ИЗПЪЛНИТЕЛНА АГЕНЦИЯ ПО ЛЕКАРСТВАТА

ИАЛ

ГОДИШЕН ДОКЛАД

2017

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BDA

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BULGARIAN DRUG AGENCY

BULGARIAN DRUG AGENCY'S ANNUAL REPORT FOR 2017

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Executive Director
of the Bulgarian Drug Agency

INSTEAD OF A FOREWORD

Dear readers,

You are holding in your hands the Annual report for the results in the main areas of activity of the Bulgarian Drug Agency (BDA) in 2017. Against the backdrop of national and international challenges, the Agency has made significant progress over the past year in a number of medicinal products regulation areas.

By implementing its core mission as a medicinal regulator, the BDA maintains continuous partnerships with the European Medicines Agency and the regulatory bodies of the other EU Member States. Part of the results presented in this annual report is precisely the expression of cooperation with the European regulation authorities. In the past year the Bulgarian Drug Agency continued to build Bulgaria's reputation as a reference country in MRPs. In 2017, BDA successfully completed another MRP as a reference member state and started two marketing authorizations via a decentralized procedure. At the same time, in compliance with an anti-trust decision and a recommendation of the European Commission, Bulgaria has accepted to be a reference member state for some procedures of a large pharmaceutical company. The decision was discussed at CMDh meetings, where relevant recommendations on the merger and division of procedures and their allocation among the Member States of the European Union were given. During the year, scientific advices on forthcoming international procedures, in which Bulgaria would be the reference member state, were prepared.

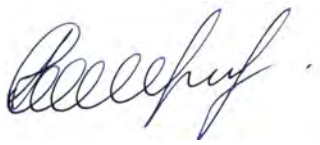
In March 2017, the BDA was successfully audited in the framework of the Joint Audit Programme - JAP Audit in relation with mutual recognition of inspections establishing the degree of compliance with the principles and requirements of the Good Manufacturing Practice in the pharmaceutical sector. The Agency was inspected by representatives of the United Kingdom (The Medicines and Healthcare products Regulatory Agency - MHRA) and Italy (dall'Agenzia Italiana del Farmaco - AIFA). Based on the Mutual Recognition Agreement between the European Commission and the USA on the results of the GMP inspections, inspectors of Food and Drug Administration (FDA) observed the audit. The audit held by the European Directorate for the Quality of Medicines & HealthCare (EDQM & Healthcare) in December 2017 found no non-compliances. The recertification audit of the Integrated Quality Management System in BDA was successful and in compliance with ISO 9001: 2015 and ISO / IEC 27001: 2013.

The Agency is a desirable partner for inspections to ascertain compliance with Good Manufacturing Practice requirements for medicines in third countries. In 2017, BDA inspectors inspected manufacturers in Iran, Vietnam, Russia and Turkey. Two of the local inspections were carried out under the supervision of inspectors from the UK, Italy and the USA in connection with the Audit under the Joint Audit Program (JAP) conducted in 2017.

In 2017, the steady trend of increasing the reporting activity of adverse drug reactions continued and for 2017 the reports are 1200 (initial and follow up). Communication with all stakeholders is of utmost importance and priority for the BDA and in 2017 we updated the software platform on the Agency's website, meeting the higher information security requirements and providing new opportunities for development and better communication

In spite of the general tendency to reduce revenues from state fees, the Agency managed to meet the planned budget (not reflecting this trend), which is a result of the additional activities and efforts of the whole BDA team, with an absolute saving of 218 950 BGN.

The results we noted in 2017 are impossible without the coordinated efforts of the BDA's staff, the external experts, the regulatory bodies of the other EU Member States, without the support by the Ministry of Health and the management of the European Medicines Agency, whom I would like to thank!



Prof. Assena Stoimenova,
PhD, MScPharm, MPH

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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 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.

Received applications

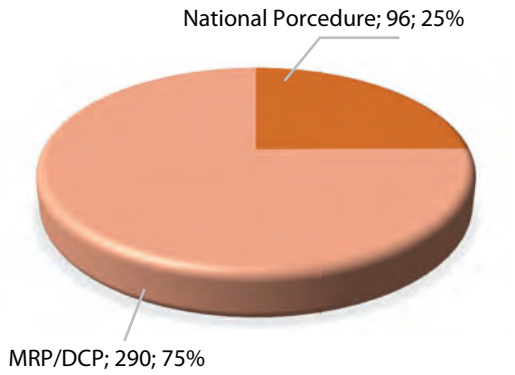


Fig. 1 **MA Applications for 2017**

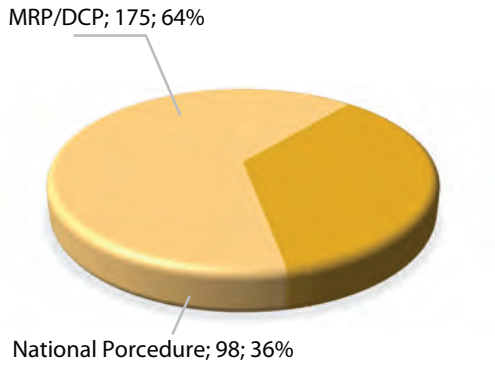


Fig. 2 **Renewal Applications for 2017**

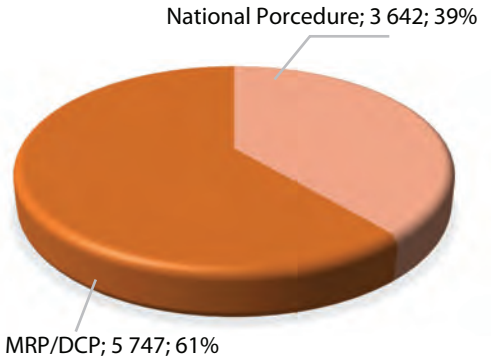


Fig. 3 **Variations Applications for 2017**

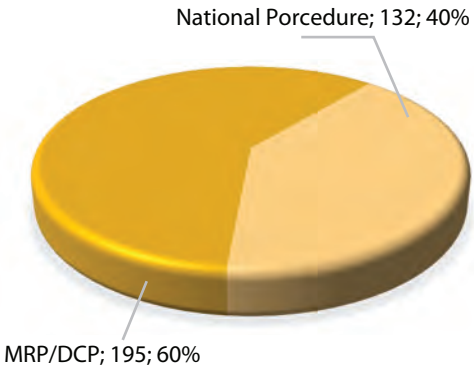


Fig. 4 **Revoked MAs for 2017**

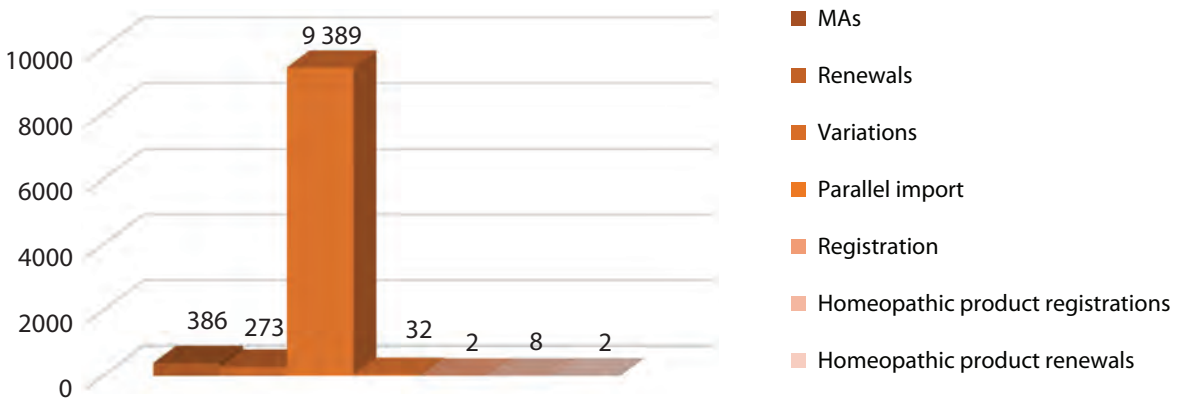


Fig. 5 **Received application in BDA for 2017**

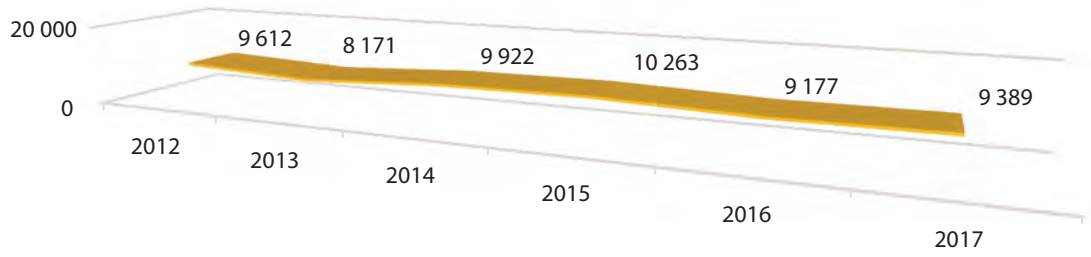


Fig. 6 **Number of received Variation applications during 2014-2017**

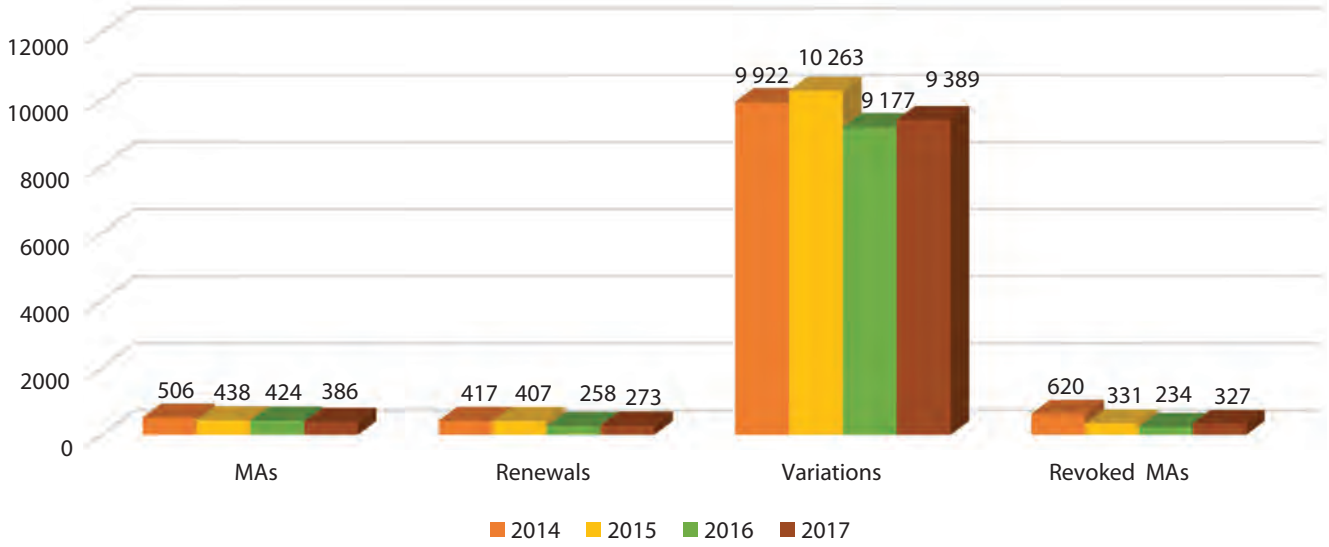


Fig. 7 **Received Applications for MAs, Renewals, Variations and Revoked MAs during 2014-2017**

Closed procedures

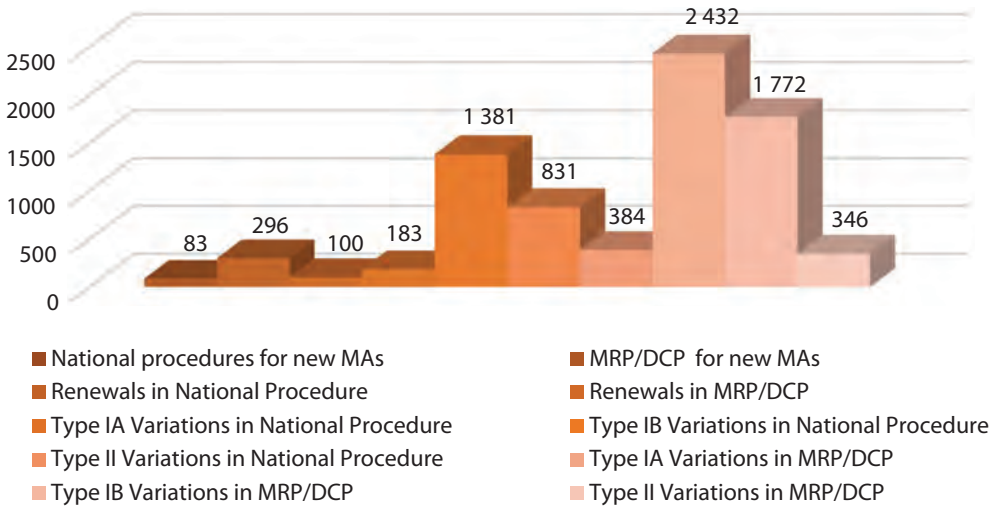


Fig. 8 **Closed procedures in 2017**

In addition, 505 applications for design changes to primary/secondary packaging of medicinal products and/or package leaflet not related to changes in the summary of product characteristics were reviewed and approved.

In 2017, 327 marketing authorizations were discontinued at the expressed wish by their marketing authorization

holders. None of the suspended marketing authorizations was associated with a serious risk to public health or because of problems with the quality of the products.

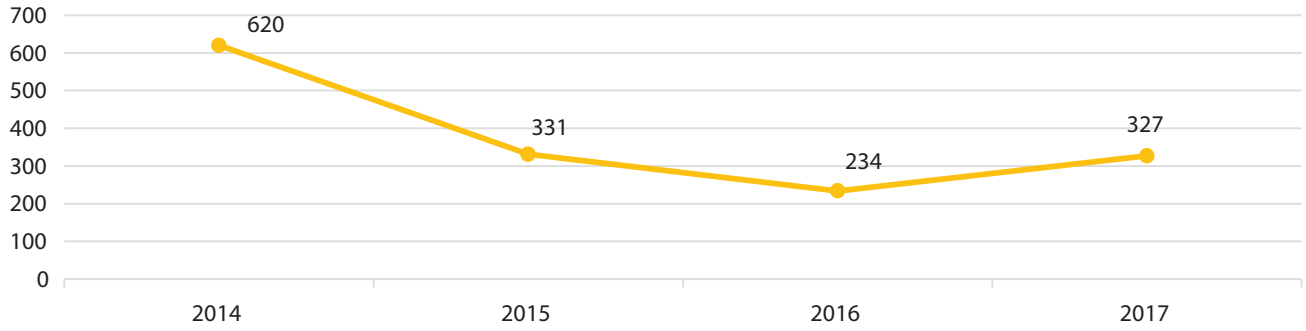


Fig. 9 **Number of revoked marketing authorizations for 2014-2017**

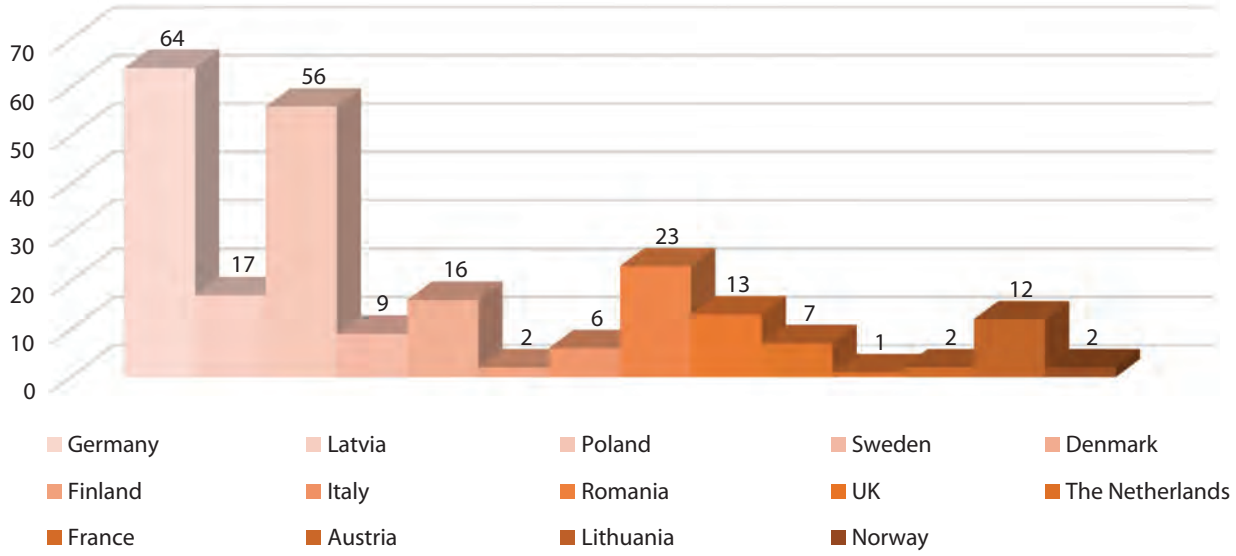


Fig. 10 **Parallel export references issued in 2017**

In 2017, BDA successfully completed another MRP as a reference member state and started two marketing authorizations via a decentralized procedure. At the same time, in compliance with an anti-trust decision and a recommendation of the European Commission, Bulgaria has accepted to be a reference member state for some procedures of a large pharmaceutical company. The decision was discussed at CMDh meetings, where relevant recommendations on the merger and division of procedures and their allocation among the Member States of the European Union were given.

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

During the year, scientific advices on forthcoming international procedures, in which Bulgaria would be the reference member state, were prepared. The BDA issued a scientific opinion on a change in the composition of medicinal products and subsequent new bioequivalence studies as well as scientific opinions on the prescription of medicinal products.

2.2 MARKET SUPERVISION

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

Manufacturing authorization and control

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

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

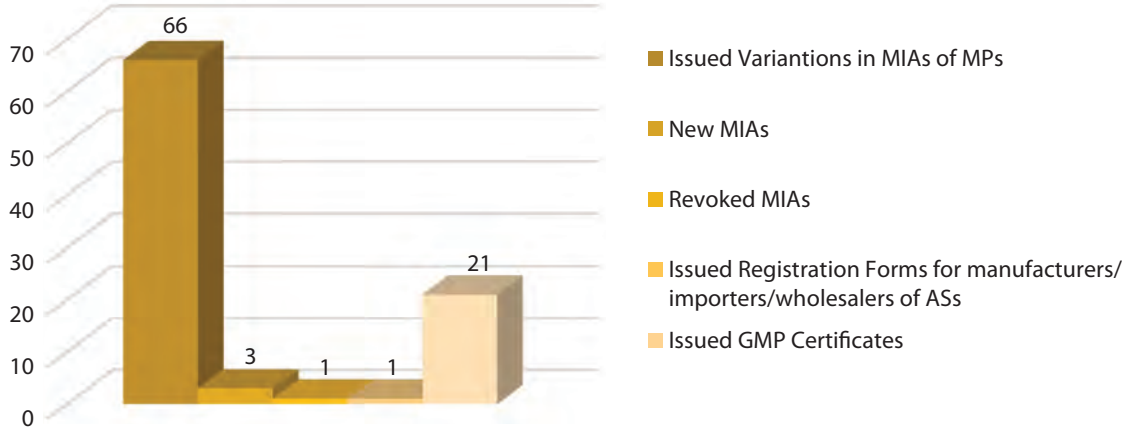


Fig.11 **Types of documents and activities**

Rapid Alert System Activities

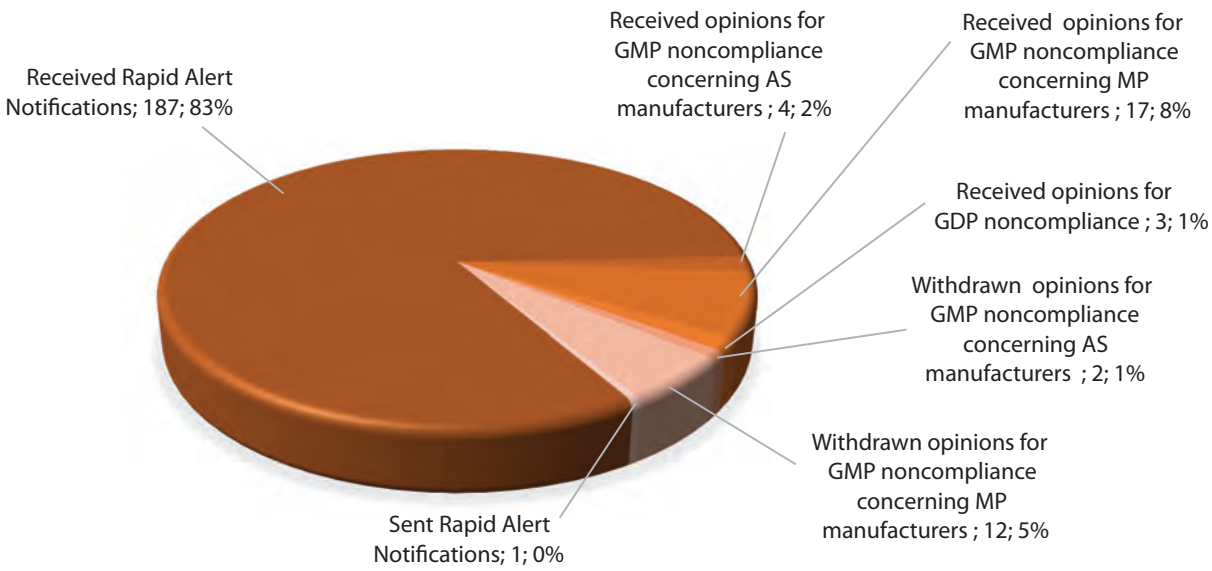


Fig.12 **Rapid Alert System**

Inspections at manufacturers

In 2017, the BDA's inspectors carried out 36 inspections at 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 2017 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.

Four of the inspections were conducted at manufacturers of medicinal products in Iran, Vietnam, Russia and Turkey. Two of them were carried out under the supervision of inspectors from the UK, Italy and the USA in connection with the Audit under the Joint Audit Program (JAP) conducted in 2017.

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

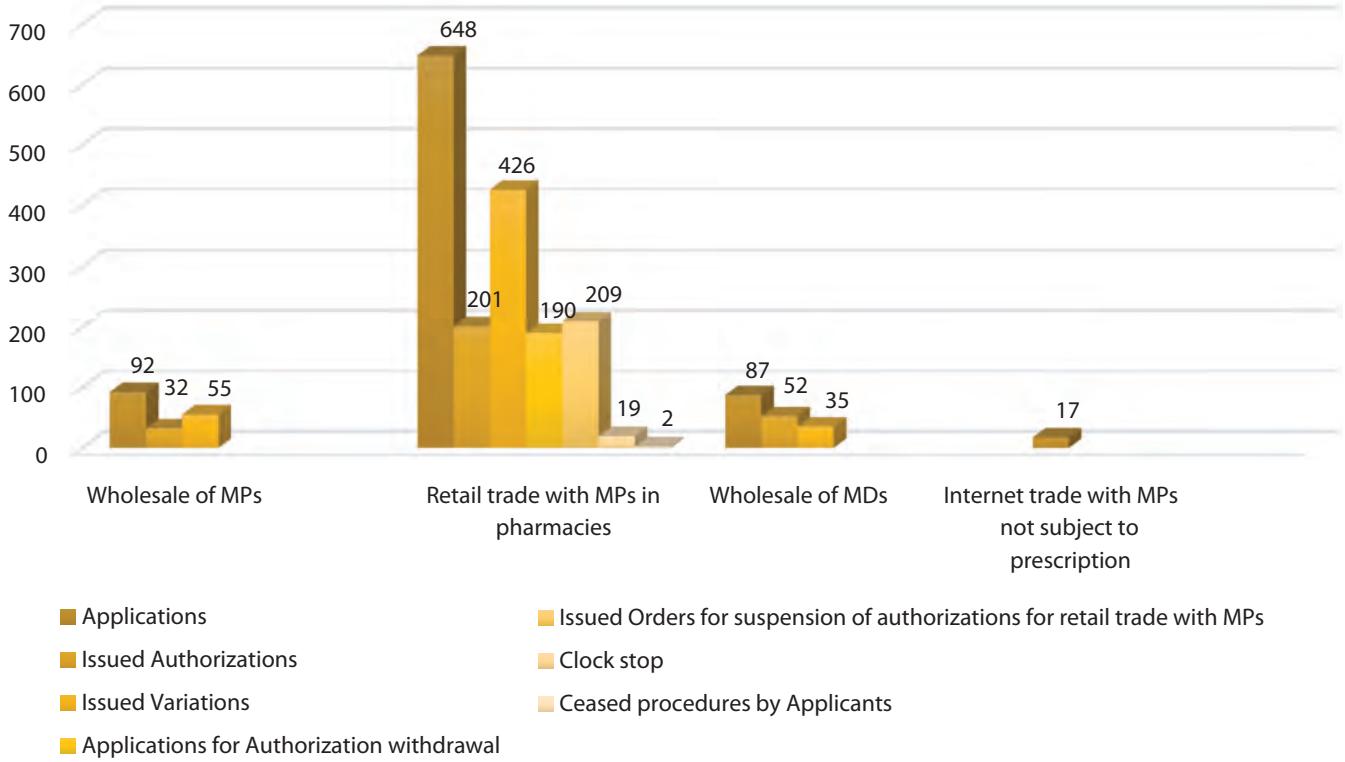


Fig. 13 **Trade Authorization Procedures**

Other activities concerning registrations and approvals

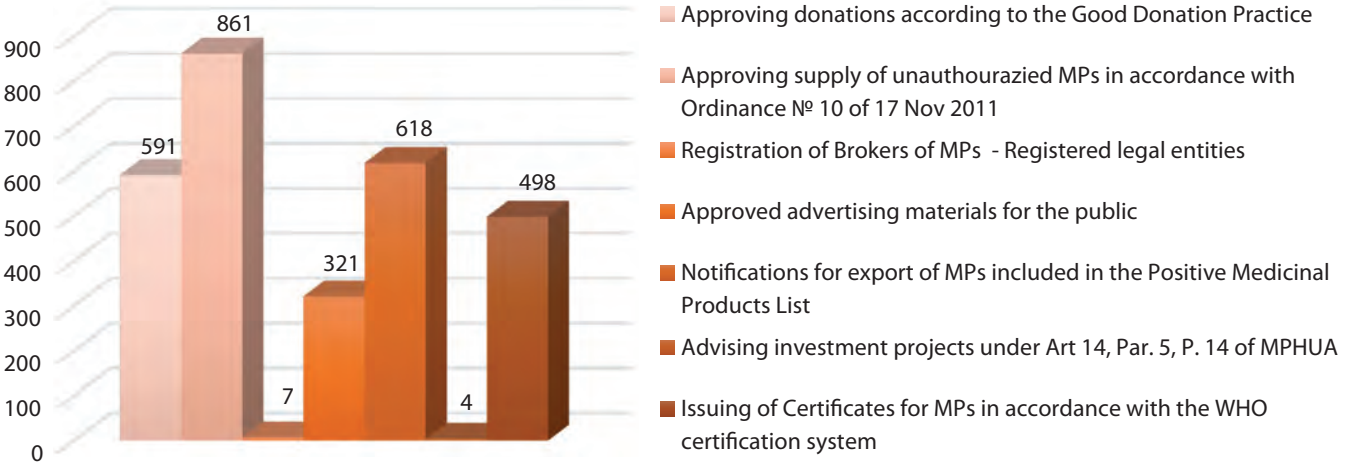


Fig. 14 **Other activities**

Medical Devices Registration

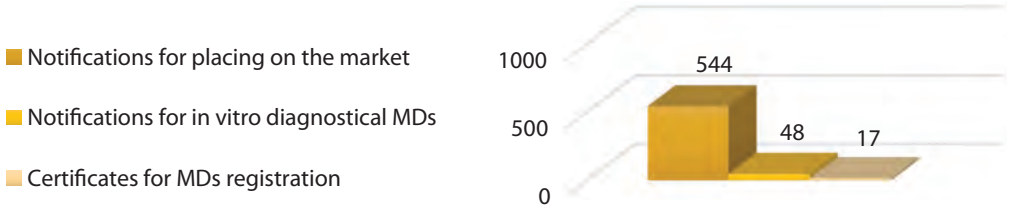


Fig. 15 **Issued Notifications and Certificates in 2017**

The 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 2017, validated records for **7 386** medical devices were made.

Medical Devices Vigilance

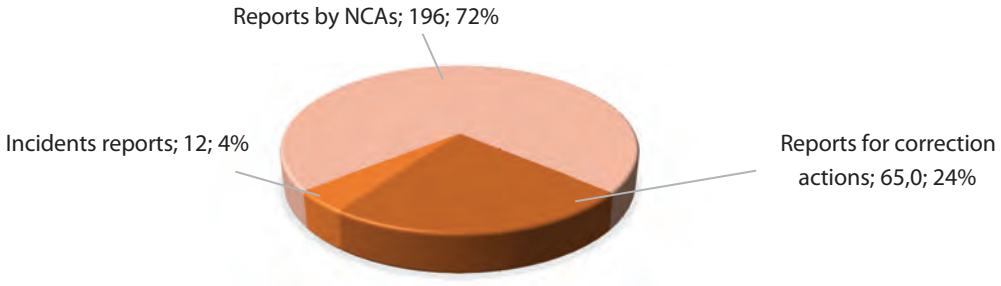


Fig. 16 **Updated information in the System for registration and medical devices vigilance**

Clinical trials of medical devices

The received documentation was assessed. As a result, 1 Clinical Trial Authorization and 1 Refusal were issued.

2.3 CONTROL AND INSPECTIONS

In 2017, 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, the 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, were carried out **392** inspections including:

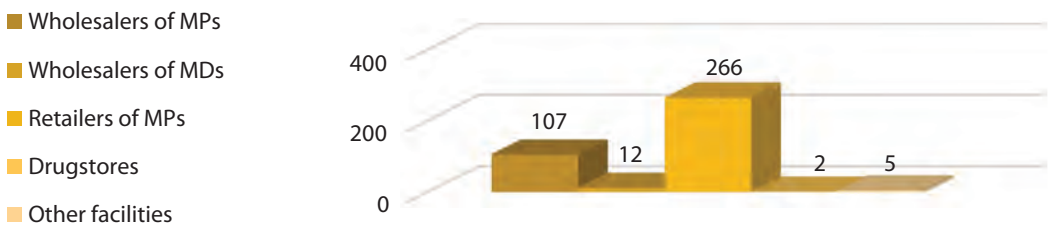


Fig. 17 **Inspections in 2017**

The most common violations in the retail trade with medicinal products

- Selling (dispensing) of medicinal product subject to medical prescription by assistant pharmacists.
- Selling (dispensing) of 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 2017, the BDA inspectors performed joint inspections together with officers from the National Revenue Agency, from the *Combating Organized Crime* Specialized Department at the *State Agency for National Security* (SANS) and the *Combating Economic Crime* Sector at Regional Department of the Ministry of Interior, and together with officials at Executive Agency *Medical Audit* executing Prosecutors' decrees after receiving signals about medicinal products trade and export violating the MPHUA and its secondary legislation.

During the market supervising inspections, 42 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 9 inspections / re-inspections of marketing authorization holders related to the pharmacovigilance system or of particular risk minimization activities for the use of certain medicinal products.

Control of clinical trials

Agency's inspectors conducted 2 inspections at two clinical trial centers for compliance with Good Clinical Practice.

Administrative-penal procedures

Given the ascertained violations, the adequate lawful measures of preventive and punitive nature were taken. By Penal Ordinances were closed 48 procedures for violations of the MPHUA and the imposed fines and financial sanctions by the BDA Executive Director were **225 000 BGN**.

Blocking, recall and destruction of medicinal products and medical devices

Fig. 18 **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 processed **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), the Medical Audit Executive Agency, Bulgarian Pharmaceutical Union (BFU), etc. The complaints and signals contained

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 and about 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.

2.4 MEDICINAL PRODUCTS ANALYSES

In 2017, 553 analyses were performed.

Fig. 19 **Number of analyses performed in 2017**

Analyses performed according the Annual plan for market surveillance 2017

Under the Bulgarian Marketing Surveillance Plan for 2017, **40** batches of medicinal products with 13 different active substances (Acetylsalicylic acid, Clopidogrel besylate, Clonazepam, Pentoxifylline, Propofol, Trimetazidine dihydrochloride, Metamizole sodium/Triacetonamine, Desloratadine, Dimetindene maleate, Omeprazole, Pantoprazole, Metformine hydrochloride, Isosorbide dinitrate) were analysed. All analysed batches of medicinal products complied with the requirements for the tests done.

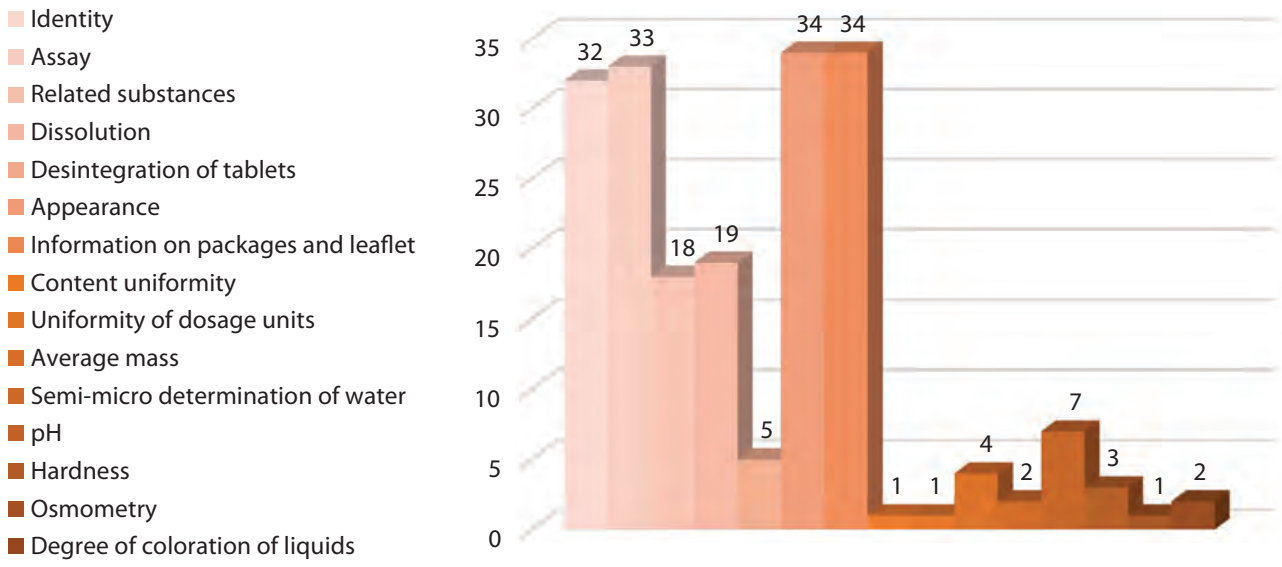


Fig. 20 **Physico-chemical and pharmaceutical analyses on batches from Bulgarian Marketing surveillance plan 2017**

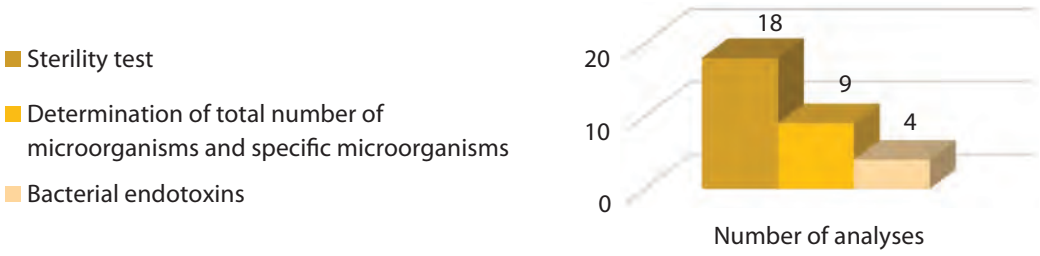


Fig. 20 **Biological and microbiological analyses performed in relation with market surveillance plan 2017 and complaints for quality non-conformities**

Sterility tests were performed on 15 samples of medicinal products. All of the results complied. Nine samples were analysed for microbiological quality (determination of total number of microorganisms and specific microorganisms). All of the results complied with the approved specification.

In connection with the testing of market surveillance samples, a task in 2017 was the assessment of eye drops sterility on the last day of the approved shelf-life after opening the package. There were analysed a group of eye drops with moisturizing effect not subject to a medical prescription and registered as medical devices. Products containing Carboximetilcellulose, Hypromellose, Sodium Hyaluronate were tested. All of the tested 6 batches met the sterility requirements on the last day of the shelf-life after opening the package.

Physico-chemical and pharmaceutical analyses

One of the BDA activities is the performance of physico-chemical and pharmaceutical analyses. In 2017, 102 batches of medicinal products were analysed.

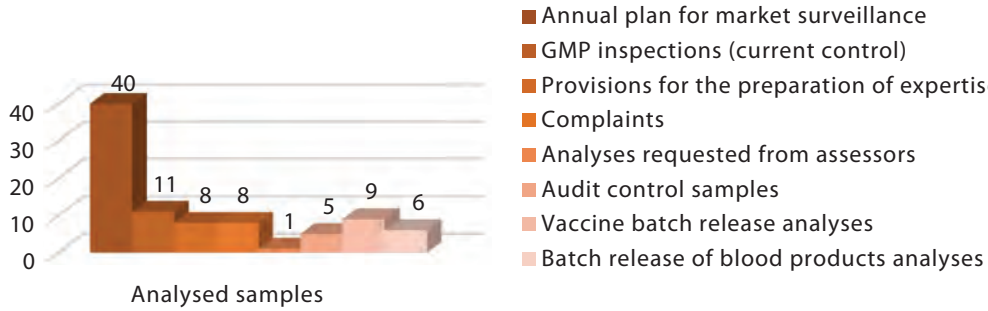


Fig. 22 **Analysed samples in 2017**

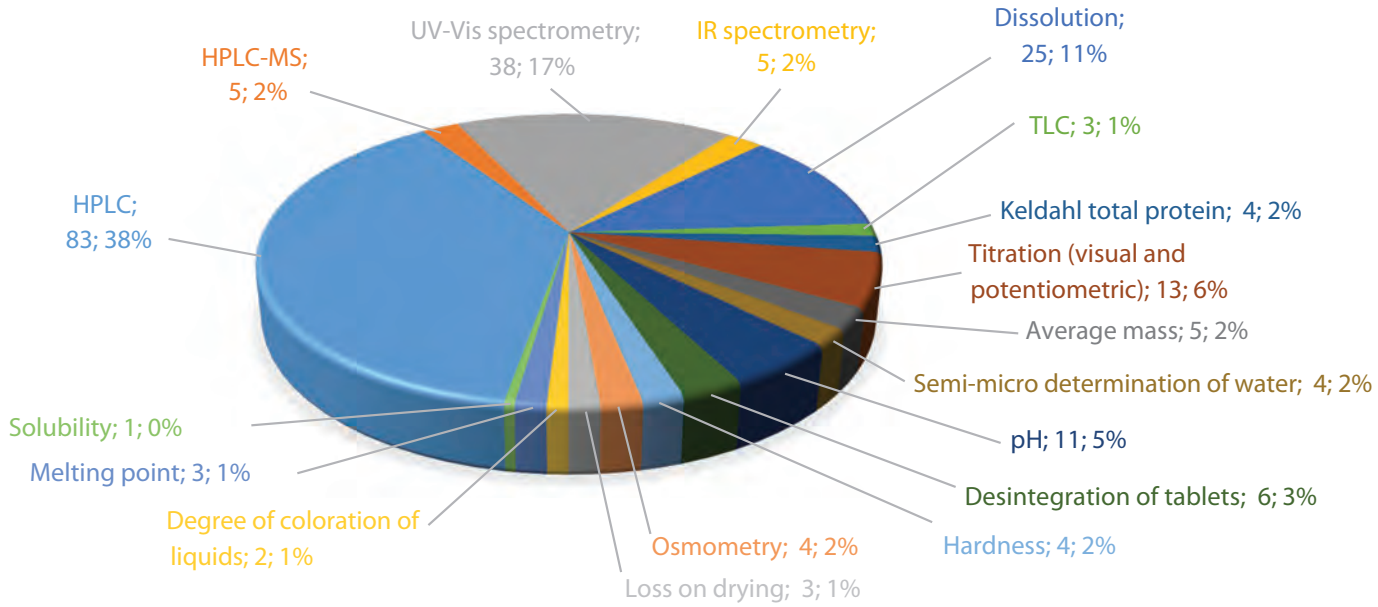


Fig. 23 **Analytical methods used for control of medicinal products batches in 2017**

The distribution of the analytical methods according to analysed parametersis as follows:

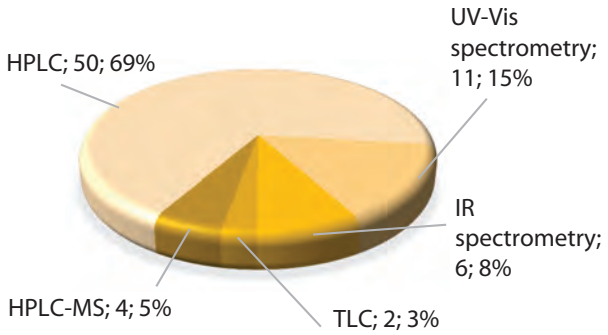


Fig. 24 **Identity of drug substance**

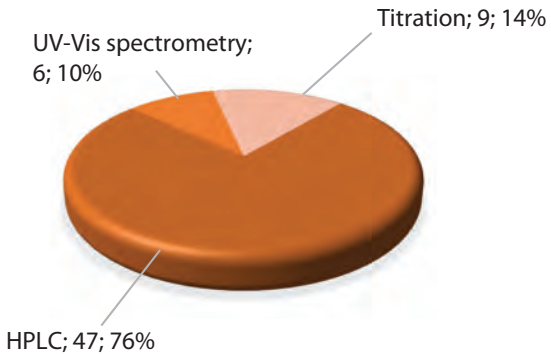


Fig. 25 **Assay of drug substance**

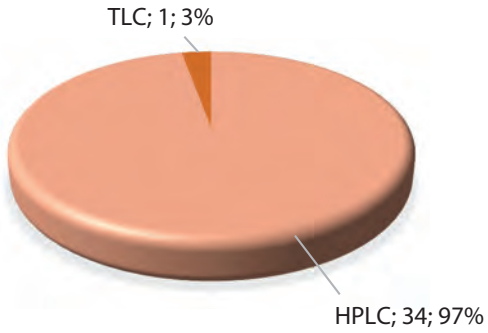


Fig. 26 **Determination of impurities in medicinal products**

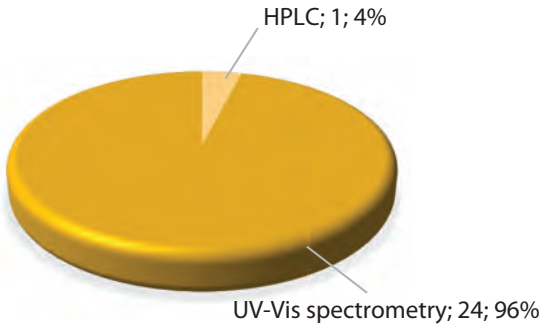


Fig. 27 **Dissolution test for solid dosage forms**

The most used analytical methods were HPLC (132 batches analysed), UV-Vis spectrophotometry (41 batches analysed) and Dissolution test (25 batches analysed).

In 2017, 2 physicochemical and pharmaceutical expertises were prepared with a police/prosecutor's decree for 8 analyzed samples. Based on quality deviation complaints, 8 batches were analysed, 6 of which were food supplements. Physico-chemical analyses of immunological and blood products were performed in connection with the batch release of 15 batches (9 batches of PPD Tuberculin Mammalian and 6 batches of blood products).

In 2017, the BDA also participated in joint programs organized by the European Directorate for the Quality of Medicines & Healthcare (EDQM).

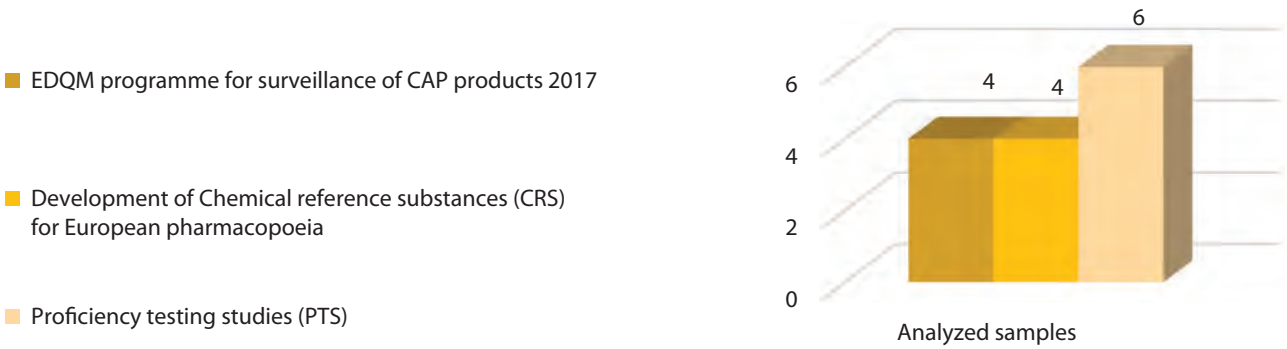


Fig. 28 **Analysed samples for European programs 2017**

Biological analyses

The Agency's 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) and according to the WHO Guideline on Batch Release of Vaccines (WHO TRS No. 978, 2013).

In 2017, 235 certificates for batch release of vaccines and medicinal products derived from human blood or plasma were issued.

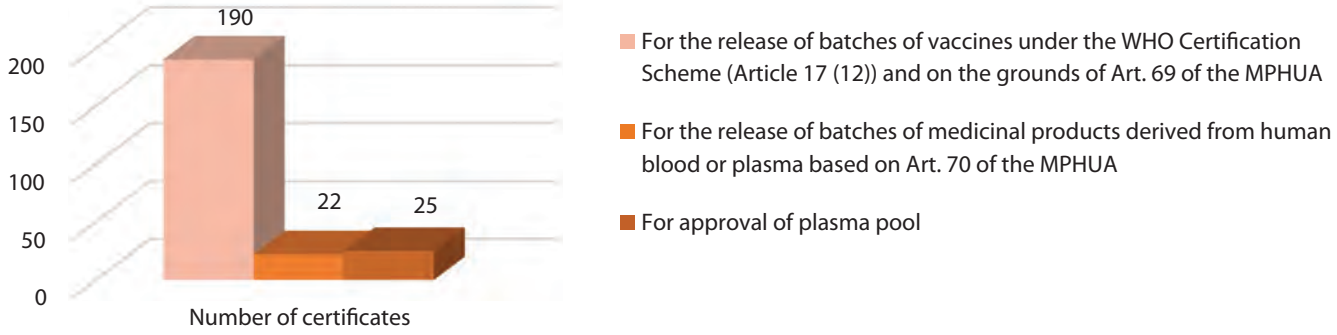


Fig. 29 **Total number of certificates issued in 2017**

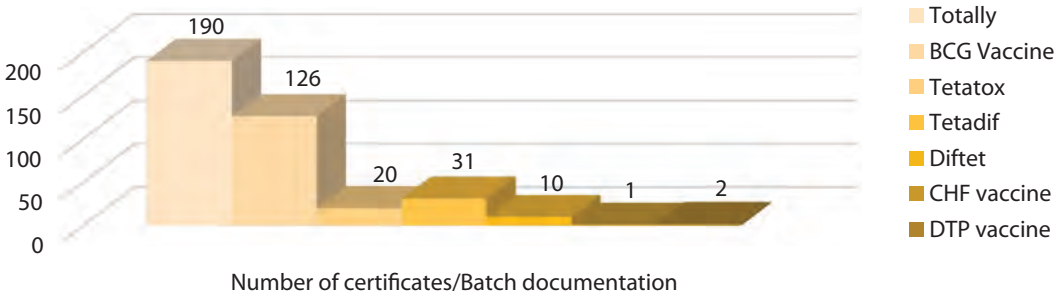


Fig. 30 **Batch release of certificates issued for 2017**

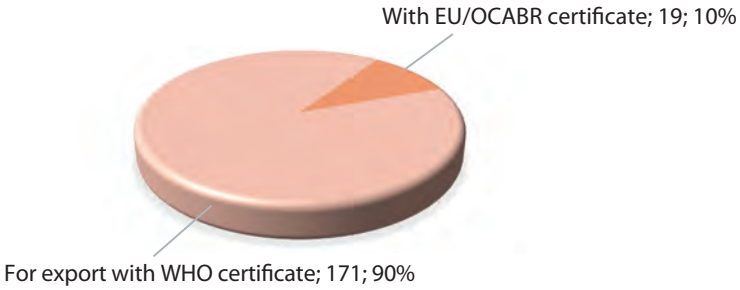


Fig. 31 **Batch release certificates issued with European / EU OCABR and WHO Certificate.**

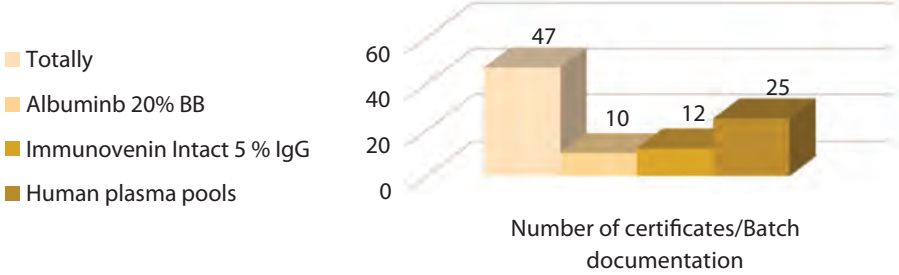


Fig. 32 **Certificates issued for the release of batches of medicinal products derived from human blood or plasma under Art. 70 of the MPHUA**

The total number of samples performed under different procedures was 334. The test results complied with the approved specifications of the medicinal products concerned, with the following exceptions:

- 2 human plasma samples submitted with applications for the issuance of certificate for approval of plasma pool;
- 1 sample of eye drops provided for signal testing;
- 3 batches of PPD Tuberculin Mammalian, which were received with applications for certificate for batch release.

For 2 human plasma pools, a positive result for hepatitis C virus RNA was obtained by the PCR method. Subsequent actions were taken according to the OCABR procedures and internal standard laboratory procedures. In connection with the requirements of the BBDBTA, Chapter V. Transfusion Surveillance and its Ordinances, as well as the recommendations of the Guideline on Plasma-derived Medicinal Products (EMA / CHMP / BWP / 706271/2010), a look-back procedure was started for the follow-up of donors associated with the positive plasma.

For 3 batches of PPD Tuberculin Mammalian, out of specification result for animal activity was obtained. The Marketing Authorization Holder has been notified in writing and no release certificates for the relevant batches have been issued.

The analyses in relation to the release of batches of vaccines and batches of medicinal products derived from human blood or plasma were **303** as follows:

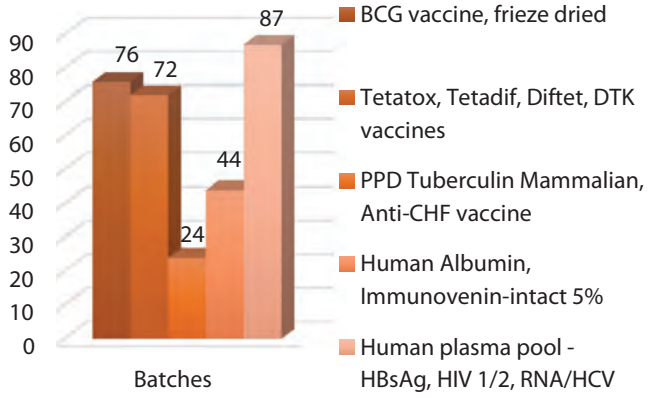


Fig. 33 **Analyzes in relation to the batch release of vaccines and medicinal products derived from human blood or plasma**

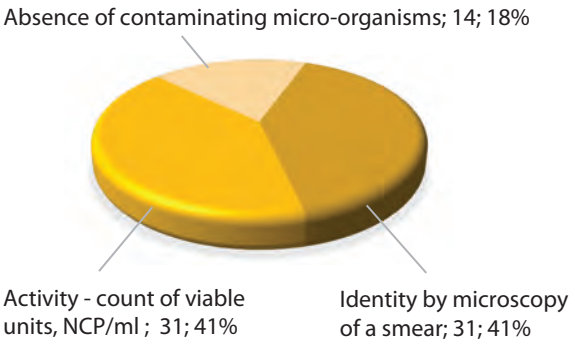


Fig. 34 **Analyses BCG vaccine, frieze dried**

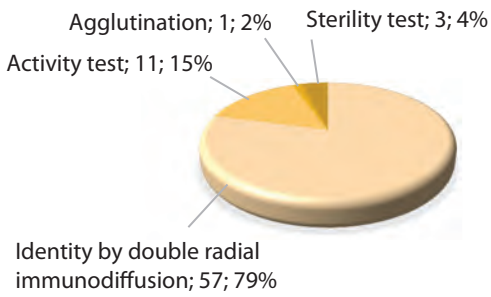


Fig. 35 **Analises of Tetatox, Tetadif, Diftet, DTK vaccines**

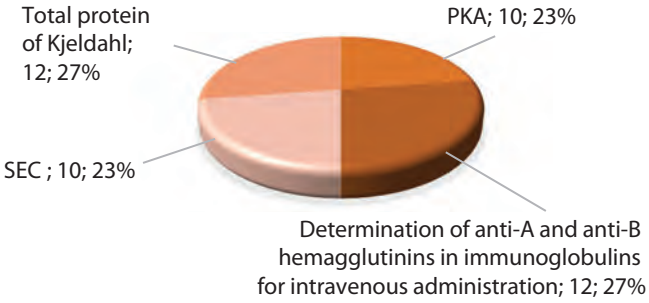


Fig. 36 **Analyses of Human Albumin, Immunovenin-intact 5%**

All batches of vaccines and medicinal products derived from human blood or plasma samples (a total of 235) were evaluated for the appearance, primary, secondary packaging and patient information leaflet.

During 2017, 82 Notifications of placing on the market of batches of vaccines and 235 Notifications of placing on the market of batches of medicinal products derived from human blood or plasma were issued.

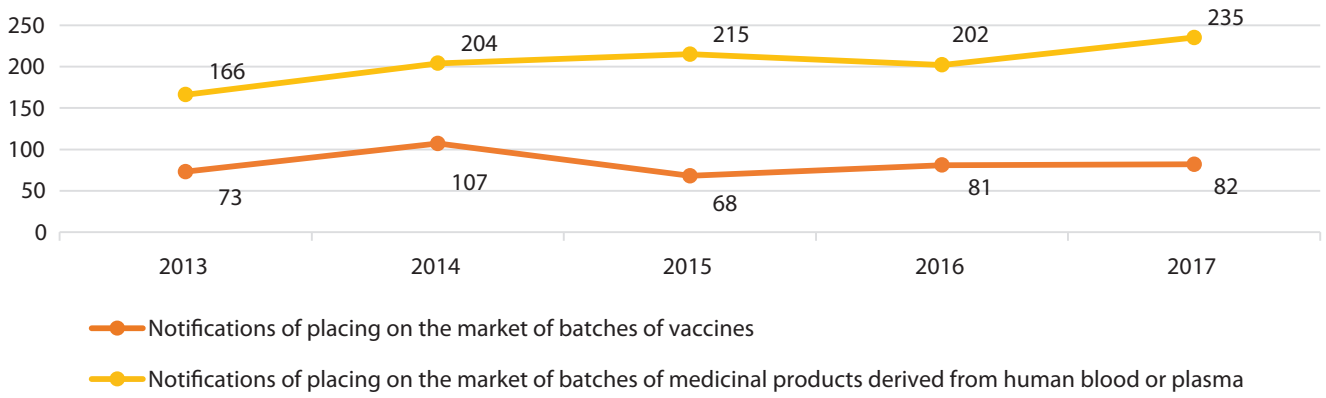


Fig. 37 **Notifications of placing on the market of batches during 2013-2017**

2.5 PHARMACOPOEIAL ACTIVITIES

The 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 for 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, the 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, a 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 Executive Director. The 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 2017, draft documents for implementation were prepared. Texts on pharmacopoeial requirements on the territory of Bulgaria were revised and deleted.

BDA's website was updated and were published:

- ✓ Order of the Minister of Health to cease the action of the following monographs:
  - *Cholera vaccine (0154);*
  - *Cholera vaccine (freeze dried) (0155);*
  - *Typhoid vaccine (freeze dried) (0157);*
- ✓ the Order of the Minister of Health to enter into force of the supplements (9.4.-9.6) to the 9th edition of the European Pharmacopoeia;
- ✓ the Order of the Minister of Health concerning the rapid implementation of the revised version of the monograph on Erythromycin ethylsuccinate (0274);
- ✓ the lists of translated monographs titles of the European Pharmacopoeia on:
  - *Herbal drugs and herbal drug preparations (up to suppl. 9.3);*
  - *Homoeopathic preparations (up to suppl. 9.3);*
  - *Vaccines for human use (up to suppl. 9.0);*
  - *Active substances and excipients (up to suppl. 9.2).*

The standard terms of dosage forms, packaging, routes and methods of administration were also translated into Bulgarian.

In connection with proposals by the European Pharmacopoeia Secretariat about the working programs of the expert groups, the BDA answered 66 surveys and sent information on substances/monographs, national pharmacopoeia requirements and good pharmacopoeial practices.

In 2017, the BDA experts participated in two meetings of the European Pharmacopoeia Commission - EDQM

in Strasbourg, France and in the annual meeting of the secretaries. Bulgarian experts participated in GR 7, GR 12, GR 13A, PaedF WP and WP EXP working groups of the European Pharmacopoeia Commission.

2.6 PHARMACOVIGILANCE

Adverse Drug Reactions Reports

A part of the BDA responsibilities includes assessment of the received Individual Case Safety Reports (ICSRs). In 2017, the number of the initial as well as the follow up reports that were received, managed and assessed increased in comparison to the previous year. The total number of ICSRs in 2017 was 1 200, the initials being **850** and the follow ups - **350**.

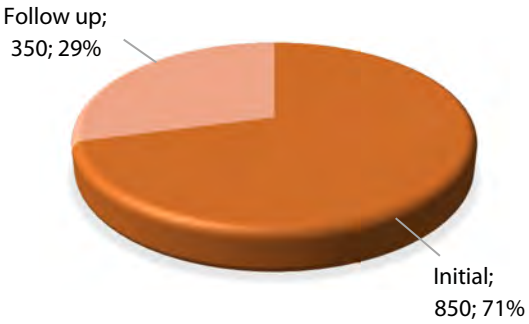


Fig. 38 **Received, processed and assessed initial Individual Case Safety Reports (ICSRs) and follow-ups – 1 200 valid reports in total**

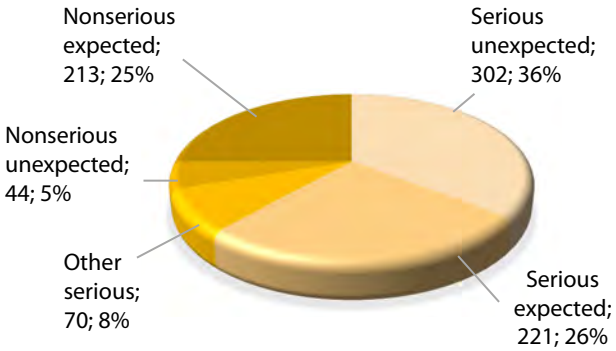


Fig. 39 **Correlation between the received ADRs in respect of seriousness and expectedness**

In relation to the announcement of the *EudraVigilance* functionality, the reporting of ICSRs to EMA was temporarily stopped in 08 -21 November 2017. It was resumed in accordance with the new rules. Before introducing the new rules, national experts were trained and the system was tested together with EMA.

A tendency is observed towards increase of the reporting activity and as result the number of valid ICSRs increased from **799** in 2016 to **850** in 2017.

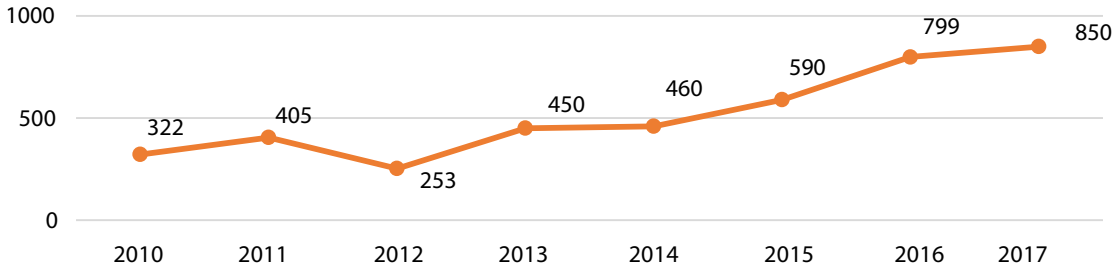


Fig. 40 **Valid ADR case reports**

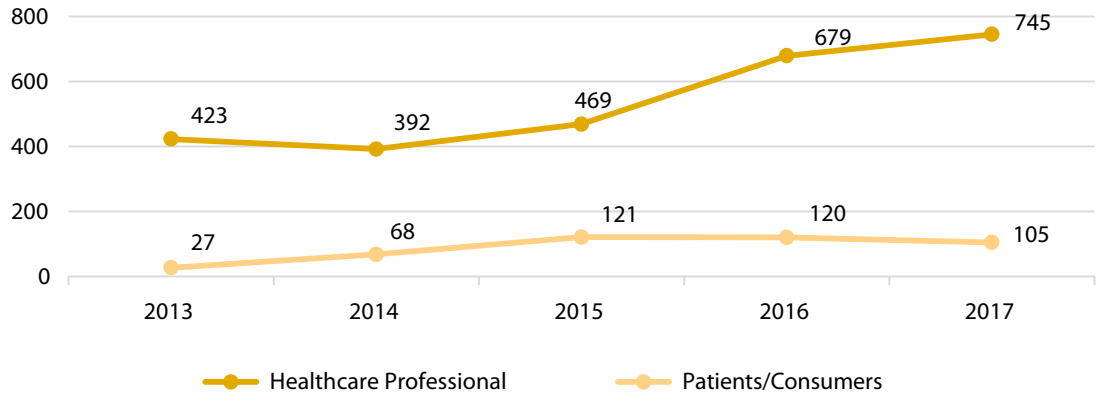


Fig. 41 **Tendency in reporting according to the primary source of information**

The reporting activity of healthcare professionals (HCPs) was continuously increasing and reached **745** reports in 2017. The number of patient's reports was **105**, which is a slight decrease compared to 2016. The Marketing Authorization Holders sent the biggest share of reports (624). Directly reported to BDA were **121** reports by healthcare professionals and 105 reports by patients.

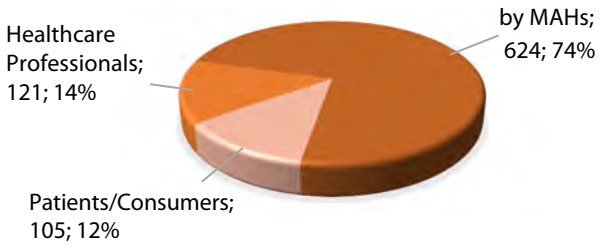


Fig. 42 **Reports received in the BDA according to the source of information in 2017**

The adverse events following immunizations (AEFIs) were 7%. The number of AEFIs by patients continued increasing and reached 50% of all reported AIFIs in 2017.

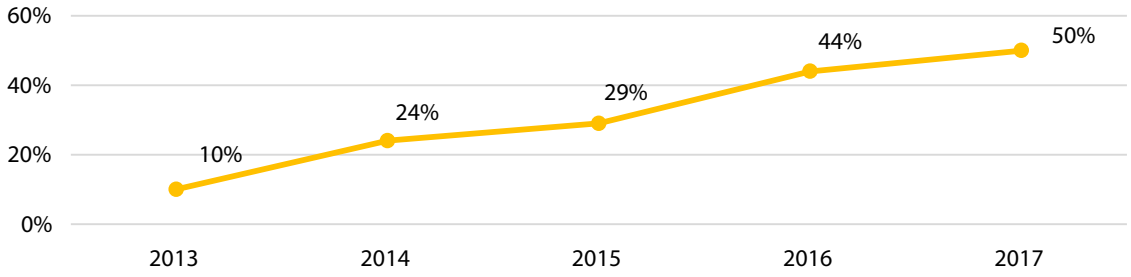


Fig. 43 **Percentage of the AEFIs reported by patients/consumers during 2013-2017**

Information activities related to pharmacovigilance and risk communication

In 2017, BDA evaluated 61 Educational Materials and additionally agreed on 25 Direct Healthcare Professionals Communication letters. On the BDA website, were published 18 press releases on safety issues and an *Adverse drug reactions* bulletin.

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

In 2017, NPRAC held 11 meetings prepared and chaired by BDA. The 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 with scientific assessment of several national ADRs cases was provided.

Training activity and participation in scientific fora

In 2017, two lectures in the field of pharmacovigilance were delivered for students at the Pharmacy faculty. A presentation within an educational program on pharmacovigilance organized by the Bulgarian Association for Drug Information was performed for industry representatives. A lecture on how to report adverse drug reactions was presented for patient's organizations.

2.7 CLINICAL TRIALS

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

In 2017, BDA received 212 Applications for Clinical trial authorization and 894 Applications for Substantial amendment approval. The total number of applications was 1 106.

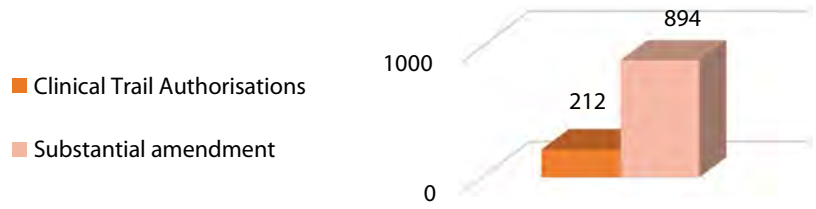


Fig. 44 **Applications received in 2017**

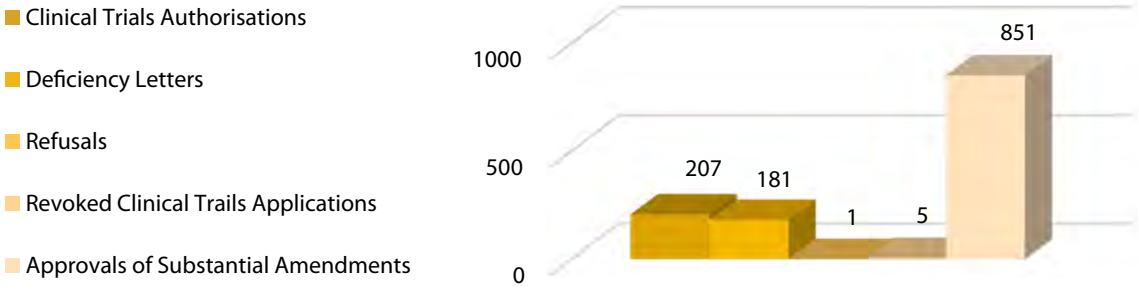


Fig. 45 **Applications assessed in 2017**

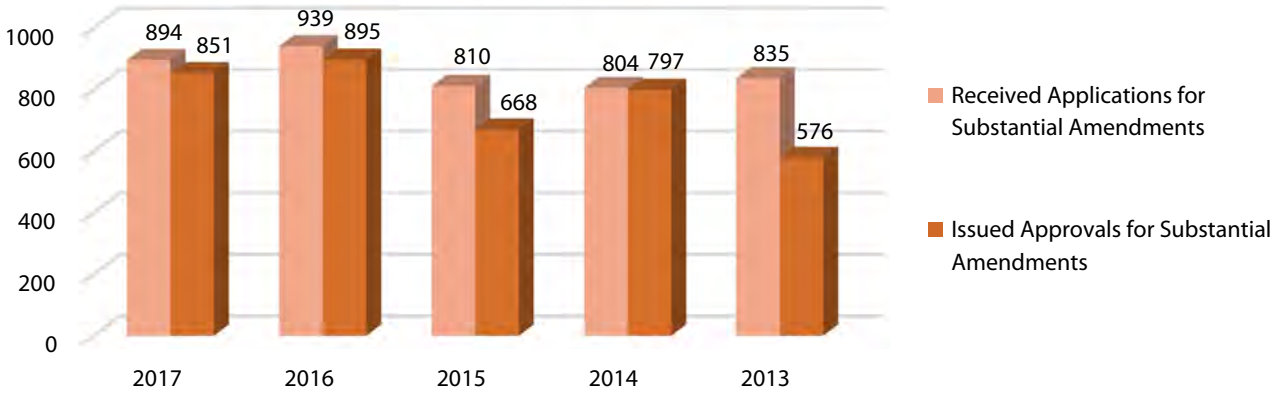


Fig. 46 **Substantial Amendments during 2013-2017**

The tendency of the higher number clinical trials in oncology, neurology, haematology and psychiatry remains the same.

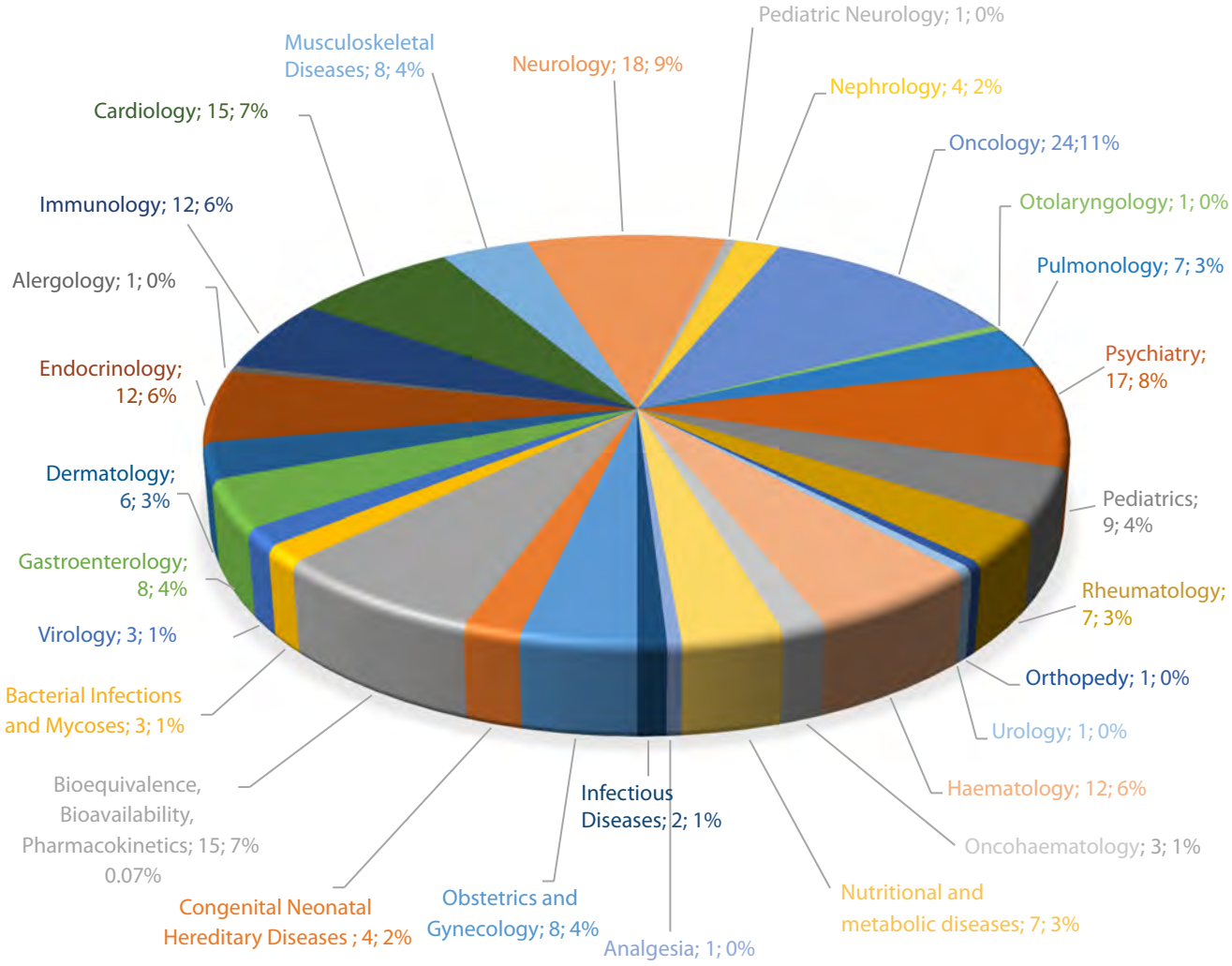


Fig. 47 **Clinical trials by therapeutical area**

The predominant type of clinical trials by phase is in phase 3.

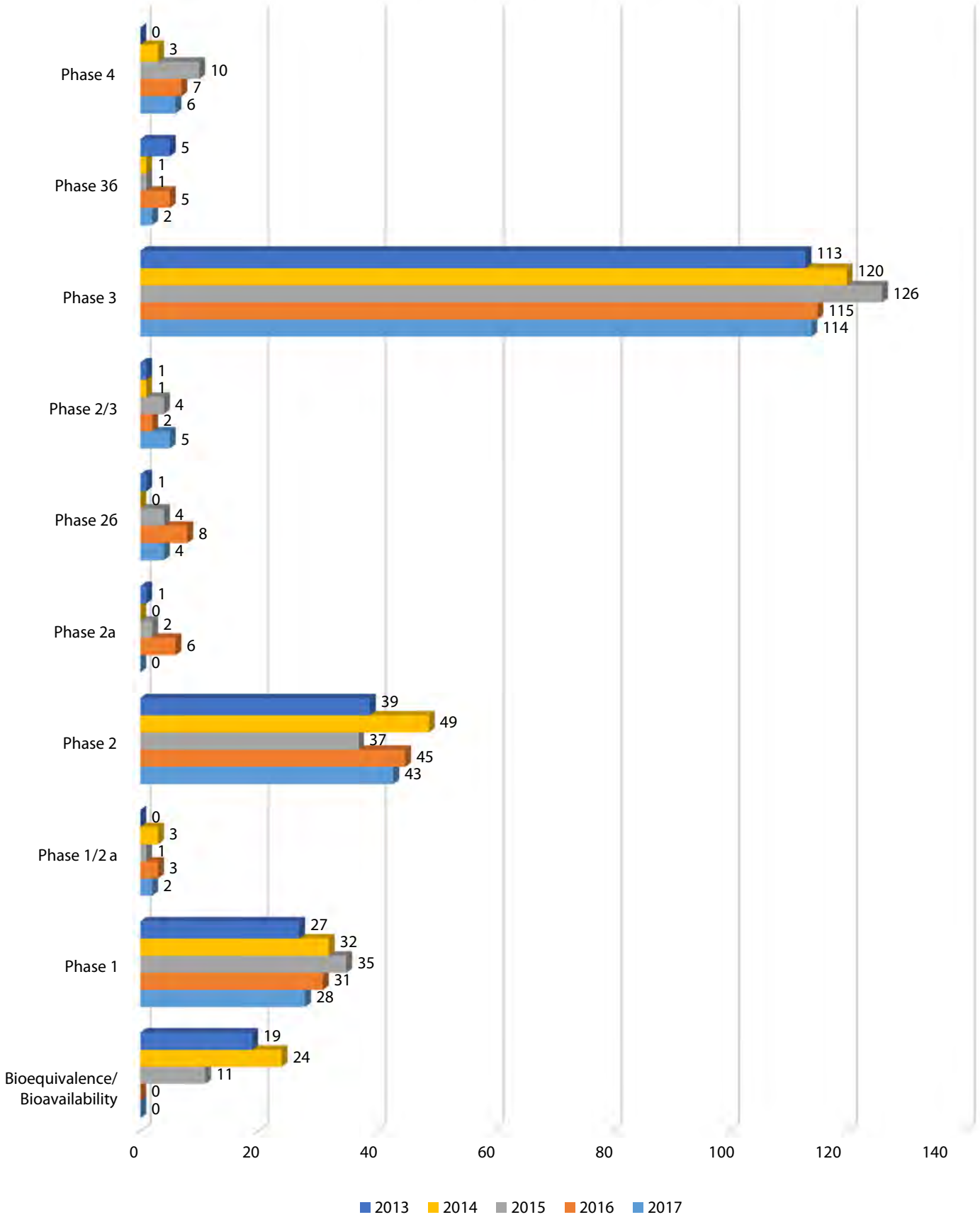


Fig. 48 **Clinical trials by phase**

Clinical Trials Safety

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

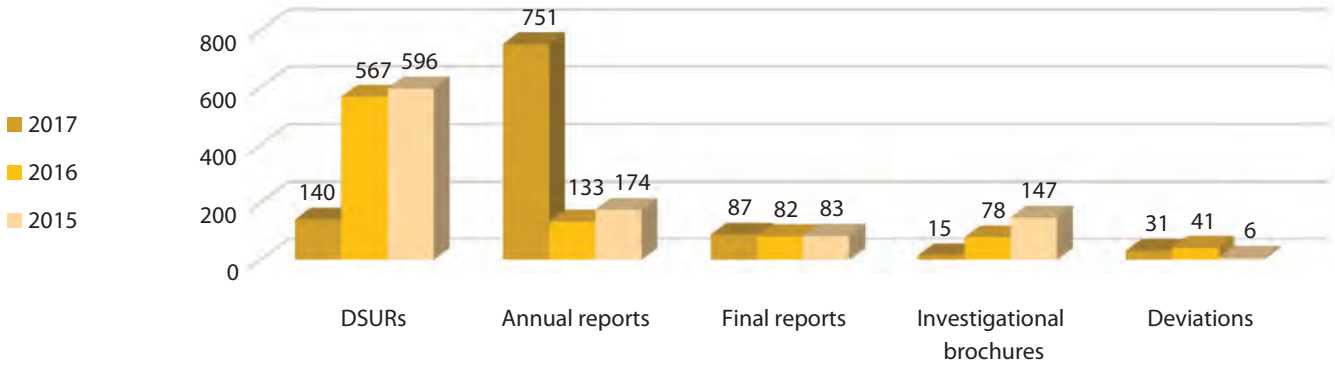


Fig. 49 **Clinical Trials Safety Documentation for 2015-2017**

2.8 NON-INTERVENTIONAL RESEARCH

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.

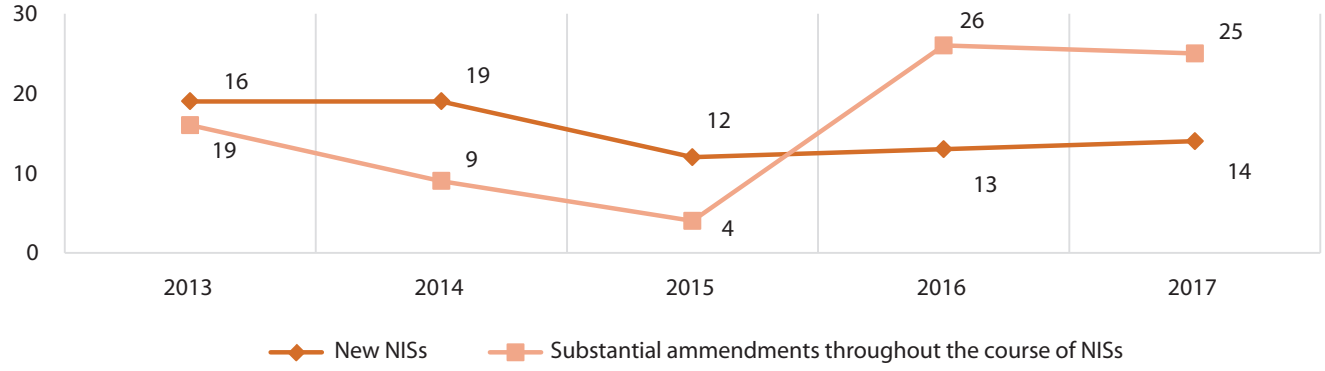


Fig. 50 **Assessment of NIS documents for the period 2013-2017**

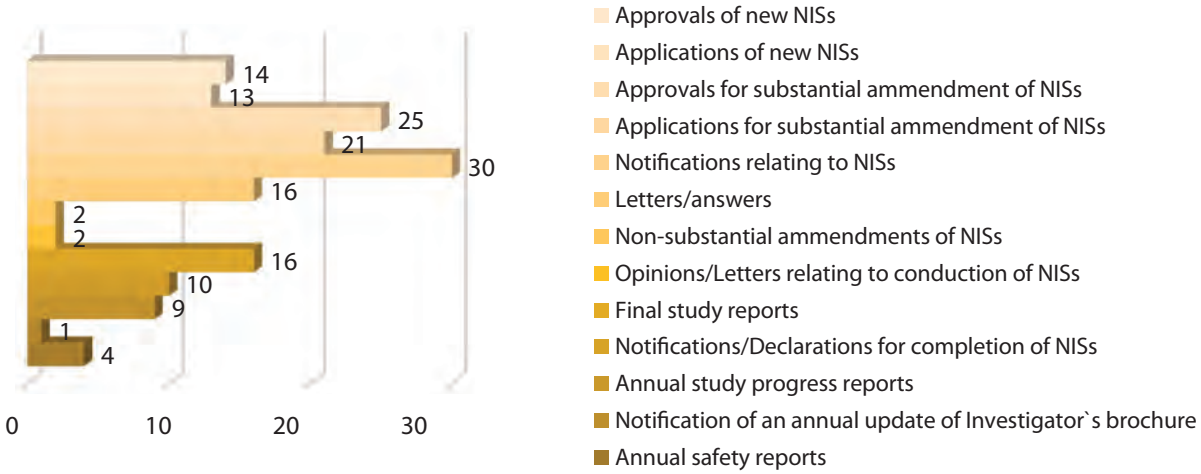


Fig. 51 **Activities on NIS assessment 2017**

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.

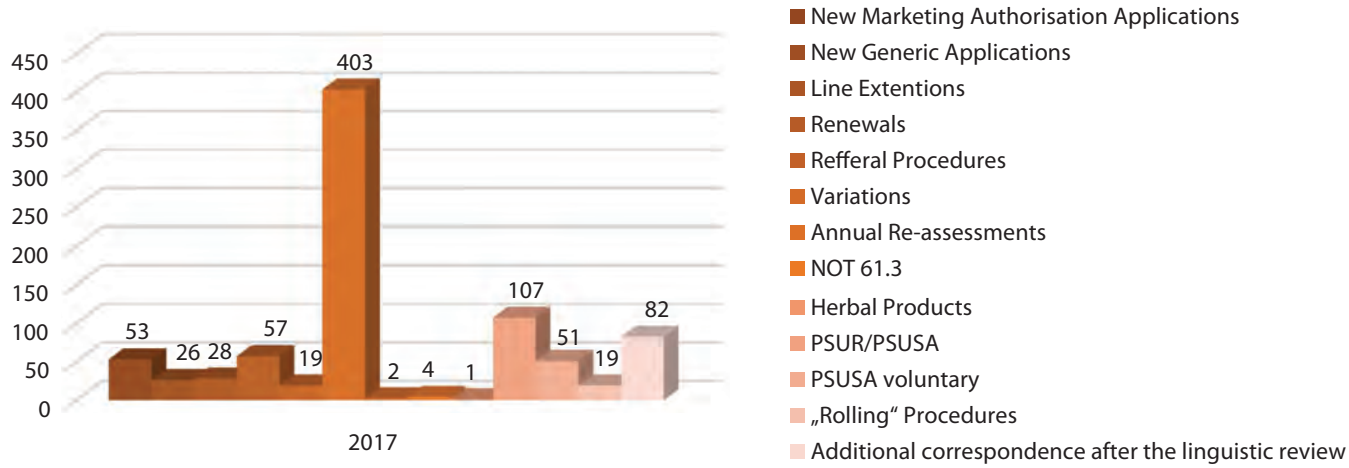


Fig. 52 **Procedures within the scope of the post-opinion linguistic review/assessment 2017**

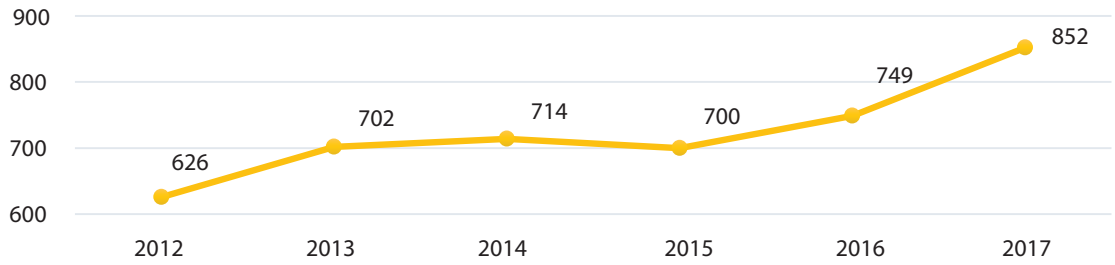


Fig. 53 **PIs reviewed under the centralised procedure 2012 – 2017**

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

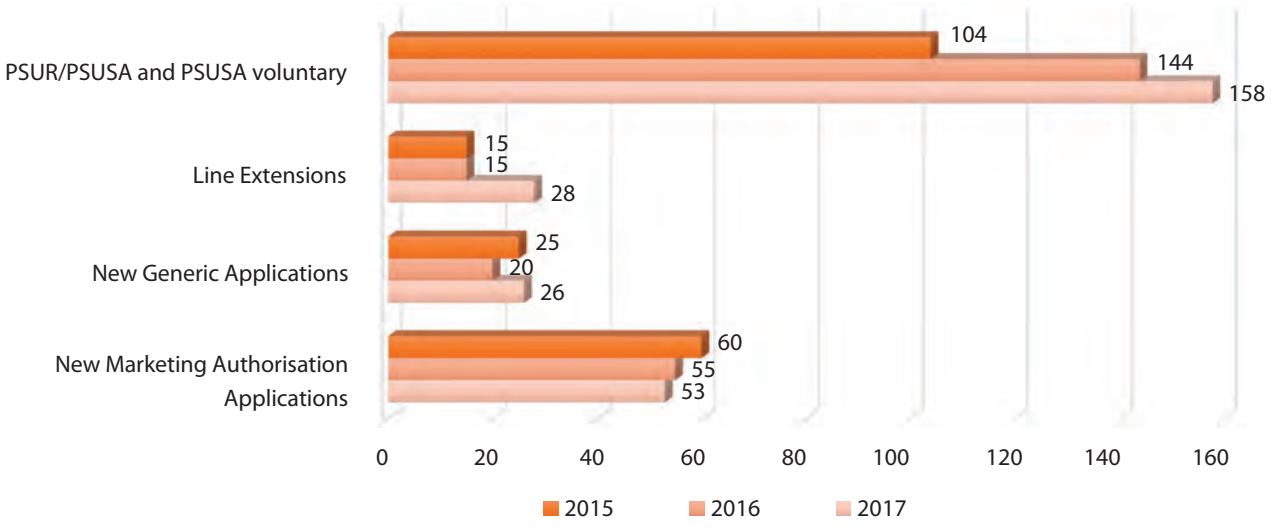


Fig. 54 **Comparative analysis 2015-2017**

For the period 2015-2017, 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.

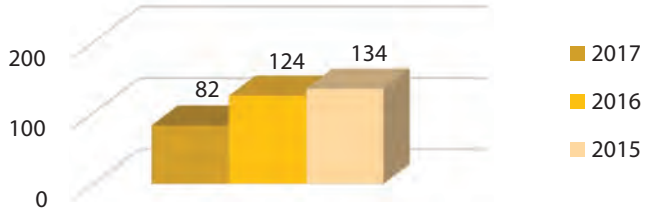


Fig. 55 **Procedures subject to further discussion 2015-2017**

Linguistic review of Product Information

According to an annual agreement with EMA, in 2017 the BDA performed linguistic review of Product Information of centrally authorised products. The Product Information consists of Summary of Product Characteristics, Labelling and Package Leaflet.

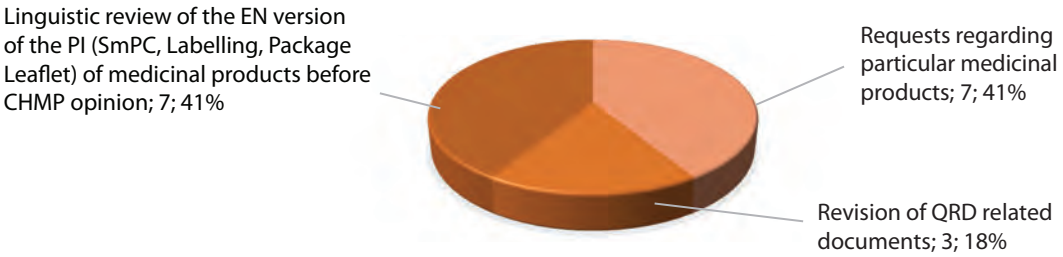


Fig. 56 **Opinions on documents and revisions of documents related to the EMA QRD activities 2017**

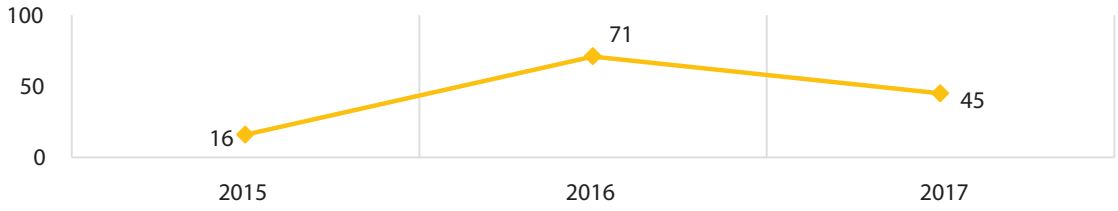


Fig. 57 **Assessment of Readability Tests of Patient Leaflets 2015-2017**

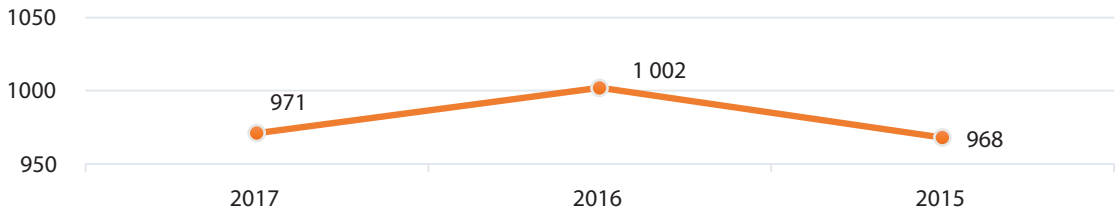


Fig. 58 **Number of updates in the List of Authorized Medicinal Products which are not subject to medical prescription 2015 2017**

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.

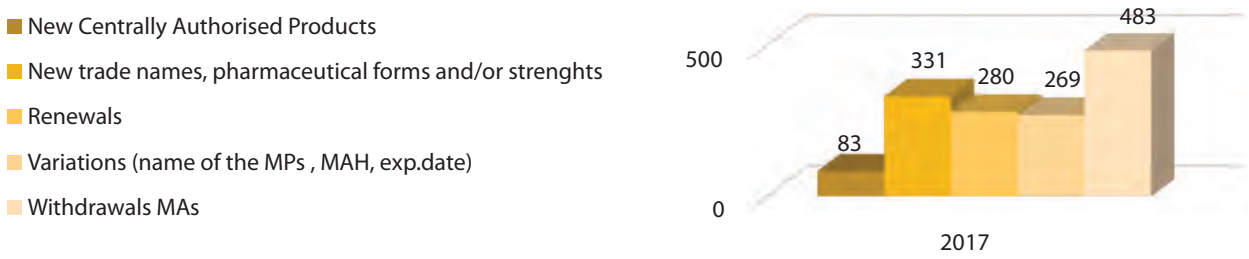


Fig. 59 **Regulatory Bulletin entries in 2017**

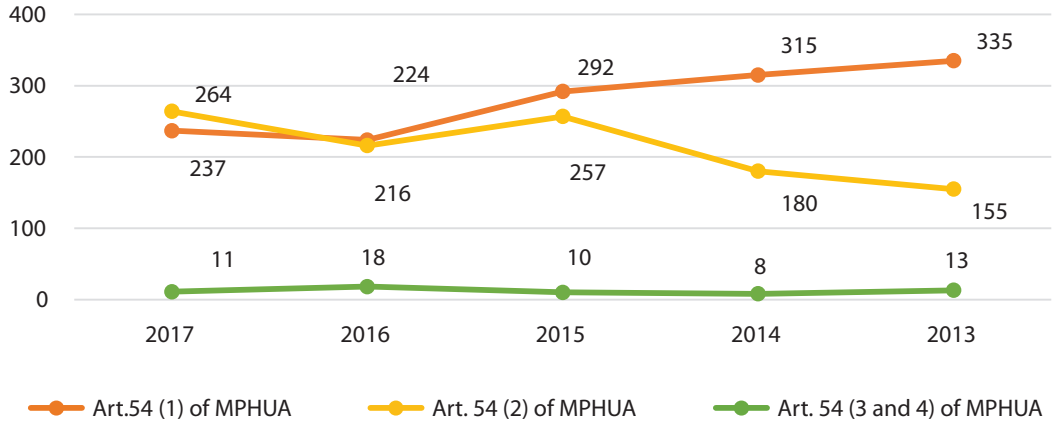


Fig. 60 **Submitted notifications 2013 2017**

In 2017, 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 2017, 790 opinions regarding the import of unauthorised in the country medicinal products under the Ordinance № 10 were issued.

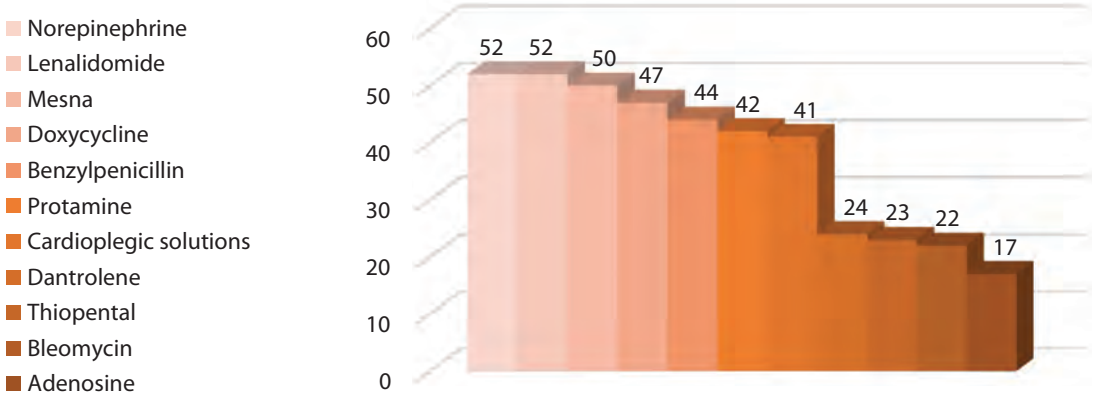


Fig. 61 **Medicines (INNs) for which opinions were most frequently issued in 2017**

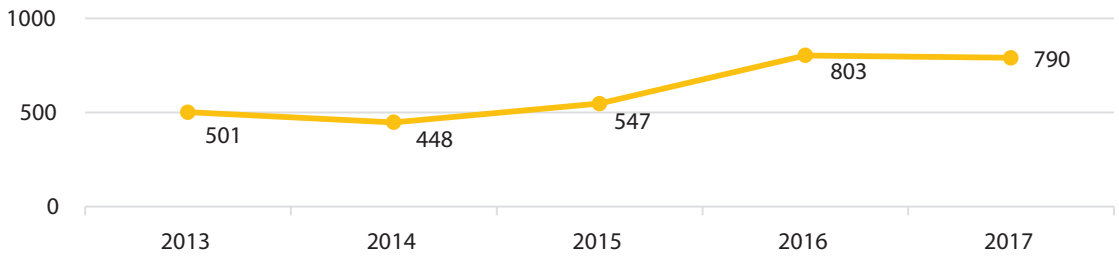


Fig. 62 **Issued opinions regarding the import of unauthorised medicinal products under Ordinance №10 2013-2017**

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.

Inspections

In compliance with the approved schedule for inspections in 2017, there were carried out 56 routine inspections in healthcare facilities 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.

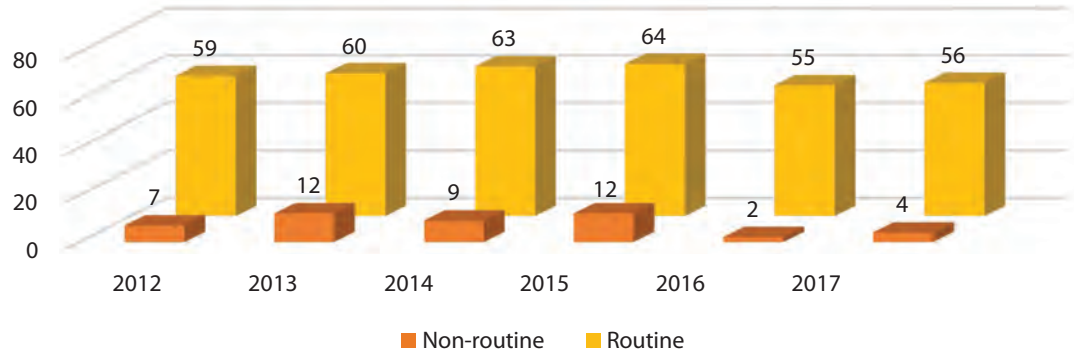


Fig. 63 **Inspections**

The subject of the inspections in 2017 were the main activities and basic characteristics of the blood establishments - Regional Centers of Haematology (RCH), the Haematology Wards (HW) and the Haemotology Laboratories (HL) 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. The clinical use of blood and blood components and haemovigilance were also inspected.

The number of the found non-compliances varies during the years as shown:

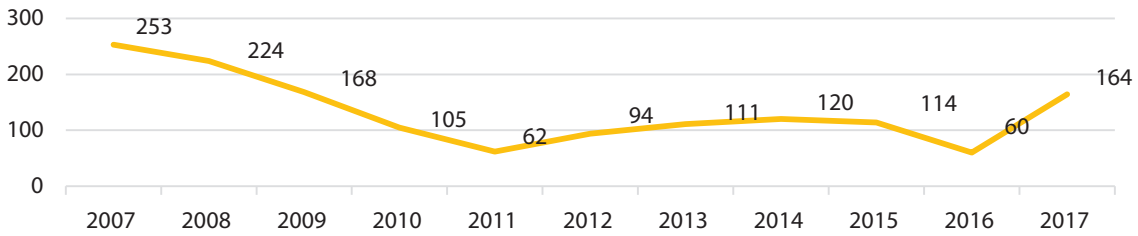


Fig. 64 **Number of non-compliances by year**

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 2017 due to the introduction of the Good Practice Guidance by the Council of Europe.

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 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 2017, the BDA received 772 reports for adverse reactions as follows:

Fig. 65 **Ratio between the adverse reactions in recipients and in donors**

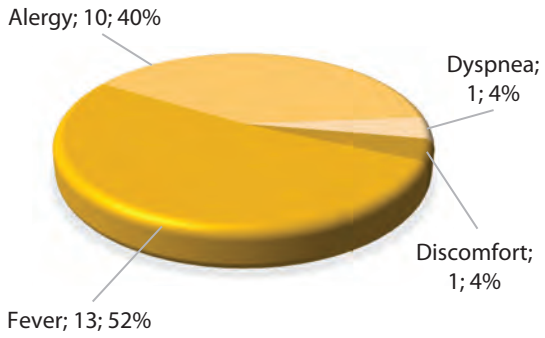


Fig. 66 **Type of adverse reactions in recipients**

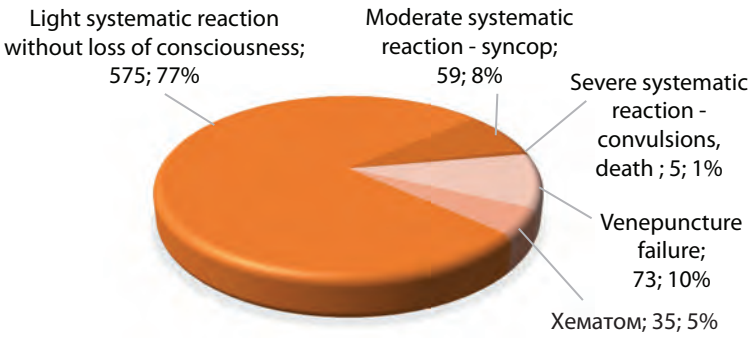


Fig. 67 **Type of adverse reactions in donors**

In 2017, the BDA received 25 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 2016, the number of the reported adverse reactions decreased as the tendency is evident from 2015.

In 2017, the BDA received 747 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. In 2017 there is an increase in the number of failed venipunctures. These reactions were reported by the

blood establishments and the information about them was received by the BDA in a timely manner.

Pursuant to the requirements of the European directives relating to the collection, testing, processing, storage and transfusion of blood and blood components 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 taken. In this regard in 2017 the BDA, after receiving information via the Rapid Alert System, has informed all transfusion units about cases of West Nile Virus (WNV) in other Member States as well as the guidelines of the measures taken by blood transfusion systems of each of the countries.

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 2017, the transfusion system disposed of or transmitted for scientific use 5 033 units of whole blood or blood components (incl. erythrocyte concentrate, fresh-frozen plasma or platelet concentrate). The comparison to 2016 shows an increase of the disposed of or handed over for scientific purposes units with 91.

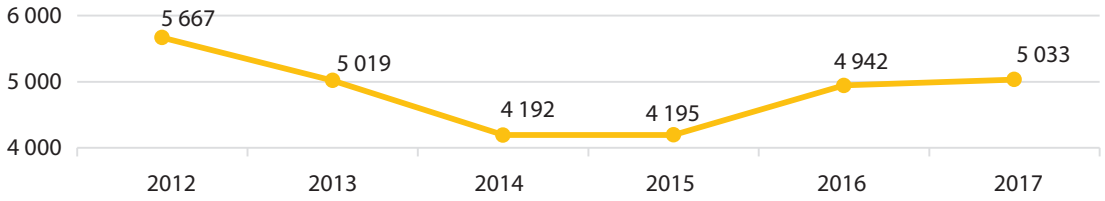


Fig. 68 **Disposal of blood and blood components during 2012-2017**

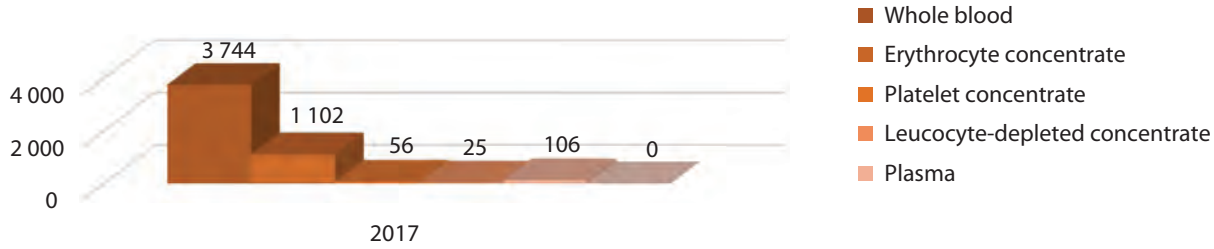


Fig. 69 **Disposal of blood and blood components by type in 2017**

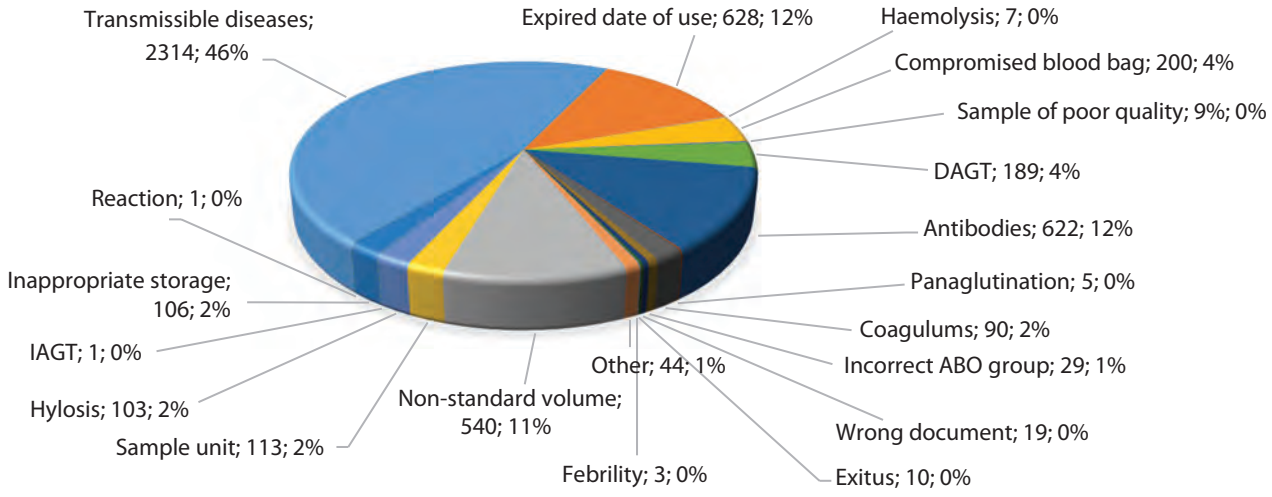


Fig. 70 **Disposal of blood and blood components by reason in 2017**

In 2017, 74% of all disposed of units were whole blood (no components were produced). The data show 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.

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 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 2017 was 21 122 180 BGN as the approved budget was 21 000 000 BGN and the implementation is 101%.

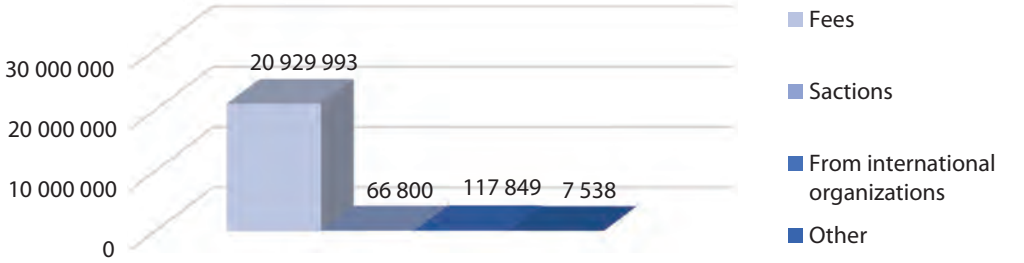


Fig. 71 **Income in 2017**

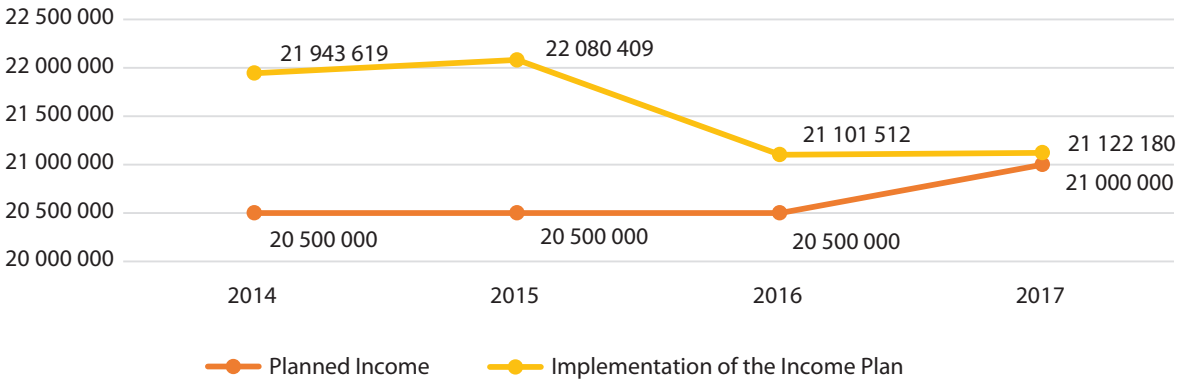


Fig. 72 **Comparison between the planned income and the implementation of the income plan during 2014-2017**

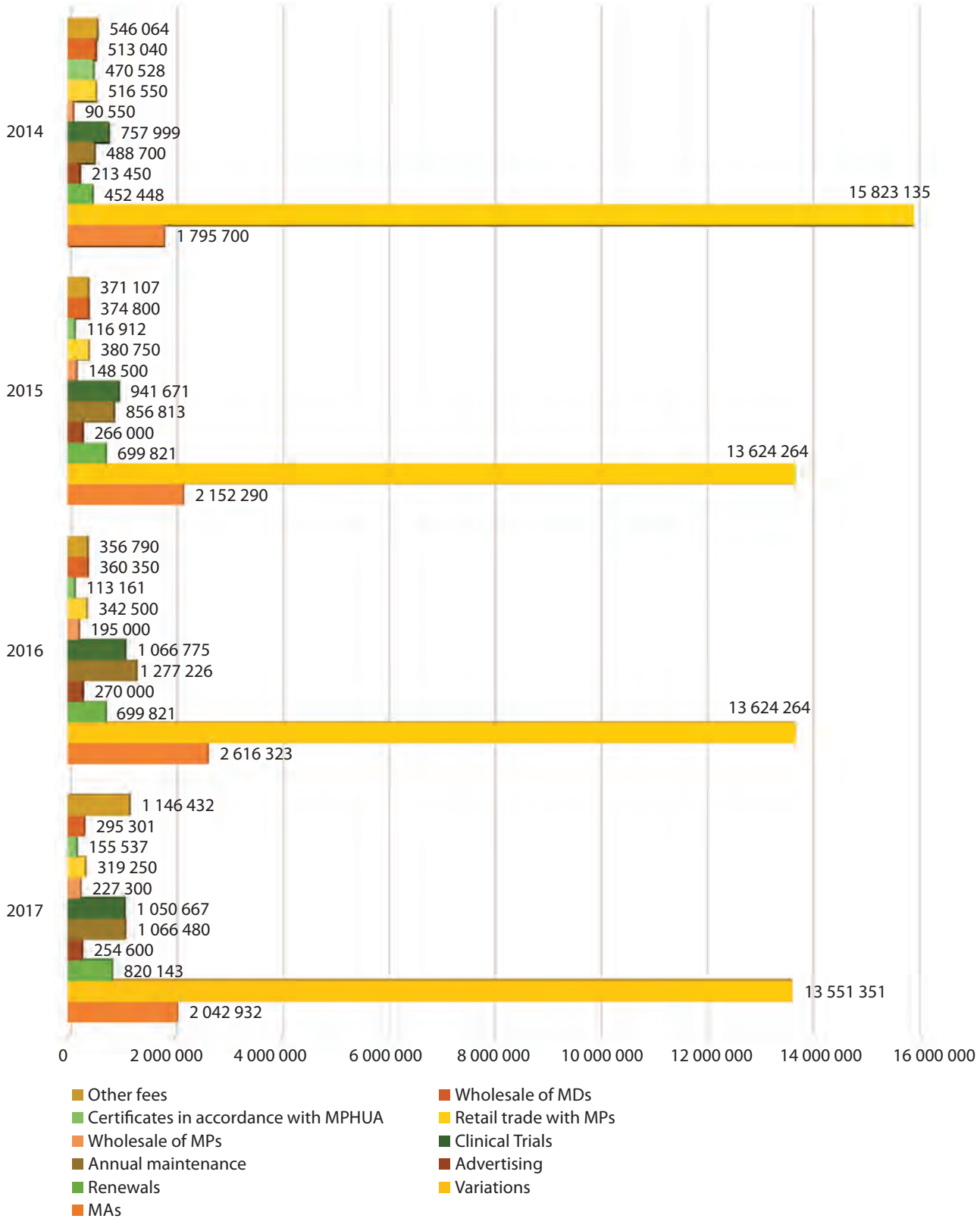


Fig. 73 **Structure of the state fees income in 2014-2017 by administrative service**

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

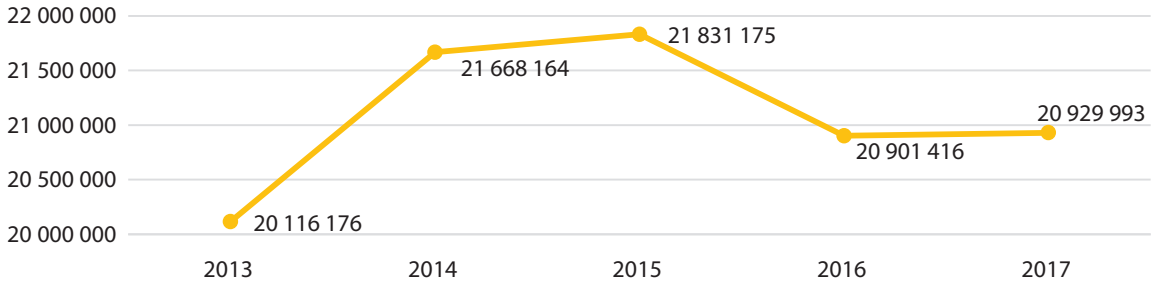


Fig. 74 **Comparison of the income from state fees during 2013-2017**

The overall trend of reduction of revenue from state fees is maintained compared to 2014 and 2015.

Expenses

The total amount of expenses for 2017 is 5 245 350 BGN as the approved budget was 5 464 300 BGN. The implementation is 96%. The saving are 218 950 BGN or 4%.

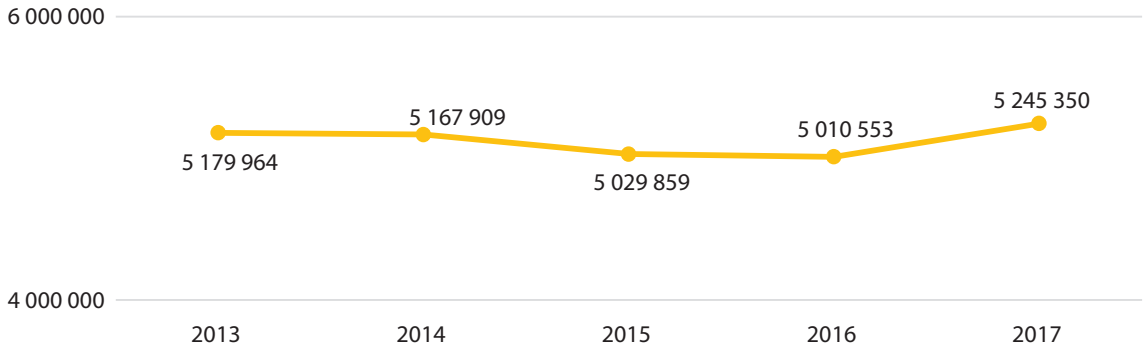


Fig. 75 **Expenses during 2013-2017**

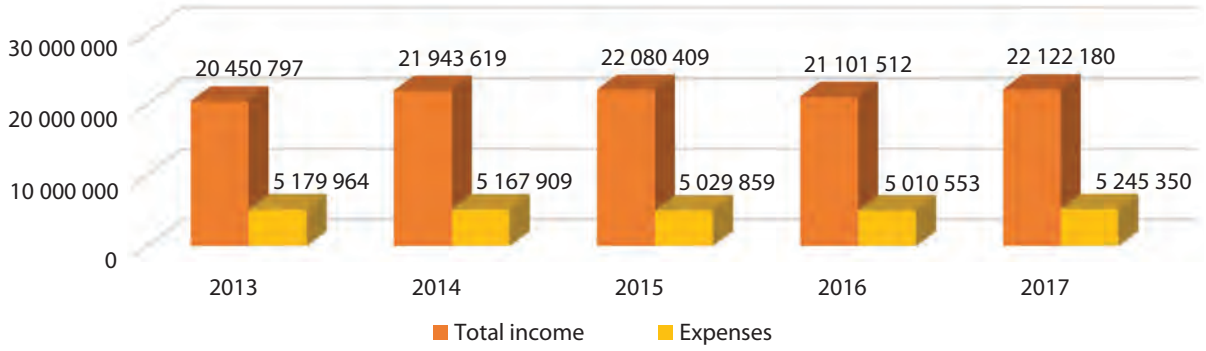


Fig. 76 **Income and expenses during 2013-2017**

Effectiveness

The efficiency of expenditure is 4.03 and the planned by the budget efficiency was 3.83. Each 1 BGN of expenses „brought" 0.20 BGN additional income. The additional effect is 5%. There is a slight decrease in efficiency justified by objective factors, namely the reduction of the revenues from state fees, the increase in the expenses due to the increase in the amount of the payment to the Pensions Fund and the raise of the Minimal Salary in 2017.

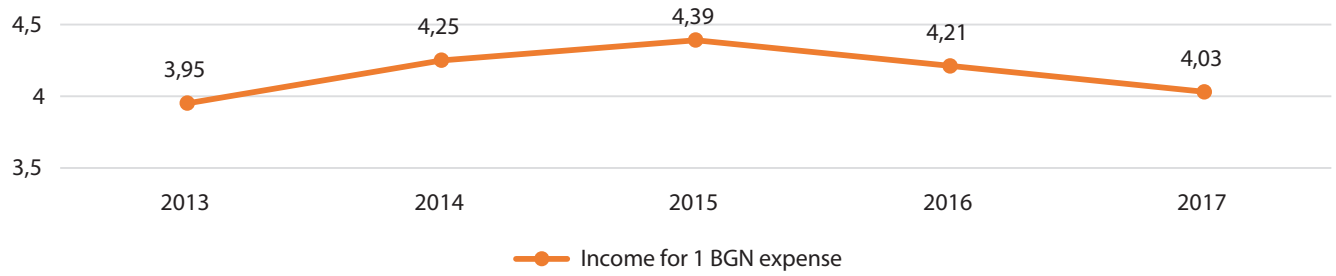


Fig. 77 **Agency's effectiveness for 2013-2017**

4. ADMINISTRATIVE SERVICES

In 2017, **57 845** documents were registered in the Automated Information System (AIS) DOCMAN©2.

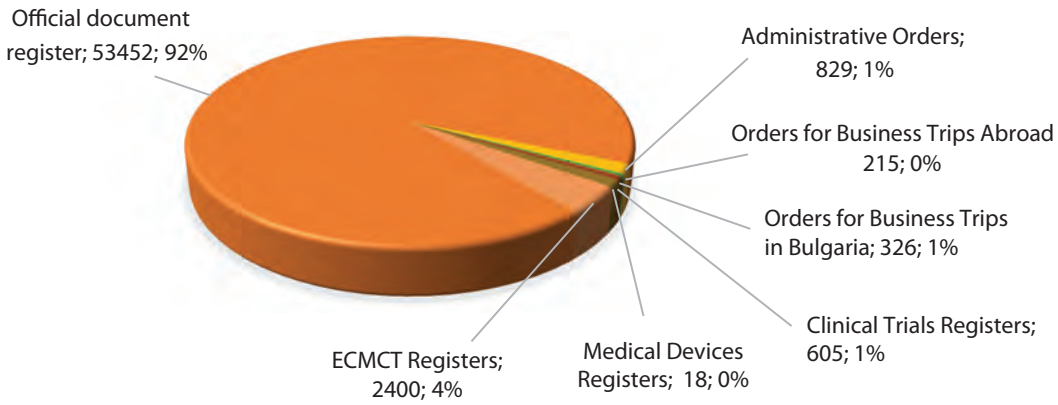


Fig. 77 **Agency's effectiveness for 2013-2017**

In July 2017, the Agency became responsible for the technical provision of the Ethical Commission for Multicenter Clinical Trials (ECMCT) activities.

5. PROCEDURES FOR AWARDING PROCUREMENTS

In 2017, the Agency conducted 3 procedures for awarding procurements under the Public Procurement Act (PPA):

1. Provision of plane tickets for transport by air of passengers and luggage, hotel reservations and accommodation in cases of business trips for the needs of the Bulgarian Drug Agency (BDA).

2. Delivery of net electric power and selection of coordinator of a balancing group for the needs of the BDA.

3. 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 Automatic Washing System for ELISA microtiter plaques.

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 Regu-

lation 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 46 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:

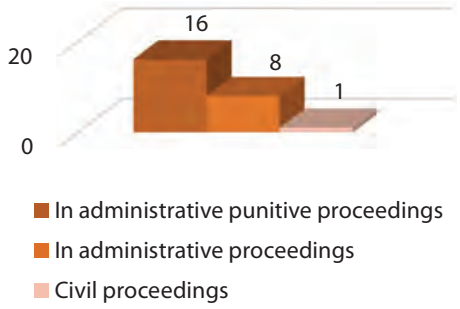


Fig. 79 **Enforced court decisions/definitions**

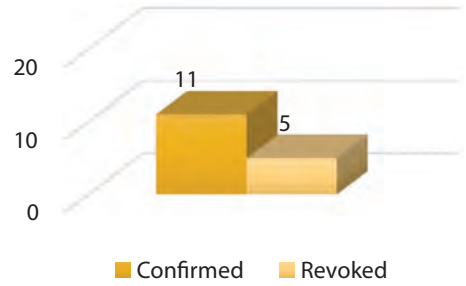


Fig. 80 **Administrative punitive cases**

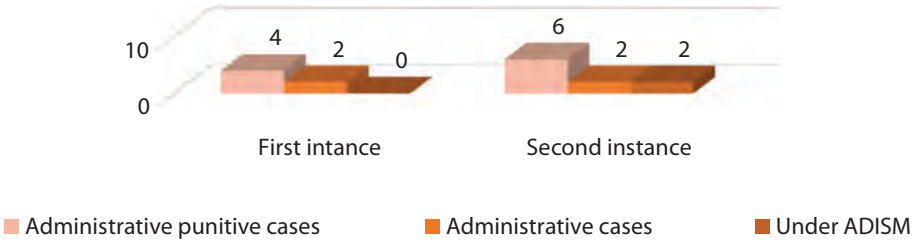


Fig. 81 **Pending proceedings**

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. Regarding filed civil claims, the responses were prepared and relevant evidence was engaged in the court proceedings.

Validation of the lawfulness of acts of the Executive Director

The legal division 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. They prepare and/or validate orders within the Executive Director's powers.

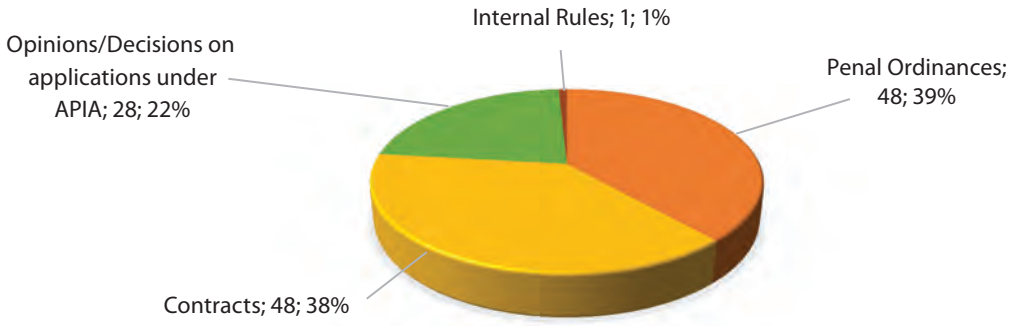


Fig. 82 **Prepared/validated documents**

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

In 2017, "Instruction on measures to protection of personal data which Bulgarian Drug Agency collects, processes, stores and provides" was developed and approved.

Participation in commissions and working groups

The legal advisors participate as chairs and members of competition commissions for conducting competitions for appointment of civil servants under Civil Servants Act and Ordinance on Conducting the Competitions of Civil Servants. They validate and control the lawfulness of employment contracts, civil contracts and other acts related to formation, alteration and termination of employment contract relationships between the Agency and the civil servants.

Other activities

The legal advisors gave day-to-day legal advice on cases in relation to the Agency's activities including inspections. They also prepared written and verbal opinions on applications, signals and complaints by citizens and legal entities, Administration of the President, National Assembly, Ministry of Health, Regional Prosecutor's Offices, Courts and Customs offices. They prepare opinions and give advice on submitted applications and the relevant procedures according to the permitting and registration regimes under the MPHUA, MDA and BBDBTA.

7. HUMAN RESOURCES MANAGEMENT

Personnel

In 2017, BDA appointed 10 new employees. There were11 employees who resigned, including those who retired.

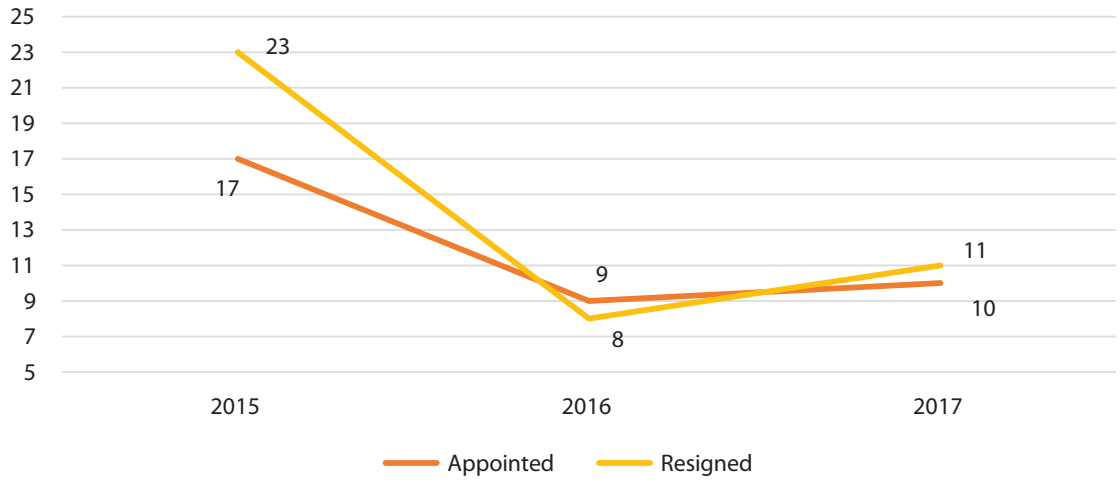


Fig. 83 **Appointed and resigned employees in 2015 - 2017**

The Agency held **9 competition procedures for vacant positions** and **8 selection procedures for promotion** as follows:

Competition procedures for vacant positions:

- **junior expert** in *Medicinal Products Information* Division at *Medicinal Products Information and Noninterventional Researches* Department;
- **junior expert** in *Validation and Community Procedures* Division at *Marketing Authorizations of Medicinal Products* Department;
- 2 competition procedures for one position of **senior expert** in *Quality, Pre-clinical and Clinical Assessment Division* at *Marketing Authorizations of Medicinal Products* Department;
- **chief expert** in *Quality Management, Administrative and Information Technology Services* Division at *Legal, Administrative, Financial Services and Quality Management* Department;

- **chief expert** in *Quality, Pre-clinical and Clinical Assessment* Division at *Marketing Authorizations of Medicinal Products* Department;
- **junior expert** in *Quality, Pre-clinical and Clinical Assessment* Division at *Marketing Authorizations of Medicinal Products* Department;
- **junior expert** in *Control of Blood Transfusion System* Department;
- **senior expert** in *Control of Blood Transfusion System* Department.

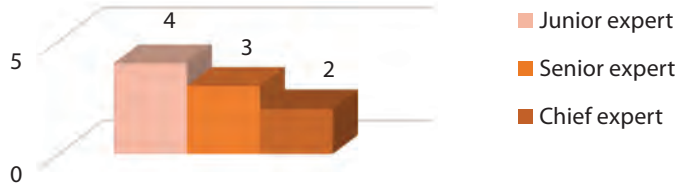


Fig. 84 **Competition procedures**

Selection procedures for promotion

- **senior inspector** in *Manufacturing Licensing and Control* Division at *Market Supervision and Inspections* Department;
- **4 senior experts** in *Quality, Pre-clinical and Clinical Assessment* Division at *Marketing Authorizations of Medicinal Products* Department;
- **senior expert** in *Validation and Community Procedures* Division at *Marketing Authorizations of Medicinal Products* Department;
- **head** of *Noninterventional Researches* Division at *Medicinal Products Information and Noninterventional Researches* Department;
- **chief expert** in *Quality Management, Administrative and Information Technology Services* Division at *Legal, Administrative, Financial Services and Quality Management* Department;
- **chief legal advisor** in *Legal Services, Human Resources and International Cooperation* Division at *Legal, Administrative, Financial Services and Quality Management* Department;
- **senior expert** in *Noninterventional Researches* Division at *Medicinal Products Information and Noninterventional Researches* Department;
- **senior legal advisor** in *Legal Services, Human Resources and International Cooperation* Division at *Legal, Administrative, Financial Services and Quality Management* Department.

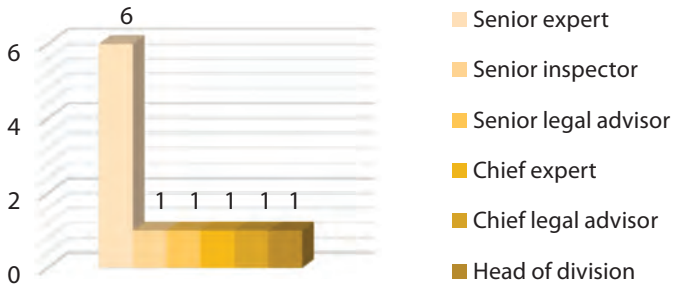


Fig. 85 **Selection procedures**

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

BDA staff participated in the following types of trainings:

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

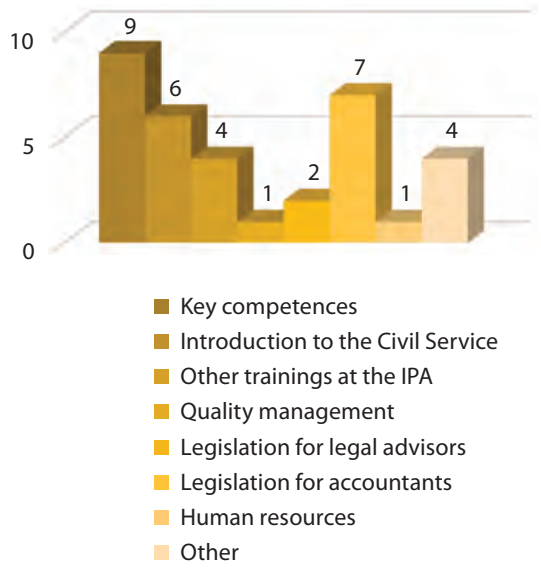


Fig. 86 **Trainings in Bulgaria**

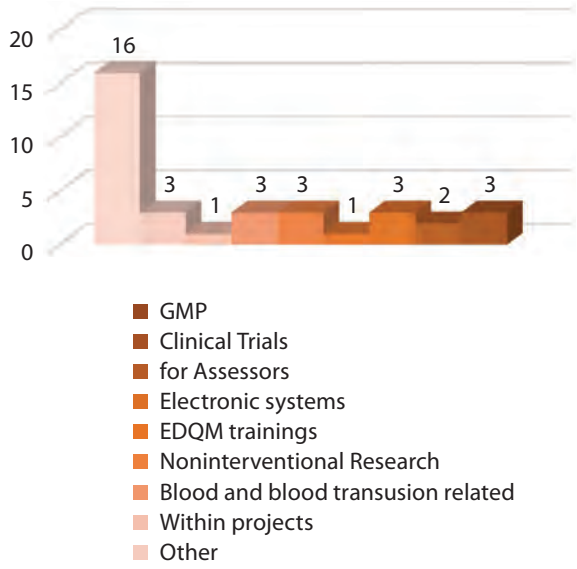


Fig. 87 **Trainings abroad**

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 2017, the maintenance and the improvement of the Integrated Quality Management, Information Security and Risk Management System was successfully continued in accordance with ISO 9001 and ISO / IEC 27001 and scope of certification: Expert evaluation and supervision of quality, safety and efficacy of medicinal products. Pharmacovigilance. Expert evaluation of advertising of medicinal products. Control of manufacturing, wholesale and retail of medicinal products. Expert evaluation, registration and market surveillance of medical devices. Supervision of blood transfusion system.

Internal and external audits

According to the *Annual Program for conducting Internal Audits for 2017* 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 March 2017, the BDA was successfully audited in the framework of the Joint Audit Programme - JAP Audit. The Agency was inspected by representatives of the United Kingdom (The Medicines and Healthcare products Regulatory Agency - MHRA) and Italy (dall'Agenzia Italiana del Farmaco - AIFA). Based on the Mutual Recognition Agreement between the European Commission and the USA on the results of the GMP inspections, inspectors of Food and Drug Administration (FDA) observed the audit. Corrective actions for eliminating the identified non-compliances and those for closing the areas for improvement were undertaken.

In June 2017, a recertification 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. There were no identified non-compliances. Actions for closing the areas for improvement were taken.

The *Medicinal Products* Analyses Department was accredited for compliance with BSS ISO/IEC 17025:2006 by Executive Agency *Bulgarian Accreditation Service* and was attested by the European Directorate for the Quality of Medicines & HealthCare (EDQM & Healthcare). In December 2017, the second planned supervision was held. The audit was successful and without non-compliances.

9. PROJECTS

VISTART

The 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 participated with two inspectors in the training in 2017. The second planned training is in 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

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.

Preparation of the Bulgarian Presidency of the Council of the European Union

The BDA will host three meetings during the Bulgarian Presidency of the Council of the European Union in 2018. These three meetings are regular meetings in the European Union Medicines Agencies Network. In Sofia, will be held:

1. Working Group of Communication Professionals (WGCP) meeting on 10-11 May 2018;

2. European Medicines Agencies Co-operation on Legal and Legislative Issues (EMACOLEX) meeting on 29-30 May 2018;

3. Heads Medicines Agencies (HMA 2) meeting on 20-21 June 2018.

In 2017, the preparation for the meetings started. The organizational activities are coordinated with the HMA Management Group and the Ministry of the Bulgarian Presidency of the Council of the European Union. Two BDA employees were trained to work with the Event Management System.

The *orphan* meetings will be hosted by other Medicines Agencies under the Bulgarian Presidency. The BDA's representatives in the committees and the working groups within the Network cooperate with the hosting agencies for the preparation of these meetings.

The BDA experts participated in committees and working groups as follows:

1. Committee for Medical Devices (MDR IVDR) which is established according to Article 107(1) of Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in-vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU and Article 114(1) of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC;
2. Ad hoc Working Group on the Interaction between GMO legislation and legislation in the field of Medicinal Products;
3. Expert Group on the Delegated Act on Safety Features for Medicinal Products for Human Use and European Medicines Verification Organisation/NCA Workshop.

11. TRANSPARENCY AND COMMUNICATIONS

Access to Public Information

In 2017, the BDA received 28 Applications under the Access to Public Information Act (APIA) as 22 of them were submitted by citizens, 4 - by legal entities and 2 - by NGOs. Also, 14 were received on hardcopy and 14 were received via e-mail.

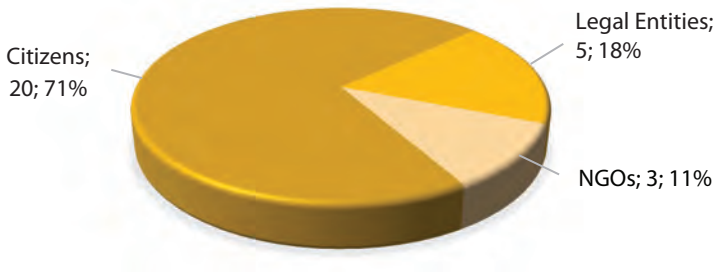


Fig. 88 **Received Applications for Access to Public Information by type of applicant**

All the required accesses were granted in the set terms except for one refusal on grounds that the information is part of the decision-making process. All applications were assessed. There was one claim against a final act under APIA.

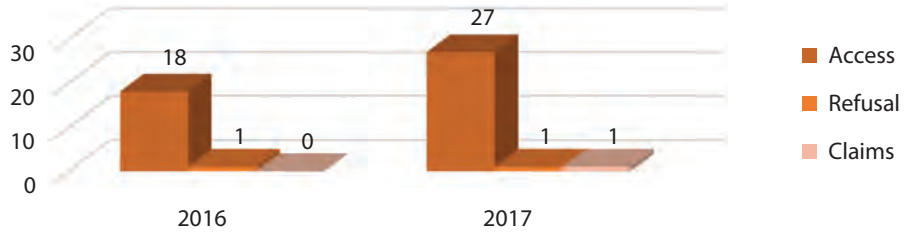


Fig. 89 **Access to Public Information**

Communications

The Agency, in pursuance of the Biannual Agreement between the Ministry of Health and the Regional Office for Europe of the World Health Organization, has developed an information brochure entitled „The Path of Medicine - Truths and Facts". It is aimed at familiarising patients with the main stages of drug development - from research laboratories to their marketing, by comprehensively clarifying the nature of generic medicines and their importance for rational and effective pharmacotherapy.

The BDA, with the assistance of partners, took an active part in the 2nd European Union-wide Adverse Drug Reaction Awareness Week campaign (20-24 November 2017) under the coordination of the Working Group of Communication Professionals (WGCP) at the HMA through the dissemination of animated infographics developed by the UMC (Uppsala Monitoring Center), Sweden. The target group was the patients and the general public, as well as community pharmacists who dispense drugs and advise on their proper use.

The BDA also published on its website materials related to the World Week on Responsible Application of Antibiotics carried out in Bulgaria by the National Center for Infectious and Parasitic Diseases.

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.

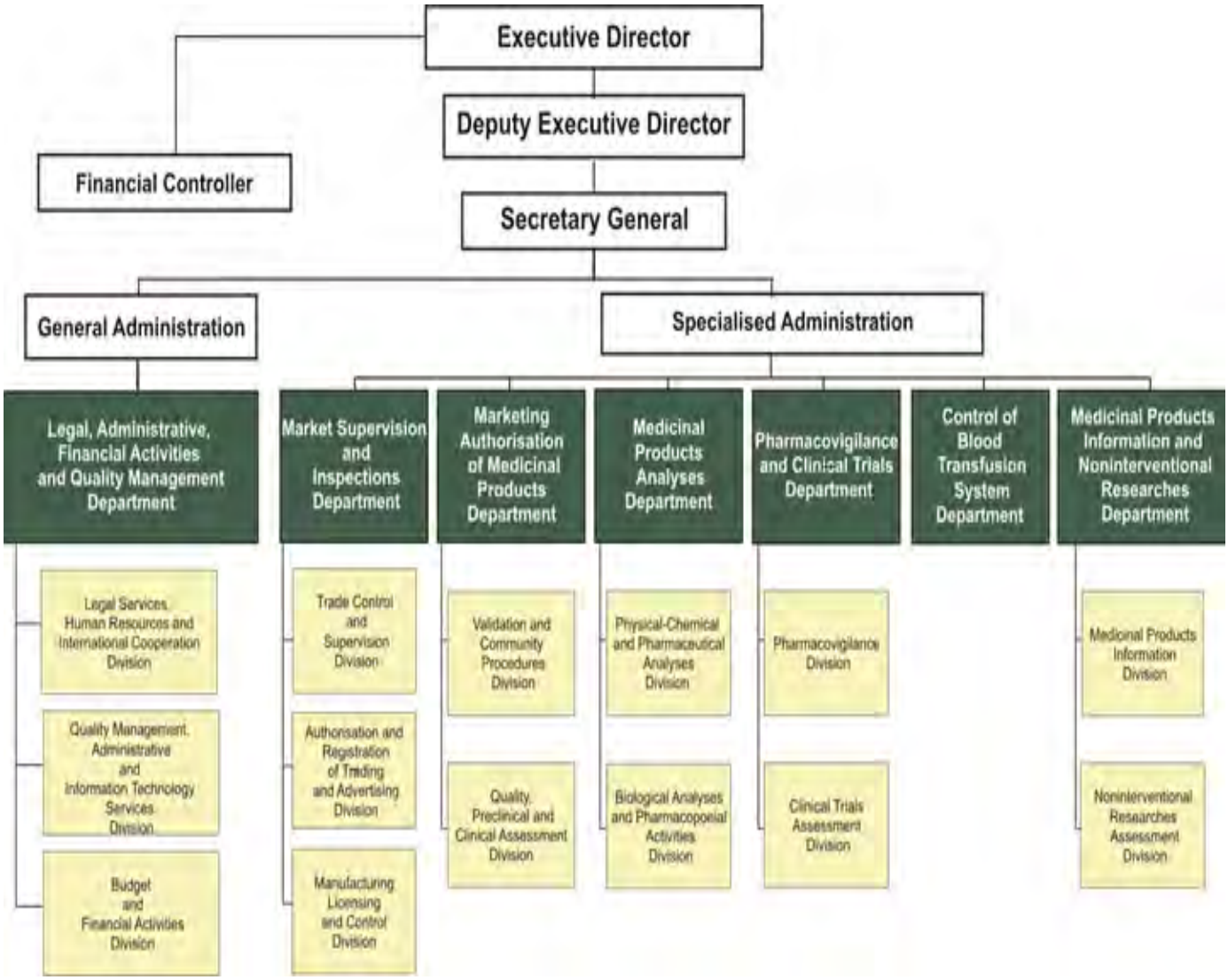
After the demonopolization, the decentralization of the production, supply and distribution of medicines in 1991, SICM turned out to be the only State institution, competent in the medicinal sector. International experience was gained and the foundation of a different institute was prepared, an institute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