REVIEW

by

PROF. ILKO NIKOLAEV GETOV, PhD

On the Dissertation Thesis for the Award of the Educational and Scientific Degree "Doctor"

Field of Higher Education: 7. Healthcare and Sports
Professional Field: 7.3 Pharmacy
Doctoral Program (Scientific Specialty): Hospital Pharmacy
Author: **VELINA HRISTOVA GRIGOROVA**
Form of Doctoral Studies: Independent preparation
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Title of the dissertation: **"CENTRALIZED PREPARATION OF MEDICINAL PRODUCTS FOR SYSTEMIC TREATMENT OF MALIGNANT DISEASES IN HOSPITAL PHARMACIES IN BULGARIA – SPECIFICS, CHALLENGES AND PERSPECTIVES"**

Scientific Supervisors: Prof. Evgeni Grigorov, PhD
Prof. Assena Serbezova, PhD, DSc

1. General presentation of the procedure and the PhD candidate

Under the present procedure, I was provided with a complete set of materials in electronic and hard copy format in accordance with Article 69 of the Regulations for the Development of the Academic Staff at MU-Varna, which includes the required documents:
- Dissertation thesis
- Abstract
- List of scientific publications
- Curriculum vitae, diplomas, orders, protocols, etc.

The PhD candidate has submitted five (5) full-text publications in Bulgarian and English, published in national (4) and international (1) peer-reviewed scientific journals.

Mag. Pharm. Velina Hristova Grigorova was enrolled as a doctoral student on an independent preparation basis by Rector's Order No. R-109-340/11.08.2022 at MU-Varna in the doctoral program "Hospital Pharmacy", accredited in the Professional Field 7.3 Pharmacy. Following a meeting of the Departmental Council of the Department of Organization and Economics of Pharmacy and a decision of the Faculty Council of the Faculty of Pharmacy, the doctoral student was discharged with the right to defend as of 18.09.2025.

The set of documents meets all requirements, and after becoming familiar with the procedure for the preparation, submission, and conduct of the doctoral program, I consider that they comply with the regulatory framework. The presented documentation proves the lawfulness and completeness of the doctoral training and procedure, which have been conducted within the statutory period and fulfill the minimum national requirements for acquiring the educational and scientific degree "Doctor" in the field of Pharmacy.

2. Brief biographical data about the PhD candidate

Mag. Pharm. Velina Hristova Grigorova holds consecutive master's degrees in Biology and Pharmacy, a professional qualification as Master Pharmacist, postgraduate specializations in Clinical Pharmacy and Hospital Pharmacy, and an additional specialization in Oncological Pharmacy from the European Society of Oncology Pharmacy (2011).

Her professional career has been long, successful, goal-oriented, and productive. She has successively worked as a biology teacher, pharmacy assistant, master pharmacist, and head of a hospital pharmacy. Her specialization in oncological pharmacy has led to gradual career development – head of the hospital pharmacy at the Specialized Hospital for Active Treatment of Children with Oncohematological Diseases, "UniHospital" Panagyurishte, ACC University Hospital "Mladost" Sofia, and currently – ACC University Hospital "Tokuda" Sofia.

It must be emphasized that Grigorova is an active member and participant in the professional guild's development, holding key positions in the Bulgarian Pharmaceutical Union – member of the Management Board, Deputy President, and Acting President. Her contribution to the advancement of hospital pharmacy in Bulgaria is significant. For ten years, she served as Chair of the Management Board of the Professional Organization of Hospital Pharmacists in Bulgaria and as Chair of the Bulgarian Association of Oncological Pharmacy. Her professional path coincides with a period of major changes in clinical and hospital pharmacy in Bulgaria, which determined her choice of topic, doctoral program, and research focus.

As a witness to her professional career, I can note that she was the first pharmacist in Bulgaria to obtain a postgraduate specialization in Hospital Pharmacy, and with her dissertation, she will also become the first to earn the degree of "Doctor" in Hospital Pharmacy in the country.

She possesses excellent computer literacy and skills for teamwork, operation of specialized equipment, and pharmaceutical software. She speaks English and Russian fluently and is a capable lecturer, mentor, and negotiator. She is an active member of the Bulgarian Pharmaceutical Union and numerous professional, scientific, and international organizations.

3. Relevance of the topic and appropriateness of objectives and tasks

The presented dissertation thesis, developed as an independent doctoral study, is titled: "Centralized Preparation of Medicinal Products for Systemic Treatment of Malignant Diseases in Hospital Pharmacies in Bulgaria – Specifics, Challenges, and Perspectives." The topic is fully within the scope of the doctoral program, highly relevant and specialized, representing a comprehensive, multi-layered study on the development, status, and perspectives of oncology and hospital pharmacy. The findings have the potential to improve

the efficiency, safety, and cost-effectiveness of the preparation, storage, and administration of cytotoxic drugs in Bulgaria. For the first time, an attempt has been made to assess the working environment and occupational hazards for hospital pharmacists, highlighting their crucial role in modern clinical practice and therapeutic outcomes.
The structure, content, and conclusions demonstrate balance, completeness, and real applicability. The recommendations, if implemented, could have significant impact on regulatory authorities and professional organizations.

4. Understanding of the problem
The PhD candidate demonstrates deep understanding of the studied topic. The dissertation is based on the hypothesis that the regulatory framework for centralized preparation of cytotoxic drugs requires improvement; aseptic preparation in hospital pharmacies is a highly specialized activity that must be performed by trained personnel under national standards and strict control.
The literature review occupies about one-third of the thesis and covers the nature of cytotoxic drugs, reasons for introducing centralized compounding, preparation techniques, training needs, and the practice in Bulgaria. It cites 139 references, mainly from the past decade, in English and Bulgarian, all of high scientific value.

5. Research methodology
The methodology section is comprehensive, describing the objects and methods used. A detailed survey was conducted on the need for specialized training of pharmacists preparing parenteral cytotoxic solutions in Bulgarian hospital pharmacies. Eighteen of the 44 hospitals treating cancer patients in the country participated (41%), ensuring statistical validity. A deeper statistical correlation analysis would further strengthen the results. Nevertheless, the applied methodological apparatus is sufficient to meet the study's goals.

6. Characteristics and evaluation of the dissertation
The dissertation is structured in a classic form – introduction, literature review, aim and objectives, materials and methods, results and discussion, conclusions, conclusion, contributions, bibliography and applications – a total of 139 pages. The formulated research tasks are comprehensively reviewed and commented on in separate subsections of the chapter with the results, and I admire the choice of the author and the scientific supervisors for a summary discussion/conclusions/conclusion at the end of the individual parts. The results of the critical review and analysis of the legal framework concerning the centralized preparation of solutions for direct administration of medicinal products for the systemic treatment of malignant diseases show that:
- Not all medical institutions comply with the regulatory framework in the country;
- Control by the competent authorities is greatly underestimated;
- There is inequality among hospitals – those that comply with the legislation are in a more disadvantageous position than those that do not. Meeting the requirements requires serious financial resources, as four years after the changes in the regulatory framework, not all

pharmacies still meet the requirements, but despite this, all medical institutions have a contract for payment of activities related to the treatment of patients with malignant diseases with public funds;

- Non-compliance with the regulatory framework is not related to ownership, but to the management of the medical institution;
- The quality of the clinical trials conducted in these medical institutions that do not meet the regulatory requirements and Good Clinical Practice is questionable, but this is not taken into account by regulators and contracting authorities and continues to be a fact;
- Currently, there is no institution in the country that actually knows the status and controls the activities of centralized preparation of drugs for the systemic treatment of malignant diseases.

The next task is to analyze the medical institutions in which medical oncology and/or clinical hematology and/or pediatric clinical hematology and oncology activities are carried out, and for me the most important results concern the study conducted on the centralized preparation of cytostatics in hospital pharmacies. 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 in order to cover the minimum requirements. The author shares her experience, observations and justifies that if a hospital prepares solutions not only for its own needs, but also for other hospitals, where they are only to be administered, an even better result will be achieved and this approach has a number of advantages in terms of equipment, personnel, residues and financial result. More patients and a larger number of solutions allow for better planning and minimization of unusable residues without resorting to underdosing of patients.

The third part of the own research is dedicated to the sensitive topic of analyzing the unusable residues from the preparation of antineoplastic drugs reported to the NHIF for the period 2020-2024. After a detailed description of the methods for calculating the dose of anti-tumor drugs, the reasons for not reporting unusable residues to the NHIF and specific indicators for 9 medical institutions, the following important conclusions were made:

- the medical institutions with the largest amount of reimbursed unusable residues for the period are shown;
- the amount of reimbursed active units of medicinal products for the studied medical institutions is shown;
- the dosage form for medicinal products with INN methotrexate, cabazitaxel, tebentafusp available on the market is reported as the leading reason for the large amount of unusable residues.

I believe that this part of the study is particularly valuable and can serve as the basis for a broad discussion on the possibilities for saving public funds by optimizing the use of cytostatics in medical institutions.

The following two parts are devoted to a study of the demographic and professional characteristics of pharmacists who prepare parenteral solutions of antitumor drugs and the training of pharmacy personnel performing centralized dilution of cytostatics. Here,

Grigorova shows her expert and professional qualities as a leader in the guild and presents us with the true state of the problems. I highly appreciate the conclusions and recommendations made on the data from this study, because they concern the vision for the development of the profession and the challenges facing the college.

Leading results are that the preparation of ready-to-use solutions of anti-tumor medicinal products in the country is carried out mainly by master pharmacists, women, aged between 36-50 years, 94% of all master pharmacists participating in the study and 44% of all participating assistant pharmacists have undergone training organized by non-profit organizations and/or professional organizations. Here we must emphasize the lack of academic training or pre- or postgraduate course on the topic, as university structures are indebted to the professional guild of hospital pharmacists.

This chapter also presents recommendations to the National Assembly, Ministry of Labour and Social Policy, Ministry of Health, Bulgarian Drug Agency, Ministry of Education and Science, universities and other institutions for improving the regulatory framework, as well as the training of pharmacists preparing solutions of antitumor drugs.

The presented dissertation contains 14 conclusions with numerous sub-points to the research tasks, which show the importance of the research and the potential impact on regulatory and professional practice. My feeling is that they are too many, they should not repeat the results and correspond to the set goals and research tasks.

7. Contributions and significance

The dissertation presents significant scientific and practical contributions in a previously unexplored interdisciplinary field. The results reflect real challenges and propose feasible improvements for hospital practice and regulation. Contributions are defined as both theoretical and practical, and I accept them fully.

8. Publications related to the dissertation

The submitted full-text publications are on the topic of the dissertation – one in English, in a foreign journal with an impact factor and 4 in Bulgarian refereed scientific publications. In four of the scientific articles, the doctoral student is the first author in teams, there is no independent publication. The publications reflect the conducted research, results and analyses of the dissertation work to a significant extent.

I have ONE joint publication with M.Pharm. Grigorova.

Participation in scientific forums in Bulgaria is a total of 14, all within the term of the doctoral program – an average of 3.5 per year. The analysis of the submitted documents shows that the doctoral student has the required scientific activity.

I accept and evaluate the scientific production on its merits, but I recommend expanding the publication activity, since I find that individual works presented in the dissertation are not designed as independent publications, as this would be a prerequisite for visibility and citation of the results by the scientific community.

9. Personal contribution of the PhD candidate

The research, analysis, and conclusions are clearly the result of the author's individual work, supported by her supervisors. The originality declaration and the depth of analysis confirm her personal involvement and expertise.

10. Critical notes and recommendations

I have no significant critical remarks. Minor terminological and formatting inconsistencies are observed but do not affect the scientific value. My main recommendation is for a more concise and structured presentation of conclusions and recommendations.

Conclusion

The dissertation contains original results and contributions and fully complies with the Law on the Development of Academic Staff in the Republic of Bulgaria and the MU-Varna Regulations.

I give my positive evaluation of the research, presented as the First doctoral dissertation in the new PhD program "Hospital Pharmacy", and recommend that the Honorable Scientific Jury award the educational and scientific degree "Doctor" to Mag. Pharm. **Velina Hristova Grigorova for her work titled:

"Centralized Preparation of Medicinal Products for Systemic Treatment of Malignant Diseases in Hospital Pharmacies in Bulgaria – Specifics, Challenges, and Perspectives."

27.10.2025