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CENTRALIZED PREPARATION OF MEDICINAL PRODUCTS FOR SYSTEMIC TREATMENT OF MALIGNANT DISEASES IN HOSPITAL PHARMACIES IN BULGARIA – SPECIFICS, CHALLENGES AND PROSPECTS

THESIS SUMMARY

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The dissertation contains a total of 139 pages, is illustrated with 54 figures and 10 tables. The bibliography includes 139 sources.

The public defense of the dissertation will take place on 10.12.2025.

The materials for the defense are published on the website of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

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Abbreviations

AHFS - American Hospital Formulary Service
ANVISA - Brazilian Health Regulatory Agency
ASCO - American Society of Clinical Oncology
ASHP - American Society of Health-System Pharmacists
BSA - Body surface area
BSC - Biological safety cabinet
CAI - Compounding Aseptic Isolator
CACI - Compounding Aseptic Containment Isolator
CCC - Complex Cancer Center
CDER - Center for Drug Evaluation and Research
CMR - Carcinogenic, Mutagenic and Reprotoxic substances
CSTD - Closed System Drug Transfer Device
EMA - European Medicines Agency
EU - OSHA - European Agency for Safety and Health at work
ESOP - European Society of Oncology Pharmacy
FDA - Food and Drud Agministration
GLOBOCAN - Global cancer statistics
HEPA - High Efficiency Particulate Air
HLA - Human leucocyte antigen
HMP - Hazardous Medicinal Products
ICH - International Council for Harmonizations of Technical Requirements for Pharmaceuticals for Human Use
ISO - International Organization for Standartization
MH - Ministry of health
MHAT - Multi-profile Hospital for Active Treatment
MTH - Methotrexate

NHIF - National Health Insurance Fund

NIOCH - National Institutes for Occupational Safety and Health

NSI - National Statistical Institute

QUAPOS - Quality Standard for the Oncology Pharmacy Service

SHATHD - Specialized Hospital for Active Treatment of Hematological Diseases

SMPSTMD - Solutions of medicinal products for the systemic treatment of malignant diseases

UMHAT - University Multi-profile Hospital for Active Treatment

WHO - Worlds Health Organization

"One in five people worldwide develop cancer during their lifetime"

International Agency for Research on Cancer, WHO

"Every year, more than 100.000 people die in the EU from cancer caused by carcinogens at work"

EU-OSHA /European Agency for Safety and Health at work/

I Introduction

Studies have linked exposure to cytotoxics in the workplace to health complications such as skin rashes, reproductive problems and the potential for developing malignant disease. It has been established that the risk depends on the duration of contact and the toxicity of the drugs.

On the other hand, the number of oncological patients is constantly increasing and new modern drugs with high value are approved, which increases the costs of treating malignant diseases every year. As early as the late 1980s, analyses showed that the centralized preparation of antitumor drugs allows for their maximum utilization while protecting personnel, which is why it is gradually starting to be implemented in different countries. Centralized preparation is the aseptic preparation of parenteral solutions of medicinal products /powdered and concentrated solutions/ in a form for direct administration to the patient in one place - most often in the hospital pharmacy /regardless of the number of units that administer them/, while adhering to strict rules and requirements. Usually, hospitals first implement centralized preparation of antitumor drugs, due to the toxicity of a large part of them and their high cost.

A legal change to introduce centralized preparation of medicinal products for systemic treatment of malignant diseases in our country was made at the end of 2015 with a change in Regulation No. 28 of December 9, 2008 of the Ministry of Health on the structure, order and organization of work of pharmacies and the nomenclature of medicinal products. Currently, there is no regulatory document in Bulgaria that specifies exactly what competencies are required to carry out activities related to the preparation of solutions of antitumor drugs.

This dissertation aims to analyze the centralized preparation of medicinal products for systemic treatment of malignant diseases in Bulgaria after its introduction in 2015.

II Aim and objectives

1. Aim - to study and analyze the process of centralized preparation of solutions of medicinal products for the systemic treatment of malignant diseases /SMPSTMD/ in hospital pharmacies in Bulgaria, as well as the training of personnel for the performance of this specific pharmaceutical activity. A secondary aim of the dissertation is the definition and presentation by the doctoral student of the prospects for the development of the process in our country.

2. Tasks for achieving the goal

- Study and analysis of the main regulatory documents concerning the centralized preparation of SMPSTMD in Bulgaria
- Analysis of the characteristics of hospitals in which activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology are performed
- Analysis of the unusable residues from the preparation of SMPSTMD reported to the NHIF in 2020–2024
- Study of the demographic and professional characteristics of pharmacists who prepare SMPSTMD
- Study of the training of pharmacy personnel performing centralized reconstitution of SMPSTMD
- Preparation of recommendations for improving the regulatory framework, as well as the training of pharmacists preparing SMPSTMD

3. Hypotheses

- A regulatory framework concerning the centralized preparation of medicinal products for the systemic treatment of malignant diseases exists in Bulgaria. The gaps and imperfections in it, identified during the ten-year period since the start of the process, need correction.

- The aseptic preparation of SMPSTMD is a highly specialized pharmaceutical activity, requiring appropriate specialized training

- The shortcomings in the legislation, the lack of established national standards, as well as inadequate process control, determine the inequality of medical institutions with regard to the conditions under which aseptic solutions of medicinal products for the systemic treatment of malignant diseases are prepared

III Materials and Methods

Of essential importance for solving the tasks set is the study of the legislative framework in the Republic of Bulgaria, which defines and regulates the centralized preparation of medicinal products for the systemic treatment of malignant diseases. The data on the medical institutions in which there are activities in medical oncology, clinical hematology and pediatric clinical hematology and oncology, available on the NHIF website, the National Framework Agreements signed between the NHIF, the Bulgarian Medical Association and the Bulgarian Dental Association from 2014 to the current one /2023 - 2025/, as well as information obtained under the Access to Public Information Act from the Ministry of Health and the NHIF, have been processed, summarized and analyzed for the purpose of this work.

The following methods have also been used in the dissertation work:

1. Historical method: collecting information on the development over the years of the topic of the influence of cytotoxics on the health of those working with them, as well as on the centralized preparation of antitumor drugs in Europe and Bulgaria. A number of publications from the 1980s to the present day have been studied, as well as the development of manuals, recommendations and guidelines during this period.

2. Documentary method: study and analysis of regulatory documents adopted in Europe regulating the centralized aseptic preparation of medicinal products, as well as established manuals and standards in the field in Europe and the USA. Study of the legal framework in Bulgaria adopted after 2015 regarding the centralized preparation of cytotoxics, as well as changes in the national framework contracts signed between the NHIF, the Bulgarian Medical Association and the Bulgarian Dental Association in the part concerning the payment of medicinal products for the systemic treatment of malignant diseases in hospital care outside the cost of clinical pathways and clinical procedures

3. Statistical method – processing and analysis of data published on the NHIF website related to the payment of medicinal products for the systemic treatment of malignant diseases in hospital care outside the cost of clinical pathways and clinical procedures. The information on medical institutions that perform activities in medical oncology and/or clinical hematology from 2019 to 2024, available in various databases /NHIF, NSI, MH/, was studied. Information obtained under the Access to Public Information Act, as well as the information obtained from the conducted study, was analyzed

4. Graphical method - presentation of the results obtained through graphs

5. Method - interview - in order to establish the need for specialized training on protection during work and the aseptic dissolution process from the perspective of master pharmacists and assistant pharmacists who prepare solutions for parenteral administration of antitumor medicinal products, an online interview was conducted, which received an positive ethical assessment by the Research Ethics Committee /REC/ at the Medical University of Varna.

Research topic

STUDY OF THE NEED FOR SPECIALIZED TRAINING OF PHARMACISTS PREPARING PARENTERAL SOLUTIONS OF ANTI-TUMORUM MEDICINAL PRODUCTS IN HOSPITAL PHARMACIES OF HOSPITALS IN BULGARIA

The aim of the study is to establish the need for specialized training on protection during work and the aseptic dissolution process from the perspective of master pharmacists and assistant pharmacists who prepare solutions for parenteral administration of anti-tumor medicinal products.

After receiving a positive opinion from Research Ethics Committee /REC/ at the Medical University of Varna, the study was conducted in the period 01.11.2024 - 31.12.2024

Study centers

Hospital pharmacies of medical institutions that have clinics or departments performing activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology throughout the country, from whose heads the researchers received a declaration of consent for the participation of master pharmacists and assistant pharmacists from the team preparing cytotoxics in an online interview. In Bulgaria in 2024, there were 44 hospitals that treat patients with malignant diseases. Contact was made with the Heads of the pharmacies of 30 of them, and a declaration of consent was received from 18 /40.9% of all 44/.

Medical institutions participating in the study:

MHAT Uni Hospital OOD, MHAT Avis Medica OOD, UMHAT "St. Georgi" EAD, UMHAT Pulmed OOD, MHAT Central Onco Hospital OOD, CCC Plovdiv EOOD, UMHAT KANEV - RUSE AD, UMHAT MEDICA RUSE OOD, UMHAT "St. Ivan Rilski" EAD, MHAT SERDIKA EOOD, Acibadem City Clinic UMHAT EOOD, SHAT "Ioan Pavel" OOD, SHATHD-EAD, Military Medical Academy, MHAT - MK "St. Iv. Rilski" EOOD Stara Zagora branch, CCC - Stara Zagora EOOD, CCC-Shumen EOOD, UMHAT "Aleksandrovska" EAD

Description of the scientific study

In Bulgaria, centralized dissolution has been launched for medicinal products for the systemic treatment of malignant diseases. This regulatory change occurred in October 2015, with the adoption of changes in Regulation No. 28/9.12.2008 of the Ministry of Health of the Republic of Bulgaria.

Cytotoxics are classified as highly active/ hazardous drugs and many scientific data show that they can have a negative effect on the health of the personnel who work with them. This effect can be minimized by using appropriate equipment, appropriate personal protective equipment and strict adherence to procedures related to all stages of the reconstitution process - washing and disinfecting hands, putting on and taking off personal protective equipment, preparing solutions and cleaning the workplace. The preparation of drugs must be carried out in compliance with aseptic technique in order to guarantee the quality of the prepared product. At present, there is no regulatory document in

Bulgaria that specifies exactly what competencies are required to carry out activities related to the preparation of drugs for the systemic treatment of malignant diseases. The procedures are developed and approved at the level of the medical institution and due to the lack of established national standards, there are differences in the basic knowledge and skills related to workplace protection and the quality of the prepared product among the staff of individual hospitals

Method of conducting the study

An online interview was conducted with master pharmacists and assistant pharmacists who work in hospital pharmacies of medical institutions performing activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology, and a questionnaire was sent

Description of the study population

Master pharmacists and assistant pharmacists who work in hospital pharmacies of medical institutions performing activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology and prepare solutions of cytotoxics. Goal - minimum number of participants - 24, maximum number - 120. Responses were received from 32 pharmacists.

Procedures for recruiting the study population

Recruitment of study participants:

Initially, contact was made with the Heads of hospital pharmacies of the medical institutions that met the criteria. They were informed of the purpose of the study and after obtaining their consent through a declaration, an online questionnaire was sent to emails of master pharmacists/assistant pharmacists who prepare cytotoxic solutions, indicated by the Head of the pharmacy. In order to be admitted to the questions, potential participants must sign an informed consent to participate in the study

Criteria for inclusion and exclusion of individuals from the study.

Inclusion criteria: working in medical institutions where activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology are performed, master pharmacists or assistant pharmacists, preparing solutions for direct administration of antitumor medicinal products

Exclusion criteria: working in medical institutions where activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology are not performed, master pharmacists or assistant pharmacists; those who work in medical institutions where activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology are performed, but do not prepare solutions for direct administration of antitumor medicinal products; those who have not given consent for the processing of their personal data or for access to their confidential information to researchers or regulatory authorities upon request.

IV Results

4.1. Analysis of the main regulatory acts determining the centralized preparation of solutions for direct administration of medicinal products for systemic treatment of malignant diseases

The main regulatory documents regulating the process are several:

1. Ordinance No. 28 of December 9, 2008 on the structure, procedure and organization of the work of pharmacies and the nomenclature of medicinal products

2. Ordinance No. 4 of March 4, 2009 on the conditions and procedure for prescribing and dispensing medicinal products

3. The Rules for Good Pharmaceutical Practice 2020

4. Law on Healthy and Safe Working Conditions

5. National Framework Agreements

The changes made to Ordinance No. 28 of December 9, 2008 on the structure, procedure and organization of work in pharmacies of the Ministry of Health of the Republic of Bulgaria are fundamental for starting the modernization of the processes of management of antitumor medications in medical institutions for hospital care in the country. To this day, the Occupational Health and Safety Act obliges employers to provide safe and healthy working conditions for employees, and they must comply with the specifics of the activity performed. However, there is no regulatory document describing specific measures that must be taken in medical institutions in all contacts with cytotoxics by the end of 2015. The introduction of centralized preparation of solutions for direct administration of drugs for systemic treatment of malignant diseases in Bulgaria also aims to protect personnel, guarantee the quality of the prepared product, protect the environment and minimize unusable residues.

At the same time, the introduction of changes made to Regulation No. 28 of December 9, 2008 on the structure, order and organization of work in pharmacies leads to difficulties for hospitals for various reasons.

According to one of the amendments, drugs for the systemic treatment of malignant diseases must be prepared in the pharmacy of the relevant medical institution in a form for direct administration to the patient, which means that such a medical institution has to have its own pharmacy. However, it is not specified what type of activity permit the hospital pharmacy must have, since according to the same regulation it can have for:

1. medicinal products, including those prepared according to magistral and pharmacopoeial recipes without the preparation of dosage forms for eyes and solutions for parenteral administration;

2. medicinal products, including those prepared according to magistral and pharmacopoeial recipes with the preparation of dosage forms for eyes and solutions for parenteral administration;

3. medicinal products with the exception of those prepared according to magistral and pharmacopoeial recipes.

A grace period of six months is given for hospitals to prepare, which is insufficient time to carry out the entire process of research, design, ordering equipment, creating procedures, hiring new staff and training, especially if the Public Procurement Act is to be complied with. When adopting the amendments to Regulation No. 28 of December 9, 2008, no standards were set out that the sector for aseptic preparation of solutions of antitumor drugs must meet, so as to ensure the safety of personnel and the quality of the prepared product. One year later, in October 2016, the Ministry of Health approved the "Rules for Amendments and Supplements to the Rules for Good Pharmaceutical Practice", which describe requirements for the activities of pharmacies in medical institutions, including the preparation of cytotoxics. This sets out the minimum standards that the unit for dissolving medicinal products for the systemic treatment of malignant diseases as part of the hospital pharmacy must meet. They are in line with the European Quality Standards in the field of oncology pharmacy /QUAPOS/. Thus, the managements of the medical institutions, when designing and renovating the pharmacies, receive the same basic criteria that must be met in order to guarantee the protection of the personnel, the quality of the prepared medicinal product and the protection of the environment. Due to the fact that the standards were approved one year later after the promulgation of the changes in Regulation No. 28 of December 9, 2008 on the structure, order and organization of the work of pharmacies and the nomenclature of medicinal products of the Ministry of Health of the Republic of Bulgaria /Article 37a/ and six months after the expiration of the grace period, the structure of the new sectors, as well as the equipment, are left to the discretion of the hospitals themselves for 12 months. As a result, there are hospitals that are familiarizing themselves with the established international standards, despite the imperfection of national legislation, and are restructuring the medical facility and its pharmacy in accordance not only with national requirements, but also with approved world guidelines. Other medical institutions do not take any action to meet the requirements of Regulation 28 of December 9, 2008 on the structure, order and organization of the work of pharmacies and the nomenclature of medicinal products and the Occupational Safety Act for various reasons, mainly financial and lack of new staff for pharmacies.

The 2018-2019 National Framework Agreement, which is concluded between the Bulgarian Medical Association, the Bulgarian Dental Association and the NHIF, introduces the requirement that a medical institution that provides medical care on clinical pathways and outpatient procedures in the field of oncology and hematology should have a pharmacy on its territory, which must have a license - "Pharmacy for meeting the needs of a medical institution under Art. 222, para. 4 of the Law on Medicinal Products in Human Medicine for medicinal products, including those prepared according to a magisterial and pharmacopoeial recipe, of dosage forms for eyes and solutions for parenteral administration and nutrition". This forces hospitals that have not done so yet to take steps to transform their hospital pharmacies in order to be able to conclude a contract with the NHIF.

Despite all these amendments to Regulation No. 28 of December 9, 2008 of the Ministry of Health of the Republic of Bulgaria, as of April 2019, 18% (7 hospitals) continue to be in violation and do not

have an amended license /i.e. do not include in their permit the activity "preparation of medicinal products according to magisterial and pharmacopoeial prescriptions, including dosage forms for eyes and solutions for parenteral administration", with 4 of them being state or municipal, and 3 being private. In 31% of the medical institutions in which medicines for the systemic treatment of malignant diseases are prescribed and dispensed, there is no centralized preparation of cytotoxics, i.e. they are prepared by nurses in the clinics or wards. This means that almost four years after a change in Regulation No. 28 of December 9, 2008 of the Ministry of Health of the Republic of Bulgaria (October 2015–April 2019), not all pharmacies still meet the regulatory requirements.

Since Regulation No. 28 of December 9, 2008 of the Ministry of Health of the Republic of Bulgaria, Art. 19, paragraph 4, states that "it is prohibited to employ persons other than master pharmacists and assistant pharmacists appointed under an employment contract with the medical institution in the pharmacies of medical institutions under Art. 222, paragraph 4 of the Pharmaceutical and Medical Devices Act", the problem of providing staff for hospital pharmacies also arises, since the preparation of solutions for direct administration requires much greater human resources, especially in hospitals with more patients. Finding and appointing new pharmacists within the six-month grace period is a challenge that not everyone manages to cope with.

In Article 39 of the same regulation with the amendments of 2015, medicinal products and medical devices intended for clinical trials shall be received, stored, prepared and dispensed by the pharmacy of the medical institution separately from other medicinal products and medical devices, with a designation of their status, according to the protocol of the clinical trial. This means that all medicinal products from clinical trials for the treatment of malignant diseases must also begin to be prepared in hospital pharmacies by pharmacists.

Also in 2015, in Regulation No. 28 of December 9, 2008 on the structure, procedure and organization of work in pharmacies and the nomenclature of medicinal products, the obligation to have at least one master's degree pharmacist with a postgraduate specialty "Clinical Pharmacy" or with a specialization in "Clinical Pharmacy" was introduced in medical institutions for hospital care. This imperative norm applies to hospitals with over 400 beds for active treatment or those that have opened at least 10 clinics/wards with beds, as well as in all those that carry out activities in medical oncology and/or clinical hematology. Although in Bulgaria "Clinical Pharmacy" as an independent specialty in the postgraduate training of master pharmacists was introduced in 1993, there are actually no clinical pharmacists in hospitals in the country in the type known in countries where this specialty is highly developed. They are part of the team of pharmacists of the hospital pharmacy and as such can provide clinical pharmaceutical services, which is the first step in the development and establishment of clinical pharmacy as an independent professional field in our country. The quality of these services is increasingly important given the constantly increasing public resources that are allocated for the payment of medicines for the systemic treatment of malignant diseases. Clinical pharmacists have a role in the multidisciplinary team in various aspects of anti-cancer treatment:

1. In oral therapy - consulting patients on the method of taking and storing the drug, as well as possible drug interactions between the anti-cancer product and existing therapy, e.g. against chronic diseases

2. In intravenous therapy

- monitoring the compliance of prescriptions and preparation with the SPC

- ensuring compliance with the required concentration of the solution and its stability

- undertaking the necessary strategies to ensure a minimum amount of unusable residues from the preparation

3. Preparing or participating in the preparation of an opinion on the safety and efficacy of a medicinal product administered outside the marketing authorization - a common practice that is observed in a wide range of therapeutic areas in both adults and children, but is much more common in the pediatric population. The opinion of a master pharmacist is part of the set of documents that the medical institution must prepare and send to the relevant institutions according to the legal framework.

From a statement received from the Ministry of Health under the Access to Public Information Act, it can be seen that in response to a letter from the Ministry of Health with reference number 09-00-135/15.09.2024, in the period 26.09.2023–11.10.2023, inspectors from the BDA carried out inspections on the territory of the city of Sofia to implement the provisions of the Law on Medicinal Products in Human Medicine, Regulation 28 of December 9, 2008 on the structure, order and organization of work in pharmacies and the nomenclature of medicinal products, as well as the instructions in Chapter III of the Rules for Good Pharmaceutical Practice (Preparation of medicinal products in pharmacies of medical institutions). 15 hospitals in Sofia that perform activities in medical oncology and/or clinical hematology were inspected for the presence of a clinical pharmacist as part of the pharmacy team and for the presence of protocols of monthly tests of microbiological purity in the box or isolator for the preparation of cytostatics in the pharmacy. The results of the inspection show that a total of 8 /53%/ of the 15 inspected pharmacies /since different pharmacies do not meet one or the other criterion/ do not meet the requirements and violate the regulatory framework. The legislation is not complied with by both private and hospitals with state or municipal participation. The lack of control of microbiological and cleanliness in the premises and equipment for the preparation of antitumor drug solutions is a lack of control over aseptic conditions, which in turn puts the quality of the prepared product at risk. The three-year grace period for the appointment of a clinical pharmacist in medical institutions that meet the requirements of Regulation No. 28 of December 9, 2008 on the structure, order and organization of work in pharmacies and the nomenclature of medicinal products expires at the end of 2018. Almost five years later, 4 of the 15 hospitals inspected in Sofia have not provided one.

Regulation No. 28 of December 9, 2008 states that the preparation of solutions is carried out in compliance with the Occupational Health and Safety Act. It contains requirements for employers, who are obliged to ensure healthy and safe working conditions for employees, by implementing the necessary measures and taking into account the specifics of the work. This is done through:

1. prevention of occupational risks;

2. providing information and training;

3. ensuring the necessary organization and resources

In essence, the above-mentioned measures correspond to the "STOP" strategy described in the "Roadmap of Carcinogens" of the European Agency for Safety and Health at Work. However, the lack of a national regulatory document that explicitly specifies actions to be taken when working with dangerous medicinal products in medical institutions also leads to non-implementation in practice of what is written in the Occupational Health and Safety Act . Ordinance No. 10 of September 26, 2003 on the protection of workers from risks associated with exposure to carcinogens, mutagens or substances toxic to reproduction at work (title amended - SG, issue 28 of 2024, in force from 05.04.2024) is a step in the right direction. The amendments adopted in the 2024 regulation somewhat specify the minimum measures that must be taken for protection when working with "hazardous drugs".

Results from the summary of the legal framework regarding the centralized preparation of solutions for direct administration of medicinal products for the systemic treatment of malignant diseases:

1. Not all hospitals comply with the regulatory framework in Bulgaria

2. Control by the competent authorities is greatly underestimated

3. There is inequality among hospitals - those that comply with the legislation are at a disadvantage compared to those that do not. Meeting the new ruls requires serious financial resources, which are not allocated by all affected medical institutions for various reasons. Almost four years after the change in Regulation No. 28 of December 9, 2008 of the Ministry of Health of the Republic of Bulgaria (October 2015–April 2019), not all pharmacies still meet the regulatory requirements, but despite this, all 39 hospitals have a contract for activities related to the treatment of patients with malignant diseases and receive payment for the administered antitumor medicinal products outside the cost of clinical pathways and clinical procedures. The data show that the paid value has increased annually in the period since the change in the regulation (end of 2015) and 2019, when the study was conducted.

4. Hospitals that have not met the requirements of the regulation and the Rules for Good Pharmaceutical Practice have different ownership - private, state and municipal, i.e. non-compliance with the regulatory framework is not related to ownership, but to the management of the medical facility

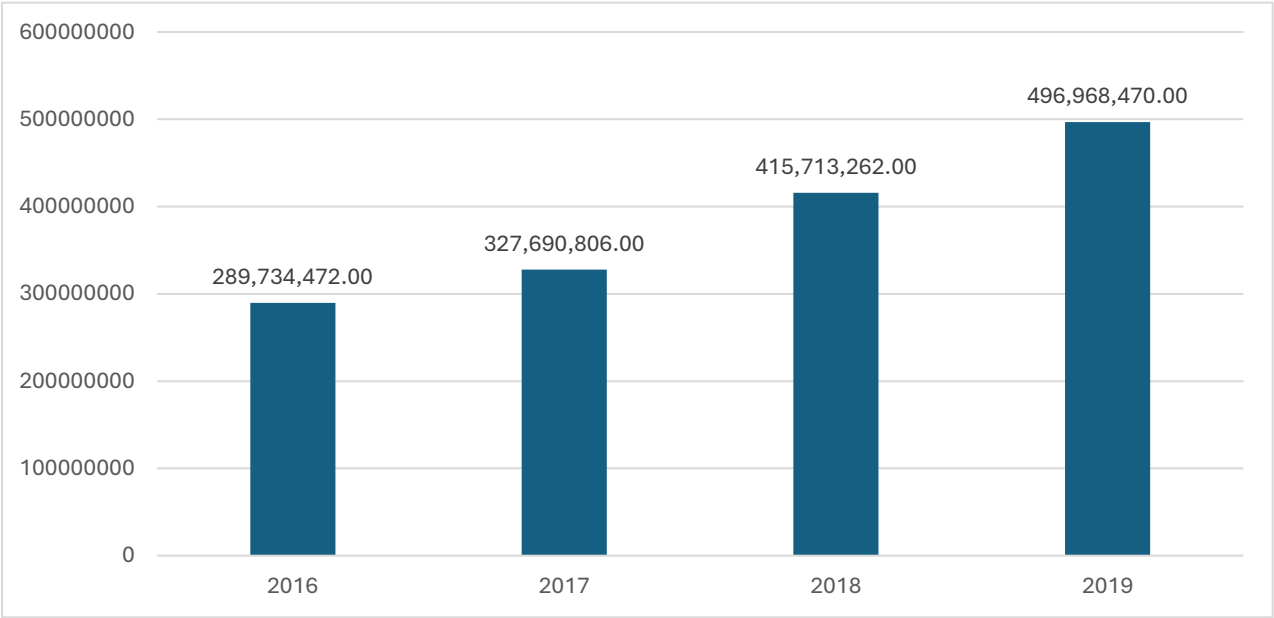

Fig. 1. Paid funds for medicinal products for the treatment of malignant diseases in hospital medical care in BGN

5. The quality of clinical trials with antitumor drugs conducted in medical facilities that do not meet regulatory requirements is questioned, as it is determined by all planned and systematic actions that are established to ensure that data are obtained, documented (recorded) and reported and that the trial is conducted in accordance with Good Clinical Practice and applicable regulatory requirements.

6. Currently, no institution in Bulgaria can actually say in all hospitals that have activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology whether:

- Solutions for systemic treatment of malignant diseases are prepared in the hospital pharmacy by pharmacists

- The equipment that the pharmacy has meets global standards for working with hazardous substances, i.e. whether the personnel working with it, the product being prepared and the environment are protected

- The sector for preparing cytotoxics has the necessary level of cleanliness according to the available equipment

- The number of pharmacists working in the pharmacy is sufficient to guarantee the quality of the process

- The aseptic technique of the pharmacists preparing the solutions meets international standards

- The personal protective equipment that is used meets the requirements and is used in the correct way.

The existence of uniform state standards and the possibility of certification of pharmacies would put all hospitals before the same conditions that must be met and would increase the quality of the pharmaceutical services provided. The institutions that can develop such standards are the Ministry of Health and the Bulgarian Drug Agency. Thus, pharmacies that are certified will unconditionally provide a safe working environment for pharmacists who prepare solutions, better quality treatment for patients and lower expenditure of public funds. Certification is related to the presence of controlled and validated working conditions in the sector for aseptic preparation of parenteral solutions and would allow for greater microbiological stability of open vials with concentrated solutions /if chemical and physical are available/, which are diluted in order to be administered to patients. This will ensure guaranteed quality of the prepared medicines and a smaller amount of unusable residues, part of which is paid for by the NHIF and part is at the expense of the hospital.

4.2. Analysis of medical institutions where activities in medical oncology and/or clinical hematology and/or pediatric clinical oncology and hematology are performed

Antitumor medicinal products providing the main treatment for malignant solid tumours and hematological diseases in accordance with the approved pharmacotherapeutic guidelines, the necessary erythro-, thrombo- and granulocyte colony-stimulating factors, immunoglobulins, immunosuppressive therapy and chelation therapy, bisphosphonates and other medicinal products affecting bone structure and mineralization for conditions/complications resulting from the main disease and treatment are included in the package of activities for systemic medicinal treatment of malignant solid tumours and hematological diseases in hospital medical care. The number of medical institutions for hospital care in Bulgaria from 2019 to 2024 has not changed - it is 341. However, contrary to the trend of the number of hospital beds decreasing in many European countries, in Bulgaria it is growing and in 2022 there are 823 hospital beds per 100,000 inhabitants compared to an EU average of 516 in 2022, making it the country with the largest number of hospital beds per 100,000 inhabitants in the EU. In second and third place are Romania and Germany. In Bulgaria, the provision of hospitals per 100,000 people is also high (Table 1). The number of hospitals that treat malignant diseases in Bulgaria has been increasing in recent years. In 2019, 2020 and 2021, we have 39 medical institutions in which activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology are carried out. After 2022, we have an increase every year and at the end of 2024, they are already 44. Hospitals in Bulgaria are equal regardless of their ownership, which means that the NHIF concludes contracts with hospitals if they meet the conditions recorded in the National Framework Agreement, regardless of whether they are state, municipal or private. If in 2019 the medical institutions that provide systematic treatment of malignant diseases are evenly distributed by ownership /33.33%/, then the increase in the number in the following years is in favor of private hospitals, which are already the largest number /41% of all/. Medical facilities that treat patients with malignant diseases are multidisciplinary, specialized or complex oncology centers.

Table 1 Comparison of the number of inhabitants and the number of hospitals in 9 EU countries

Country	Population 2022*	Number of hospitals	Hospital coverage rate per 100,000 inhabitants
Romania	19 350 000	535	2,76
Netherlands	17 564 000	95	0,54
Sweden	10 551 000	115	1,08
Portugal	10 270 000	200	1,94
Bulgaria	6 847 000	341	**4,98**
Ireland	5 018 000	46	0,91
Croatia	4 060 000	40	0,98
Lithuania	2 749 000	62	2,25
Estonia	1 322 000	17	1,28

* https://worldpopulationreview.com

Table 2 Hospital coverage rate for cancer and oncohematology patients per 100,000 inhabitants for 9 European countries

Bulgaria	Estonia	Ireland	Lithuania	Netherlands	Portugal	Romania	Croatia	Sweden*
0,59	0,45	0,51	0,22	0,54	0,48	0,56	0,27	0,23

* Only central oncology hospitals were taken into account

In addition to being the country in the EU with the most hospital beds, Bulgaria also has the highest provision of hospitals and hospitals for the treatment of patients with malignant diseases per 100,000 people in 9 European countries according to data from 2022. Despite their large number, the distribution of medical institutions carrying out activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology in Bulgaria by region is uneven.

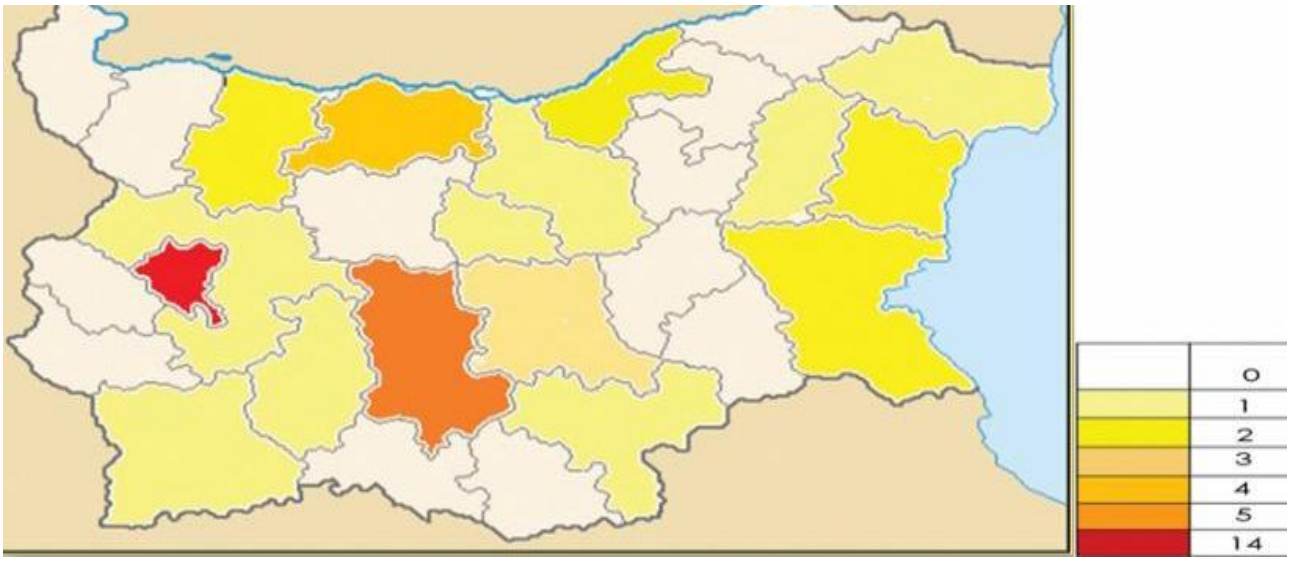

Fig. 2. Distribution of hospitals for the treatment of malignant diseases by region in Bulgaria as of October 2024.

There are no hospitals for the treatment of malignant diseases in 12 districts in Bulgaria (in white):

- Vidin
- Montana
- Lovech
- Targovishte
- Razgrad
- Silistra
- Sliven
- Yambol
- Kardzhali
- Smolyan
- Kyustendil
- Pernik

In 2019, 2020 and 2021 we have 39 hospitals in which activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology are carried out. The five hospitals after 2021 until the end of 2024, which start treating malignant diseases, are located in districts in which there is already at least one such medical institution /Pleven, Stara Zagora, Ruse and Plovdiv/. As of October 2024, 44% of medical institutions providing anti-tumor treatment are concentrated in two districts – Sofia City and Plovdiv. Most of the top 6 hospitals that receive the most funds from the NHIF for payment of anti-tumor medicinal products outside the cost of clinical pathways are also located in Sofia and Plovdiv.

Table 3 The first 6 hospitals that received the most funds from the NHIF for payment of medicinal products for the treatment of malignant diseases and medicinal products for life-threatening bleeding in patients with congenital coagulopathy, arranged in descending order

2019	2020	2021	2022	2023	2024
CCC Plovdiv	CCC Plovdiv	CCC Plovdiv	CCC Plovdiv	MHAT Uni Hospital Panagyurishte	CCC Plovdiv
MHAT Serdika Sofia	MHAT Uni Hospital Panagyurishte	MHAT Uni Hospital Panagyurishte	MHAT Uni Hospital Panagyurishte	CCC Plovdiv	MHAT Uni Hospital Panagyurishte
UMHAT "St. Marina" Varna	SHATHD	SHATHD	SHATHD	ACC UMHAT Tokuda	UMHAT "St. Ivan Rilski" Sofia
UMHAT "G.Stranski" Pleven	UMHAT "G.Stranski" Pleven	UMHAT "St. Ivan Rilski" Sofia	ACC UMHAT Tokuda	SHATHD	ACC UMHAT Tokuda
SHATHD	UMHAT "St. Marina" Varna	ACC UMHAT Tokuda	USHAT oncology Sofia	USHAT oncology Sofia	UMHAT "St. Marina" Varna
ACC UMHAT Sofia	UMHAT "St. Ivan Rilski" Sofia	USHAT oncology Sofia	UMHAT "St. Marina" Varna	UMHAT "St. Ivan Rilski" Sofia	USHAT oncology Sofia

Data from the NHIF show that every year the funds for paying for medicinal products for the treatment of malignant diseases and drugs for life-threatening bleeding in patients with congenital coagulopathy increase for all specified drugs.

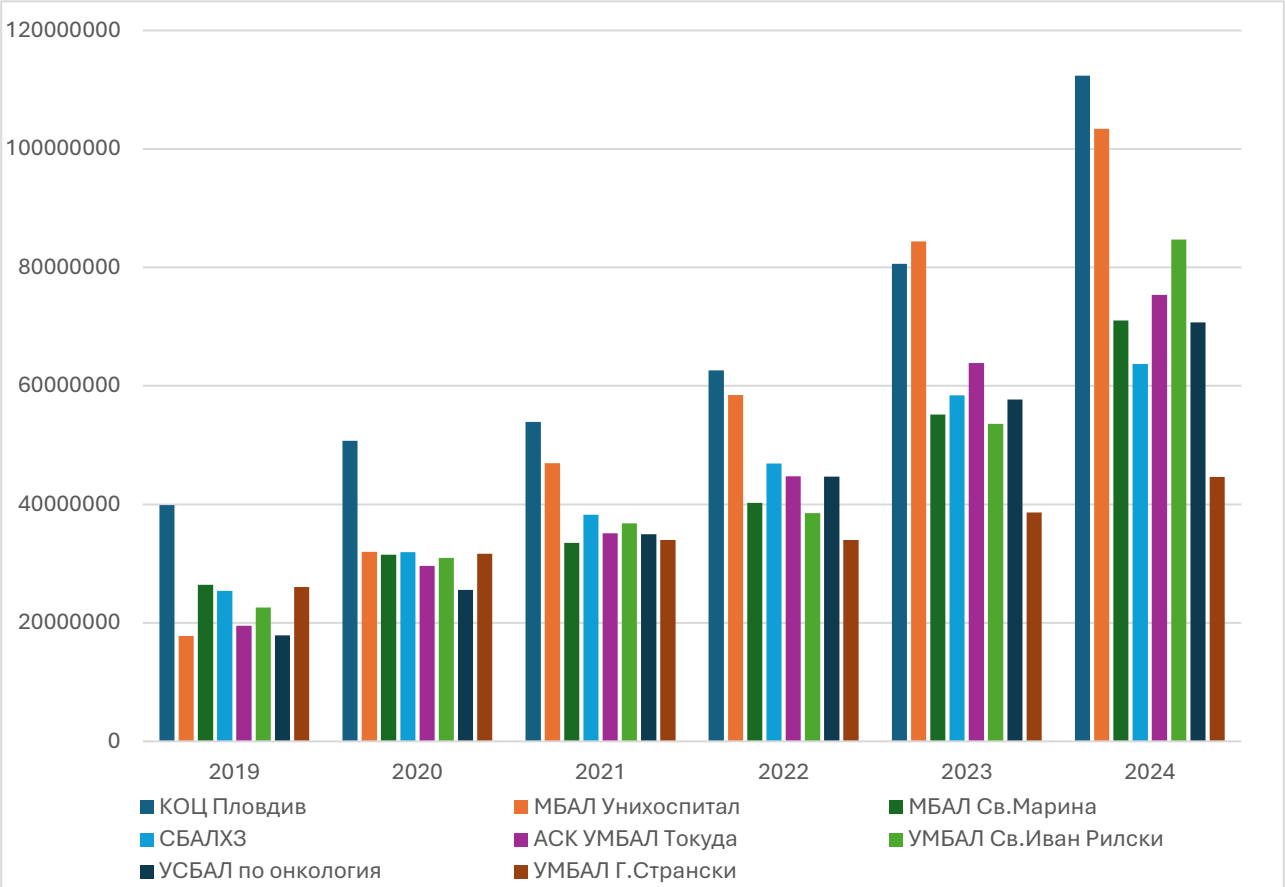

Fig. 3. Financial parameters of the medical institutions that, in the period 2019 – 2024, were in the top six for at least two years receiving the most funds from the NHIF for payment of medicinal products for the treatment of malignant diseases and LP for life-threatening bleeding in patients with congenital coagulopathy

Results of the data analysis:

1. In the period from 2019 to 2024, only 8 hospitals were in the top six for at least two years that received the most funds from the NHIF for payment of medicinal products for the treatment of malignant diseases and medicinal products for life-threatening bleeding in patients with congenital coagulopathy

2. Four of these medical institutions are located in Sofia and one in Plovdiv, i.e. 62.5% of hospitals that received the most funds from the NHIF for payment of medicinal products for the treatment of malignant diseases and medicinal products for life-threatening bleeding in patients with congenital coagulopathy are located in the regions with the most medical institutions for the treatment of malignant diseases

3. Only two of these 8 medical institutions are private

4. From the public register of medical institutions on the website of the Ministry of Health, it is seen that all have at least two units that prescribe and administer medicinal products for the systemic treatment of malignant diseases, most often three - medical oncology, clinical hematology and radiotherapy. University Hospital "St. Marina" Varna also has a clinic for pediatric clinical hematology and oncology.

5. From the study conducted in 2019 on the centralized preparation of cytotoxics in hospital pharmacies and inspections carried out in the period 26.09.2023–11.10.2023 by inspectors from the Bulgarian Drug Agency on the territory of the city of Sofia for the implementation of the provisions of the Law on Medicinal Products in Human Medicine, Regulation 28 of December 9, 2008 on the structure, order and organization of work in pharmacies and the nomenclature of medicinal products, as well as the instructions in Chapter III of the Rules for Good Pharmaceutical Practice (Preparation of medicinal products in hospital pharmacies), it is clear that violations of the legal framework occur in medical institutions with different ownership and in different locations in the country.

6. The construction of a room for aseptic preparation of solutions for direct administration of medicinal products for systemic treatment of malignant diseases, its equipment and finding personnel, represents a serious investment for the medical institution, if even the minimum requirements set out in the Bulgarian legislation are to be met. Compliance with them would be a serious challenge for hospitals with more limited resources. The large financial investment raises the question of whether it is justified when the number of patients with malignant diseases treated in a hospital is small. On the other hand, the number of oncological patients is increasing every year, both due to the aging of the population and due to better diagnostics, and a way must be sought to facilitate access to quality treatment. Experience in a number of European countries shows possible other solutions. It is a widespread practice in Scandinavian countries for a hospital to prepare solutions not only for its own needs, but also for other hospitals, where they will only be administered. This way of working has a number of advantages:

a. Investments in premises and equipment are made in fewer places, which allows more funds to be invested and all criteria to be covered without making compromises for financial reasons

b. Staff shortages in medical institutions are a common phenomenon, both in the wards and in the hospital pharmacy. Concentrating aseptic preparation of solutions in fewer places will only allow these pharmacies to maintain a larger staff with longer working hours

c. More patients and a larger number of solutions allow better planning and minimization of unused residues without resorting to underdosing patients.

d. It will also allow the appointment of drugs that form a large unused residue, which is currently avoided by many hospitals

4.3.Analysis of unusable residues from the preparation of medicinal products for the systemic treatment of malignant diseases reported to the NHIF in the period 2020 – 2024

There are several ways to calculate the dose of antitumor drugs:

- Dosing based on body surface area (BSA) - Body surface area (BSA) was first used in the late 19th century, when the German physiologist Karl M. Mee formulated the first formula for BSA. Mee's formula, based on weight (BSA = 12.312 x weight$^{2/3}$), was originally derived for animals and later adapted for humans. However, the formula inaccurately reflects the complex relationship between body size and physiological processes. The Du Bois and Du Bois formula was later developed by the American physician Eugene Floyd Du Bois and his wife and collaborator Delafield Du Bois to address this limitation. The new formula includes height as a variable.

BSA (m2)=0.007184×weight (kg)$^{0.425}$×height (cm)$^{0.725}$

Dosing based on body surface area does not take into account the complex processes of elimination of cytotoxic drugs. This leads to unpredictable variations in effect. Overdose is easily recognized, but unrecognized underdosing is likely to be more common and may occur in 30% or more of patients receiving a standard regimen. Patients who are inadvertently underdosed are at risk of significantly reduced antitumor effect. This formula may also not be accurate in obese individuals and children.

- Weight-based dosing - another way to dose antitumor drugs. ASCO recommends the use of full, weight-based doses of cytotoxic chemotherapy for the treatment of obese adults with cancer.

- Glomerular filtration rate dosing - used with Carboplatin. Since renal excretion is the major variable determining the pharmacokinetics of this drug, a dosing formula based on glomerular filtration rate (GFR) has been proposed and is increasingly used in the dosing of carboplatin. This dosing method is critically dependent on accurate measurement of GFR.

- Fixed dose – commonly encountered with monoclonal antibodies. This is because they are generally distributed only in blood plasma and extracellular fluids, which increase less than proportionally with increasing body weight. Elimination occurs by proteolytic catabolism, a nonspecific immunoglobulin G elimination pathway, and intracellular degradation after binding to the target. The latter is the major route of elimination and is related to target expression levels rather than body size. Taken together, the small effects of body size on the distribution and elimination of monoclonal antibodies and their generally wide therapeutic window do not support dosing based on body size. This is the reason for the increasingly widespread use of fixed doses for monoclonal antibodies.

In cases where dosing is based on weight or body surface area, during the preparation of antitumor drug solutions, residues may form in the vials, which must be destroyed due to disruption of the physical, chemical and/or microbiological stability of the drugs. These residues are called unusable residues. The National Framework Agreement 2020-2022 states that the National Health Insurance Fund pays for unusable residual quantities of medicinal products, which are reflected in Annex No. 8f of Regulation No. 4 of 2008, in the amount of up to 5% of the total amount of active substance

administered to all health insured persons by the contractor for the given medicinal products by ATC code for the relevant month. According to the National Framework Agreement, residues are formed by those whose primary packaging contains a dose of the active substance that does not provide the prescribed individual therapeutic dose according to the protocol, according to the dosage according to the approved SPC. Which means that not all drugs form residues. There are different strategies for reducing residues in Bulgarian hospitals, and their implementation requires joint work of doctors and pharmacists.

1. Planning and schedule for patient admission, which ensures the least surplus of infusion forms and is approved by the Head of the clinic/department. Given the fact that most SPCs state that opened vials have microbiological stability for up to 24 hours, there are two options for patient planning:

- If there are more patients treated with one medicinal product, then the smallest residue will be obtained if there are patients every day and then there will be a shortage of this medicinal product only on Friday or Saturday, depending on the pharmacy's working hours.

- If there are few patients treated with one medicinal product, then the aim is to combine them in one day or two consecutive days, which is not always possible, since the course, although planned, can be postponed due to the patient's condition

2. Using different dosage forms of one drug, which allows for a choice or to make a combination in order to reduce the residue. Combinations can only be made between different dosage forms of the same commercial product from one manufacturer. Often, a prerequisite for the formation of a residue is the inappropriate dosage form that is authorized for use and available in the country.

3. Certification of the premises and equipment to allow for a longer use of opened vials, where the SPC allows it.

With a strategy and a large number of patients, unusable residues can be reduced to 1-2% of the administered amount, with hospitals with more cancer patients having greater opportunities to reduce discarded residues. There is a dosing method, the so-called "dose restriction", which uses predefined body surface area (BSA) ranges to calculate the dose for each patient, using a single BSA value per range. In this way, drugs with sufficient long-term stability can be prepared in advance. The main advantages of dose restriction are reduced waiting time for patients and improved planning of pharmacy capacity; additional benefits include reducing medication errors, reducing medication waste, and prospective quality control. This method was developed to optimize medication preparation, and research has shown that this is possible for some medications.

Although hospital pharmacies have been reporting unused medication since January 2020, the first amounts reimbursed by the NHIF were from March 2020, meaning that the amount for 2020 is not actually for a full year. The observed trend of increasing the amount of unused medication reimbursed by the NHIF from 2020 to 2024 is logical given the increasing number of patients each year, the opening of new cancer treatment units, and the availability of funds to pay for medications for the systemic treatment of malignant diseases in hospital settings. At the same time, oral antitumor drugs

and those with a fixed dose /for subcutaneous or intravenous administration/ are increasing, which has a positive impact on unusable residues, since they do not form any.

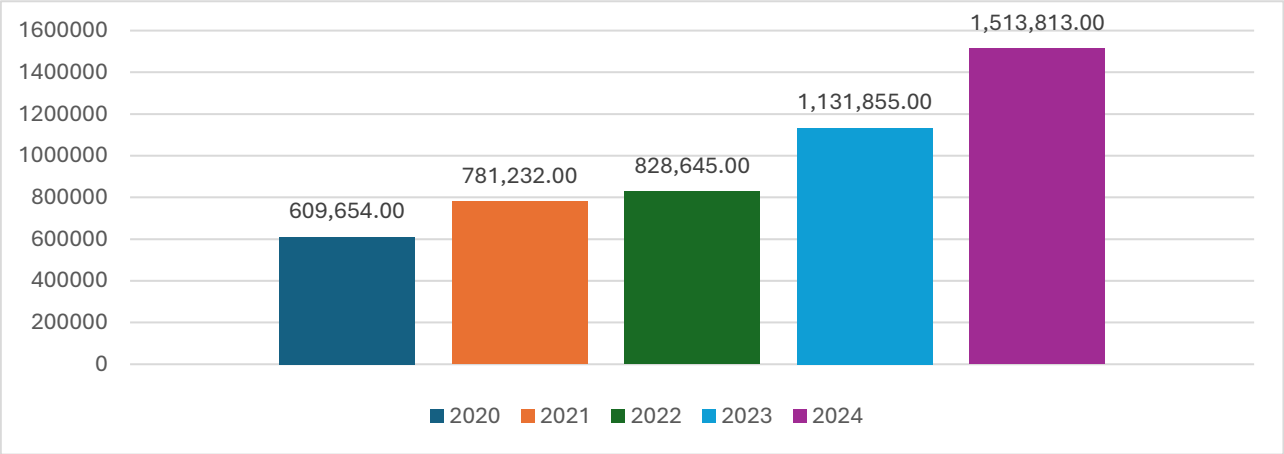

Fig. 4 Reimbursed unusable residues from the NHIF, obtained during the preparation of solutions of medicinal products for the systemic treatment of malignant diseases in the period 2020 - 2024 throughout the country

The amount of reimbursed unused residues is different from that reported by hospitals, since the NHIF pays up to 5% of the total amount of active substance administered to all health insured persons by the contractor for the given medicinal products under the ATC code for the respective month. This means that with a large number of patients and proper planning, it is possible for the entire amount of reported unused residues for certain medicines to be reimbursed by the NHIF, while respecting the accurately calculated individual dose. However, it is not possible for all unused residues for all INNs to be reimbursed, i.e. to fall within the 5% limit for 2 reasons:

- There are medicinal products that are administered to a small number of patients and they can hardly be combined

- In Bulgaria, there is currently no hospital pharmacy with a certified sector for aseptic preparation of solutions of antitumor medicines. This is so because there are no standards developed in the country that the sectors for the preparation of cytotoxics would meet. Therefore, it is not possible to use a vial with a few days of physical/chemical stability for more than the usually 24-hour microbiological stability specified in the SPC, since it is not opened, dissolved (if powdered) and stored under controlled and validated conditions, which is a requirement for greater microbiological stability

However, there are medical institutions that do not report unusable residues to the NHIF. The data were obtained under the Access to Public Information Act from the NHIF. There is a tendency for the number of these medical institutions to decrease, and in 2020 /when the reimbursement of unusable residues begins/ they are the most. It is striking that these are mainly hospitals that received relatively little funds from the NHIF to pay for medicinal products for the treatment of malignant diseases and

medicinal productss for life-threatening bleeding in patients with congenital coagulopathy, with the exception of 2020.

Table 4. Hospitals that did not report unusable residues from the preparation of antitumor drug solutions

2020	2021	2022	2023	2024
CCC Veliko Tarnovo	CCC Veliko Tarnovo	CCC Veliko Tarnovo	CCC Veliko Tarnovo	MHAT “Hristo Botev” Vratza
MHAT “Hristo Botev” Vratza	MHAT “Hristo Botev” Vratza	MHAT “Hristo Botev” Vratza	MHAT “Hristo Botev” Vratza	MHAT Avis Medica Pleven
MHAT Avis Medica Pleven	MHAT Avis Medica Pleven	MHAT Avis Medica Pleven	MHAT Avis Medica Pleven	SHAT “Ioan Pavel” Sofia
UMHAT “St.Georgi” Plovdiv	UMHAT “St.Georgi” Plovdiv	UMHAT “St.Georgi” Plovdiv	SHAT “Ioan Pavel” Sofia	SHAC Oncology Sofia area
UMHAT “Tzaritza Ioanna” Sofia	SHAT “Ioan Pavel” Sofia	SHAT “Ioan Pavel” Sofia	SHAC Oncology Sofia area	UMHAT Medica Ruse
MHAT”St.Sofia” Sofia	SHAC Oncology Sofia area	SHAC Oncology Sofia area	UMHAT Medica Ruse	
SHAT “Ioan Pavel” Sofia		MHAT “St.Ivan Rilski” St.Zagora		
SHATHD				

The reasons for not reporting unusable residues to the NHIF may be different:

1. A large number of patients - they have activities in medical oncology, clinical hematology, pediatric clinical hematology and oncology, radiotherapy, the pharmacy works without a day off and prepares solutions daily

2. Lack of technical ability to report unusable residues - in 2020. some of the hospital software providers were still not technically ready to report unusable residues

3. Lack of training for reporting residues and lack of interest on the part of the staff

4. Lack of centralized reconstitution of cytotoxics

5. Rounding of individual doses to whole vials

The available information is not sufficient to understand the real reason for not reporting unusable residues in the indicated medical institutions

The analysis of the data received from the NHIF under the Access to Public Information Act shows that the medicinal products from which the largest amount of unusable residues were reported belong to the classic cytostatics. The registered dosage forms are usually large, since the individual doses are also very often high and small dosage forms are inconvenient to work with most cases, as they take a lot of time for the person preparing the solutions.

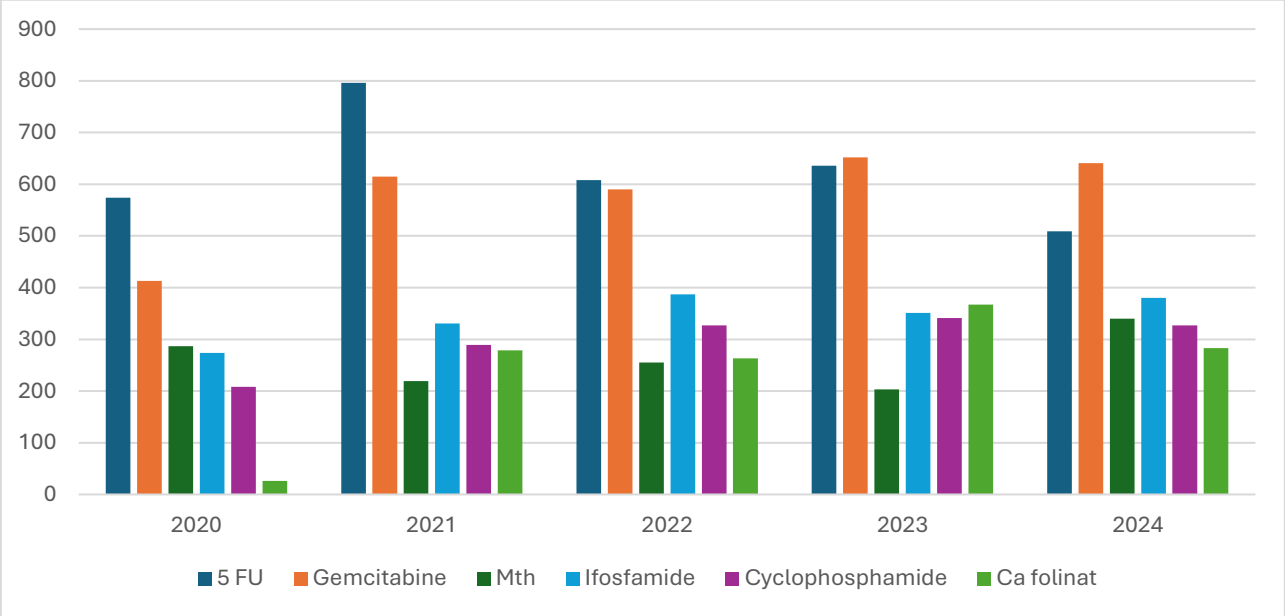

Fig. 5. Medicinal products with the largest amount of reimbursed active units of unusable residues for the entire country /according to information from the NHIF received under the Access to Public Information Act / - the amount is presented in grams

Comparing the five years during which unusable residues were reported, no drastic difference was observed in the reimbursed amounts of active units of the 6 mentioned drugs. The very low amounts of Ca folinate in 2020 are probably due to the fact that only dosage forms of 50mg and 100mg are available, which at the high doses administered by this medicinal product require more time for dissolution, but allow dosing to whole vials/ampoules and less unusable residues /but formation of more hazardous waste from the empty vials or ampoules/. This also determines the small amount of unusable residues of Ca folinate reported. In 2021, a 1000mg dosage form appeared, which is much more convenient for preparing solutions, but accordingly forms an unusable residue in the event of an incorrect work strategy. The number of patients and the schedule for their administration are of great importance for obtaining unusable residues when preparing a medicinal product. As can be seen from Table 5, the number of patients varies greatly.

Table 5. Number of patients in the country in a randomly selected month from 2020 to 2024 according to data from the NHIF for the six medicinal products with the largest amount of active units of reimbursed unused residues

	11.2020	11.2021	11.2022	11.2023	11.2024
5 FU	1674	1748	1895	2063	1941
Gemcitabine	420	501	540	558	531
Methotrexate	62	72	79	65	85
Ifosfamide	94	74	84	101	105
Cyclophosphamide	887	927	968	886	825
Ca folinate	1319	1471	1654	1840	2051

Since the indicated drugs belong to classical chemotherapy, i.e. they were discovered a long time ago, generic medicinal products are, at a low price, which accordingly determines the low value of their unusable residues. The indications and regimens for which they are applied are different, which also determines the different number of patients.

Table 6 Medicinal products with the largest amount of active units of reimbursed unused residues for the entire country /according to information from the NHIF received under the Access to Public Information Act / - presented as value

	2020	2021	2022	2023	2024
5 FU	2526,86	3030,71	2307,23	2660,18	2489,69
Gemcitabine	12643,11	17143,85	15029,03	16947,70	16497
Methotrexate	8963,29	6529,97	7528,12	5946,47	9479,48
Ifosfamide	25770,85	31219,53	36477,45	34657,25	38361,72
Cyclophosphamide	10954,88	15142,47	17116,24	18868,90	16179,31
Ca folinate	3119,55	31731,56	30517,57	42 977,34	32321,93
Sum	**63 978,54**	**104 798,09**	**108 975,64**	**122 057,84**	**115 329,28**

The six drugs with the largest amount of active units of reimbursed unused balances do not form a major part of the amount paid by the NHIF.

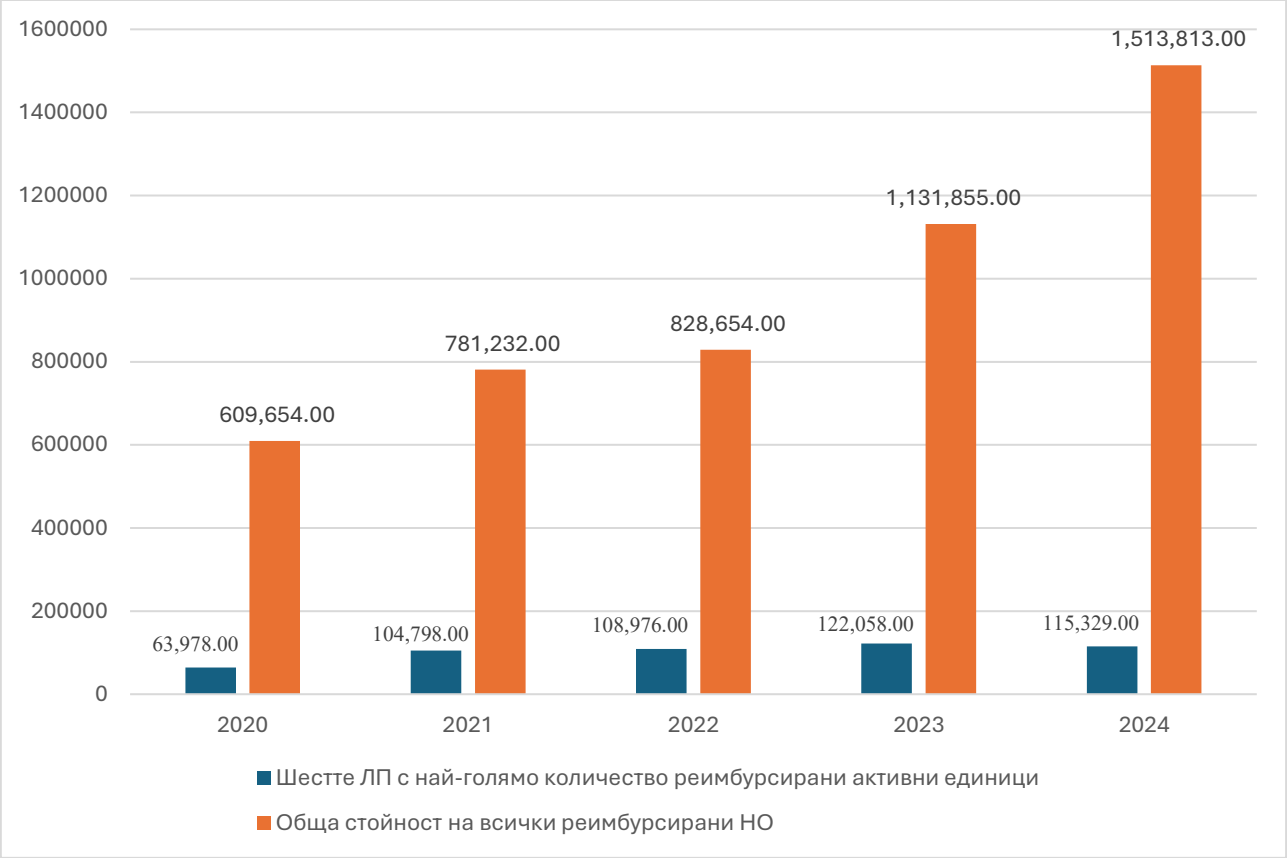

Fig. 6. Comparison of the growth of the six medicinal products with the largest amount of active units of reimbursed unused residues for the entire country compared to the reimbursed unused residues of all medicinal products in the period 2020 -2024.

Accordingly, the medicines, the reimbursed unused residues of which are of the greatest value, are mainly innovative, often biological molecules. Unlike the six medicinal products with the largest amount of reimbursed active units of unused residues, where the increase is very small, and in 2024 we even have a decrease, these medicines are experiencing a constant increase / with a difference every year in the medicinal products whose reimbursed unused residues are of the greatest value /. The following graph shows the medicinal products whose reimbursed unused residues are of the greatest value for each year / the first 6 /.

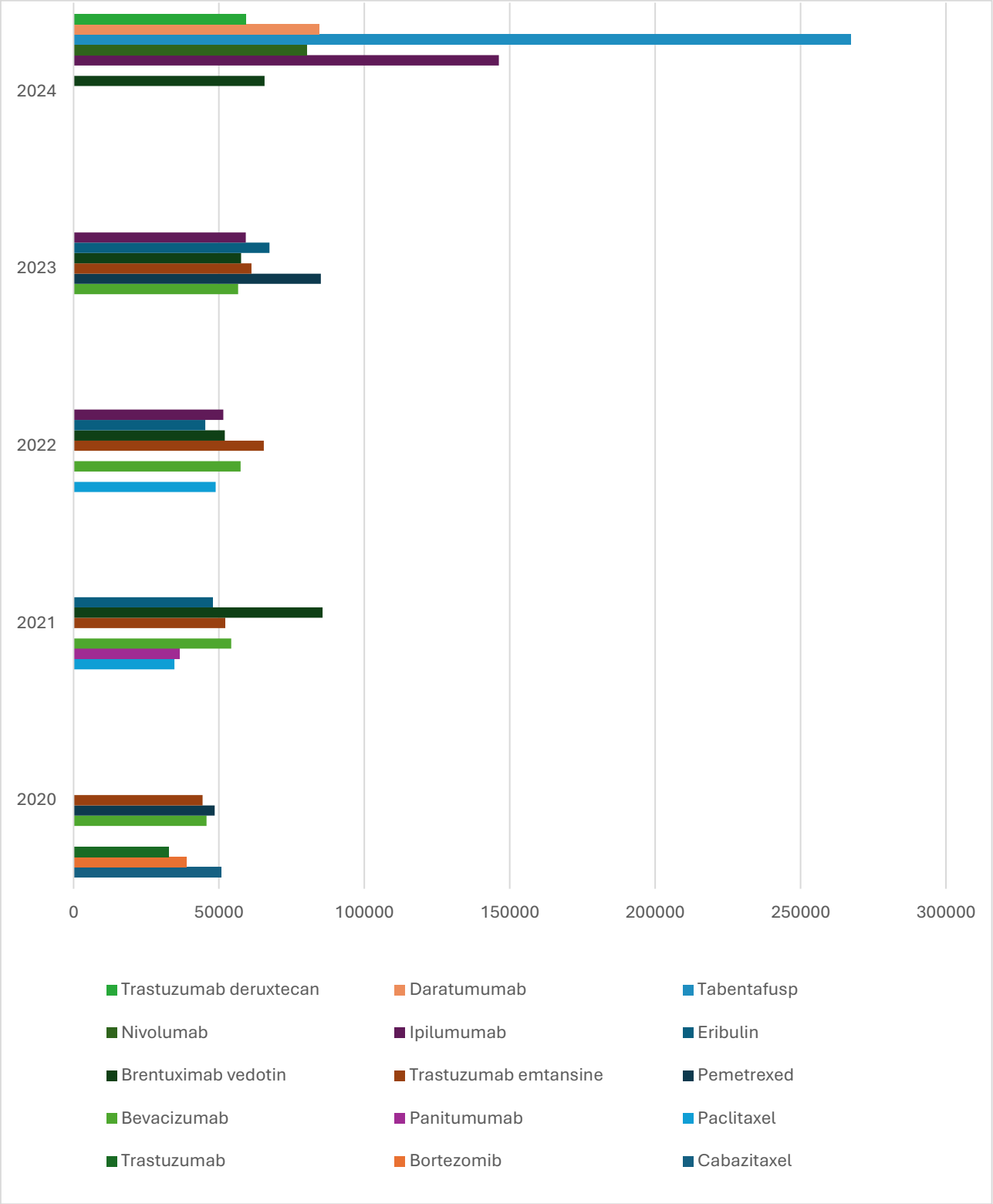

Fig. 7. Medicinal products whose reimbursed unused residues have the highest value for the respective year

Result of the general analysis of reimbursed unusable residues:

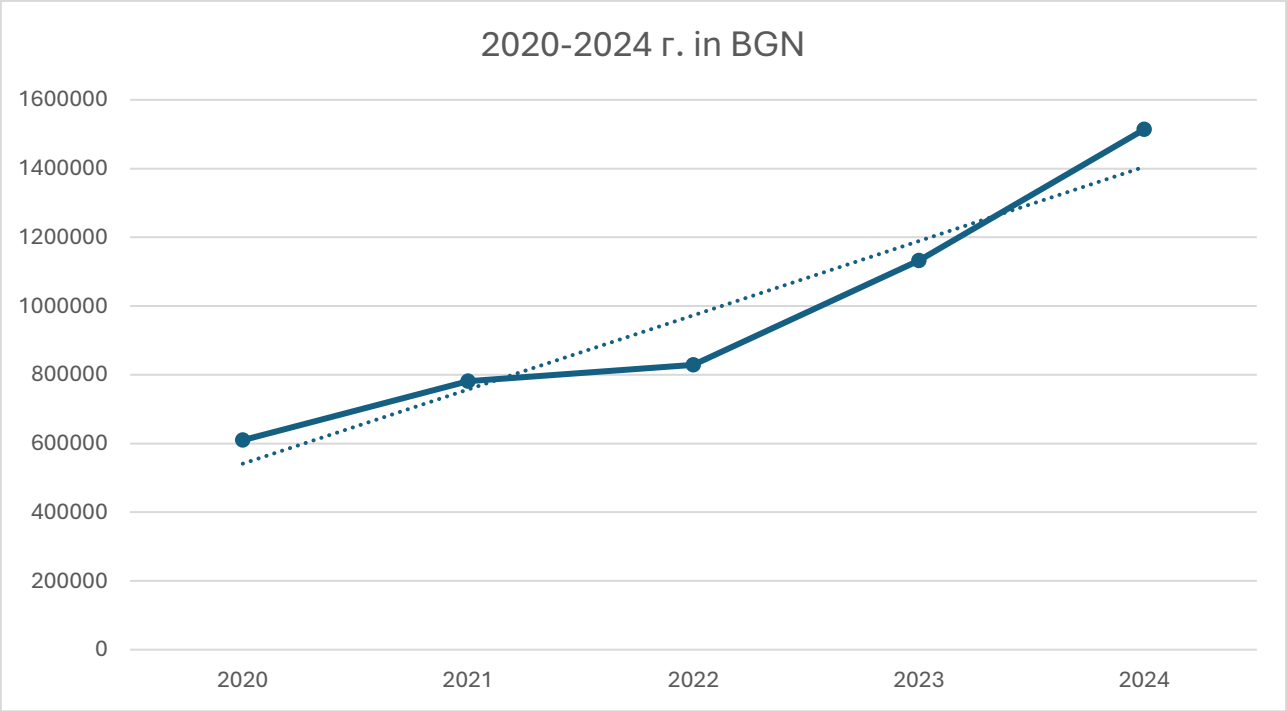

Fig. 8 Graph of the trend in the value of reported unused balances in BGN in the period 2020 – 2024.

1. The value of reimbursed unused residues of all medicinal products in 2020 is lower, since their payment starts in March, i.e. the numbers are for 10 months, not for a year. This year, the largest number of hospitals that did not report residues at all is 8 out of 39 (about 20%), some of which are very active - such as the University Hospital "St. George" Plovdiv and the SHATHD.

2. The trend in the value of reported unused residues in leva in the period 2020 - 2024 is constantly upward throughout the entire period, which is understandable, because every year new, innovative medicinal products are introduced, new indications for existing therapies are approved, the number of patients increases, i.e. the consumption of anti-tumor drugs increases. There is a clearly expressed upward trend in the value of reimbursed unused balances – from 609 thousand BGN in 2020 to over 1.5 million BGN in 2024. The total increase for the 5-year period is +148%, or about +904 thousand BGN. The largest growth compared to the previous year is in 2024 – over +382 thousand BGN. The smallest growth compared to the previous year is in 2022, i.e. absolute growth +47 thousand BGN. The largest absolute growth in the value of reported unused balances in BGN compared to the previous year is in 2024 (+382 thousand BGN), and the highest growth rate is in 2023 (36.59%).

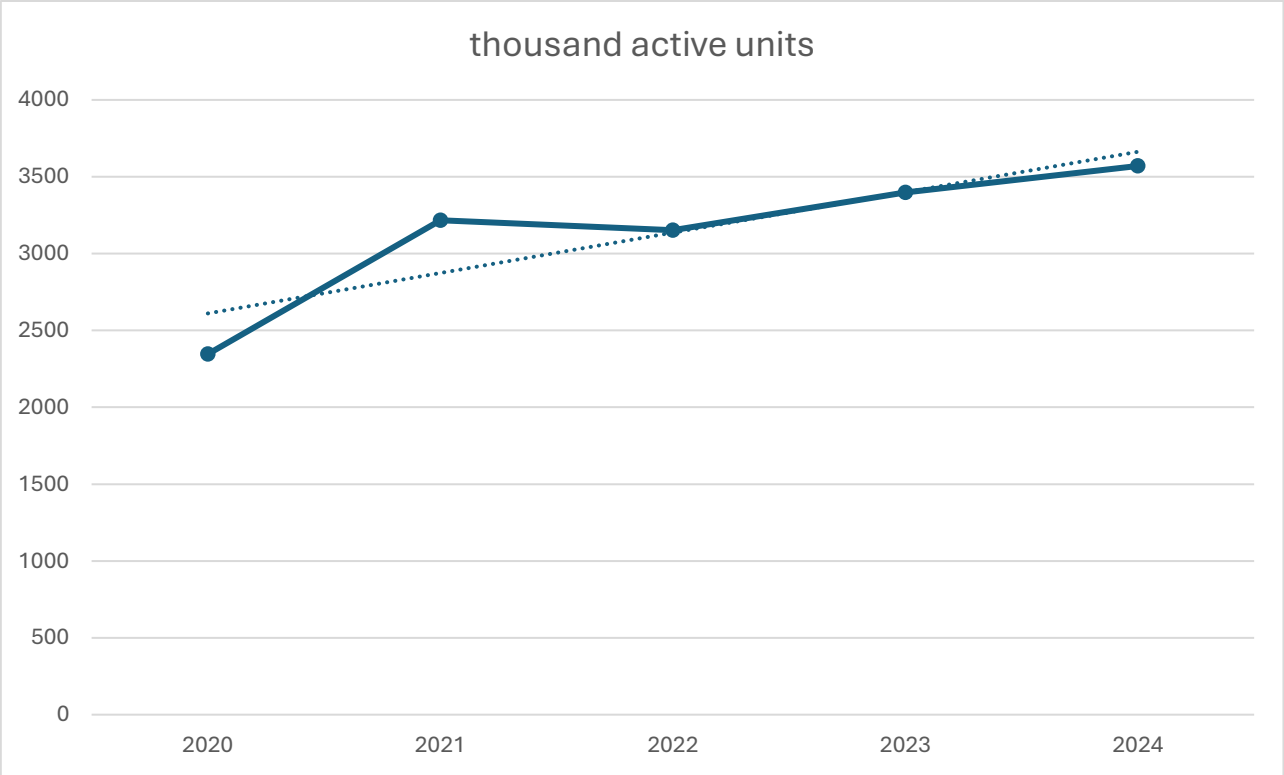

Fig. 9. Trend graph in reimbursed active units of reported unused balances in the period 2020 – 2024.

3. The trend in the reimbursed active units of the reported unusable residues for the period is also upward, but the trend of change is much smaller. The total growth in the amount of unused residues in act. units in the period 2020 - 2024 changes from 2,346 thousand act. units to 3,570 thousand (an increase of 1,224 thousand units +52%), and in 2022 we have a negative growth of - 2.08%. This means that the reimbursed unusable residues with a high value and a smaller number of active units are increasing.

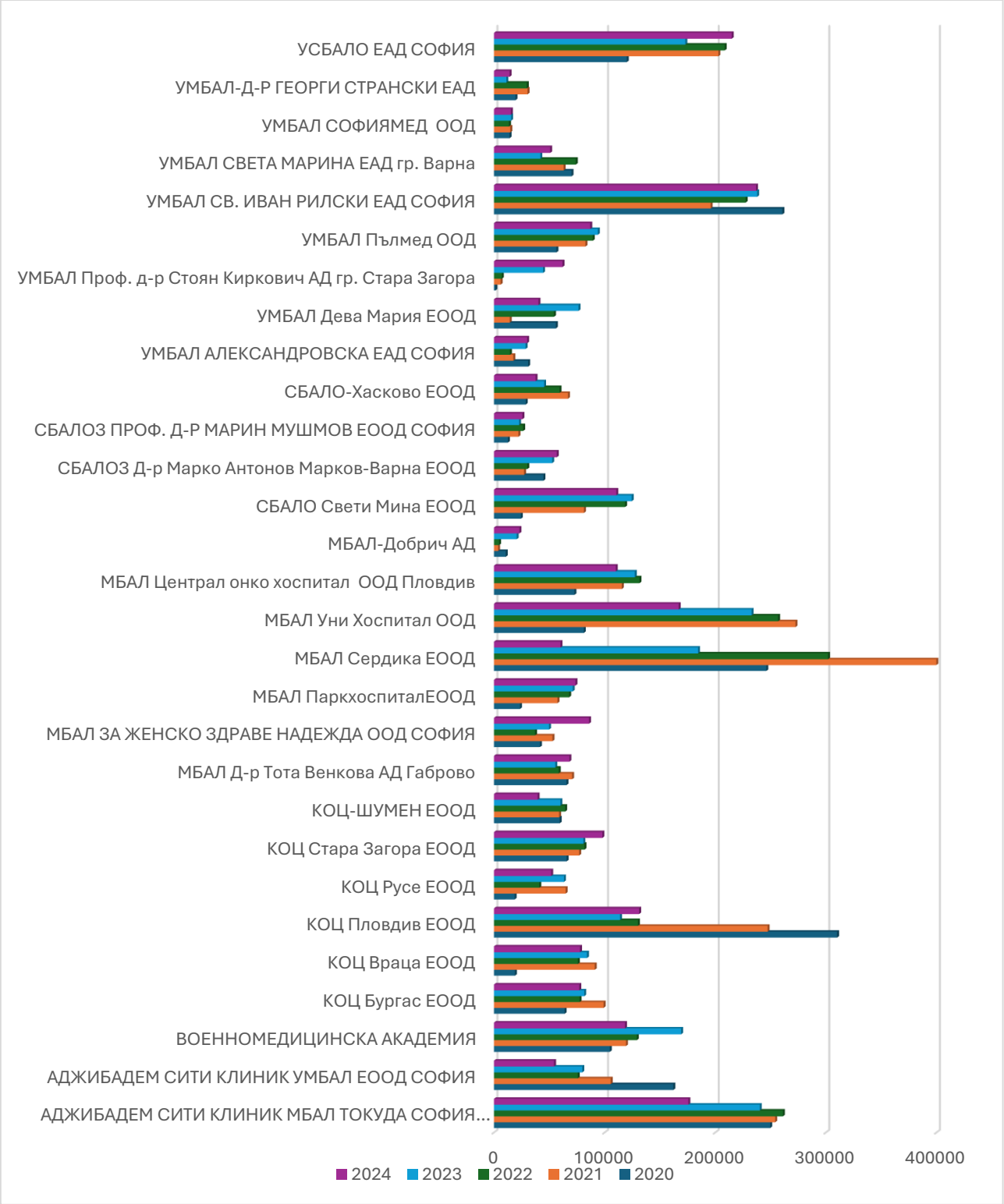

Fig. 10. Graph of reimbursed unusable residues /in actual units/ for all medical institutions that reported residues during the period 2020 – 2024.

Table 7. Medical institutions with the largest amount of reimbursed unusable residues for the period 2020 – 2024.

Hospital	UMHAT "Ivan Rilski" Sofia	MHAT Uni Hospital Panagyurishte	USHAT oncology Sofia	CCC Plovdiv	SHATHD*	ACC UMHAT Tokuda
Sum	**791 547,95**	**748 139,11**	**494 695,29**	**384 674,92**	**340 607,58**	**244 861,23**

*Includes data for the period 2021-2024, as no residuals were reported for 2020

Data analysis result:

From the presented data for specific hospitals, we can draw several conclusions:

1. The hospitals with the largest amount of reimbursed unused residues for the period 2020-2024 are the University Hospital "St. Ivan Rilski" Sofia and the University Hospital "Uni Hospital" Panagyurishte. A significant increase for both medical institutions was observed in 2023 and 2024. For the University Hospital "St. Ivan Rilski" Sofia in both years, the medicinal products with the largest relative share were Daratumumab and Ipilimumab. For the University Hospital "Uni Hospital" in 2023 - Pemetrexed and Bevacizumab, and in 2024 - Tebentafusp /represents 69.51% of the total amount for 2024/ and Eribulin.

2. The largest amount of reimbursed active units of medicinal products for the indicated medical institutions are those that are valid for the entire country (Fig. 5), with the medicines themselves varying according to the medical institution. At CCC Plovdiv, MHAT Uni Hospital, Acibadem City Clinic UMHAT Tokuda and SHATHD, Pemetrexed is also among the medicines with the largest amount of reimbursed units. The SPC of 5FU, Gemcitabine, Ifosfamide and Cyclophosphamide describes the stability of the products, as their physical and chemical stability is greater than 24 hours. In such a case, the microbiological stability is decisive for the shelf life of the opened or prepared concentrated and diluted solutions, which in the absence of controlled and validated conditions, such as the conditions in all hospital pharmacies in Bulgaria, is a maximum of 24 hours. This determines the need after this period, unused residues to be discarded according to the regulatory framework. With 5 Fluorouracil and Ca folinate, the number of patients is large (Table 5), the amount of medicinal product administered is large and, subject to all strategies, the amount of unused residue will be small and in most cases below 5% of the total amount administered per month. With Cyclophospamide, Ifosfamide, Gemcitabine and Methotrexate, the number of patients is smaller and depends on the medical institution - whether it has activities only in medical oncology or also clinical hematology, as well as on the implementation of strategies for reducing unused residues.

4. The reason for the large amount of unused residues may be the dosage form. Registration of more dosage forms of one medicinal product from one manufacturer is a prerequisite for reducing unused residues and improving access to the given treatment.

- Methotrexate - the dosage form appearing in the PLS, Appendix 2, in Bulgaria is 1000mg. When we talk about medical institutions that only have activities in medical oncology, when choosing therapy with Mth, the hospital discards between 80 and 90% of each vial. Methotrexate according to the SPC is used in the field of oncology for the treatment of breast cancer at a dose of 40mg/m2. With an average height and weight of a patient - 165cm and 65kg, her body surface area is 1.72m2. The individual dose will be:

D = 1.72 x 40 = 68.80 mg

The therapeutic regimen is on the 1st and 8th day of the cycle. Even if there are two or three patients with this therapy in one hospital and they manage to come on the same day and their condition allows the application of the therapy, about 800mg /80%/ will be discarded.

4.4. Study of the demographic and professional characteristics of pharmacists who prepare parenteral solutions of medicinal products for systemic treatment of malignant diseases

To achieve the task set in this work, a study was conducted STUDY OF THE NEED FOR SPECIALIZED TRAINING OF PHARMACISTS PREPARING PARENTERAL SOLUTIONS OF ANTI-TUMO MEDICINAL PRODUCTS IN HOSPITAL PHARMACIES OF MEDICAL INSTITUTIONS IN BULGARIA, for which a positive opinion was received from the Research Ethics Committee at the Medical University of Varna. The study was conducted in the period 01.11.2024 - 31.12.2024.

In Bulgaria in 2024, there were 44 hospitals that perform activities in medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology. From 18 of them /40.9% of all/ a declaration - consent was received from the Heads of the hospital pharmacies for participation in an online interview of the pharmacists in the pharmacy who prepare solutions of antitumor drugs. University Hospital "Kanev" Ruse was excluded from the study, since there is no centralized preparation of antitumor drugs, although it has a II level in clinical hematology.

Of the research centers from which a declaration - consent was received, 9 /50%/ are private hospitals, 6 /33.33%/ are state hospitals and 3 /16.66%/ are municipal /complex oncology centers/, including University Hospital "Kanev". Some of the participants in the study did not answer this question, which means that they are not familiar with the ownership of the medical institution in which they work.

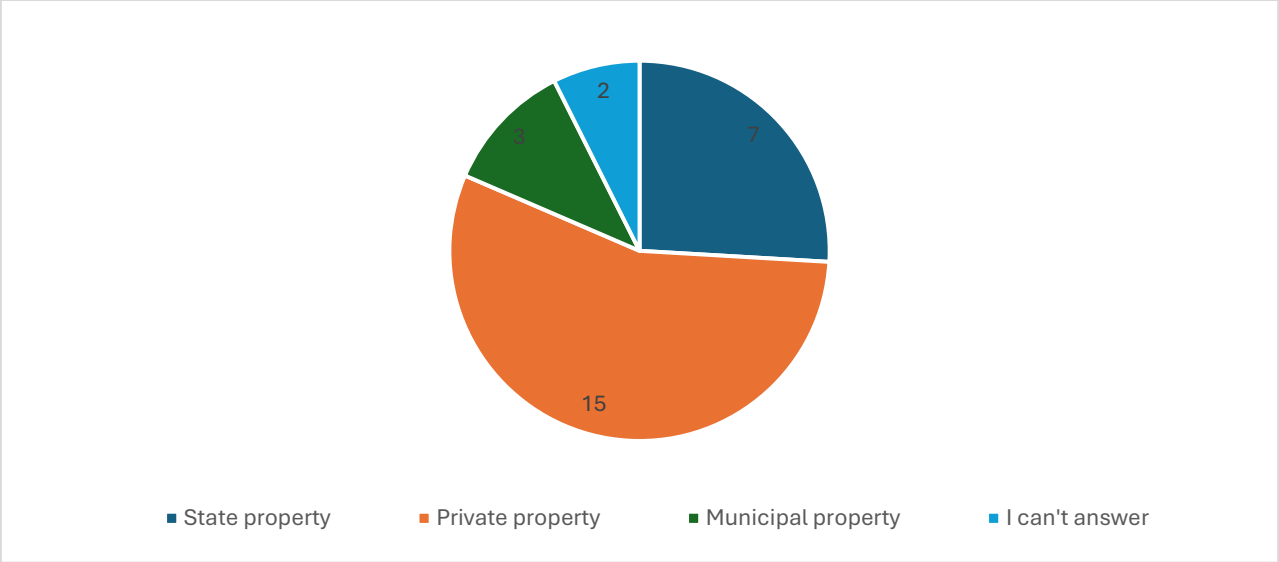

Fig. 11. Distribution of medical institutions by ownership according to participants' responses

From the remaining 17 medical institutions /after excluding University Hospital "Kanev" Ruse/ responses were received from 32 pharmacists /20 master pharmacists and 12 assistant pharmacists/, with 5 people excluded from the study because they did not give permission for access to their confidential information to researchers or regulatory authorities upon request. Of the remaining 27 pharmacists – 18 /66.66%/ are master pharmacists, and 9 /33.33%/ are assistant pharmacists. Of the master pharmacists – 13 /72.22%/ are women, and 5 /27.77%/ are men. All assistant pharmacists /100%/ are women.

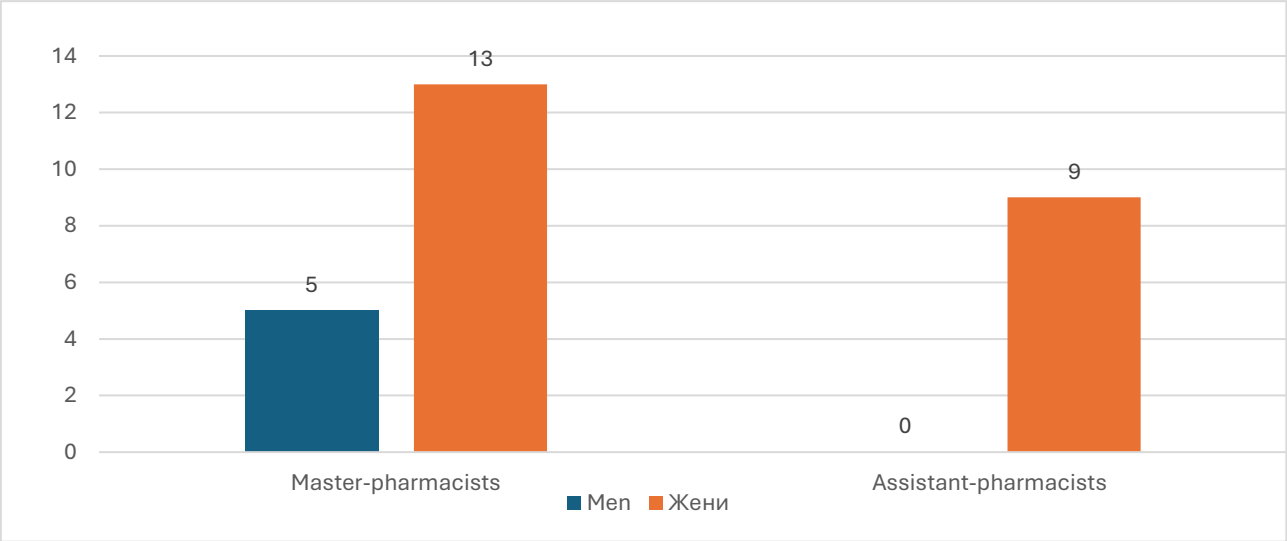

Fig. 12. Distribution of survey participants by education and gender

The age of the respondents is divided into three groups:

1. 18 – 35 years old - 22.22%
2. 36 – 50 years old - 48.15%
3. 51 – 65 years old - 29.62%

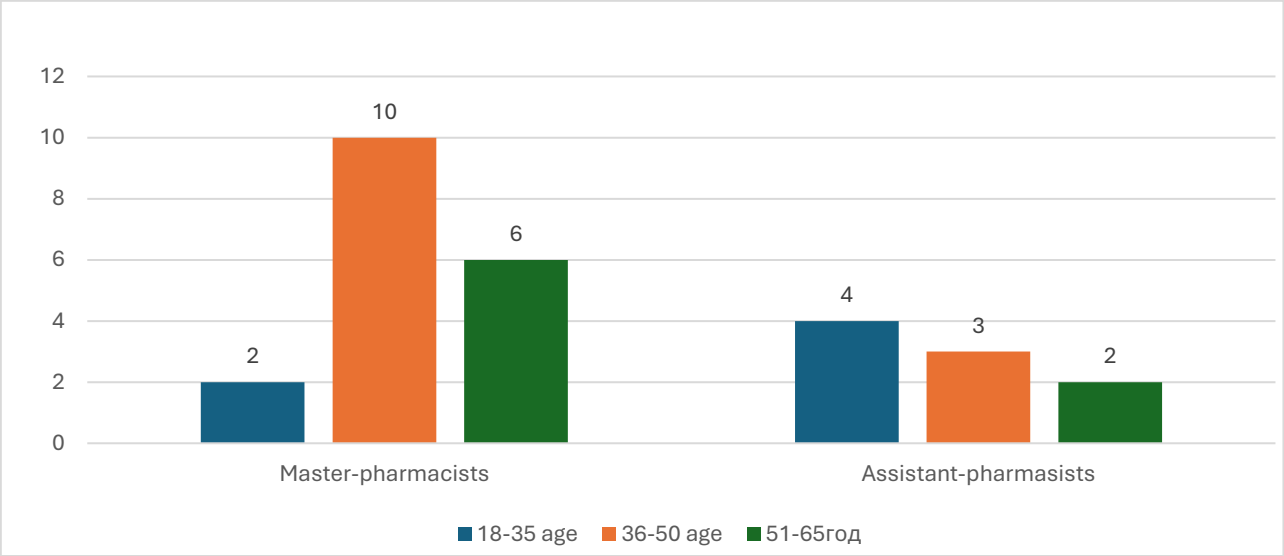

Fig. 13. Distribution of survey participants by education and age

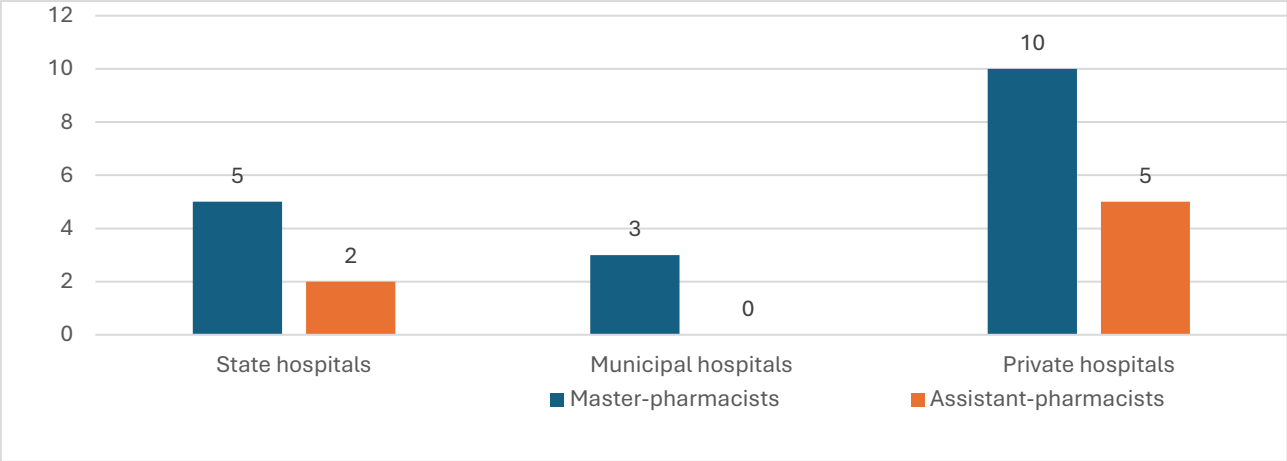

Fig. 14. Distribution of survey participants by education in healthcare facilities with different ownership[1]

1 These graphs do not take into account the responses of two pharmacist assistants, as they cannot determine the ownership of the hospital in which they work.

Results of the study on the demographic and professional characteristics of pharmacists who prepare parenteral solutions of medicinal products for the systemic treatment of malignant diseases:

1. Solutions are prepared by both master pharmacists and assistant pharmacists.

2. In medical institutions that prepare solutions of cytotoxics more master pharmacists work than assistant pharmacists

3. Pharmacists preparing solutions of antitumor drugs are predominantly women, with men being mainly master pharmacists

4. The largest part of the pharmacists participating in the study /masters and assistants/ are in the age group from 36 to 50 years

5. Young pharmacists, aged between 18 and 35, work mainly in private hospitals, which can be explained by better pay

6. The predominant age of master pharmacists preparing cytotoxics is between 36 and 50, followed by the age group 51 - 65 years, and the least are those between 18 and 35 years. In contrast, assistant pharmacists aged 18 to 35 predominate, while the group aged 51 to 65 is the smallest.

7. The preparation of ready-to-use solutions of antitumor medicinal products in the country is carried out mainly by master pharmacists, women, aged between 36-50

8. One of the reasons why fewer pharmacists aged 18-35 prepare solutions of medicinal products for the systemic treatment of malignant diseases is the fear of the toxic effects of cytostatics and their potential effect on the reproductive capabilities of those working with them. In the conditions of Bulgaria, this is not without reason, given the lack of established detailed standards for equipment in this area and their adequate control.

4.5. Study of the training of pharmacy staff performing centralized preparation of cytotoxics

The preparation of ready-to-use solutions of medicinal products for the systemic treatment of malignant diseases is a specific, highly specialized pharmaceutical activity that requires special knowledge and skills. Currently, there is no regulatory document in Bulgaria that specifies exactly what competencies are required to perform this activity, as well as a single approved national training program that covers both theoretical and practical aspects of the process. The training of employees is decided at the level of the medical institution and is usually voluntary, although it is critically important for the protection of personnel and the quality of the prepared product. The aim of the study is to collect information in the participating hospitals on the training of pharmacists performing centralized preparation of cytotoxics.

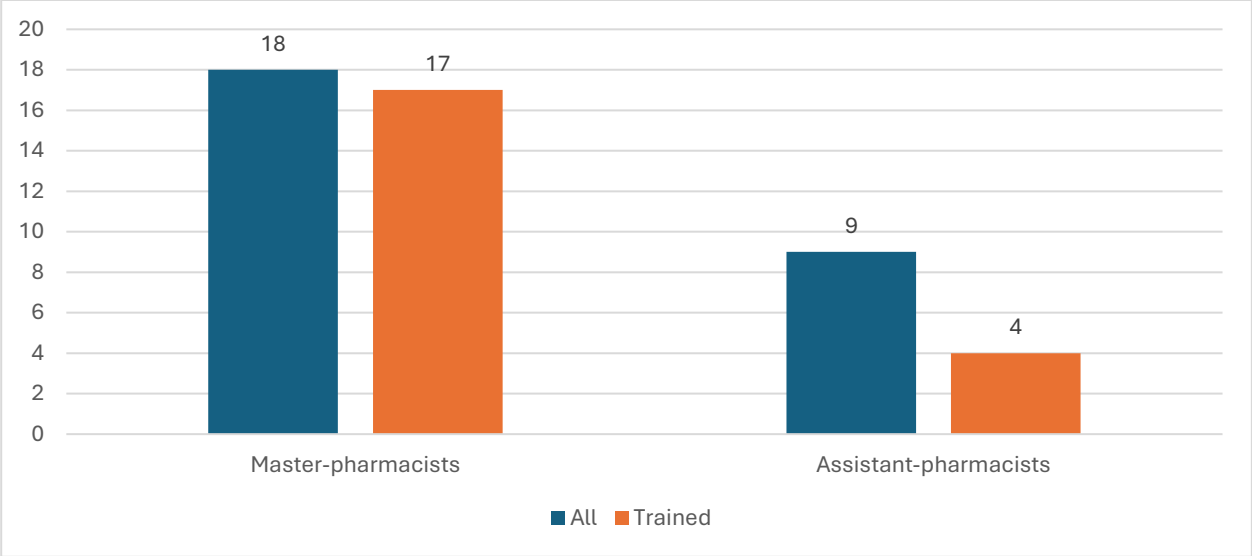

Fig.16 Comparison of those who have completed training compared to the total number of pharmacists participating in the study

The ownership of the medical facility is not decisive for attending courses, as pharmacists from hospitals with different ownerships included in the study have undergone training.

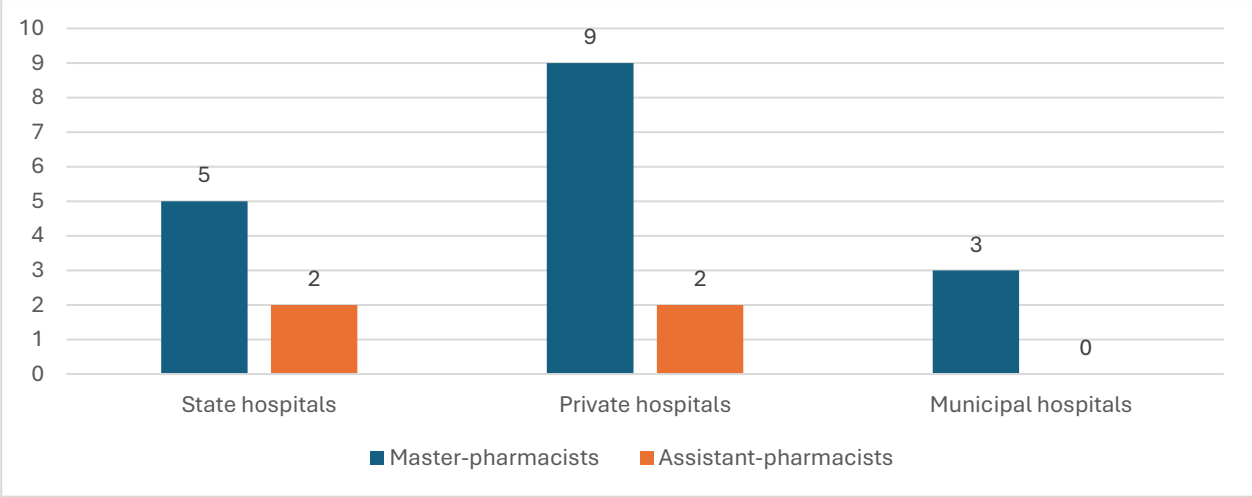

Fig.17 Distribution of pharmacists who participated in training according to their place of work[1]

1 These graphs do not take into account the responses of two pharmacist assistants, as they cannot determine the ownership of the hospital in which they work.

The training courses that are mainly attended by Bulgarian pharmacists are those organized by the European Society of Oncology Pharmacy /ESOP/ and the Bulgarian Society of Oncology Pharmacy /BSOF/, with the Bulgarian program being shorter and mainly covering basic knowledge and skills. Some of the pharmacists have attended both trainings.

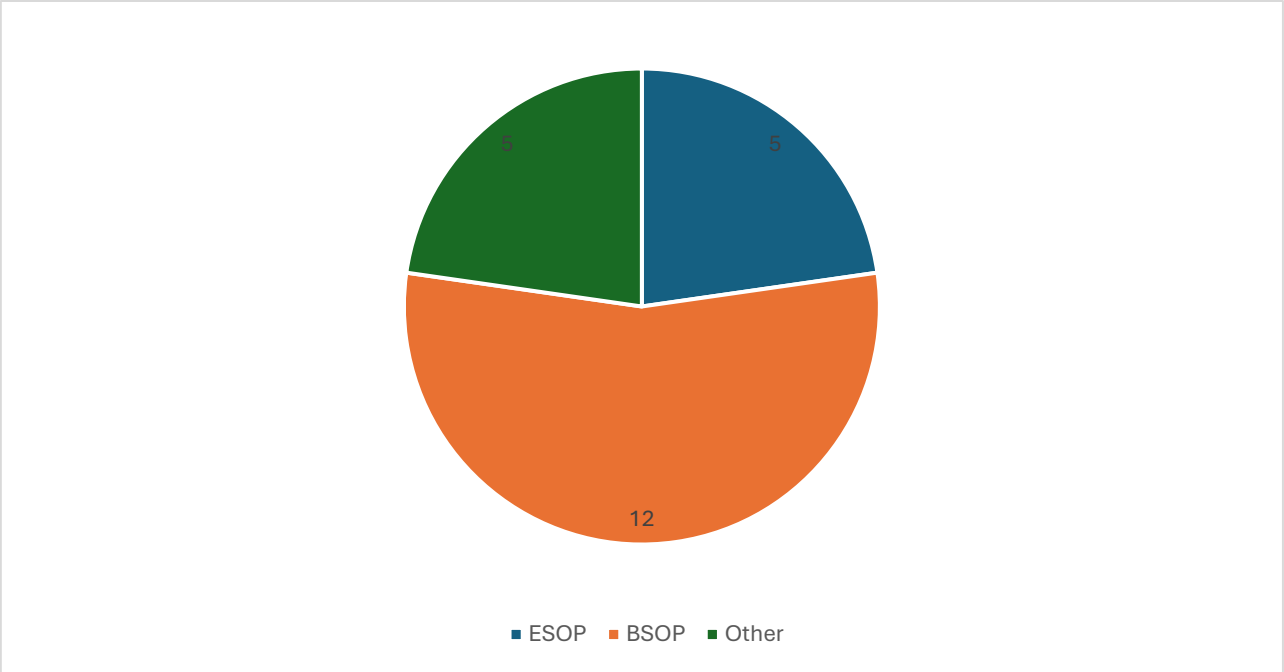

Fig.18 Types of training attended by the pharmacists participating in the study

The participants in the study indicated that practical training was conducted by:

- fellow pharmacists
- company representatives
- nurses

One of the participants trained himself.

According to European practice, the training of pharmacists related to working with hazardous drugs is of two types - training of new staff and upgrading training. Particular attention should be paid to the training of new staff, the main topics of which are: types of personal protective equipment, the standards they must meet and their correct use, as well as aseptic technique /theory and practice/ in the preparation of parenteral solutions of antitumor drugs. PPE is the last level of the hierarchy of controls, but employees rely heavily on them. Aseptic technique determines the quality of the product. Two of the questions in the study are related to the self-assessment of pharmacists regarding their knowledge in these two areas. As expected, almost all of those who attended some training believe that they are well prepared.

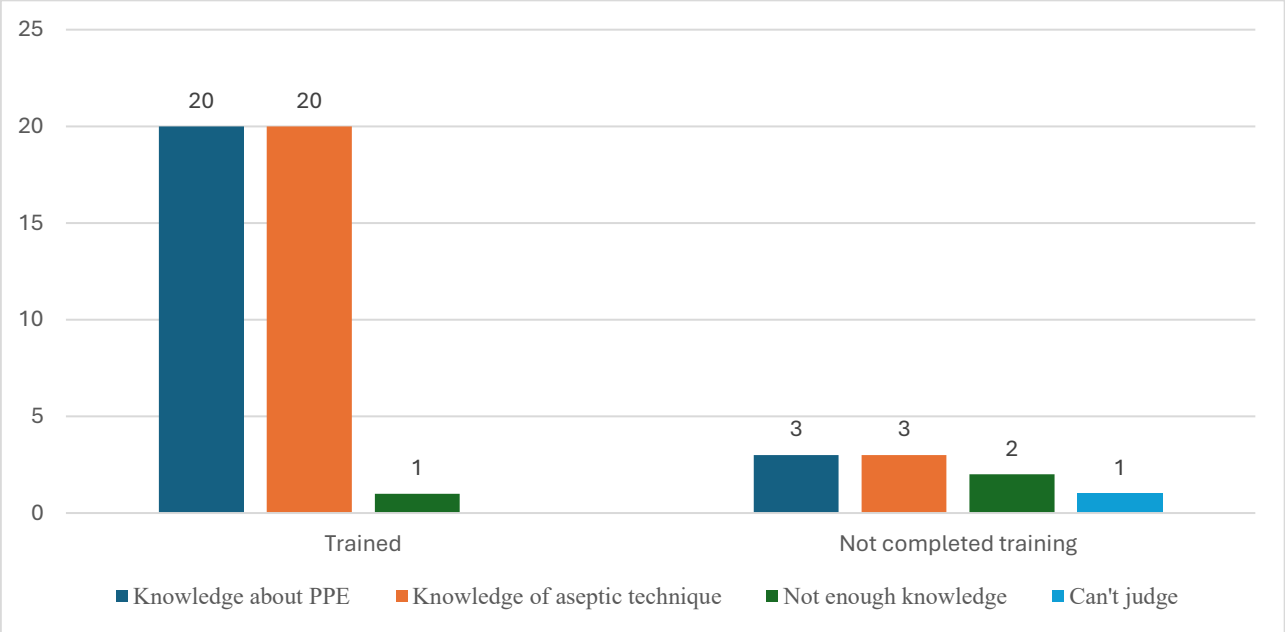

Fig. 19. Self-assessment of pharmacists preparing parenteral solutions of antitumor drugs regarding their knowledge of PPE and the aseptic technique they use

Results of a study on the training of pharmacy staff performing centralized dilution of cytostatics:

1. 94.44% of all participating master pharmacists and 44.44% of all participating assistant pharmacists have undergone some training, which shows its importance for employees who prepare solutions of antitumor drugs.

2. The main trainings that the interviewed pharmacists attended were organized by non-governmental, professional organizations - ESOP and BSOP

3. Almost all those who attended the training assessed their knowledge of PPE and aseptic work technique as sufficient

4. Since there are no national mandatory criteria developed regarding knowledge and skills in this area in order to have comparability, and there is no developed and approved control system, the self-assessment of pharmacists related to their knowledge of the type and use of PPE and aseptic work method is largely subjective, without being based on validated results.

4.6. Recommendations for improving the regulatory framework, as well as the training of pharmacists preparing solutions of antitumor drugs

After the introduction of changes in Regulation 28 of December 9, 2008 on the structure, order and organization of the work of pharmacies and the nomenclature of medicinal products of the Ministry

of Health of the Republic of Bulgaria, in October 2015 and the launch of the centralized preparation of ready-to-use parenteral solutions of medicinal products for the systemic treatment of malignant diseases, the practice is developing. A number of problems and issues arise that have no solution in the current regulatory framework. Amendments to the legislation would lead to a number of positive changes in the sector, concerning both better working conditions and protection of personnel, guaranteed quality of the prepared products and increased efficiency in the use of antitumor medicinal products.

1. Ministry of Labor and Social Policy

A large part of antitumor drugs are classified as "hazardous drugs" according to NIOSH and employees who work with them must be protected by introducing a hierarchy of controls. What is written in the Health and Safety at Work Act and Ordinance No. 10 of September 26, 2003 on the protection of workers from risks associated with exposure to carcinogens, mutagens or substances toxic to reproduction at work (title amended - State Gazette, issue 28 of 2024, effective 05.04.2024) is a step in the right direction. The amendments adopted in the 2024 ordinance somewhat specify the minimum measures that must be taken for protection when working with "dangerous drugs". However, several practical problems can be identified:

- due to the lack of a direct link between carcinogens, mutagens or substances toxic to reproduction and "hazardous drugs" in the cited regulation, the point of view of medical institutions on the issue is too individual and has a great freedom of action, which does not always guarantee the protection of personnel who are in daily contact with antitumor drugs

- we do not have an officially recognized list of "hazardous" drugs in Bulgaria. The fact that a given list is recommended means that employers in most cases neglect it

- the adopted regulation is not known among the institutions and responsible persons in the field of labor protection in medical institutions, so that at least some of the described measures can be introduced as soon as possible

2. Ministry of Health

Specifically for hospital pharmacies, the requirements that the sector for the preparation of cytotoxics must meet are specified in the Rules for Good Pharmaceutical Practice. Considering that Regulation 28 of December 9, 2008 on the structure, order and organization of the work of pharmacies and the nomenclature of medicinal products is the regulatory act that describes the structure of pharmacies, the standards that a hospital pharmacy in which there is centralized preparation of medicinal products must meet should be listed in it. Now the existing ones need to be expanded, deepened and detailed, so that the medical institution has clear criteria that must be met in order for the pharmacy to receive a license.

The research team recommends specifying the standards for structure and equipment that the centralized dilution sector must have. The “Rules for Good Pharmaceutical Practice” can serve as a

basis, but they need to be expanded. When developing the requirements, it should be borne in mind that centralized preparation can be not only of antitumor drugs, but also of others that do not fall into the “dangerous” group – e.g. antibiotics. The two groups of drugs cannot be prepared in the same sector due to the risk of contamination of antibiotics with toxic drugs. The exception is parenteral drugs that do not have CMR properties, but are used in the therapy of oncological patients. This makes it necessary to develop criteria for a sector for centralized preparation of "dangerous drugs" and for those that are not dangerous. It is mandatory to indicate the necessary class of primary engineering controls according to good European and world practices, as well as the requirements for secondary controls / premises /, which depend on the primary ones.

3. Bulgarian Drug Agency and the Ministry of Health

Certification of the pharmacy for GMP to guarantee:

- the quality of the prepared product

- the possibility of longer microbiological stability of open vials with concentrated or dissolved, but not yet used drugs, which reduces the amount of unusable residues when preparing the solutions

Certification must be carried out by an independent authorized institution / e.g. Ministry of Health or Bulgarian Drug Agency / according to previously developed, approved and validated standards. Documents and guidelines of the EU and individual countries where this has been practiced for a long time can serve as a basis

4. Ministry of Education and Ministry of Health

To introduce a requirement that pharmacists who prepare solutions of antitumor drugs must have undergone initial specialized training under an approved national program. And currently, the Health and Safety Act states that the employer must provide training. Given the fact that there is no regulatory document that specifies exactly what competencies are required to perform this activity, the employer is left with the discretion of what training to provide. The survey conducted clearly shows that pharmacists consider it necessary to undergo specialized training, which is not carried out during university studies, which is why most of the interviewees underwent such training voluntarily.

5. Medical universities with Faculties of pharmacy

The development and approval of a specific training program, which must be completed by all pharmacists before they start dissolving cytostatics, will undoubtedly ensure equal access to the necessary basic knowledge and skills related to workplace protection and the quality of the prepared product, regardless of their place of work. The training must necessarily include two modules: theoretical and practical and be of several days' duration. The theoretical part must necessarily include the following topics:

- Quality control and risk management system;

- Knowledge of national and regional laws, rules, regulations and best practices;

- Safe work with hazardous substances within the sector;

- Hazards and protective equipment, equipment and disposal of contaminated material;

- Prevention and control of incidents;

- Work with hazardous waste;

- Drugs and dosage forms;

- Stability and incompatibilities;

- Preparation management;

- Working in an aseptic environment; Technical equipment required for reconstitution and handling of cytostatics;

- Drug effects and pharmacology;

- Pathology and dose response;

- Management of clinical trials with cytostatics;

- Quality control;

The practical part should include:

- Aseptic working techniques and their validation in a work process simulation;

- Working with single-use medical devices;

- Simulation of incidents and their management;

- Working with various documentation systems;

- Packaging, quality control systems for delivery and destruction of contaminated material;

- Methods for assessing practical training;

- Working with a decontamination kit;

The question arises as to who will conduct the training. In different countries there are different options – they can be private or public institutions, professional organizations – independently or in cooperation with universities. While the theoretical part could be conducted in higher education institutions, the practical part must necessarily be conducted in the real environment of a hospital pharmacy, by practicing, certified master pharmacists, in order to have the desired effect. The training should end with an exam and a certificate certifying the completed course.

6. National Assembly

If we learn from the experience of other countries in increasing the efficiency of the use of antitumor drugs, we can consider amendments to the legislation that would allow a hospital pharmacy to prepare solutions for parenteral administration for other nearby medical institutions, following the example of the Scandinavian countries. This would allow large investments in material resources and personnel to be made by fewer hospitals, but they would meet all the requirements. Also, the preparation of more solutions by a certified pharmacy would lead to the avoidance of underdosing of patients in order to reduce unusable residues, respectively to compromising the treatment of patients, lack of the expected effect and a greater economic burden on the health system due to non-compliance with therapeutic guidelines. This is especially true for hospitals with a small number of beds, a lower level of competence and a lack of personnel. Creating a sector for the preparation of cytotoxics that meets all standards is too large an investment, which is also economically unjustified with a small number of patients. With the current lack of control, many hospital pharmacies do not even meet the existing minimum requirements, but nevertheless continue to operate. The result is inadequate protection of personnel with a potential risk of developing many diseases in the future as a result of exposure at work and treatment that does not meet therapeutic guidelines and therefore has a questionable effect, but is nevertheless paid for with public funds. Given the fact that the country is not a large territory and has a large network of hospitals, the use of certain anti-tumor drugs could even be expanded to regions where this is currently not done, if the decision for treatment and preparation of solutions is made in hospitals that meet all standards.

Summary of recommendations for improving the regulatory framework, as well as the training of pharmacists preparing solutions of antitumor drugs:

1. Expanding, deepening and detailing the standards for equipment and facilities that the centralized dilution sector must have, and developing them separately for "hazardous" drugs and those that do not have CMR properties

2. Certification of the hospital pharmacy for GMP, as well as developing procedures for controlling and validating processes

3. Introducing a requirement that pharmacists who prepare solutions of antitumor drugs must have completed initial specialized training, consisting of a theoretical and practical part according to an approved national program, which must be certified with a certificate. The practical part must be conducted in a real environment, in an accredited hospital pharmacy for the purpose.

4. Changes in legislation that would allow a hospital pharmacy to prepare parenteral solutions for other medical institutions.

V. Conclusions

1. In the period from 2019 to 2024, only 8 hospitals were in the top six for at least two years that received the most funds from the NHIF for payment of medicinal products for the treatment of malignant diseases and drugs for life-threatening bleeding in patients with congenital coagulopathy. Only two of these 8 medical institutions are private. Four of them are located in Sofia and one in Plovdiv, i.e. 62.5% of hospitals that received the most funds from the NHIF for payment of medicinal products for the treatment of malignant diseases and drugss for life-threatening bleeding in patients with congenital coagulopathy are located in the regions with the most medical institutions for the treatment of malignant diseases.

2. A study conducted in 2019 on the centralized preparation of cytotoxics in hospital pharmacies and inspections carried out in the period 26.09.2023–11.10.2023 by inspectors from the Bulgarian Drug Agency on the territory of the city of Sofia for the implementation of the provisions of the Law on Medicinal Products in Human Medicine Regulation 28 of December 9, 2008 on the structure, order and organization of work in pharmacies and the nomenclature of medicinal products, as well as the instructions in Chapter III of the Rules for Good Pharmaceutical Practice (Preparation of medicinal products in pharmacies of medical institutions), show that not all medical institutions comply with the regulations in Bulgaria related to the centralized preparation of solutions for the systemic treatment of malignant diseases. They have different ownership and are located in different parts of the country.

3. There is inequality of hospitals – those that comply with the legislation are at a disadvantage compared to those that do not, as they have invested significant financial resources to meet the requirements regarding the centralized preparation of cytostatics, which is not shared by all affected medical institutions for various reasons. Given the fact that this continues for years after the change in the legislation, it means that the offending hospitals are not sanctioned, therefore, the control of the competent authorities is greatly reduced.

4. Hospitals that have not met the requirements of the regulation and the Rules for Good Pharmaceutical Practice have different ownership – private, state and municipal, i.e. non-compliance with the regulatory framework is not related to ownership, but to the management of the medical facility

5. The quality of clinical trials with antitumor drugs conducted in medical facilities that do not meet regulatory requirements is questioned, as it is determined by all planned and systematic actions that are established to ensure that data are obtained, documented (recorded) and reported and that the trial is conducted in accordance with Good Clinical Practice and applicable regulatory requirements.

6. Currently, no institution in Bulgaria can realistically say in all hospitals that have activities in medical oncology and/or clinical hematology and/or pediatric hematology and oncology whether:

- Solutions for systemic treatment of malignant diseases are prepared in the hospital pharmacy by pharmacists

- The equipment that the pharmacy has meets global standards for working with hazardous substances, i.e. whether the personnel working with it, the product being prepared and the environment are protected

- The sector for the preparation of cytotoxics has the necessary level of cleanliness according to the available equipment

- The number of pharmacists working in the pharmacy is sufficient to guarantee the quality of the process

- The aseptic technique of the pharmacists preparing the solutions meets international standards

- The personal protective equipment that is used meets the requirements and is used in the correct manner.

7. The reimbursement by the NHIF of the unused residues meeting the requirements that are formed during the preparation of parenteral solutions of antitumor drugs begins in 2020. The trend in the value of the reported unused residues in leva in the period 2020–2024 is constantly upward throughout the entire period, which is understandable because every year new, innovative products are introduced, new indications for existing therapies are approved, the number of patients increases, i.e. the consumption of antitumor drugs increases. The total increase for the 5-year period is +148%, or about +904 thousand BGN

8. The trend in reimbursed active units of reported unused residues for the period is also upward, but the trend of change is much smaller. The total growth in the amount of unused residues in act. units in the period 2020–2024 changes from 2,346 thousand act. units to 3,570 thousand (an increase of 1,224 thousand units +52%), and in 2022 we have a negative growth of -2.08%. This means that medicinal products with a high value of reimbursed unused residues and a smaller number of active units are increasing.

8. The medical institutions with the largest amount of reimbursed unusable residues for the period 2020-2024 are the University Hospital "St. Ivan Rilski" Sofia and the University Hospital Uni Hospital Panagyurishte. A significant increase for both medical institutions was observed in 2023 and 2024. For UMBAL "St. Ivan Rilski" Sofia in both years with the largest relative share were the medicinal products Daratumumab and Ipilimumab. For MHAL "Uni Hospital" in 2023 - Pemetrexed and Bevacizumab, and in 2024 - Tebentafusp /represents 69.51% of the total amount for 2024/ and Eribulin.

9. In the SPC of a large part of the drugs forming residues, a physical and chemical stability longer than 24 hours is noted. In such a case, the microbiological stability is decisive for the shelf life of the opened or prepared concentrated and diluted solutions, which in the absence of controlled and validated conditions, such as the conditions in all hospital pharmacies in Bulgaria, is a maximum of

24 hours. This determines the need after this period for unused residues to be discarded in accordance with the regulatory framework. With a large number of patients and the implementation of strategies to reduce unused residues, the amount of unused residue formed will be small and in most cases below 5% of the total amount administered per month. The reason for the large amount of unused residues may be the dosage form. Registration of multiple dosage forms of a medicinal product from a single manufacturer is a prerequisite for reducing unused residues and improving access to the given treatment.

10. The preparation of solutions for direct administration of drugs for the systemic treatment of malignant diseases is an activity requiring specialized training according to European practices. Currently, there is no regulatory document in Bulgaria that specifies exactly what competencies are required of pharmacists working in the sector for the preparation of cytostatics. The study conducted for the purpose of this work shows that 94.44% of all participating master pharmacists and 44.44% of all participating assistant pharmacists have voluntarily undergone some training, which shows its importance for employees who prepare solutions of antitumor drugs. The main trainings that the interviewed pharmacists attended were organized by non-governmental, professional organizations - ESOP and BSOP

11. Almost all pharmacists who attended training assess their knowledge of PPE and aseptic work technique as sufficient. Since there are no national mandatory criteria developed regarding knowledge and skills in this area in order to have comparability, as well as there is no developed and approved control system, the self-assessment of pharmacists related to their knowledge of the type and use of PPE and aseptic work method is largely subjective, without being based on validated results.

12. According to the research conducted for the purpose of this work, the preparation of ready-to-use solutions of antitumor medicinal products in the country is carried out mainly by master pharmacists, women, aged between 36-50 years.

13. The existing regulatory framework in the field of centralized preparation of medicinal products for the systemic treatment of malignant diseases has a number of shortcomings and does not cover all aspects of the process. There is a serious need to revise it in several areas:

1. Expanding, deepening and detailing the standards for equipment and facilities that the centralized dilution sector must have, and they must be developed separately for “dangerous” drugs and those that do not have CMR properties

2. Certification of the pharmacy for GMP, as well as development of procedures for controlling and validating the processes

3. Introducing a requirement that pharmacists who prepare solutions of antitumor drugs must have completed initial specialized training, consisting of a theoretical and practical part according to an approved national program, which must be certified with a certificate. The practical part must be conducted in a real environment, in a certified hospital pharmacy.

4. Changes in legislation that would allow a hospital pharmacy to prepare parenteral solutions for other medical institutions. This way of working has a number of advantages:

a. Investments in premises and equipment are made in fewer places, which allows more money to be invested and all criteria to be covered without making compromises for financial reasons

b. Staff shortages in medical institutions are a common phenomenon, both in the wards and in the hospital pharmacy. Concentrating aseptic preparation of solutions in fewer places will allow only these pharmacies to maintain a larger staff with longer working hours

c. More patients and a larger number of solutions allow for better planning and minimization of unused residues without resorting to underdosing patients.

d. It will also allow for the appointment of drugs that form a large unused residue, which will improve patients' access to quality treatment.

VI Conclusion

The introduction of centralized preparation of ready-to-use solutions of antitumor drugs raises hospital pharmacy in Bulgaria to a new level. The protection of personnel, the quality of the prepared product and increasing the efficiency of the use of antitumor drugs paid for with public funds are prioritized, with the hospital pharmacy already playing a significant role in the process. Changes in the regulatory framework oblige all medical institutions that treat patients with malignant diseases to invest in their hospital pharmacies, and the pharmacists who work in them to acquire new knowledge and skills. A number of problems also arise. The delay of the criteria that the sector for the preparation of cytostatics must meet by one year after the introduction of centralized preparation gives freedom to medical institutions to choose what standards to cover. The approach of individual hospitals is different - if some decide to cover established European guidelines, others do not even introduce the process for various reasons, most often financial and personnel. The lack of adequate control puts medical institutions at a disadvantage – regardless of whether centralized preparation of antitumor drugs has been introduced or not, all of them conclude a contract with the NHIF and carry out activities in medical oncology, clinical hematology and pediatric clinical hematology and oncology. During the research period, 2016–2024, despite the difficulties and challenges, largely thanks to the efforts of hospital pharmacists, the process has developed and improved. The staff of pharmacies is increasing, since the centralized preparation of parenteral solutions requires the presence of a sufficient number of pharmacists, who must have adequate theoretical training and appropriate practical skills.

VII Contributions

1. Scientific and theoretical

- For the first time, an analysis of the centralized dissolution of drugs for the systemic treatment of malignant diseases in Bulgaria is being carried out after its introduction in 2015;

- The regulatory documents in Bulgaria that regulate the centralized preparation of drugs for the systemic treatment of malignant diseases have been systematized and analyzed;

- The gaps and incompleteness in the legislation in our country regarding the work with cytostatics in hospital pharmacies have been summarized;

- Data on medical institutions performing activities in medical oncology, clinical hematology and pediatric clinical hematology and oncology have been analyzed;

- For the first time, a study is being conducted on the demographic characteristics of pharmacists preparing parenteral solutions of antitumor drugs;

- For the first time, a study is being conducted on the training that pharmacists preparing parenteral solutions of antitumor drugs have undergone;

- For the first time, an analysis is being conducted on the reimbursed unusable residues by value and active units that are obtained during the dissolution of medicinal products for the systemic treatment of malignant diseases from the start of reimbursement by the NHIF in 2020 to 2024;

2. Scientific and practical

- Proposals are made for legislative amendments in the sector, which will lead to ensuring full protection of personnel, high quality of prepared products and effective use of public funds in all medical institutions that treat malignant diseases;

- A proposal is made to create a nationally approved and recognized training program for pharmacists preparing solutions for systemic treatment of malignant diseases;

VIII Publications and participation in scientific forums related to the dissertation work

1. Publications related to the dissertation work

Drenska, M., V. Grigorova, S. Elitova, E. Naseva, I. Getov. The off-label use of medicines in pediatric outpatients in Bulgaria based on an analysis of their prescription data. Drugs & Therapy Perspectives (ISSN print: 1172-0360 , e-ISSN: 1179-1977), 2019;35(10): 391-395.

DOI: 10.1007/s40267-019-00638-4

Cited in Scopus I Web of Science, Impact factor= 0.7

Grigorova, V., Ts. Stefanova, E. Grigorov. Introduction of centralized reconstitution of cytostatics in Bulgaria. Yearbook of Hospital Pharmacy (ISSN print: 2367-8763, ISSN online: 2603-3852), 2019;5(1):19-23.

DOI: 10.14748/ahp.v5i1.6140

Grigorova, V., E. Grigorov. Analysis of centralized preparation of drugs for systemic treatment of malignant diseases in 9 European countries. Yearbook of Hospital Pharmacy (ISSN print: 2367-8763, ISSN online: 2603-3852), 2022;8(1):17-22. DOI: 10.14748/ahp.v8i1.8607

Grigorova, V., A. Serbezova, E. Grigorov, Ts. Valchanova. Clinical pharmaceutical services in hospitals for the treatment of malignant diseases in Bulgaria. JOURNAL OF THE BULGARIAN ONCOLOGICAL SCIENTIFIC SOCIETY (ISSN print:2367-797X), 2024;3:34-40.

Grigorova, V., E. Grigorov. How to work safely with dangerous drugs Yearbook of Hospital Pharmacy (ISSN print: 2367-8763, ISSN online: 2603-3852), 2025;11(1):@-@. (in press)

2. Participation in scientific forums related to the dissertation work

- Bulgarian National Congress on Oncology with international participation 29.12.22 – 01.10.2022, Sofia – lecturer

- XVI National Conference on Hospital Pharmacy 07.10.2022 – 09.10.2022, Plovdiv - lecturer

- VIII Congress on Pharmacy with international participation 27.04.2023 – 30.04.2023, Rila Hotel, Borovets - lecturer

- XI National Conference on Oncology Pharmacy 01.06.2023 – 03.06.2023 – lecturer

- Bulgarian Pharmaceutical Days 2023 23.06.2023 – 25.06.2023, Rila Hotel, Borovets - lecturer

- XVII National Hospital Pharmacy Conference - 13 - 15.10.2023, Burgas - lecturer

- IX Pharmaceutical Business Forum - 20 - 21.10.2023, Varna - report

- Ist SINDFARM international conference - 03 - 05.11.2023, Bucharest, Romania - lecturer

- 28th EAHP Congress Bordeaux 20 - 22,03,2024 - oral poster presentation

- National Oncology Conference - new medicinal products, new indications and preliminary diagnostics in medical oncology 29 - 30.03.2024 - lecturer

- XII National Conference on Oncology Pharmacy and Master Class on Oncology Pharmacy – 07 - 09.06.2024 – lecturer

- XVIII National Conference on Hospital Pharmacy – 18 – 20.10.2024 – lecturer

- Fourth National Scientific Conference on Immuno-Oncology with International Participation – 21 – 24.11.2024 – lecturer

- National Conference on Oncology: New Medicinal Products, New Indications and Preliminary Diagnostics in Medical Oncology 21 -22.02.2025

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