Review

By Prof. Zlatka Dimitrova Dimitrova, D.Sc, Head of TRL in Social Pharmacy, Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at Sofia University “St. Cl. Ohridski ”-Sofia, appointed a member of the Scientific Jury by order №-PD-38-627 / 22.12.2021 of Prof. Anastas Gerdjikov, Rector of Sofia University“ St. Kliment Ohridski ”.

Subject: procedure for defense of a dissertation on the topic: "Study of the role and participation of pharmacists in clinical trials of medicinal products" for the acquisition of ESD "Doctor" of M. Pharm. Vladimir Antonov Atanasov, PhD student in self-study in the field of Higher Education 7. Healthcare and Sports, Professional Field 7.3 Pharmacy, under the PhD program “Social Medicine and Organization of Healthcare and Pharmacy” in the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at Sofia University “St. Kliment Ohridski ” with supervisors: Assoc. Prof. MD Emil Ivanov Christov,PhD and Prof. Ilko Nikolaev Getov,PhD.

This review has been prepared in accordance with the requirements of Law on the Development of the Academic Staff in the Republic of Bulgaria /LDASRB/, Regulations for application of the Law for the development of the academic staff in the Republic of Bulgaria/RALDASRB/ and the Regulations on the terms and conditions for acquiring scientific degrees and holding academic positions at Sofia University "St. Kliment Ohridski ”, Chapter II. Acquisition of the ESD "Doctor" and the scientific degree "Doctor of Science", Section III. Conditions and procedure for obtaining the educational and scientific degree "Doctor".

Details of the procedure. With Order №-PD-20-700 / 30.04.2020 m. pharm. Vladimir Antonov Atanasov is enrolled as a doctoral student in independent training in the field of of Higher Education 7. Healthcare and Sports, Professional Field 7.3 Pharmacy, under the PhD program “Social Medicine and Organization of Healthcare and Pharmacy” in the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at Sofia University “St. Kliment Ohridski ”. Presented is Certificate №5, issued by the Dean of FChPh from 05.01.2022. for successfully passed the exam for covering the doctoral minimum in the specialty, as well as Order № PD-20-2630 /12.20.2021 for early dismissal of the PhD student with the right to defend his dissertation after its discussion by the Department Council and a decision on its readiness for referral for public defense. The folder with the PhD student's documents contains all the required documents for the defense of the dissertation.

At the first meeting of the Scientific Jury, which took place on 4.02.2022, Friday at 1 PM were elected: Chairman of the Scientific Jury - Assoc.prof. Sava Ognyanov, Ph.D. and two reviewers: Prof. Zlatka Dimitrova, D. Sci. and Prof. Valentina Petkova, D.Sci, and the other members of the scientific jury to present statements. The deadline for submitting reviews and statements is February 25, 2022. SJ decided to admit the candidate for evaluation and the date of the defense is March 25, 2022 at 2 PM in the FChPh.

Biographical data and career development of the candidate: M. Pharm. Vladimir Antonov Atanasov was born on August 1, 1991. He graduated in pharmacy and obtained a master's degree in pharmacy in July 2015 at the Faculty of Pharmacy at MU-Sofia. He has worked as a Master Pharmacist - Clinical Research Specialist at Verum Clinical Ltd., Sofia from January 2013 to May 2015, from May 2015 to May 2016 - in the company GlaxoSmithKline and from May 2016 until now and continues - in HT Research BG. During the period 09.2016 - 07. 2018 he completed a master's degree in Public Health and Health Management at the Faculty of Public Health at the Medical University of Sofia.

Relevance and significance of the dissertation. Until the socio-economic changes in our country at the end of 1989, the opportunities for professional realization of M. Pharmacists were severely limited - over 82% of newly graduated pharmacists came to work in pharmacies, Caressed packaging laboratories/CPL/ and pharmacy warehouses at the district pharmacy enterprises of the State Pharmacy Association/ SPhA/ system. They also worked in the management of SPhA, in the system for control of

medicinal products / State Institute for Control of Medicinal Products and Control and analytical laboratories /, about 10% were employed in the system of SEA "Pharmachim" - in the production and control of drugs and in research units / Research Institute of Chemistry and Pharmacy and bases for research and development activities at pharmaceutical plants / and about 8% as military pharmacists and in the registered in our country representations of foreign pharmaceutical companies as well as in the only one in the country Faculty of Pharmacy at the Medical Academy. After the privatization of pharmacies and pharmaceutical plants and especially after the adoption of the first in the history of our country independent Law on Medicinal Products and Pharmacies in Bulgaria on 16.04.2005 and especially after the accession of Bulgaria as an equal member of the EU on 1.01.2007 and adopted new Law on Medicinal Products in Human Medicine-LMPHM in 2007 these opportunities have expanded dramatically.Significantly increased the number of the pharmacists working in the BDA, which controls all activities and stages of the drug supply process - from the marketing authorization, through the import and export of medicinal products, distribution and their release to patients from hospitals and open pharmacies.

The harmonization of the Bulgarian MP legislation with that of the EU countries, on the one hand, and on the other - the introduction of new mandatory disciplines in the training of master pharmacists in the 5 FPh in the country , the approval of new specialties for m. pharmacists / clinical pharmacy (1994), hospital pharmacy / (2016), the need to change the pharmacy services in both hospital and community pharmacies and the changes in the relevant regulations are the main prerequisite for the new functions of M. Pharmacists - experts in MP regulation, participation in clinical trials and studies, pharmacoeconomic and pharmacoepidemiological studies, providing pharmaceutical care for certain groups of patients with chronic diseases, elderly patients and children, etc. The introduction of new biological therapies in medicine and the biotechnological revolution in the pharmaceutical sector have necessitated the unification of human studies from pre-registration clinical trials, non-interventional and interventional post-registration studies, epidemiological and pharmacoepidemiological studies, etc.

In addition, the new Regulation (EU) № 536/2014 on clinical trials on medicinal products is part of the European regulatory framework through which the European Commission has given a strong impetus to research and industrial progress. This is new legislation that has filled a number of regulatory gaps in clinical trials to date in the EU by creating a single framework for authorizing clinical trials by all Member States concerned with a single evaluation of results.

That is why I believe that the dissertation of the M. Pharm. Vladimir Antonov Atanasov has a significant and topical in scientific and practical terms topic, as he considers the role of the pharmacist for compliance with scientific, regulatory and ethical requirements in the planning, conduct, and reporting of clinical trials in accordance with the GCP and Regulation (EU) № 536/2014 and the production of the tested LP in accordance with the GMP and GLP. It is dedicated to a significant issue of public health and is relevant and original, as such a comprehensive study has not been conducted in our country and in other countries.

The dissertation presented to me for review is in the volume of 93 pages / with 3 appendices /, and is illustrated with 6 tables and 48 figures. The bibliography includes 164 sources, of which 27 are in Cyrillic and 137 in Latin.

General characteristics of the research and applied research activities of the candidate.

The dissertation was discussed, accepted and directed for defense by an extended council of the Department of Physical Chemistry at the Faculty of Chemistry and Pharmacyl at Sofia University "St. Kliment Ohridski ".

In the first chapter of the literature review the doctoral student presents a comprehensive analysis of the problem of clinical trials in historical terms, and in the next chapter discusses the place and role of the pharmacist in the preparation of the research drug dossier and its evaluation and concludes that

much of all these stages and assessments are still performed traditionally by specialists with pharmaceutical education.
In my opinion, Chapter Three of the review is of some interest, providing relatively new information on the role of hospital pharmacists in conducting clinical trials and non-interventional studies based on the review of scientific publications and the European Standard for Hospital Pharmacy, which is recommended. In this regard, the Bulgarian authorities have made changes to the Law on Medicinal Products in Human Medicine, the Law on Medical Devices, Ordinance №28 of 09.12.2008 on the structure, order and organization of pharmacies and the nomenclature of medicinal products and the Rules for good pharmacy practice. These legal changes determine the conditions and the order under which MPs and medical devices are received, stored, prescribed and dispensed. The next 2 chapters of the review discuss the place and functions of the pharmacist in the regulatory processes and in the monitoring process. The review clearly shows the wide professional awareness of the doctoral student on the issues under discussion, as throughout his career so far he has worked as an expert in clinical research - a relatively new field for professional development of mag. pharmacists in our country. The serious challenges for hospital pharmacists and the good knowledge of the unsolved problems in their implementation in this new field determine the purpose and objectives of his dissertation. The aim and tasks of the peer-reviewed dissertation are well-founded and an adequate methodology for the research has been selected. The PhD student sets a significant goal: “To analyze and identify the scientific, regulatory, scientific-applied and legal opportunities for pharmacists to participate in clinical trials, research and non-interventional studies of drugs, their functions and responsibilities, rights and obligations, opportunities for professional realization and to determine the actual participation of pharmacists in Bulgaria in clinical trials for the period 2016 - 2019 incl.
As a result of the documentary analysis of the current regulatory framework for clinical trials of medicinal products in Bulgaria, the doctoral student came to the conclusion that since the Regulation is a legislative act of the European Union, which is immediately enforceable, as a rule, in all Member States. and Its main goal is to achieve homogenous law throughout the European Union in the field of clinical trials, pharmacists are recognized, as the only medical professionals who have the necessary knowledge and competencies to ensure the storage and release of investigational medicinal products can participate in all stages of process documentation, as well as in their monitoring and control.
The competent analysis of the data obtained from the respondents in the three surveys, processed with descriptive statistical methods with the software product SPSS version 19, convincingly justifies the need to overcome some weaknesses in the current practice of conducting clinical trials in our country:
-The first survey included 98 masters of pharmacy working as hospital pharmacists in hospitals across the country. About 50% of the respondents have acquired an additional specialty in three main scientific fields - "Clinical Pharmacy", "Organization and Economics of Pharmacy" and "Hospital Pharmacy", approved only in 2016. The majority of the respondents / 65% / have not participated in clinical trials so far, as well as have not conducted training in Good Clinical Practice, which must precede their inclusion in clinical trials. It is logical that they do not know the nature and differences between interventional and non-interventional clinical trials. BUPh and the Association of Hospital Pharmacists must commit to additional training for pharmacists working in pharmacies at hospitals regarding the GCP and the new EU regulation and the resulting new professional responsibilities. In addition, the majority of pharmacists surveyed indicated that the medical establishments had not taken the necessary actions to bring their organization to work in accordance with the adopted regulatory changes.

-According to the results of the second survey, the majority / 60% / of the main researchers / doctors or dentists / indicate that they have difficulties in the overall process of storage of investigational medicinal products as part of clinical trials or non-interventional studies. At the same time, more than half of the respondents indicated that they are not or are not fully aware of the changes in Ordinance № 28 of

December 9, 2008, as amended./ GJ. No. 81 of October 20, 2015 /, regulating the mandatory participation of hospital pharmacists as part of the research team of each clinical trial. Also, some of the respondents have some reservations about the implementation of the mandatory participation of pharmacists as part of their research teams.

Based on the experience in developed countries, however, it can definitely be argued that the inclusion of pharmacists in conducting clinical trials will improve the storage of the investigational product under appropriate conditions, tracking the availability of the investigational medicinal product, receiving and dispensing the investigational product, monitoring the overall condition of patients and identifying, reporting drug interactions, and in some more specific cases the pharmacist is no blinded and he is aware of what drug each patient takes, unlike part of the research team (including the principal investigator) who are blinded and do not know which product the patient is taking.

There are specialized pharmacies in the United States for clinical trials, which is due to their large number.

- The target group in the third survey included 48 associates / specialists in clinical trials, who participated in clinical trials of drugs as monitors, throughout the country. / All have a master's degree and 62% of them have a medical specialty /. Respondents categorically declare that a large part of the hospitals with which they work in their daily practice, the hospital pharmacy is not responsible for the storage and release of the tested medicinal products. This puts at risk the overall process of dispensing and storing medicinal products used in clinical trials. Most of the respondents state that they are not fully informed about the regulatory changes, but also assess the current organization of storage and release of investigational medicinal products as unsatisfactory.

This analysis is particularly relevant in the scientific and applied aspect, as it reveals serious shortcomings in the conduct of clinical trials in our country.

The conclusions in the dissertation work follow from the conducted analyzes and from the obtained results and are clearly and precisely formulated. I accept the reference for the doctoral student's contributions.

Main scientific and scientific-applied contributions. In the most generalized form, in my opinion, the contributions and merits of the dissertation of the M. Pharm. Vladimir Antonov Atanasov are the following: *Contributions of original character:*

● The idea and purpose of the study are original. For the first time in Bulgaria, a retrospective analysis of the regulations for conducting clinical trials is being made, which includes an analysis of the content of the new Regulation (EU) № 536/2014.

● On the basis of a large number of foreign and Bulgarian literary sources / publications and the European standard in hospital pharmacy / are revealed the expanded possibilities for pharmacists working in hospital pharmacies or in pharmaceutical companies for active and professionally responsible inclusion of the indicated positions in the conduct of clinical trials of investigational medicinal products or in non-interventional clinical trials.

In my opinion, the precisely conducted analyzes, well illustrated with numerous figures and conclusions will contribute to better communication and teamwork in conducting clinical trials, and the recommendations made for additional training of master pharmacists will ensure their competent involvement in future clinical trials.

Contributions of scientific and applied nature:

● There are presented and thoroughly analyzed the results of the 3 surveys of the opinion and assessment of leading specialists in the field of clinical research in our country - research doctors and specialists - monitors on the introduced legislative changes for the inclusion of master pharmacists in clinical trials, and hospital pharmacists to establish their readiness to cope with their new responsibilities as direct participants in the conduct of clinical trials of MP or as monitors.

● The 3 questionnaires developed by the doctoral student have a certain methodological contribution. The developed methodology allows its direct use by researchers who show a specific interest in assessing and analyzing the progress in the readiness of the master pharmacists to be fully involved in accordance with their competence in clinical trials of medicinal products , adds a scientific and applied contribution to the methodology.

The presented contributions and merits of the dissertation are a valuable contribution to the Bulgarian pharmaceutical literature and give rise to ideas for new similar future research on the topic. The doctoral student presents a well-designed dissertation, which is structured correctly and synthetically reflects the most important results of research in accordance with the tasks.The abstract contains a brief description of the main studies, conclusions and contributions of the dissertation.

Reflection of the candidate's scientific publications in the specialized scientific literature

On the topic of the dissertation are presented 2 published scientific articles in journals, which are *referenced in Scopus:/* Arch Balk Med Union. (2021) 56(Supplement 1): S68-69. and PHARMACIA, vol. 63, No. 2/2016, and 1 publication in the Bulgarian journal Science Pharmacology 2016 1 (7): 19-24. ,1 participation with a report abroad:CBU International Conference on Innovations in Science and Education, Prague, March 23-25, 2016, Vol.4 (2016) 767-772, *referenced in Web of Science* and 2 more participations with reports at scientific forums in our country with international participation / 6th Congress of Pharmacy with International participation, Sandanski Bulgaria, 2016 / and abroad / Congress of Pharmacy in Macedonia, Madeconian pharmaceutical bulletin, 62 (suppl) 73-74 (2016), ISSN 1409-8695, UDC:615.065(497) /.

Critical remarks and questions to the candidate.

There are small omissions and spelling mistakes in the dissertation, which in no way reduce its value.

Thus, for example. in my opinion, it would be good to note in the first chapter of the review that Galen tested his compound medicines first on the peasants of his ancient Greek homeland before giving them to his patients of the Roman aristocracy.

In addition, only 3 publications are considered on page 23, which according to the doctoral student view the role and participation of the pharmacist in clinical trials partially and incompletely. But in fact only Article 3th fully correlates with the topic of the dissertation, as the study of J. John and team in 2016 considered the pharmacy's involvement as a focal point in conducting multicenter clinical trials by managing activities related to the investigational medicinal product. The other 2 publications, and I found over 30 in the bibliographic list, evaluate the results of pharmacotherapy of patients as a result of PhC/pharmaceutical care/ performed through clinical trials, but they are not the subject of his study.

I will formulate my last note as a question: why some publications in connection with the dissertation, in some of which the PhD student V. Atanasov is even the first author, are not reflected in the text of the dissertation and the abstract?

Conclusion. The doctoral student M. pharm. Vladimir Antonov Atanasov presents a dissertation dedicated to a topical and important issue for our healthcare. The results of the research conducted in the dissertation and their interpretation are at a good scientific level, they are published in the specialized literature and are reported at pharmaceutical scientific forums.

The dissertation of M. Pharm. Vladimir Antonov Atanasov on the topic: "Study of the role and participation of pharmacists in clinical trials of medicinal products" for the acquisition of ESD "Doctor" contains a number of scientific and scientific contributions and is an original medico-social analysis. Well-substantiated conclusions and recommendations have been made, logically arising from the specific analysis in the dissertation and are directly oriented to practice.

The dissertation shows that the candidate has in-depth theoretical knowledge in the scientific specialty and abilities for independent research. This work meets all the requirements of LDASRB and the Regulations for its implementation / RALDASRB / and the Regulations on the terms and conditions for obtaining scientific degrees and holding academic positions at Sofia University "St. Kliment Ohridski ”for

acquiring ESD“ Doctor ”. I give a positive assessment of the dissertation and will fully support the award of the ESD "Doctor" in Pharmacy to the M.Pharm. Vladimir Antonov Atanasov in the PhD program "Social Medicine and Organization of Health and Pharmacy" by voting "Yes".

20.02.2022г. Reviewer: .....

/проф. Зл. Димитрова, дфн/