.

According to the Annual Inspection Plan for 2016, 41 batches of medicinal products with 15 different active substances (Levonorgestrel, Amlodipine besilate, Loperamide hydrochloride, Ceftriaxone sodium, Nifedipine, Glucose, Sodium chloride, Cinnarizine, Phenazone/Lidocaine hydrochloride, Acyclovir, Neomycin, Gliclazide, Acetylcysteine, Isosorbide dinitrate, Betahistine hydrochloride) were analysed. The following tests were done: assessment of appearance, of primary package, of secondary package and of patient information leaflet. Also, identity, assay, purity, dissolution test for solid dosage forms, average mass and uniformity of mass were tested. Three of the batches did not comply with the requirements for primary and secondary packages and one batch did not comply with the approved MAH specification for the assay and a sample of the same batch kept by the manufacturer (museum sample) was analysed. The actions taken for those samples were in compliance with the Quality System at *Medicinal Products Analyses* Department.

In connection with the inspections, 5 samples were tested as two of them were active substances.

In 2016, **6** physico-chemical and pharmaceutical Experts' Reports for **32** tested samples were drawn up. They were assigned by the Police/Prosecutor's Office.

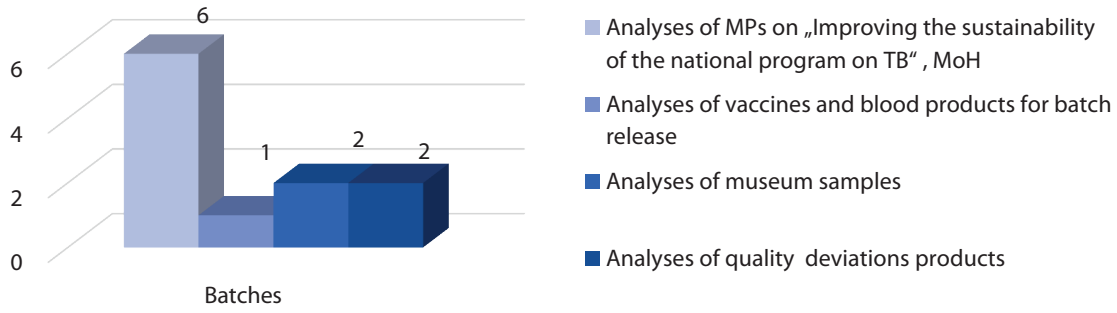


Fig. 21 **Types of analyses in 2016**

Analyses of two batches of museum samples were demanded in connection with a research on suspicion for non-complying result with the approved specification of MAH. One batch did not comply with the test for dissolution of solid dosage form.

The two batches that were analysed for quality deviations complied with the requirements for the tests.

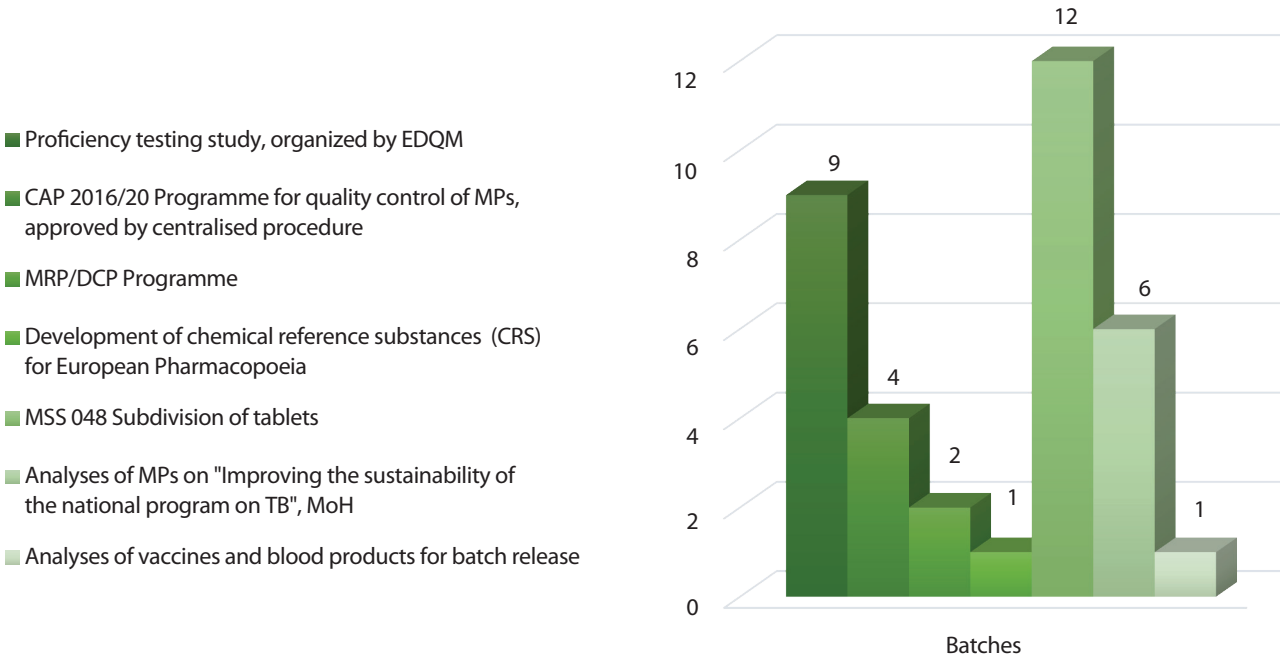


Fig. 22 **Analysed batches by international programmes in 2016**

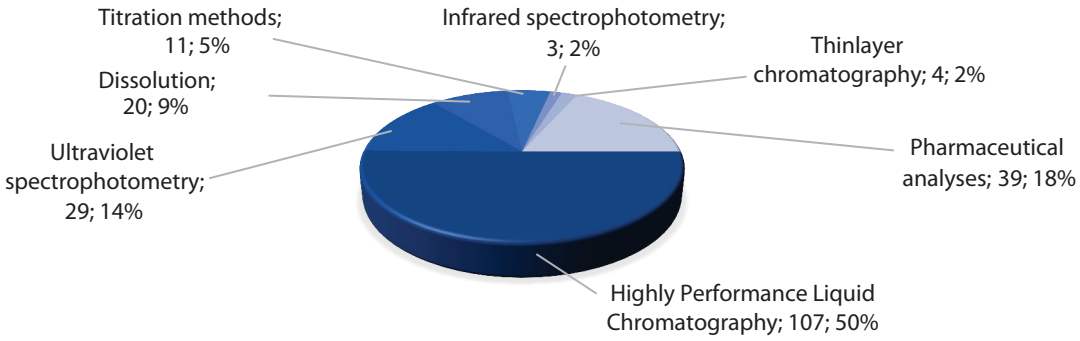


Fig. 23 **Applied methods for analyses by batches**

Biological analyses

The BDA laboratory performs Official batch release of vaccines and medicinal products derived from human blood or human plasma according to the EU Administrative procedure for batch release (Official Control Authority Batch Release - OCABR). The total number of analysed samples submitted by different procedures is **262**. The results from all the tests are within the relevant specifications for the corresponding medicinal products, except one sample of plasma pool submitted with an Application for Certificate of Approval of plasma pool. The major part of the analyses were related with batch release of vaccines and medicinal products derived from human blood or plasma, **243 in total**:

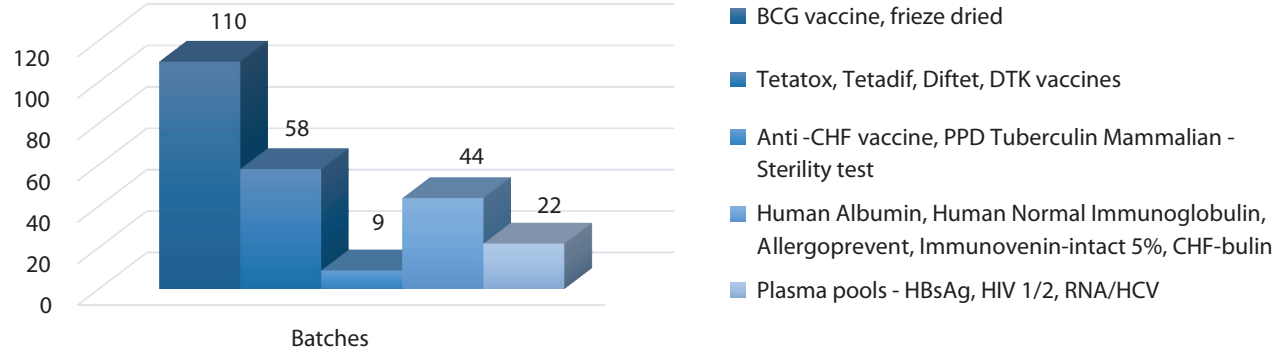


Fig. 24 **Analyses related to batch release of vaccines and medicinal products derived from human blood or plasma**

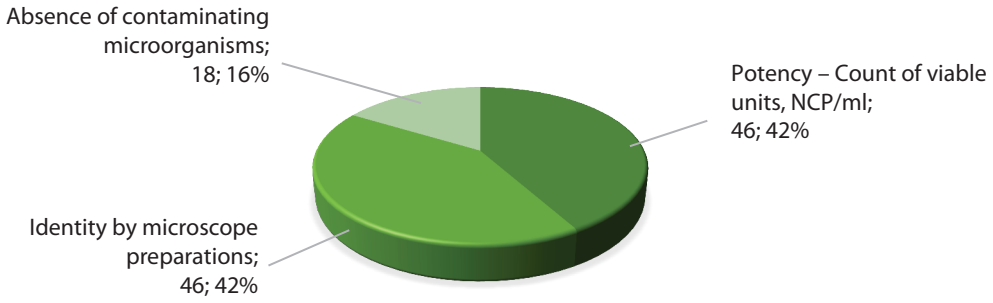


Fig. 25 **Analyses of BCG vaccine, freeze-dried**

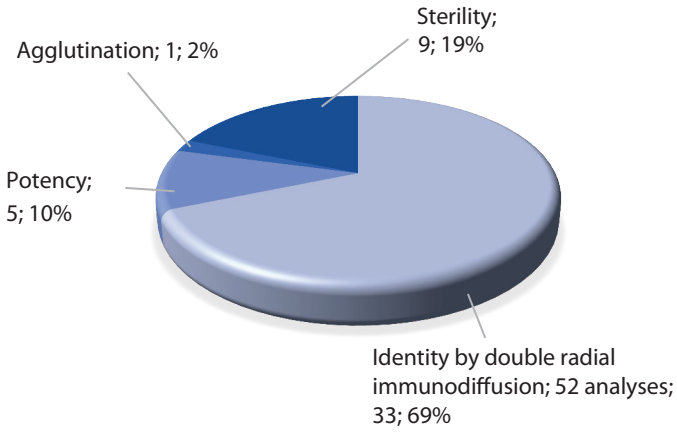


Fig. 26 **Analyses of Tetatox, Tetadif, Diftet, DTK vaccines**

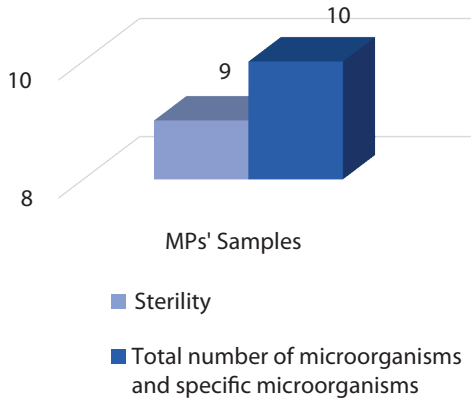


Fig. 28 **Analyses carried out in relation with market supervision and with signals for non-conformities to the quality requirements**

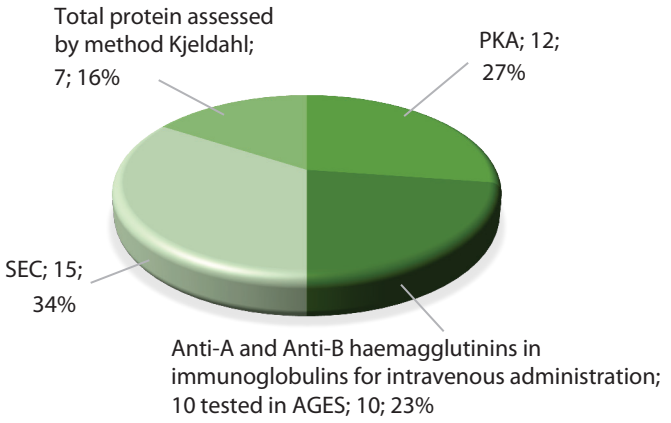


Fig. 27 **Analyses of Human Albumin, Human Normal Immunoglobulin, Allergoprevent, Immunovenin-intact 5% IgG, CHF- bulin**

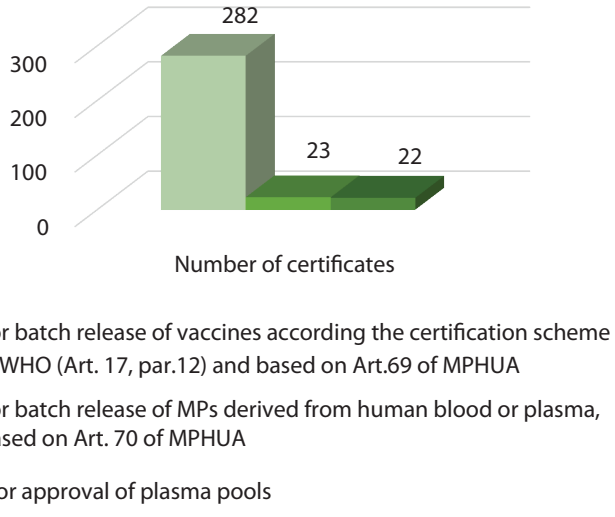


Fig. 29 **Certificates issued in 2016**

For 1 sample of human plasma was obtained a positive result for Hepatitis C viral RNA. The follow-up actions were completed in accordance with the OCABR and the internal procedures of the laboratory. For all the submitted samples from vaccines or medicinal products derived from human blood or plasma, appearance testing of the dosage form, assessment of the primary and secondary package and leaflet were carried out.

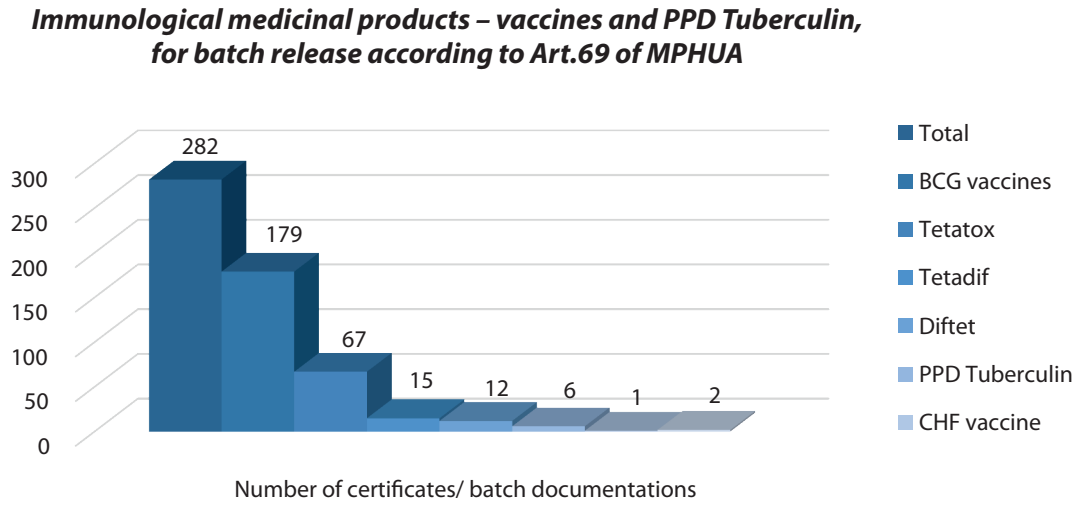


Fig. 30 **Certificates for batch release of vaccines issued after evaluation of batch documentation**

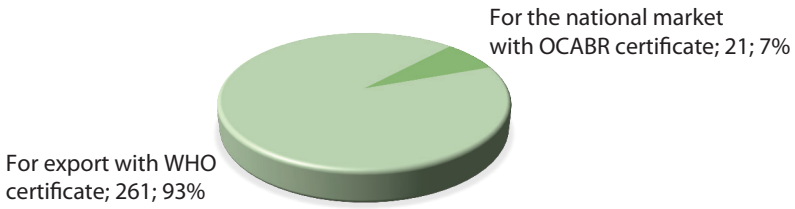


Fig. 31 **Certificates for batch release of vaccines issued according to the certification scheme of WHO, based on Art. 17, par. 12 of MPHUA and on Art. 69 of MPHUA**

The number of the Applications for batch release of vaccines for 2016 is comparable to those of the last three years and has increased since 2012.

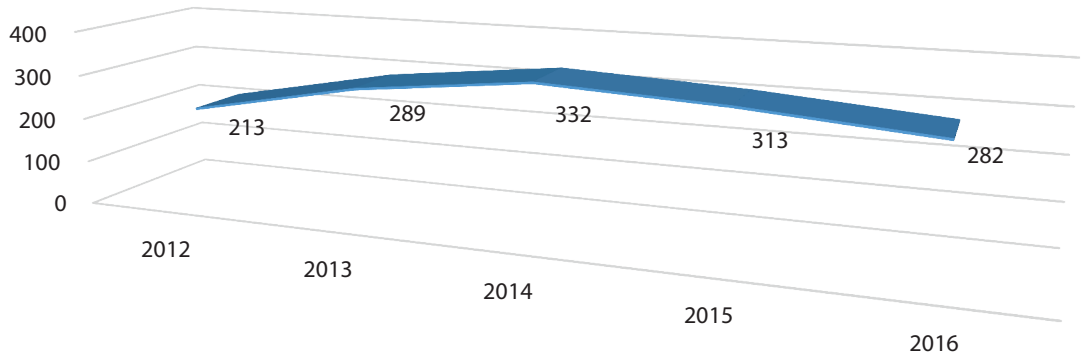


Fig. 32 **Notifications for placing on the market of batches of vaccines issued in 2012-2016**

In 2016, **81** Notifications for placing on the market of batches of vaccines were issued.

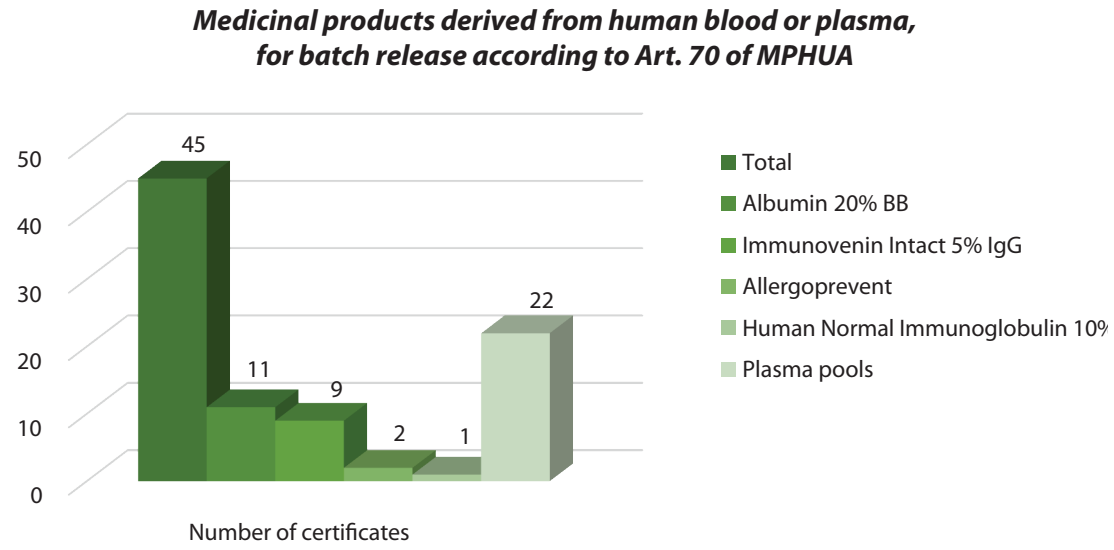


Fig. 33 **Certificates for batch release of medicinal products derived from human blood or plasma, issued after evaluation of the batch documentation**

In 2016, **202** Notifications for placing on the market of medicinal products derived from human blood or plasma were issued.

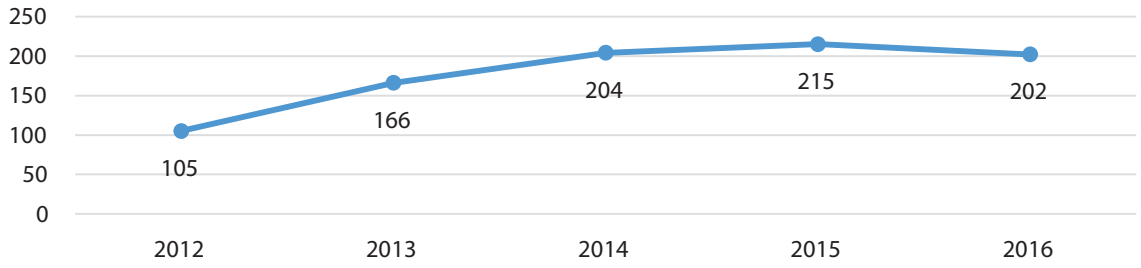


Fig. 34 **Notifications for placing on the market of medicinal products derived from human blood or plasma issued in 2012-2016**

2.5 PHARMACOPOEIAL ACTIVITIES

Pharmacopoeia is a collection of articles with mandatory standards and requirements to ensure the quality, safety and efficacy of medicinal products. It has the features of a legal act as its provisions are binding on all subjects related to the manufacturing, control, storage and application of medicines. The European Pharmacopoeia is applicable in Bulgaria.

As a party to the Convention № 50 of the Council of Europe for the development of the European Pharmacopoeia, Republic of Bulgaria is obliged to participate in scientific and technical work necessary for the development of pharmacopoeial requirements and standards for medicinal substances and medicinal products.

At the national level, Pharmacopoeia Committee was established. It is an advisory body to the Minister of Health on matters relating to the pharmacopoeia. The Head of the Committee is the BDA's Executive Director.

BDA, in the capacity of a national pharmacopoeial Secretariat, shall provide consultations on pharmacopoeial and terminological issues, update and regularly review translations of monographs, lists of controlled terms, etc.

In 2016, draft documents for implementation were prepared, texts, concerning pharmacopoeial requirements on the territory of Bulgaria were revised and deleted.

The information on the BDA's website is updated and the Orders of the Minister of Health were published so that the Ninth Edition of the European Pharmacopoeia and supplements (9.1.-9.3) to enter into force as well as the date of revoking the general chapter on *Test for neurovirulence of poliomyelitis vaccine (oral) (2.6.19)*.

In connection with proposals of the Secretariat of the European Pharmacopoeia for the work program of expert groups, BDA answered 56 surveys and sent information on substances/monographs, national phar-

macopoeia requirements and good practice and a proposal to elaboration a monograph of the European Pharmacopoeia.

In 2016, a BDA expert participated in a meeting of the European Pharmacopoeia Commission - EDQM in Strasbourg, France. The nominations of Bulgarian experts for the next three years for the European Pharmacopoeia Commission's groups, namely GR 7, GR 12, GR 13A, PaedF WP and WP EXP, were adopted.

The standard terms of dosage forms, packaging, routes and methods of administration were translated in Bulgarian and were introduced into the EDQM database.

As a national pharmacopoeia Secretariat, BDA provides consultations on pharmacopoeial and terminology issues. Reviews and updates of translations of monographs, lists of controlled terms, etc., were performed.

2.6 PHARMACOVIGILANCE

Adverse Drug Reactions Reports

The BDA's responsibilities include assessment of the received Adverse Drug Reactions (ADR) Reports. Most of the safety reports received in 2016 cover the criteria for seriousness and expectedness of the ADRs.

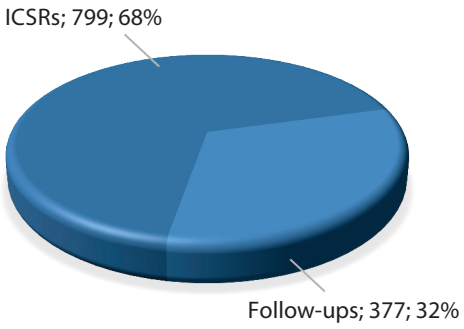


Fig. 35 **Received, processed and assessed initial Individual Case Safety Reports (ICSRs) and follow-ups – 1 176 valid reports in total**

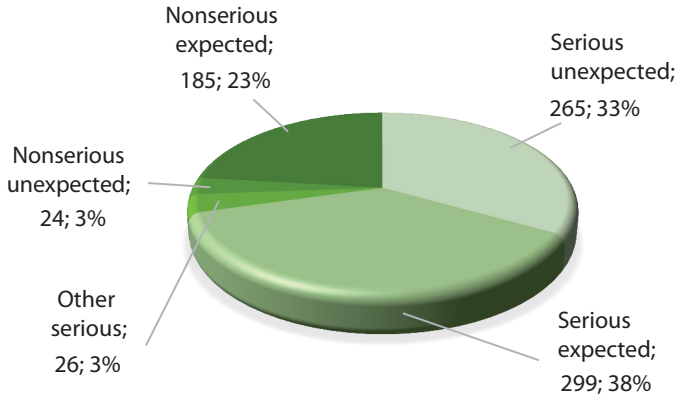


Fig. 36 **Correlation between the received ADRs in respect of seriousness and expectedness**

The reporting activity tends to increase over the years resulting in a corresponding increase in the reported cases of suspected ADRs.

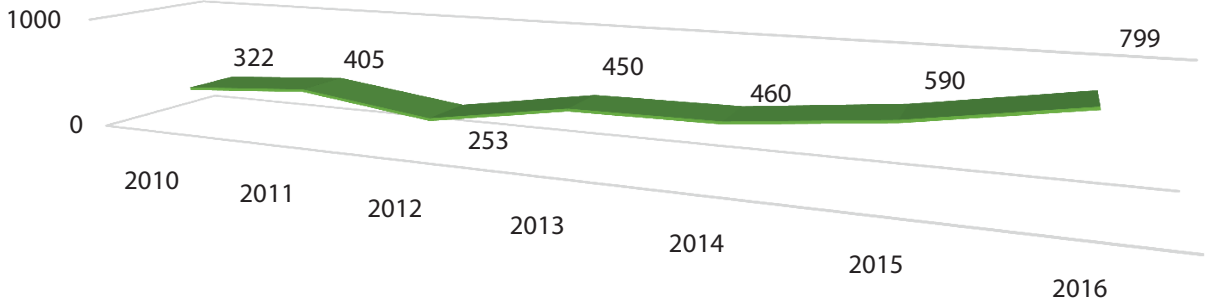


Fig. 37 **Valid ADR case reports**

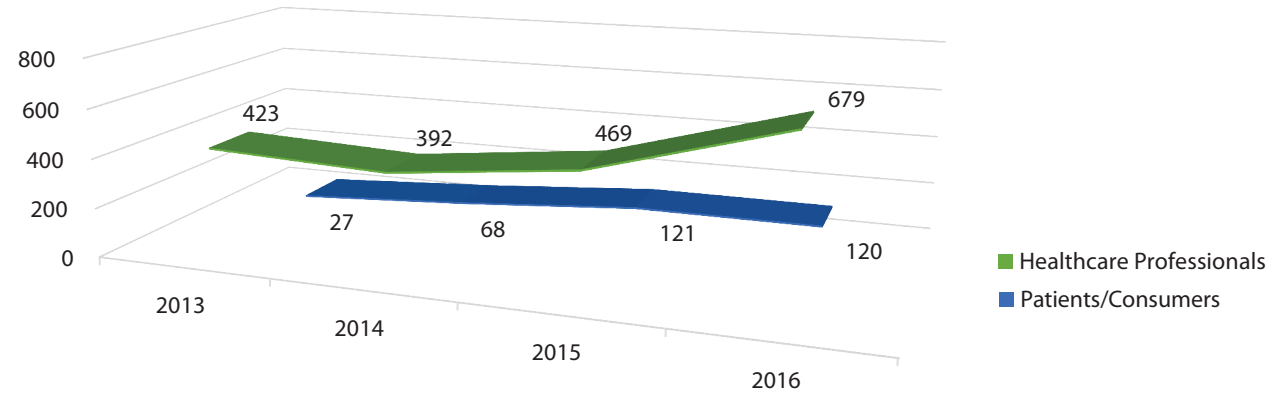


Fig. 38 **Tendency in reporting according to the primary source of information**

The number of directly received by the BDA cases reported by healthcare professionals and patients remains relatively small compared to the reports by Marketing Authorization Holders (MAHs).

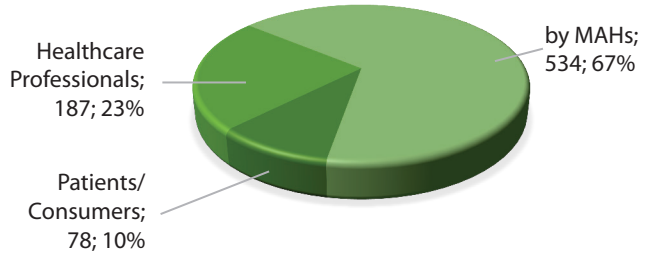


Fig. 39 **Reports received in the BDA according to the source of information in 2016**

The number of the valid reports of Adverse Events Following Immunisation (AEFI) was 49 in 2016, which represents 6% of the total number of reports and confirms the ratio of 6-7% over the years. The trend in the reporting of AEFIs is a sharp increase in patients' reporting activity reaching 44% of patients' reports in 2016 compared to 29% in 2015 and 10% for 2013.

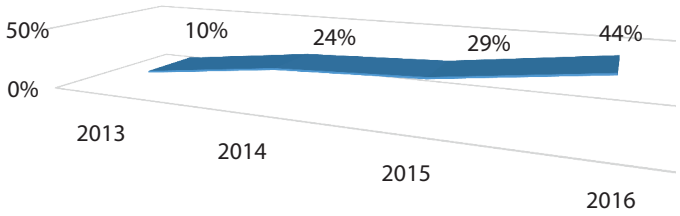


Fig. 40 **Percentage of the AEFIs according the source of information during 2013-2016**

The ICSRs, received from the territory of Bulgaria, were not sufficient to generate a safety signal by qualitative or quantitative detection methods.

Periodic Safety Update Reports (PSURs)

The BDA registered and processed 107 PSURs in the first half of 2016, before the entry into force of the requirement for mandatory submissions to the PSUR Repository.

Information activities related to pharmacovigilance and risk communication

20 responses to EU countries/EMA in the NUI/EPITT system containing national data on medicinal products subject to referral procedures, potential referrals, a generated safety signal or other safety concerns were prepared and sent.

Upon MAHs requests, four references regarding ICSRs received at the BDA for 59 medicinal products were drawn up.

BDA assesses and agrees on information to healthcare professionals regarding pharmacovigilance drafted by the MAHs. BDA approved 35 Direct Healthcare Professional Communications (DHPC – approval of texts, addresses and time of distribution) and Educational materials for 65 products in total.

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

In 2016, the NPRAC held 10 meetings, prepared and chaired by BDA. In the course of year-round activities, the NPRAC provided recommendations for the Bulgarian position regarding safety issues discussed at PRAC meetings at the EMA. In addition, NPRAC made recommendations on national implementation of the adopted EU decisions. The NPRAC also supported the BDA's work regarding the assessment of ADRs generated from the territory of Bulgaria.

Training activity and participation in scientific fora

In 2016, 6 reports were presented to the medical healthcare professionals, patients and professional organizations. Two articles were published in scientific journals. Two posters were presented at an International Congress of Pharmacy.

2.7 CLINICAL TRIALS

BDA exercises control over the ongoing clinical trials. The activity includes assessment of the documentation for clinical trial authorization and follow-up control on the implementation. BDA keeps and updates a Register of the authorized clinical trials and a Register of Ethics Committees and electronically submits data for clinical trials in the Eudra CT database.

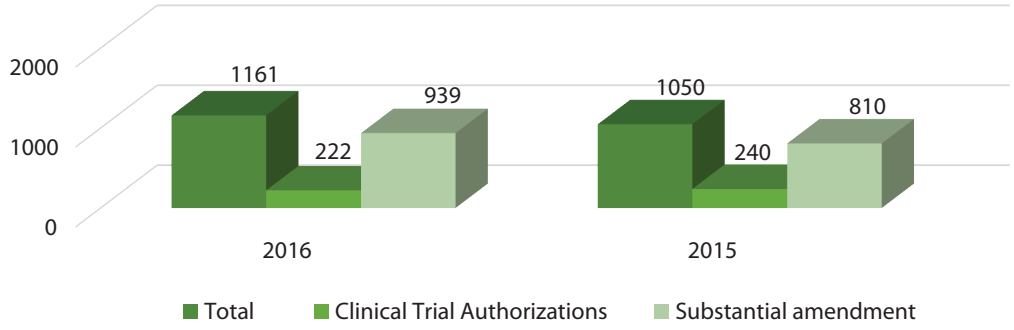


Fig. 41 **Applications received in 2016**

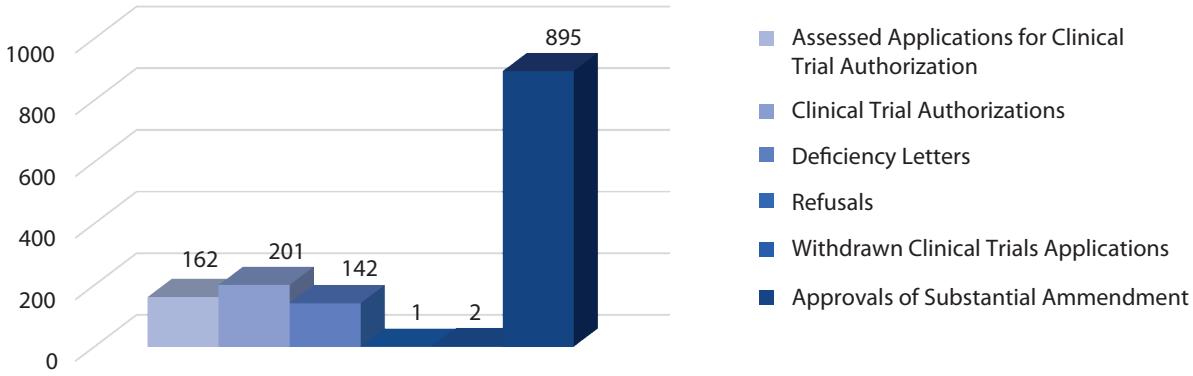


Fig. 42 **Applications assessed in 2016**

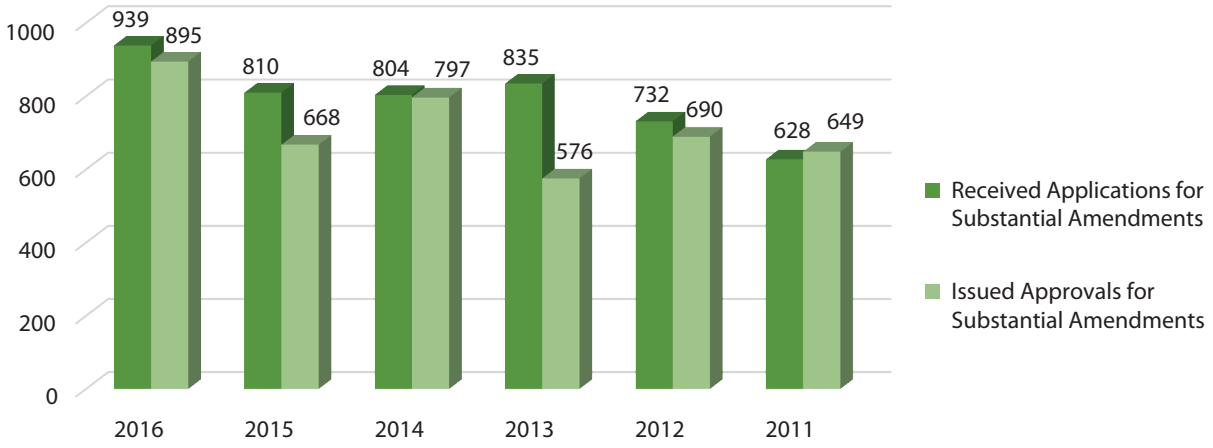


Fig. 43 **Substantial Amendments during 2011-2016**

In 2016, 209 clinical trials were closed and the information was sent to the EudraCT.

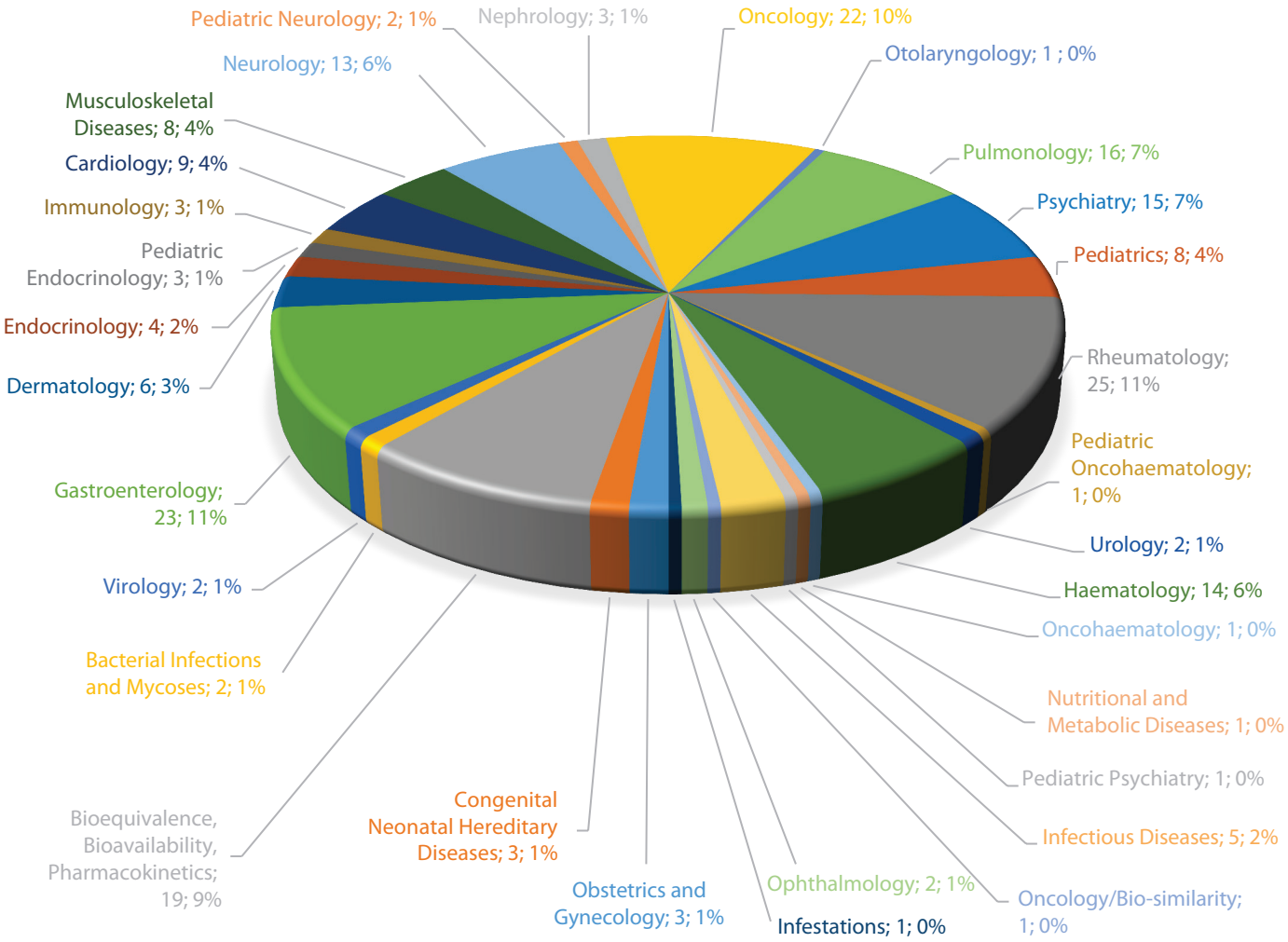


Fig. 44 **Clinical trials by therapeutical area**

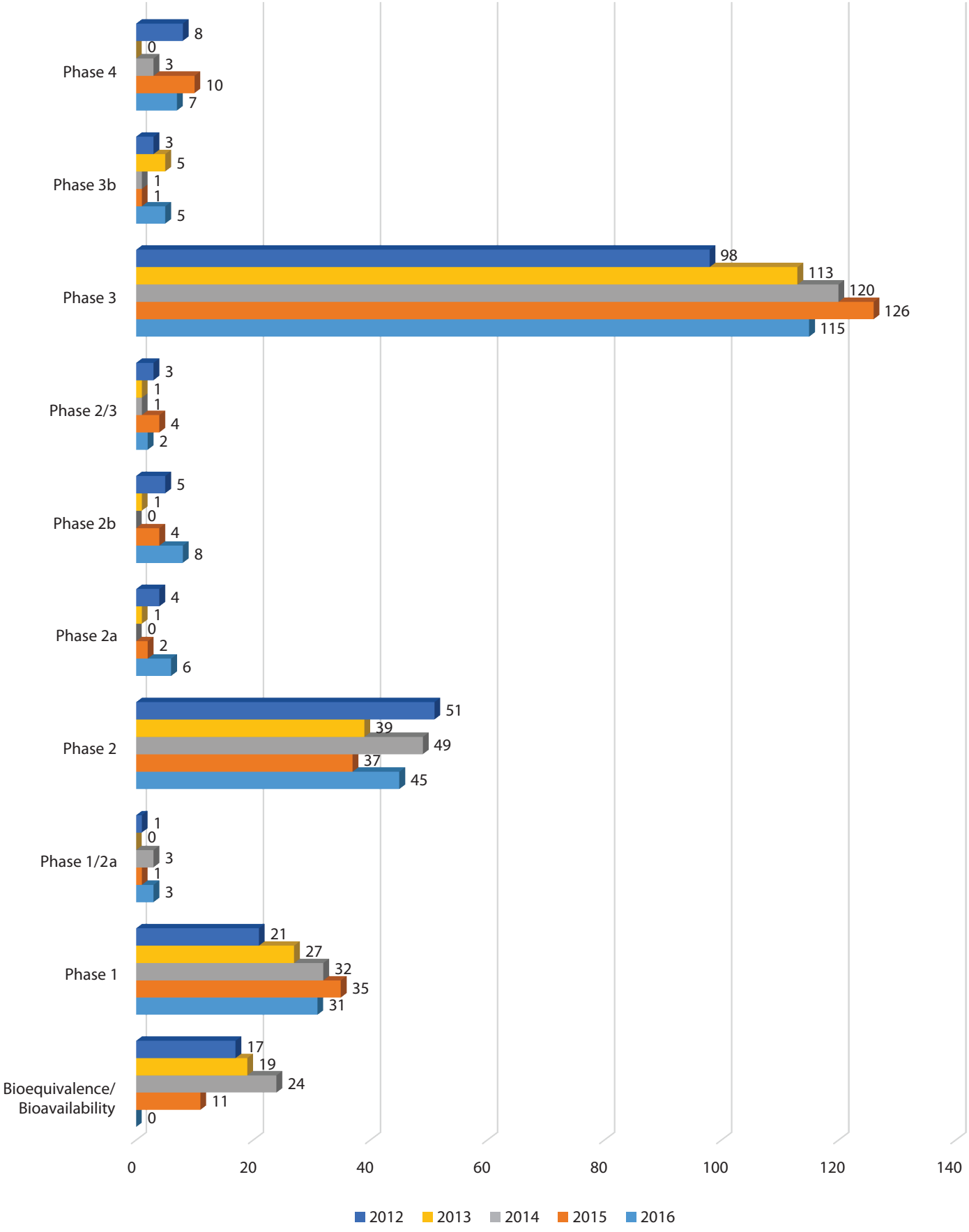


Fig. 45 **Clinical trials by phase**

Clinical Trials Safety

BDA monitors the investigational medicinal products by assessing the received Annual Reports, Development Safety Update Reports (DSURs), the Final Reports and other documentation.

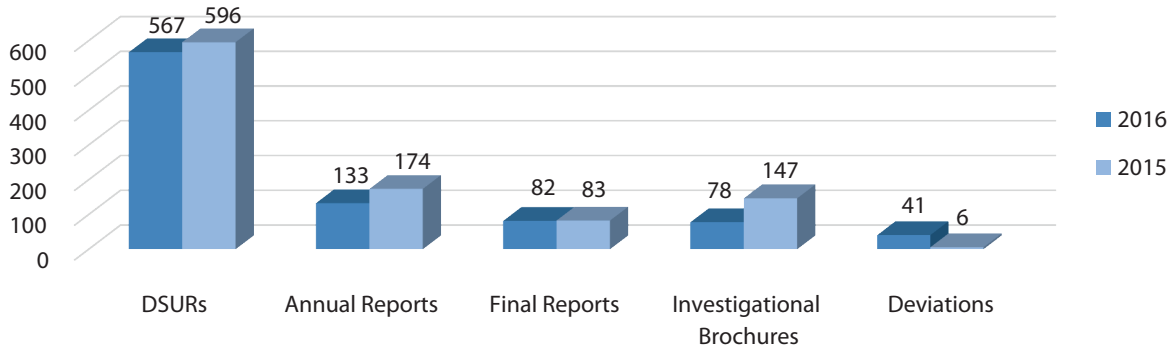


Fig. 46 **Clinical Trials Safety Documentation**

Other documents

The Agency provided five written Statements and one Scientific Advice in connection to the submitted requests by other competent authorities and institutions, including determining the regulatory regime of planned projects and reports.

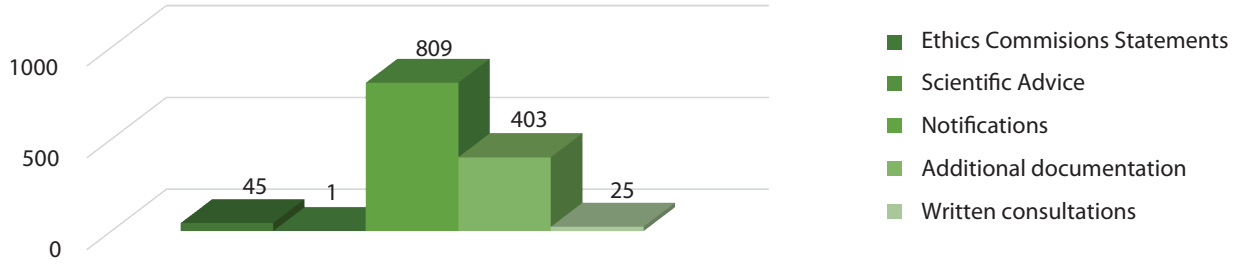


Fig. 47 **Other documents in 2016 r.**

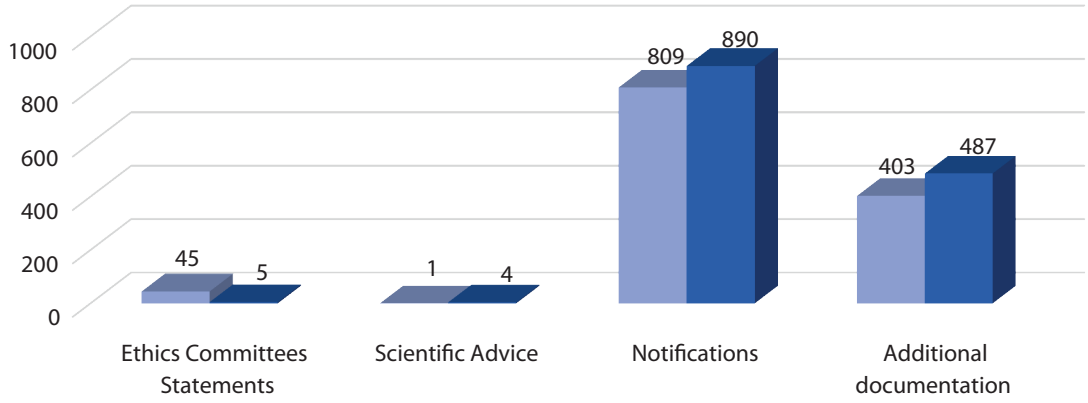


Fig. 48 **Other documents in 2015-2016**

Databases

BDA maintains a Register of the Authorized Clinical Trials in Bulgaria. All available information about the applications and the status of the ongoing trials was promptly submitted to EudraCT – **1 750** entries in total.

In connection with the electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to Eudra Vigilance, BDA sent 169 confirmations for received SUSARs that occurred in the development of ongoing clinical trials in Bulgaria.

Local Ethics Committees

BDA maintains a public Register of the Healthcare Establishments with Ethics Committee. In 2016, BDA has received 160 documents in total connected with the work of the local Ethics Committees. The Agency's Executive Director approved SOPs of 49 Ethics Committees. BDA also assessed Staff Update documents for 63 Ethics Committees.

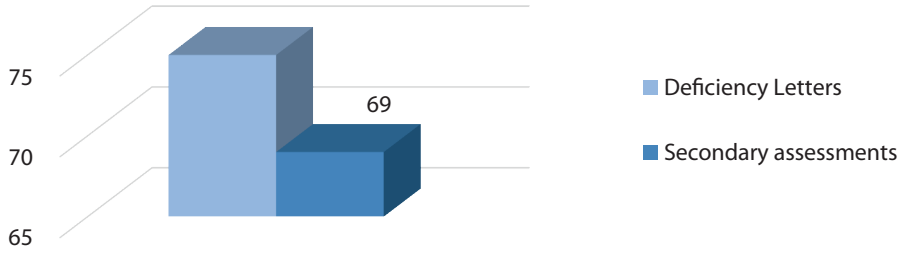


Fig. 49 **Deficiency Letters to Local Ethics Committees and secondary assessment of SOPs in 2016**

2.8 NON-INTERVENTIONAL RESEARCH

Assessment of submitted documents for conducting non-interventional researches (NIRs) on medicinal products as well as maintenance of a Register of the approved non-interventional researches in Bulgaria fall within the scope of the BDA responsibilities.

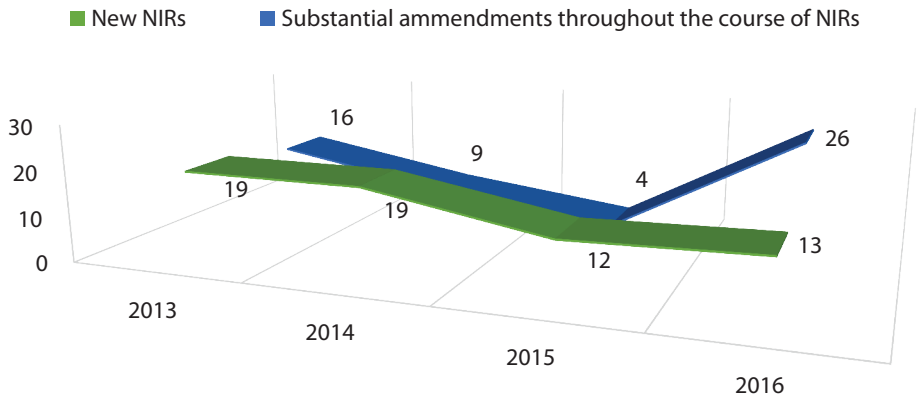


Fig. 50 **Assessment of non-interventional researches documents during 2013-2015**

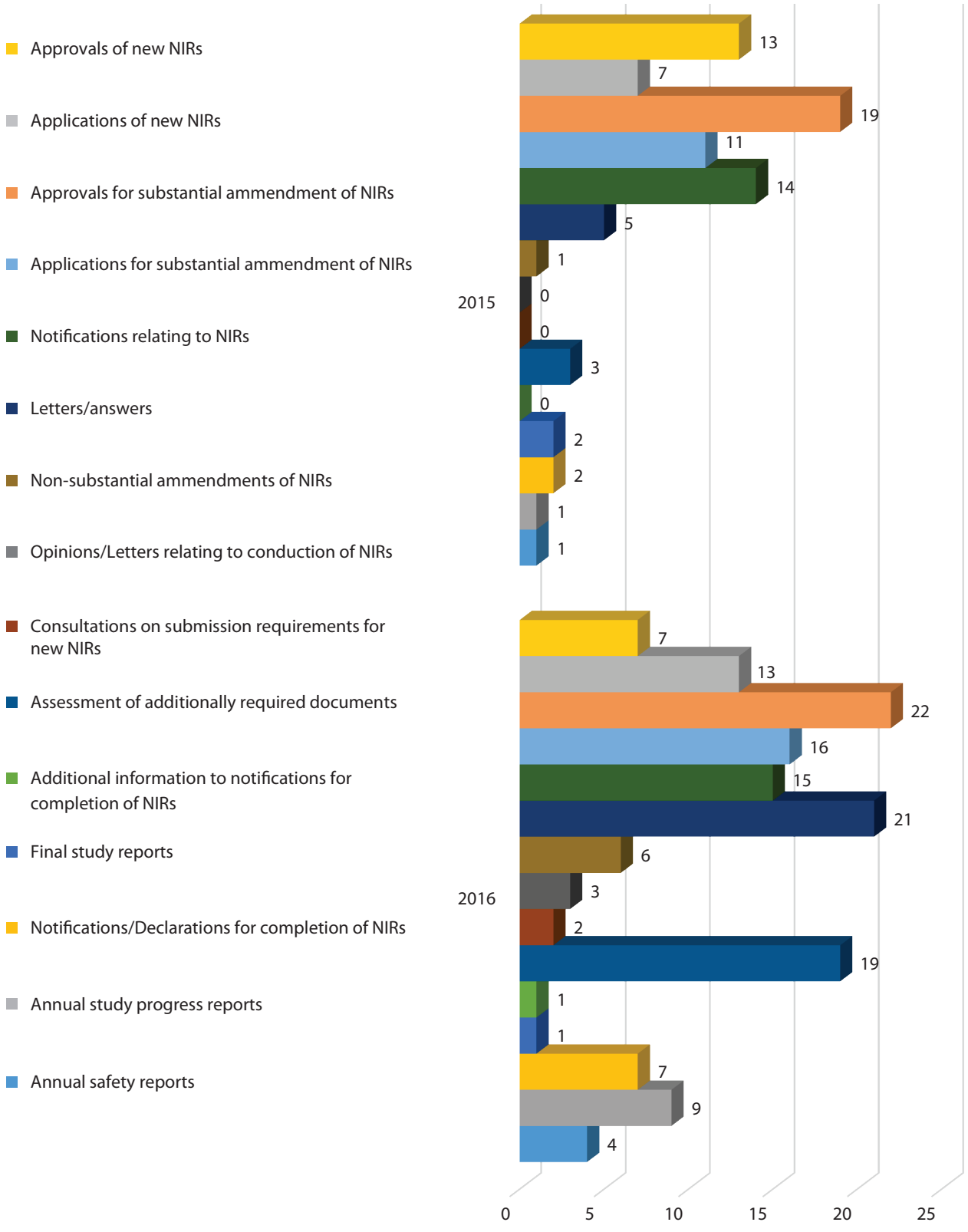


Fig. 51 **Activities on NIR assessment during 2015-2016**

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.

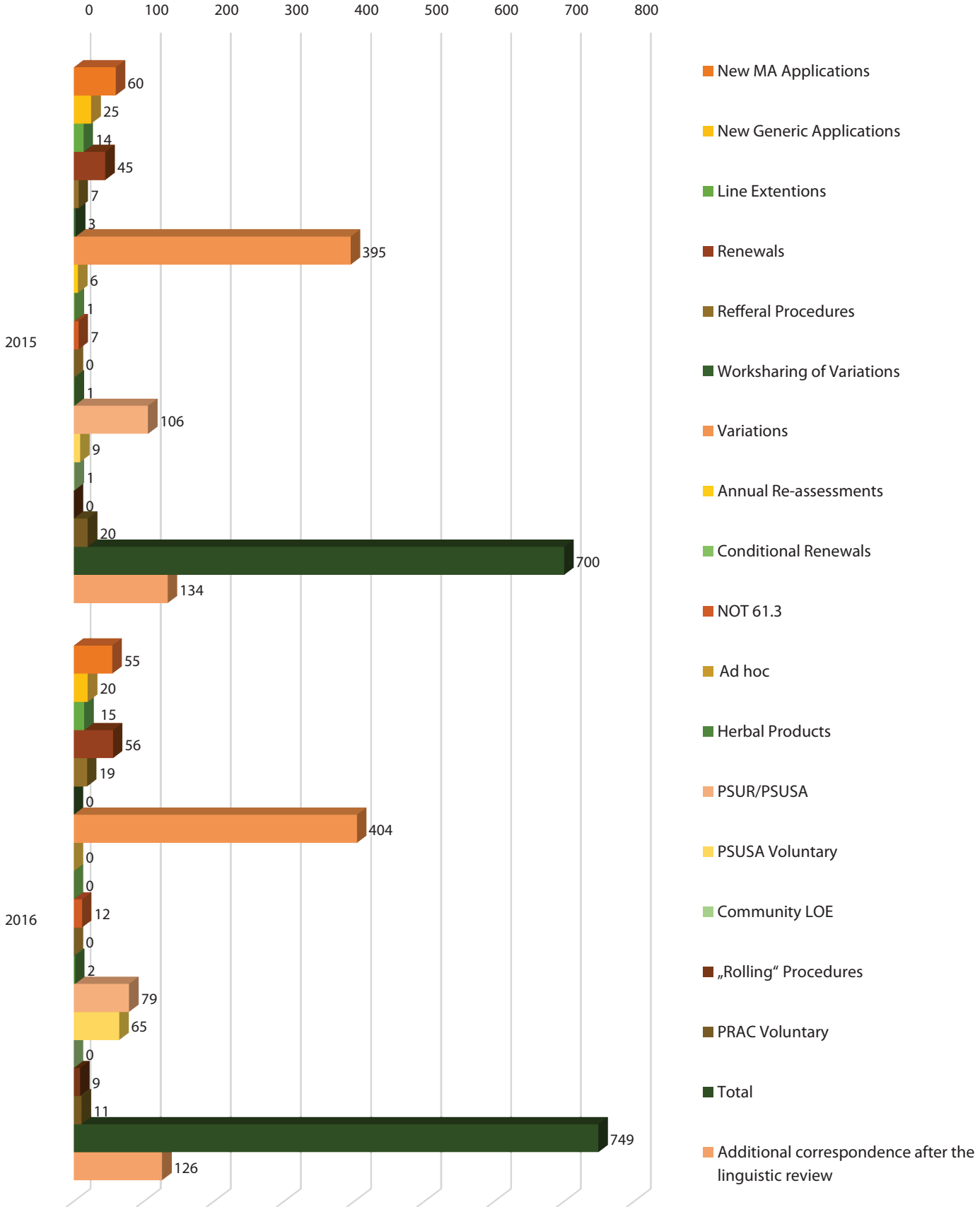


Fig. 52 **Procedures within the scope of the post-opinion linguistic review/assessment**

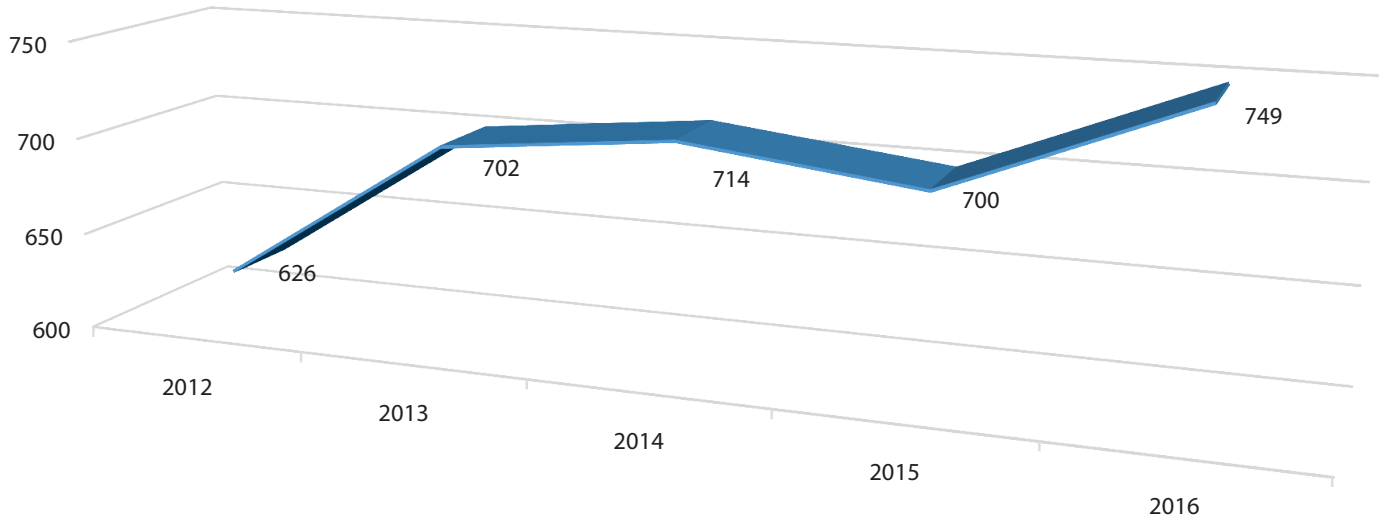


Fig. 53 **PIs reviewed under the centralised procedure during 2012 – 2016**

There is a trend of increase in the number of procedures: New Marketing Authorisation Applications, New Generic Applications, Line Extensions and PSUR/PSUSA.

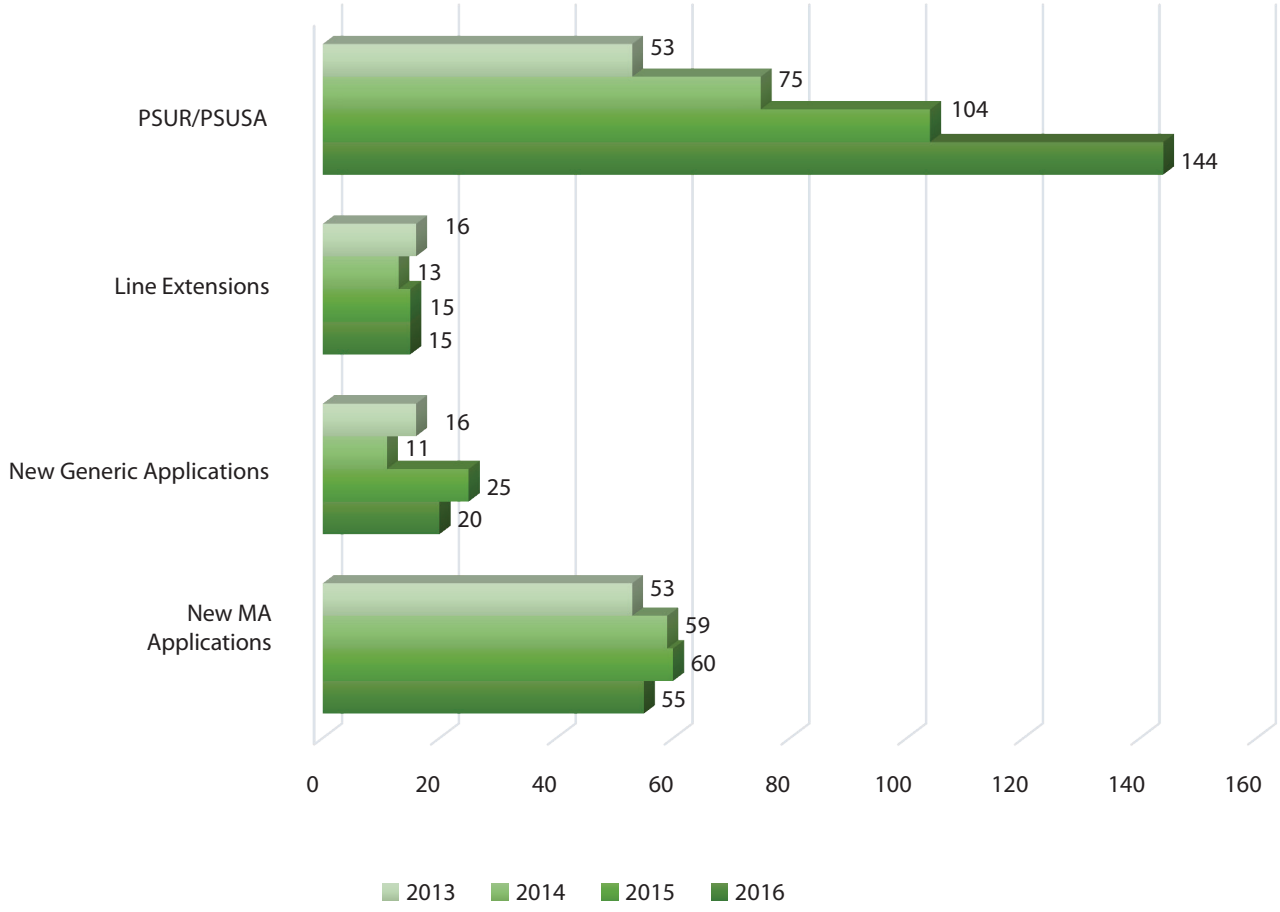


Fig. 54 **Comparative analysis 2013- 2016**

Linguistic review of Product Information

According to an annual agreement with EMA, the BDA performed in 2016 linguistic review of Product Information of centrally authorised products. The Product Information consists of Summary of Product Characteristics, Labelling and Package Leaflet.

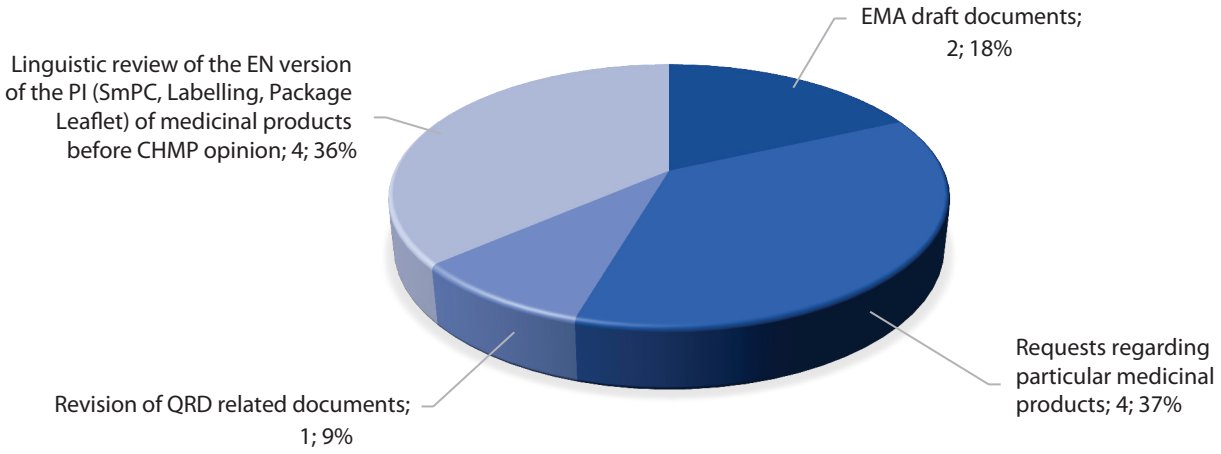


Fig. 55 **Opinions on documents and revisions of documents with regard to the EMA QRD activities**

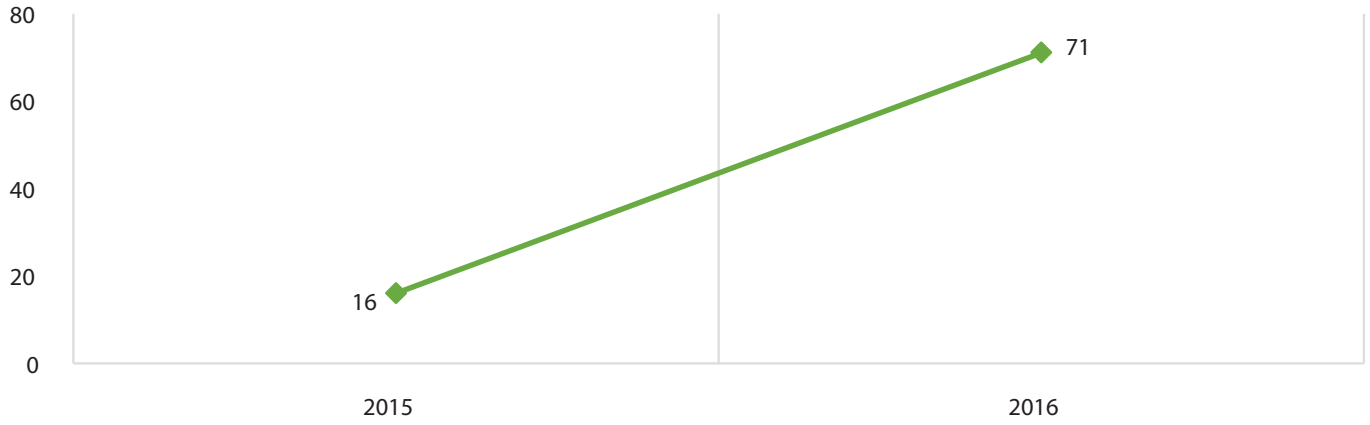


Fig. 56 **Assessment of Readability Tests of Patient Leaflets for the period 2015-2016**

BDA maintains a List of OTC medicinal products authorised in Bulgaria, a List of the suspended marketing authorisations, and a List of medicinal products containing new active substances and combinations (for the country), new trade names, new pharmaceutical forms and strengths, renewals and variations of MAs. All the lists are updated on a monthly basis and are published online in a Regulatory Bulletin.

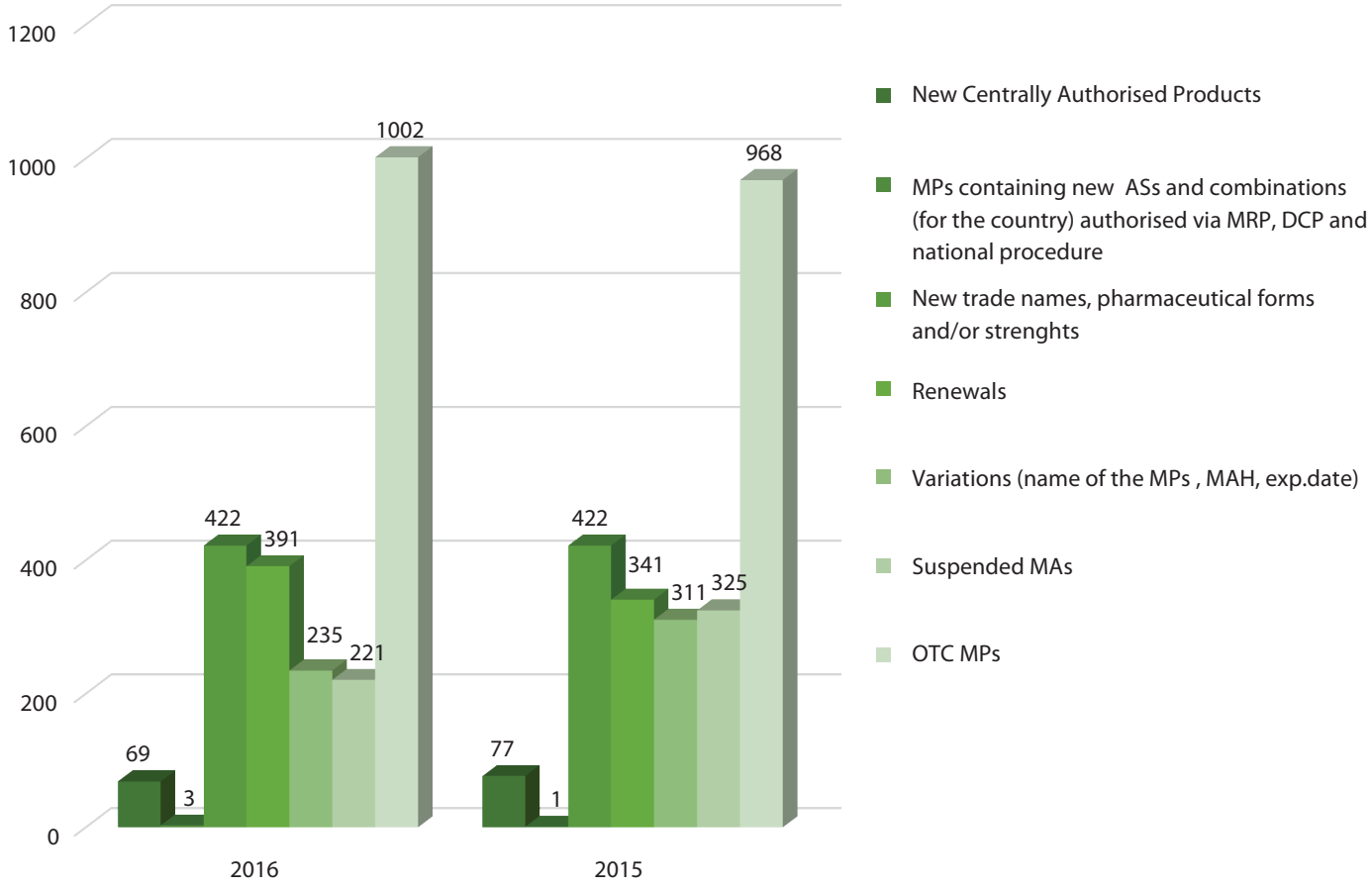


Fig. 57 **Regulatory Bulletin entries during 2015-2016**

Opinions regarding the import of unauthorised in the country medicinal products

In 2016, 803 opinions regarding the import of unauthorised in the country medicinal products under the Ordinance № 10 were issued.

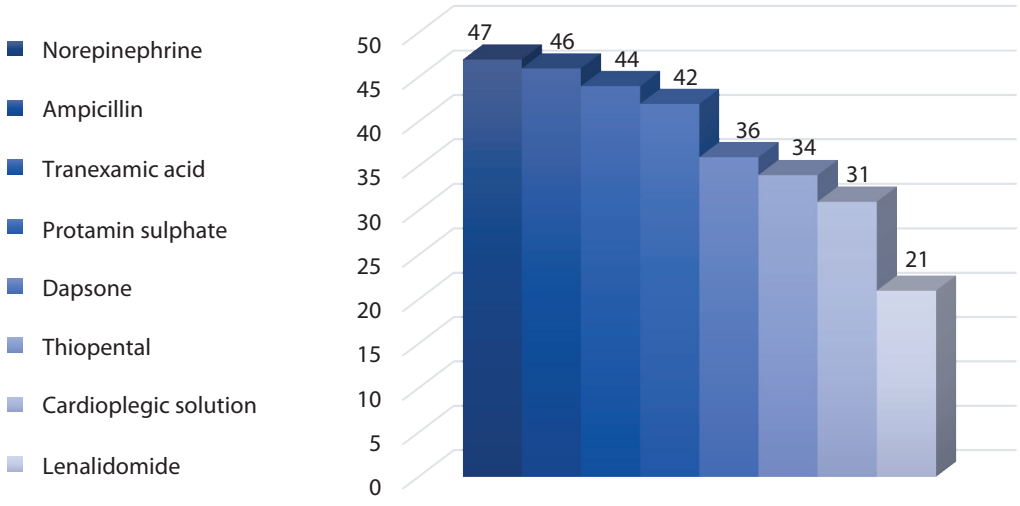


Fig. 58 **Medicines (INNs) for which opinions were most frequently issued in 2016**

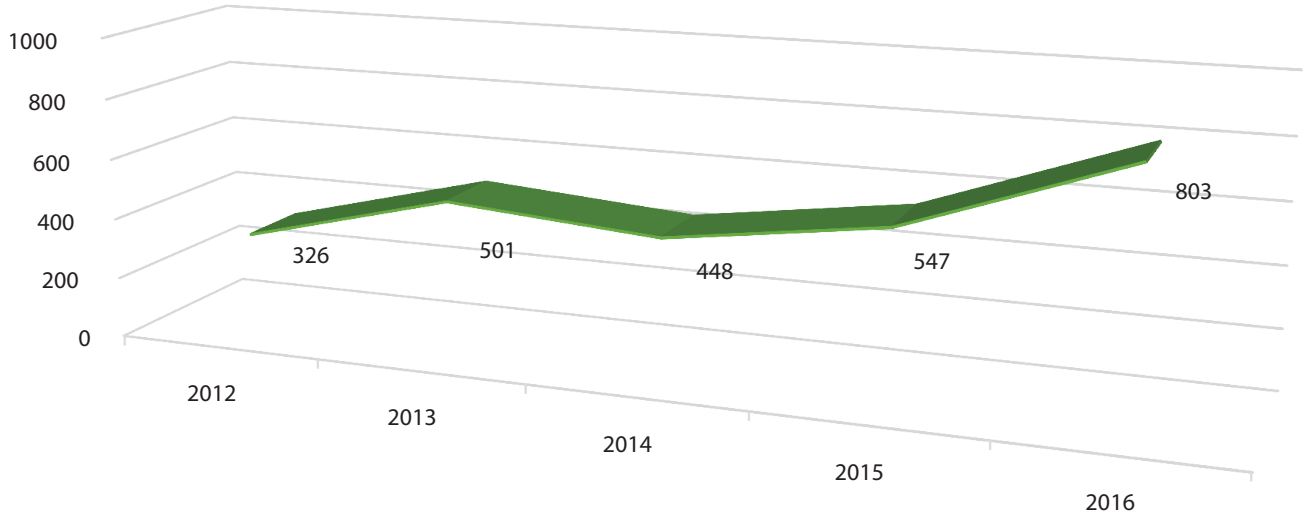


Fig. 59 **Issued opinions regarding the import of unauthorised medicinal products under Ordinandce №10 during 2011-2016**

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

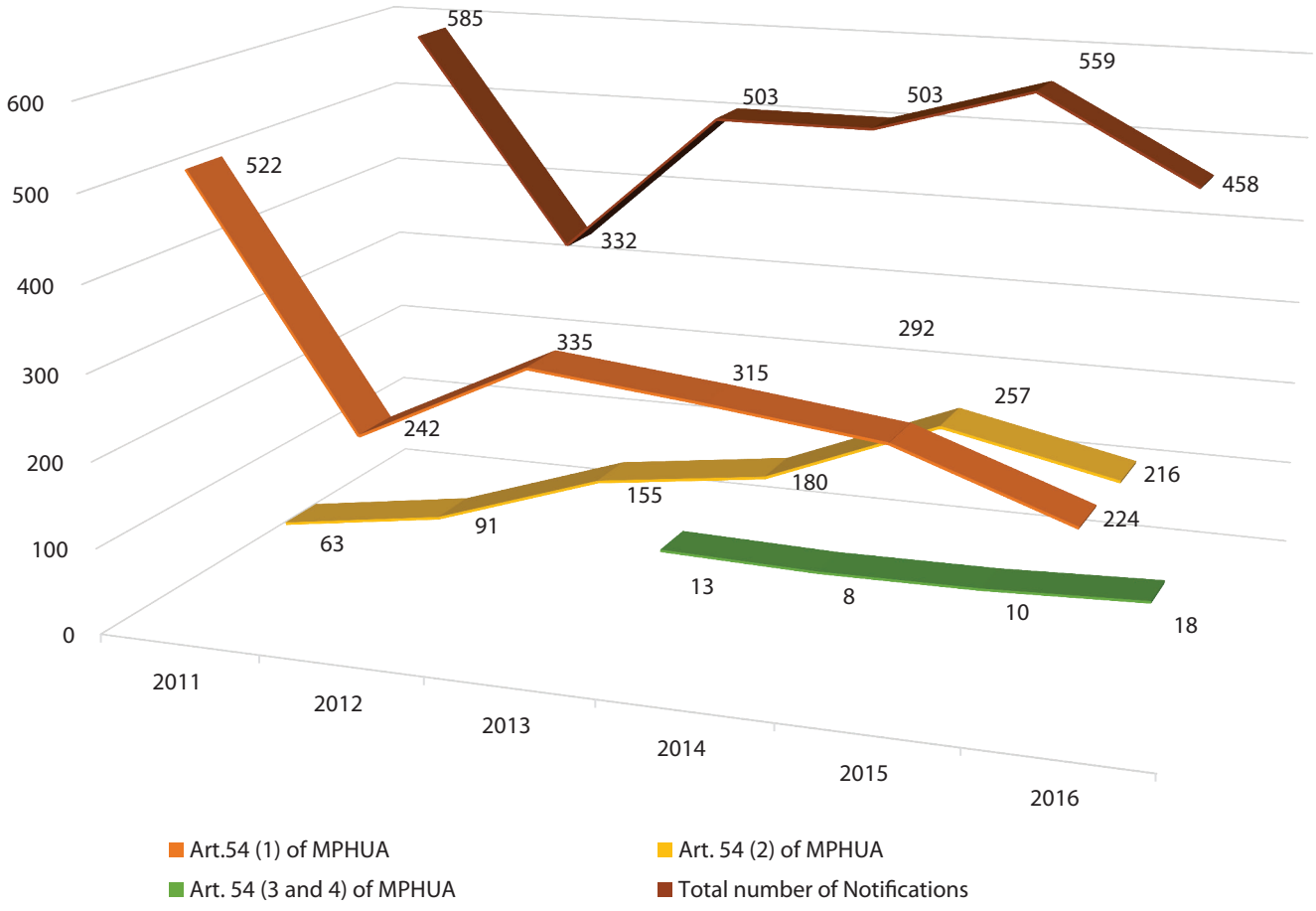


Fig. 60 **Submitted notifications during 2011-2016**

2.10 BLOOD TRANSFUSION SYSTEM SUPERVISION

The Agency's Executive Director shall act as the competent authority for the operation of the healthcare facilities collecting, testing, processing, storing, distributing, using, and ensuring 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.

Haemovigilance

BDA maintains a Register for serious adverse reactions and events occurring during collection and use of blood and blood components. Persons, engaged in collecting, diagnosing, processing, transfusing and storing blood or blood components, are required to report immediately serious adverse reactions and events or suspected serious adverse events/reactions. In 2016, the BDA received 729 reports for adverse reactions as follows:

- 37 reports for adverse reactions after transfusion of blood or blood components. All of them 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 2015, the number of the reported adverse reactions decreased.
- 692 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.

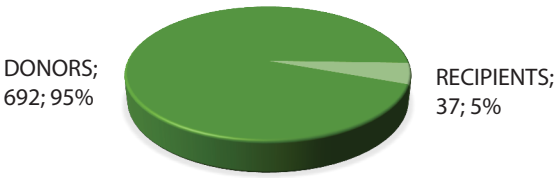


Fig. 61 **Ratio between the adverse reactions in recipients and in donors**

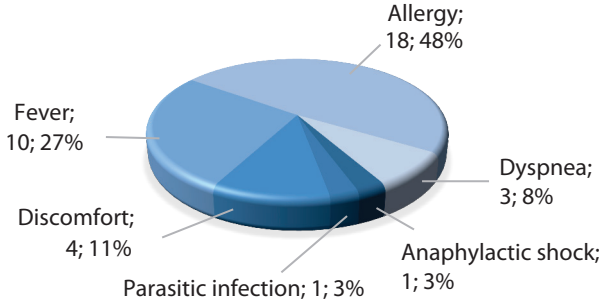


Fig. 62 **Type of adverse reactions in recipients**

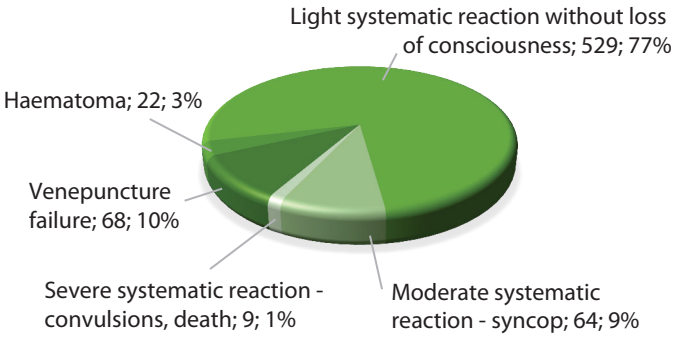


Fig.63 **Type of adverse reactions in donors**

In 2016, the Agency confirmed the information for a serious adverse reaction associated with the quality of the blood or blood components distributed by Hematology Centres. The patient was infected with a transmissible disease (malaria) after receiving blood transfusion. According to the European and national legislation, the blood donations are not subject to compulsory examination for malaria. BDA held an exceptional inspection regarding the case and appropriate measures under BBDBTA were taken.

Pursuant to the requirements of the European directives relating to the collection, testing, processing, storage and transfusion of blood and blood components and the Decision taken at the Annual meeting of the national authorities in the field of blood donation and transfusion held in October 2007 in Brussels, in the event of an outbreak of a dangerous transmissible infection anywhere in the EU, the stakeholders in the system should be informed about the particular case and measures. In this regard in 2016 BDA, after receiving information via the Rapid Alert System, has informed all transfusion units about cases of West Nile Virus (WNV) in Italy, Hungary and Austria, as well as the guidelines of the measures taken by blood transfusion systems of each of the countries.

In 2016, the Agency received an Action Plan in Case of Zika Virus Infection Outbreak in the EU Member States. The document recommends actions and measures at the national level (general measures) and in the affected areas (local measures).

Inspections

In compliance with the approved schedule for inspections, in 2016 were carried out 55 routine inspections in healthcare facilities collecting, testing, storing, processing, distributing and using blood and blood components under Art. 15 of BBDBTA. Two non-routine inspections were also carried out.

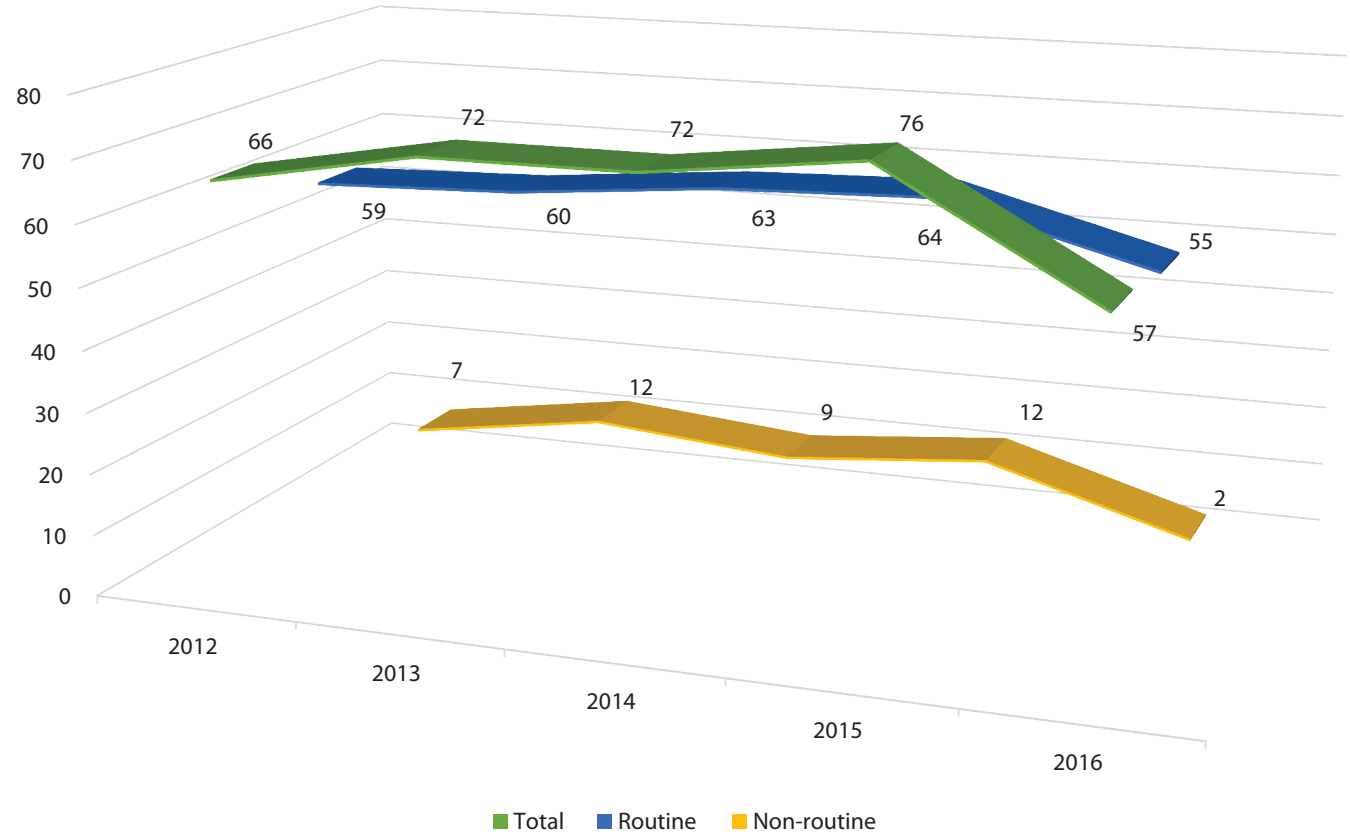


Fig. 64 **Inspections**

The subject of inspections were the main activities and basic characteristics of the blood establishments - Regional Centers of Haematology (RCH) and the Haematology Wards (HW) as well as clinical use of blood and blood components, the blood establishments quality systems, and haemovigilance. The object of the routine inspections were all the sectors in the blood establishments: blood donation sectors (donors selection, blood collection), testing sectors (laboratories) for the donated blood and the blood for transfusion, blood components processing sectors, including the transportation between the blood establishments; the quality control sectors, blood components distribution by the RCH as well as the blood establishments quality management systems.

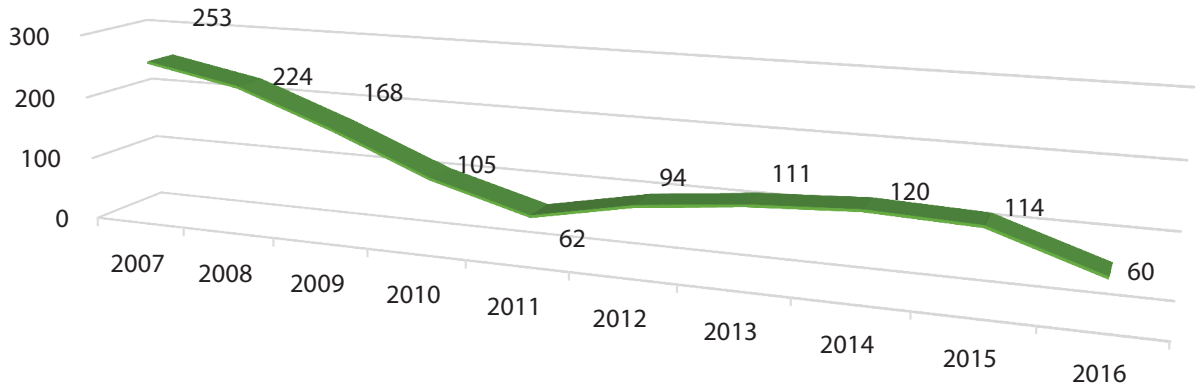


Fig. 65 **Number of non-compliances by year**

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

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

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

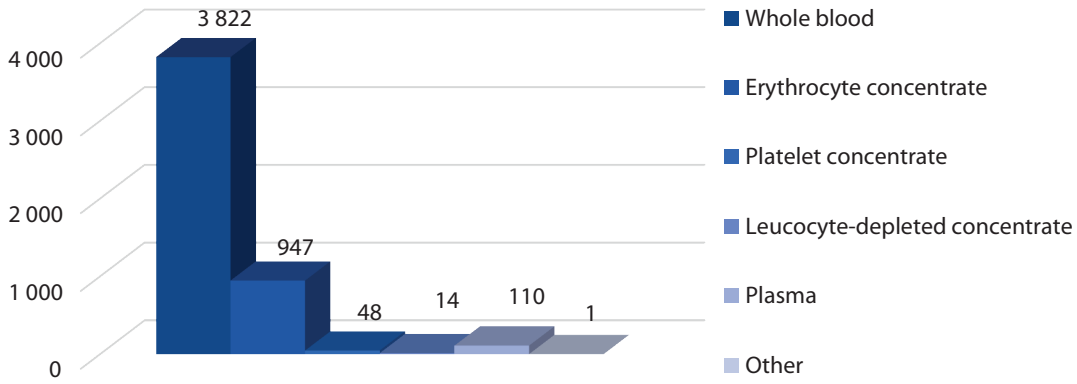


Fig. 66 **Disposal of blood and blood components by type in 2016**

After analysing all the received information for the year the following conclusions could be drawn up:

In 2016, the transfusion system disposed of or transmitted for scientific use 4 942 units of whole blood or blood components (incl. erythrocyte concentrate, fresh-frozen plasma or platelet concentrate). The comparison to 2015 shows an increase of the disposed of or handed over for scientific purposes units with 747.

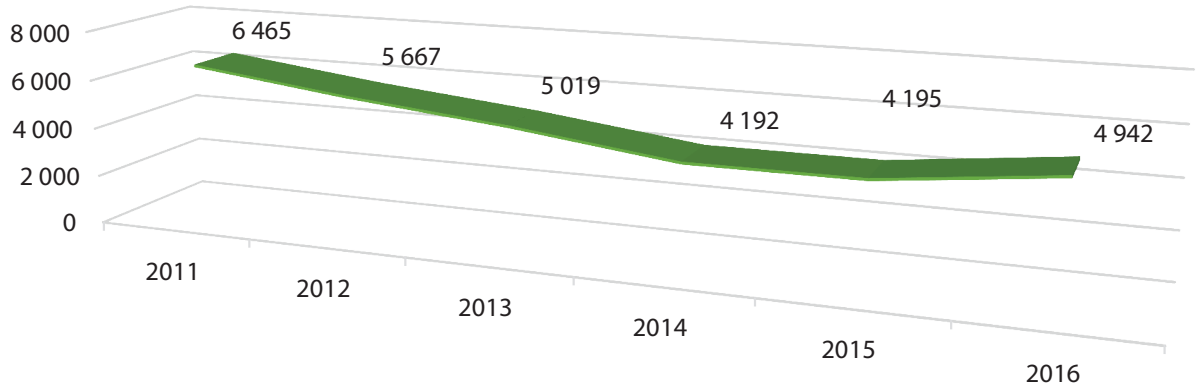


Fig. 67 **Disposal of blood and blood components during 2011-2016**

The data shows that the main part of the reasons for disposal of almost 80% of the units are factors found in the early stages of processing and examination of the blood in the blood establishments (transmissible infections, non-standard volume of the collected blood and detection of antibodies).

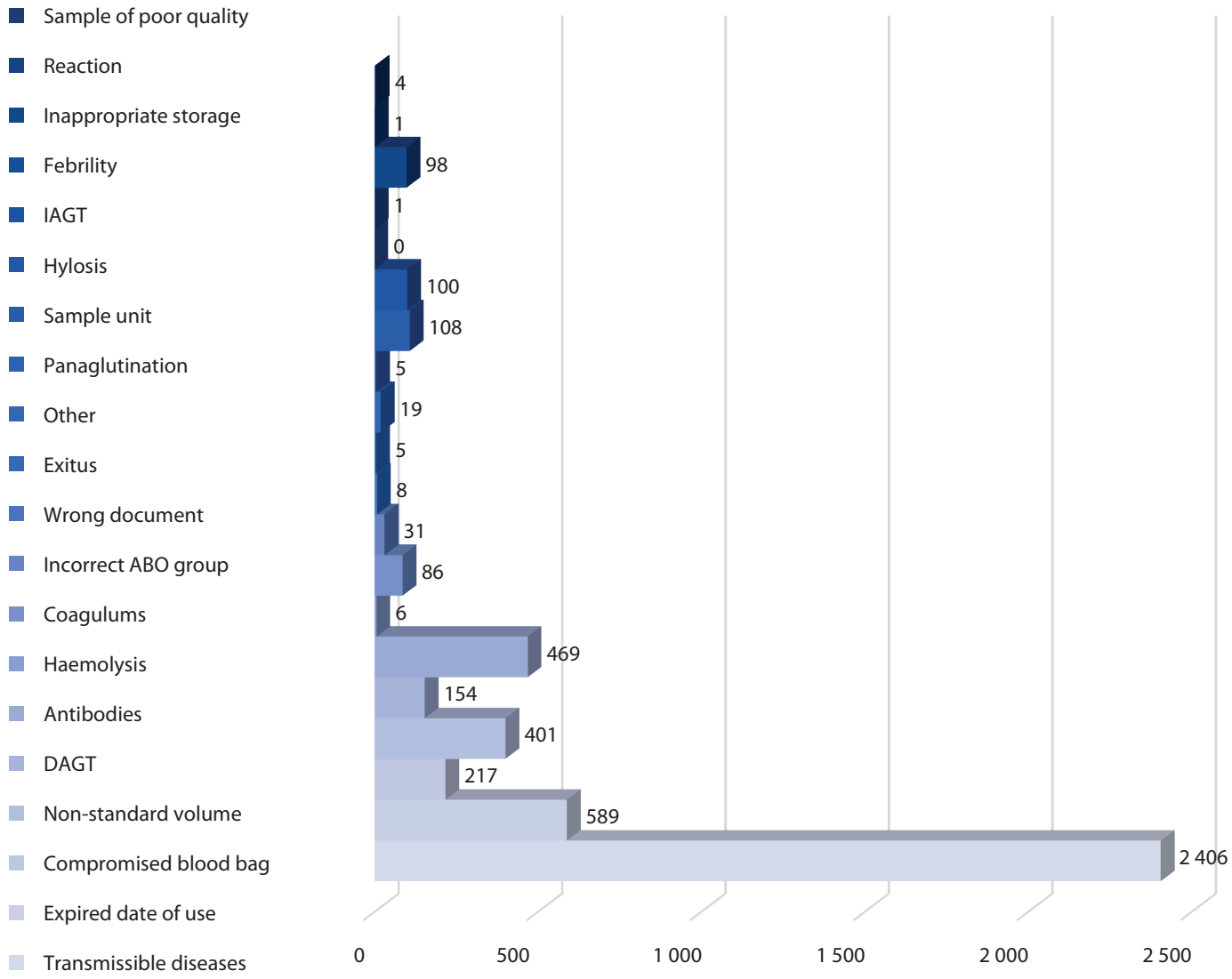


Fig. 68 **Disposal of blood and blood components by reason in 2016**

2.11 SPECIALIZED COMMITTEES TO THE AGENCY'S EXECUTIVE DIRECTOR

According to Art. 47 of 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.

BDA's officials participate in the national commissions and expert councils such as National Commission for evaluation of Adverse Events Following Immunisation, Transparency Commission, Expert Council on Advertising, Health Technology Assessment Commission, Interdepartmental Commission on the Composition, Characteristics and Names of Infant Formulas and Follow-on Formulas, Commission for Determining Product Affiliation, Higher Pharmacy Council 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 2016 was 21 101 512 BGN as the approved budget was 20 500 000 BGN.

The implementation of the income is nearly 602 000 BGN more than planned, i.e. there is 3% overfulfilment of the income part of the budget. The types of income are shown in the chart below:

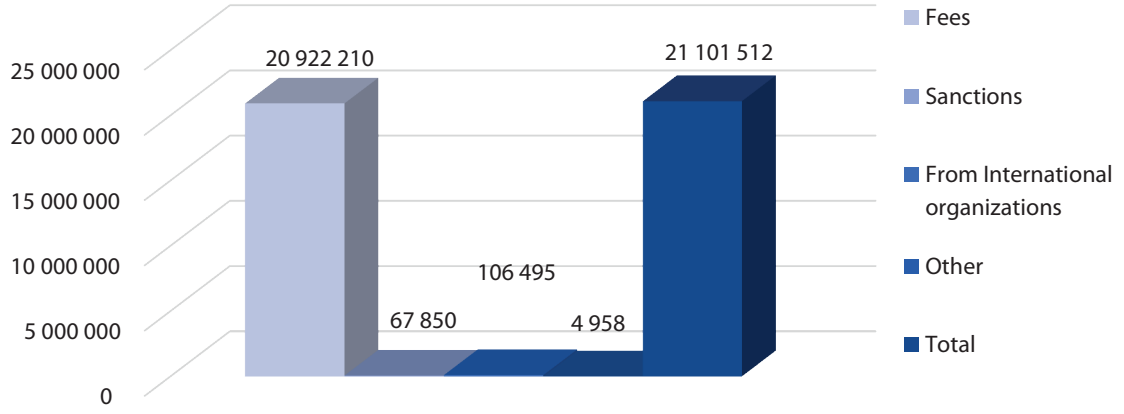


Fig. 69 **Income in 2016**

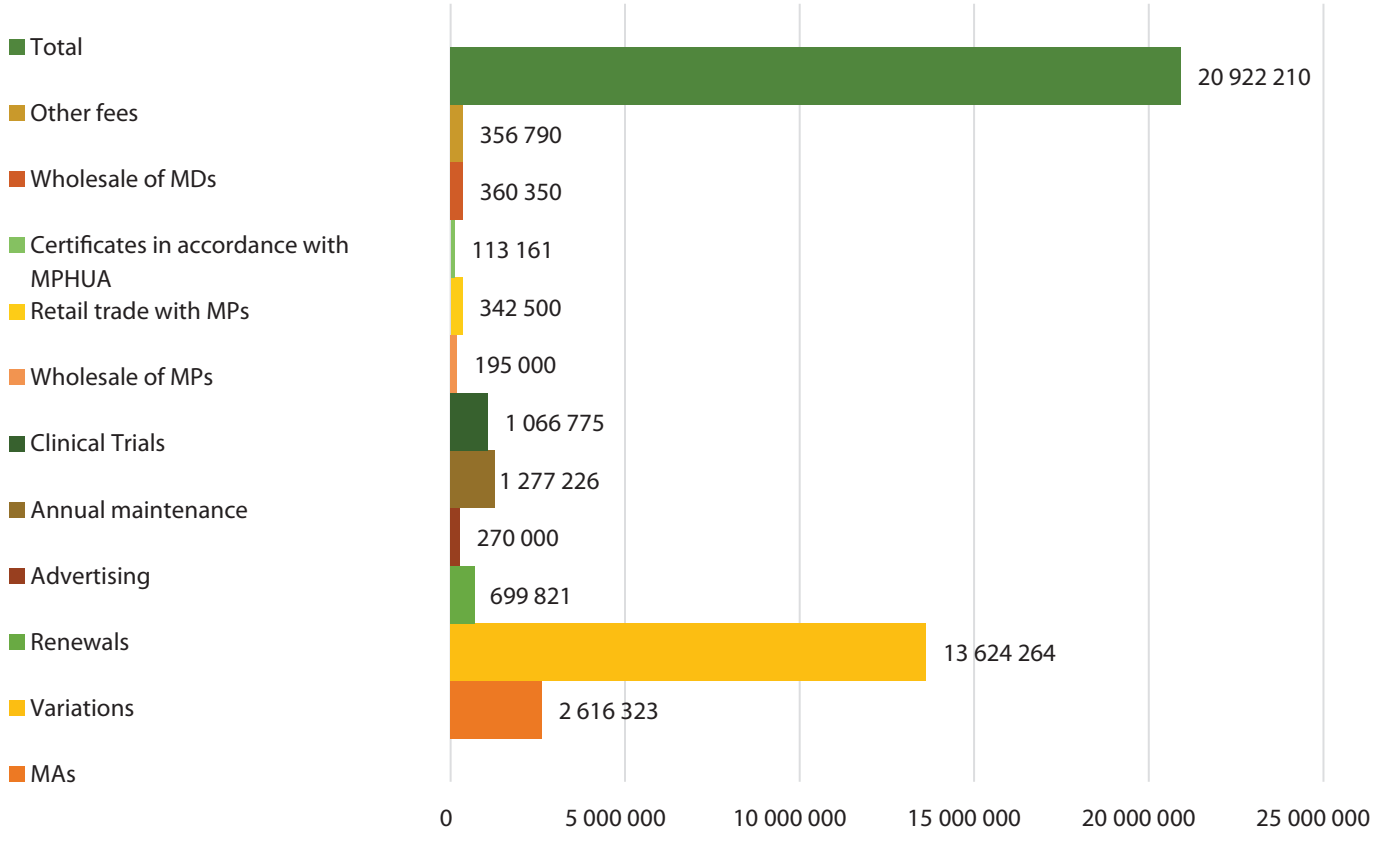


Fig. 70 **Income from state fees in 2016 by administrative service**

The values in the above two charts show that the largest share of income from fees is for issuing Variations which is over 65% of the BDA's income.

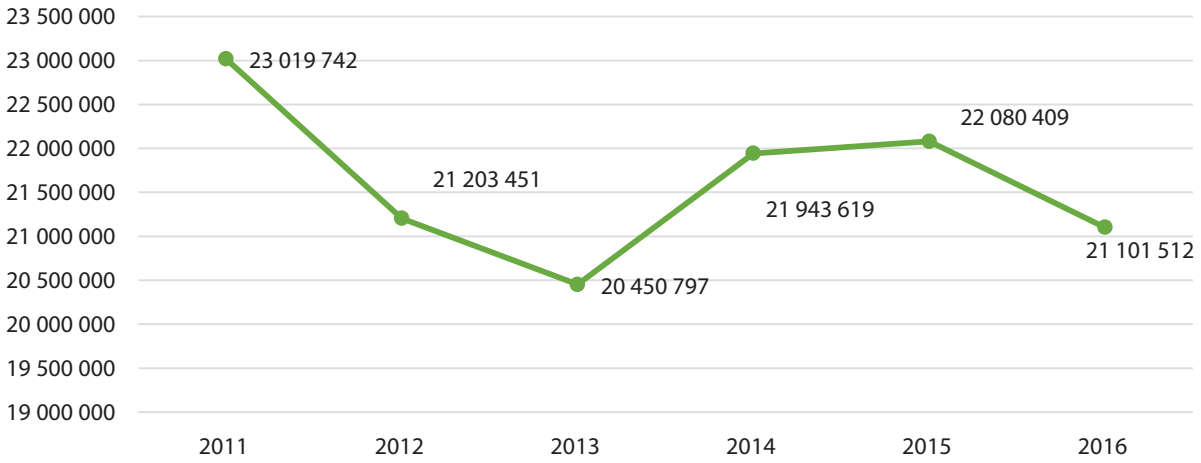


Fig. 71 **Comparison of the income during 2011-2016**

Although there is an overfulfilment of the income for 2016, there is a decrease in the income compared to 2014 and 2015. The analysis shows that the reason is primarily due to drop of the income from state fees for Variations as a consequence of the revoked 1 185 MAs upon request by the MAHs in 2014-2016.

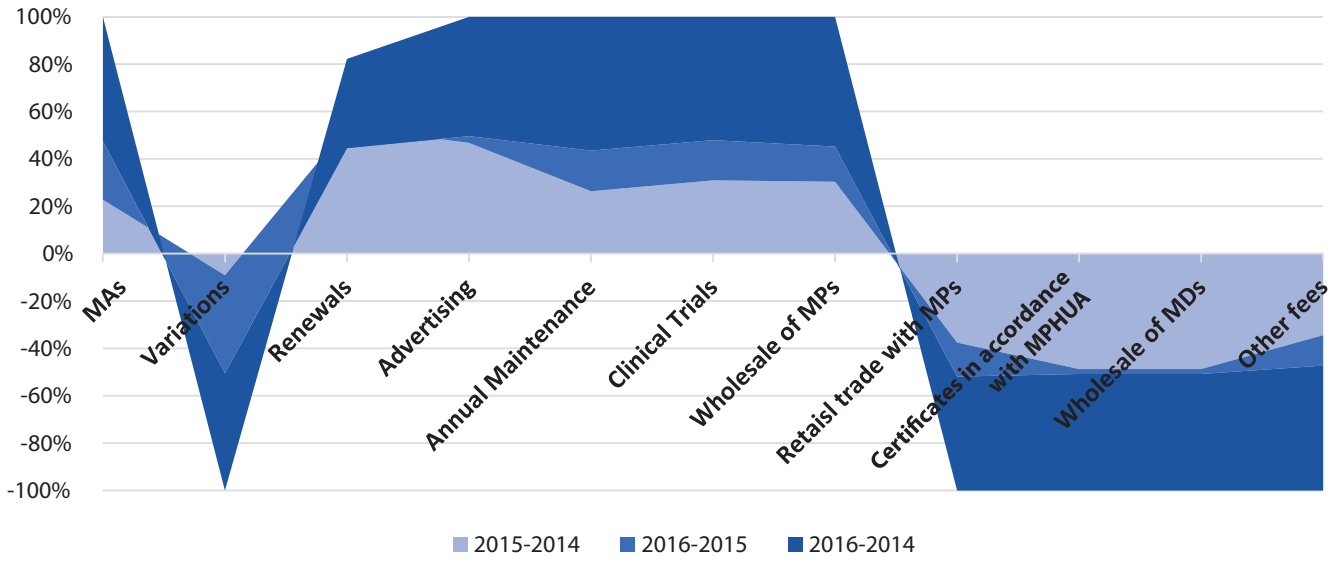


Fig. 72 **Fluctuations of the income from state fees**

The comparative analysis of income from state fees for 2014-2016 shows the following trends:

- **Increase** of the income from state fees for administrative services for MAs, clinical trials, wholesale of medicinal products, advertising of medicinal products, and annual maintenance of MAs.
- **Reduction** of the income from state fees for administrative services for Variations, Renewals, retail trade with medicinal products, wholesale of medical devices, certificates in accordance with MPHUA.

Expenses

The total amount of expenses for 2016 is 5 010 553 BGN as the approved budget was 5 362 000 BGN. 351 447 BGN were saved, as the implementation of the expenditure side of the budget was 93 %, with savings of 7%.

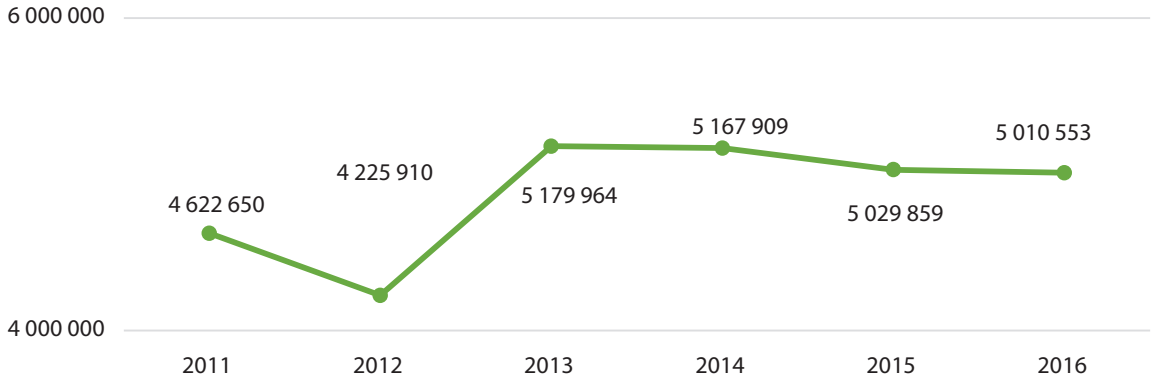


Fig. 69 **Income in 2016**

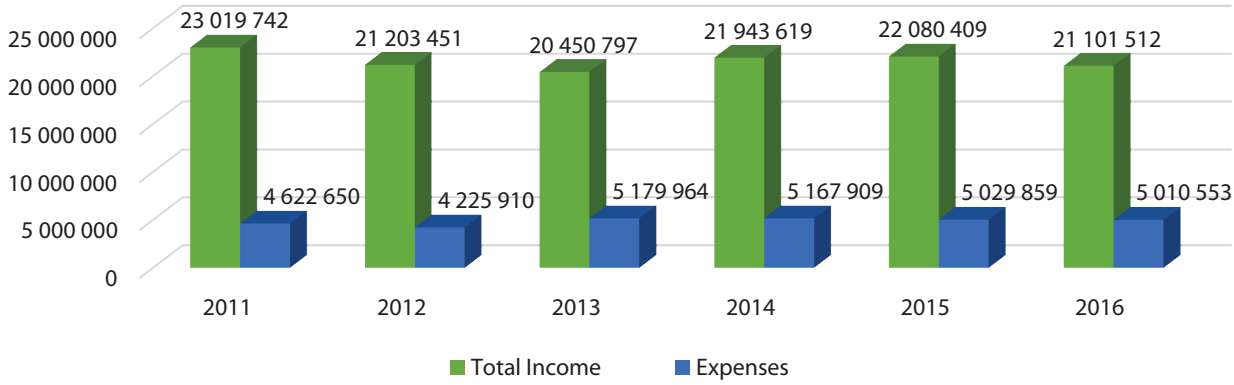


Fig. 74 **Income and expenses during 2011-2016**

Effectiveness

The efficiency of expenditure is 4.21 and the planned by the budget efficiency was 3.81. Each 1 BGN of expenses „brought" 0.40 BGN additional income. The additional effect is 10%.

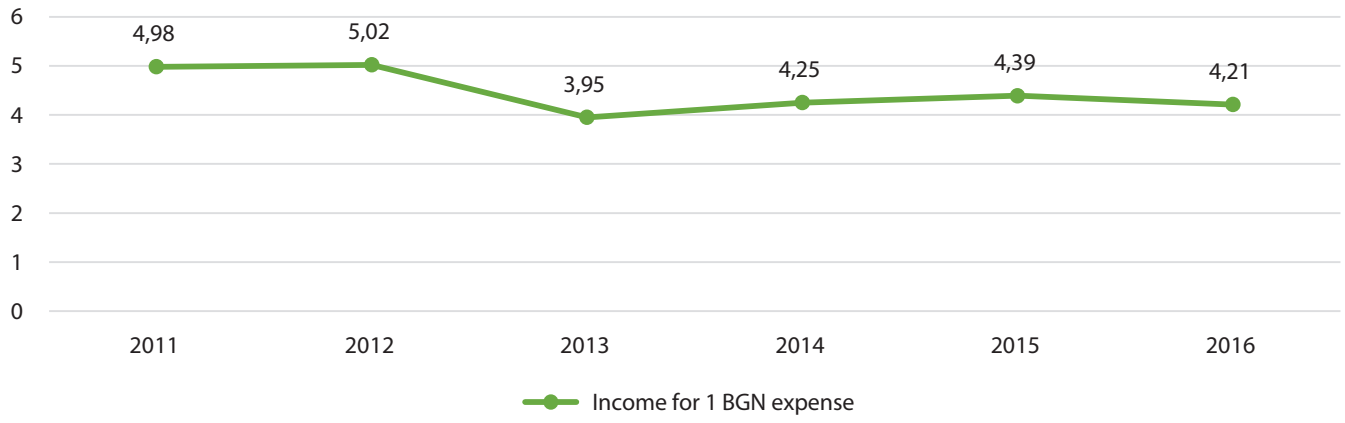


Fig. 75 **Agency's effectiveness for 2011-2016**

4. ADMINISTRATIVE SERVICES

From 1st Jan 2016 until 31st Dec 2016 in the Automated Information System (AIS) DOCMAN©2 were registered **60 122** documents.

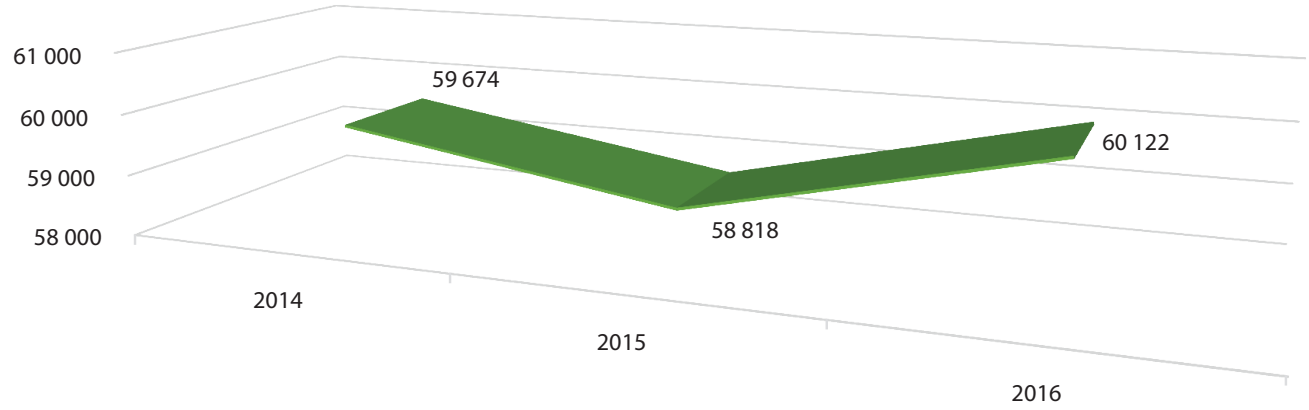


Fig. 76 **Document flow during 2014-2016**

Feedback from the BDA's customers

The BDA's Management apprehends transparency as an effective management tool and a way to provide the necessary information to the service consumers.

During June-August 2016, a survey through a questionnaire published on the website was carried out. The analysis for the customer satisfaction with BDA's administrative services and according to the measured indicators, shows that the level of satisfaction is high. In 2016, there were not received any complaints and reports relating to the activities of the Agency's employees, which is one of the satisfaction indicators.

5. PROCEDURES FOR AWARDING PROCUREMENTS

In 2016, the Agency prepared and conducted procedures for awarding procurements under the Public Procurement Act (PPA), as follows:

Public call

Provision of plane tickets for transport by air of passengers and luggage in cases of business trips for the needs of the Bulgarian Drug Agency (BDA)

Awarding procurements through collecting offers with an invitation

Delivery, installation, configuration, commissioning and warranty support for border router, three servers and a license for virtual infrastructure for the needs of the BDA

Public competition under PPA

Delivery, installation, operation and commissioning of laboratory equipment in three separate positions: Separate position № 1 – Delivery, installation, operation and commissioning of PCR Device for amplification of nucleic acids; Separate position № 2 - Delivery, installation, operation and commissioning of Device for horizontal gel electrophoresis for separation and detection of nucleic acids; Separate position № 3 - Delivery, installation, operation and commissioning of High Performance Liquid Chromatography System HPLC

6. LEGAL PROVISION

The main priority in the legal advisors' work 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 the duties under 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 75

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:

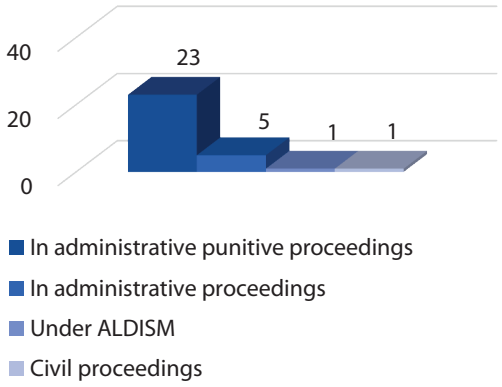


Fig. 77 **Enforced court decisions/definitions**

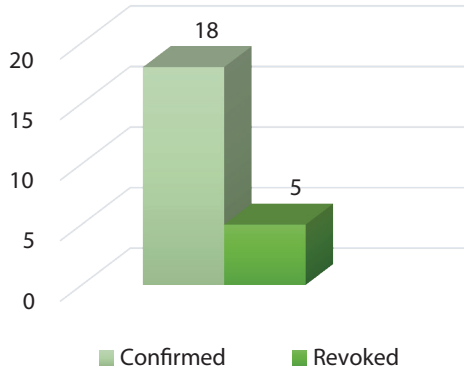


Fig. 78 **Administrative punitive cases**

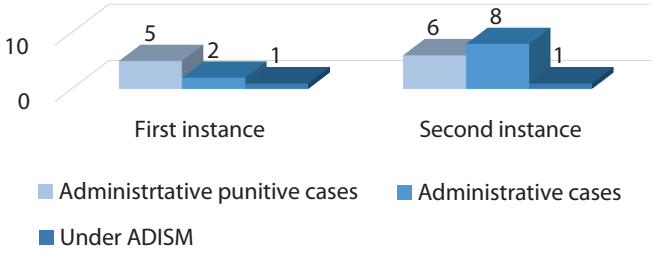


Fig. 79 **Pending proceedings**

Cassation appeals were drafted in cases of unfavorable court decisions. Regarding filed civil claims, the legal advisors prepared responses and relevant evidence was engaged in the court proceedings.

Validation of the lawfulness of acts of the Executive Director.

The legal advisors develop and validate the lawfulness of the Executive Director's Acts. This activity includes Penal Ordinances imposing fines and sanctions, as well as preparation of internal rules regulating the activities of the BDA, orders, contracts, opinions, etc. The legal advisors also assist in the preparation of answers to the European Medicines Agency, European Commission and the National Competent Authorities.

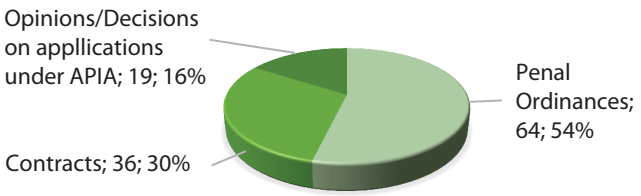


Fig. 80 **Prepared/Validated documents**

7. HUMAN RESOURCES MANAGEMENT

As a continuation of the policy for optimizing and unifying the business processes and for enhancing the administrative capacity in 2016, part of the specialized administration was restructured. Within the *Market Supervision and Inspections* Department all inspection activities on the wholesale and retail of medicinal products and medical devices, on pharmacovigilance and on clinical trials were fused in one structural unit.

Personnel

In 2016, the BDA has appointed nine new employees. There were 8 employees who resigned, including those who retired.

The Career Start Programme for employment of youths was successfully finished. As a result, one employee was appointed on an expert position.

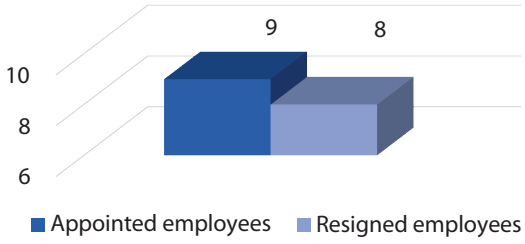


Fig. 81 **Appointed and resigned employees in 2016**

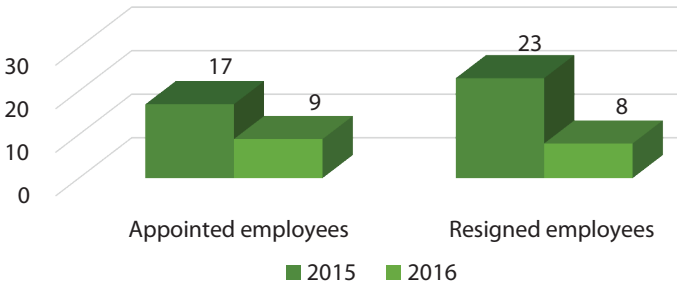


Fig. 82 **Ratio of resigned and appointed employees in 2015 and in 2016**

The Agency held 5 competition procedures for vacant positions and 4 selection procedures for promotion as follows:

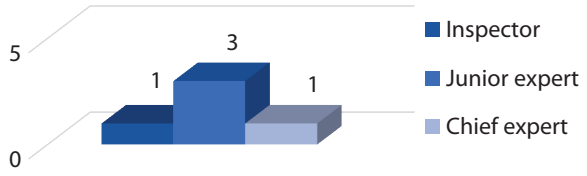


Fig. 83 **Competition procedures**

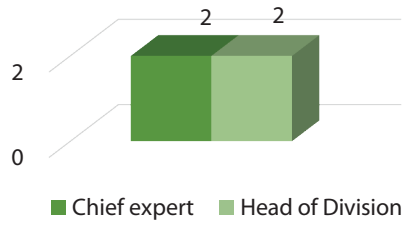


Fig. 84 **Selection procedures for promotion**

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.

One expert was appointed EU NTC Training Champion and Local Administrator for the online Learning Management System (LMS). EU NTC is aimed at exchanging information and knowledge and carrying out regulatory research and scientific trainings across the EU regulatory network to ensure its quality and thus promote the harmonization of evaluation standards. In 2016, BDA partook in the testing of the e-learning platform. LMS is a centralized online learning platform 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. The online platform is used for coordinating, monitoring and conducting trainings for all staff in the regulatory network.

BDA's 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's 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

In 2016, the maintenance and the improvement of the Integrated Quality Management, Information Security and Risk Management System was successfully continued according to 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. The migration to the new version of ISO 9001:2015 was successfully completed. In this regard, many of the internal IMS documents were changed.

In June 2016, a control audit of the IMS was held by the accredited organization Intertek. On the basis of the findings, it was ascertained that the IMS is operating effectively and efficiently. The auditor's assessment shows that the BDA maintains the IMS in accordance with ISO 9001:2015 and ISO/IEC 27001:2013.

In May 2016 in the *Medicinal Products Analysis* Department, the Executive Agency *Bulgarian Accreditation Service* held the first planned supervision by on-site assessment after received accreditation for compliance with BSS ISO/IEC 17025:2006. As a result the certificate was reissued until July 2019.

In September 2016, the BDA was successfully assessed under the comparative Benchmarking of European Medicines Agencies (BEMA IV) Program to the Heads of Medicines Agencies (HMA).

9. PROJECTS

SCOPE

BDA partakes in the Strengthening Collaborations for Operating Pharmacovigilance in Europe Project – SCOPE financed by Joint Action 2013 of Consumers, Health and Food Executive Agency (CHAFEA) at the European Commission. The project's goal is supporting the NCAs in the implementation of the new pharmacovigilance legislation. SCOPE is aimed at applying consistent approach by the Member States in the European pharmacovigilance and communication network, which will lead to better healthcare.

Bulgaria is an active party in Work Package 7 focused on the development of common quality standards for the pharmacovigilance systems. Until the end of 2016, the Good Practices documents were finished. The Agency's experts took part in the trainings under Work Package 5 Signal Management, Work Package 7 Quality Management и Work Package 8 Lifecycle Pharmacovigilance. A project extension till April 2017 is being discussed.

VISTART

BDA is a collaborating partner in Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation Project – **VISTART**. The key objectives of the Action are to promote and facilitate harmonisation of inspection, authorisation and vigilance systems for blood, tissues and cells and to increase inter-MS collaboration and confidence in each other's inspection and vigilance programmes.

The Agency partakes in Work Package 7 Training of blood, tissues, and cells inspectors with sharing of expertise across Member States. The package leader is the Italian National Blood Centre. So far, within the working package in collaboration with the Work Package 6 team, targeted training for inspectors in tissues and cells as well as in transfusion system were developed. BDA will train two inspectors respectively in 2017 and 2018. The Agency also participates in Work Package 5 International collaboration for Vigilance Communication and Preparation Process Development aimed at creating a NOTIFY Library as a case study didactic tool. At this stage, the criteria for including different cases in the Library are being discussed.

10. INTERNATIONAL COOPERATION

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 the EMA, the European Commission, the EDQM, the European Pharmacopoeia and other bodies and institutions. BDA regularly attends meetings of the HMA and the EMA, committees and working groups of the two organizations, as well as their joint initiatives.

11. TRANSPARENCY

In 2016, BDA received 19 Applications under the Access to Public Information Act (APIA) as 10 of them were submitted by citizens, 5 - by legal entities and 4 - by NGOs. The Applications are divided as follows: 17 were received on hardcopy and 2 were received via e-mail; 8 of the Applications regard official information and 11 concern administrative information.

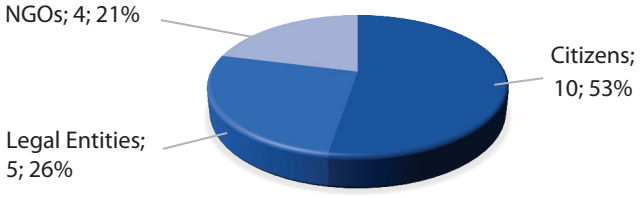


Fig. 85 **Received Applications for Access to Public Information by applicant**

All the required accesses was granted in the set terms except for one refusal on grounds that the information is part of the operative preparation of an act and has no relevance of its own. All applications were assessed. There were no claims against the final acts under APIA.

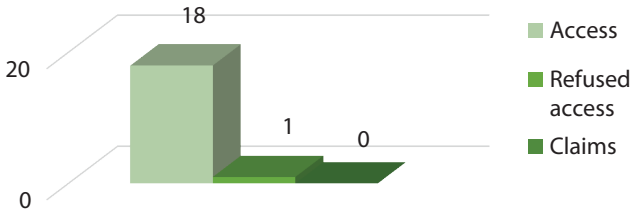


Fig. 86 **Access to Public Information**

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.

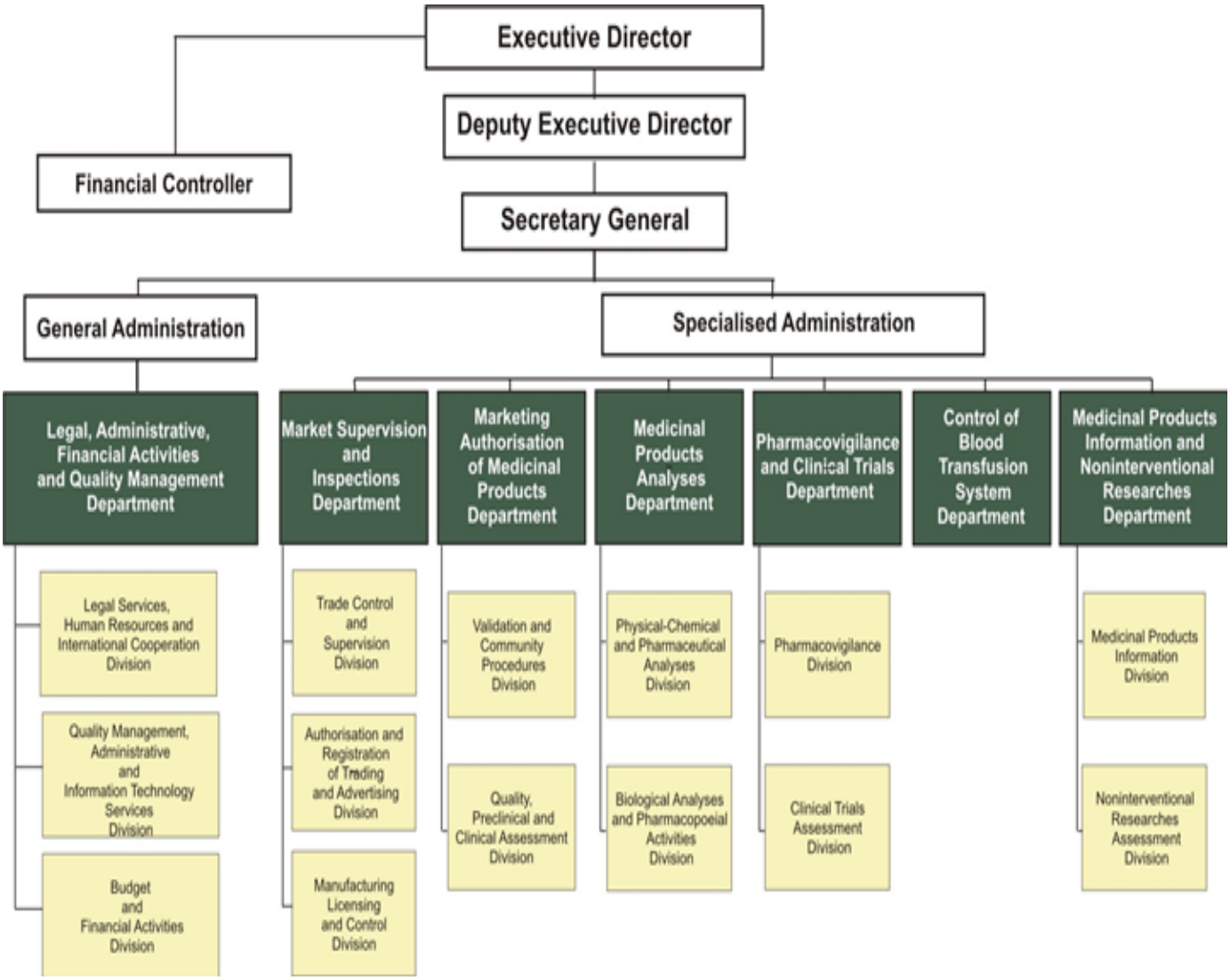
After the demonopolization, the decentralization of the production, supply and distribution of medicines in 1991, SICM turned out to be the only State institution, competent in the medicinal sector. International experience was gained and the foundation of a different institute was prepared, an institute 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



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