WRITTEN STATEMENT

from assoc. prof. Evgeni Evgeniev Grigorov, MScPharm, PhD

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(Internal member of the Scientific Jury, approved by Order No. P-109-12 / 21.01.2020 of the Rector of MU-Varna)

Subject: Procedure for the defence of a dissertation for obtaining a scientific degree "Doctor of science" in the specialty "Pharmacology (including pharmacokinetics and chemotherapy)", FHE 7. Healthcare and sports, PF 7.3. Pharmacy.

Thesis topic:
"IDENTIFICATION, ANALYSIS AND EVALUATION OF PHARMACOKINETIC AND PHARMACODYNAMICS DRUG INTERACTIONS"

Author of the dissertation:
Assoc. prof. Kaloyan Dobrinov Georgiev, MScPharm, PhD - Lecturer at the Faculty of Pharmacy, Medical University-Varna.

Significance of the topic: The rapid development of the pharmaceutical industry nowadays has led to the emergence of many innovative products that reach the market, usually without a thorough examination of their pharmacokinetic and pharmacodynamic drug interactions. The studies conducted in the dissertation give very important information and idea about the integration of computer technologies in the evaluation and analysis of drug interactions.

Actuality of the topic developed: Kaloyan Georgiev's dissertation is devoted to the identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions. After a detailed literature review, the numerous up-to-date data sources pointed by the author unambiguously proves that the topic under development is in a field, which has been developing extremely active scientifically in the last decade. K. Georgiev was able to trace the many aspects of pharmacokinetic and pharmacodynamic drug interactions and to draw important practical conclusions and recommendations.

Structure of the thesis: Kaloyan Georgiev's dissertation is very well designed and structured with respect to its main parts. It starts with an introduction and contains a total of 7 separate chapters:

- Introduction

- Purpose and objectives
- Selection, isolation and analysis of plant extracts / fractions. Design, synthesis and analysis of oligopeptides
- Study of pharmacokinetic drug interactions
- Study of pharmacodynamic drug interactions
- Study and analysis of pharmacokinetic and pharmacodynamic drug interactions in clinical practice
- Conclusion over the place of computer technology in the identification, analysis and evaluation of drug interactions
- Conclusions;

They are followed by contributions, bibliographies, and applications. The dissertation covers a total of 320 standard typing pages, including 77 figures and 78 tables. There are 441 references cited, 1 of which is in Bulgarian.

The literature review contains a sufficient volume of summarized and analyzed material that reflects a wealth of historical and experimental data and research information of the topic to date. It is systematically exposed and reveals very good knowledge of the substance related to pharmacokinetic and pharmacodynamic drug interactions. Particular attention is given to a detailed description of drug interactions associated with the inhibition and induction of drug-metabolizing enzymes and transport proteins. Logically, the literature review concludes with a summary, on the basis of which the purpose and tasks of this dissertation are formulated.

The main goal of the dissertation is to study, analyze and evaluate drug interactions at the pharmacokinetic and pharmacodynamic level. It is clearly presented and specifically worded. Good scientific understanding of the problem under development has allowed the purpose and tasks to be properly defined.

The tasks are 11 in number and they emanate from the goal. They are formulated accurately, selected precisely, and logically justified, and their solution enables them to properly achieve the goal.

The methods used in the dissertation work are extremely diverse, worth noting is the use of world-renowned software platforms. The overall design of the study is a testament to the in-depth knowledge and mastery of the dissertant of the current methodological approaches in pharmacology and clinical pharmacy.

The results obtained are presented clearly and well-structured for each aspect of the study, accompanied and clearly illustrated by figures and tables.

Conclusions. The scientific results obtained in the dissertation are systematized in formulated conclusions, in accordance to the collected and analyzed data. It is quite reasonable to state that to reduce the risk of potential drug interactions in high-risk patients, appropriate software should be used to analyze the prescribed therapy. I strongly support and appreciate that the inclusion of a highly qualified specialist such as a clinical pharmacist in the multidisciplinary team will be of significant benefit in anticipating pharmacokinetic and pharmacodynamic drug interactions and will improve the pharmaceutical care of the patient.

I accept all the other conclusions that objectively reflect the results obtained in the dissertation developed.

Contributions of the thesis

Scientific-theoretical contributions:

- Pharmacokinetically and pharmacodynamically isolated methylxanthine fractions from Bancha leaf and Pu-erh tea have been characterized for the first time.

- Added new pharmacokinetic characteristics for newly synthesized oligopeptides, endomorphin-2 analogues and RGD.

- Pharmacokinetically and pharmacodynamically isolated fractions (polysaccharide, pectin-free and total extract) of L.barbarum (Goji berry) have been characterized for the first time.

- For the first time, epicrises of patients with heart failure for a two-year period (2014-2015) were processed to investigate drug-drug interactions between standard therapy received and low-latitude drugs.

Scientific-practical contributions:

- Guidelines for the use of simulation models are presented to predict pharmacokinetic behavior and to evaluate pharmacokinetic drug interactions in herbal preparations based on the determination of a major component in the isolated fraction.

- Guidelines for the use of in silico generated physicochemical and pharmacokinetic data are presented to build simulation models and evaluate pharmacokinetic drug interactions in newly synthesized oligopeptide preparations.

- Recommendations are made for the use of software programs and / or the inclusion of clinical pharmacists in multidisciplinary teams in high-risk patients and the ongoing polypharmacy to reduce the risk of adverse drug interactions.

Summary of dissertation and publications. The summary of dissertation has been prepared in accordance with the requirements of the Rules for the development of the academic staff of the Medical University of Varna and correctly reflects the obtained results and the scientific contributions of the dissertation.

Eleven publications in scientific journals related to the dissertation are presented. In ten of them K. Georgiev is the first author, which is indisputable proof of his leading participation in the development, discussion and presentation of the results obtained.

Conclusion. I positively appreciate Kaloyan Georgiev's dissertation work and believe that in content and scientific contributions it fully meets the requirements of LDAS in the Republic of Bulgaria and the Rules for the development of the academic staff of Medical University-Varna. Good methodological preparation, thorough theoretical knowledge and practical experience of the dissertant in the field of pharmacology are an excellent proof for his successful establishment as a scientist. All this gives me reason to persuade the members of the distinguished Scientific Jury to award **Kaloyan Dobrinov Georgiev** the **scientific degree "Doctor of science".**

Varna
17 February 2020

Member of the Scientific Jury:.....

(Assoc. prof. Evgeni Evgeniev Grigorov, MScPharm, PhD)

By signing here, I declare that I am not related to the candidate and that I have no private interest that may affect the impartial and objective performance of the opinion given in the present procedure for the defense of a dissertation for obtaining a scientific degree "Doctor of science".