OPINION
by Prof. Denitsa Momekova, PhD

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Member of the scientific jury, regarding the procedure for the defense of the dissertation of doctoral student Emanuil Plamenov Yordanov, for the awarding of the educational and scientific degree "DOCTOR" in professional direction 7.3 Pharmacy and the doctoral program "Social Medicine and Organization of Health Care and Pharmacy".

Topic of the dissertation: *„Retrospective study of medicinal use, availability and accessibility of biosimilars containing monoclonal antibodies in Bulgaria“*
Scientific supervisor: Prof. MD Emil Hristov, PhD

This Opinion is prepared in response to Order № РД-38-116 от 08.02.2023 issued by the Rector of Sofia University “St. Kliment Ohridski” for the appointment of a scientific jury and the decision of the first meeting of the jury, held on April 12, 2023. The Opinion is in compliance with the law of Development of Academic Staff in the Republic of Bulgaria Act (DASRB), the General regulation on its implementation and the Institutional regulations for the application of the aforementioned law at Sofia University “St. Kliment Ohridski”.

I declare that all necessary documents have been submitted in accordance with the requirements of the aforementioned regulatory documents.

Characteristics and evaluation of the thesis

The dissertation of PhD student Emanuil Yordanov is written in 129 pages and includes the following sections: introduction, literature review, aim and objectives, materials and methods, analysis of the results, discussion, conclusions, references used, including 126 sources, almost all of which are from the last 10 years. The dissertation is illustrated with 48 figures, 15 tables and 1 appendix in which the research results are presented correctly and in a very good manner.

Relevance and significance of the dissertation

The dissertation aims to define the use, availability and accessibility of biosimilar medicinal products based on monoclonal antibodies in Bulgaria at a macro level, as well as to evaluate the use of this therapeutic modality in specific therapeutic areas - rheumatology and gastroenterology through an analysis of medicinal usability in representative nosological entities - rheumatoid arthritis and inflammatory bowel diseases ulcerative colitis, Crohn's disease and undifferentiated colitis.

The dissertation of M.Sci. Yordanov is focused on an extremely important aspect of modern clinical medicine in a constellation of socially significant diseases in which biological therapy is the dominant therapeutic modality. Such a study is timely and largely innovative not only for Bulgaria, but considering the multifaceted analyzes for the EU in general. Regardless of the availability of modern highly effective drugs, the translation of data from clinical trials into real benefits detectable in the conditions of their current use is a function of accessibility, the absence of therapeutic inertia when prescribing them, and of course adherence to therapy. In this regard, the in-depth analysis of the rational medicinal use,

availability and accessibility of biosimilar medicinal products based on monoclonal antibodies in Bulgaria, which are highly effective means of treating chronic socially significant diseases, deserves a high evaluation even at the level of a conceptual paradigm.

The aim of the presented doctoral thesis is clearly formulated, and the tasks related to its implementation adequately reflect the problem laid down in the topic of the dissertation. The methodological set is rationally selected, as the evaluation and analysis methods are modern, precisely described and allow the acomplishment of the tasks at a high scientific level.

The literature review is in itself an independent study, because unlike most literature reviews in dissertations in our country, it is based in its first part on a systematic analysis of scientific publications, identified and selected in accordance with the recommendations of the Cochrane Collaboration, the Guide to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The systematic review was conducted according to a pre-designed protocol as required by the PRISMA 2009 Checklist, redefining the thematic scope, design, search strategy, inclusion and exclusion criteria, data collection methods, data analysis and statistical processing. The second part of the section provides an in-depth review of rational approaches for pharmacotherapy of the nosological entities targeted for the study, presented in light of their importance, main characteristics and pathophysiological mechanisms. The review is written with excellent knowledge and handling of the complex terminology associated with biologics and biosimilars.

The results of own research are described according to the main directions defined in the goals and tasks of the work. The main results and conclusions can be summarized as follows:

In the Republic of Bulgaria, as a full member of the EU, the availability of quality, safe and effective biological and biosimilar medicinal products is ensured for Bulgarian citizens.

The average length of time from the authorization for the use of biological and biosimilar medicinal products to their effective reimbursement and respective implementation in the treatment of patients in our country is 6 months. Access to biological and biosimilar medicinal products is ensured, and their availability, affordability and usability at the macro level, evaluated through budgetary indicators can be considered excellent.

The implementation of biosimilar products in the reimbursement system is associated with an expected reduction in total treatment costs within the NHIF budget and expands access to these highly effective funds.

The analyzes show some negative trends that require active intervention: regardless of their higher cost, reference medicinal products remain the preferred means of prescribing, dispensing and treatment, respectively, the use of biosimilar products remains at a negligible low level of only 4.75% of the total prescription estimated through the budget expenditures of the NHIF. This trend is not observed only with infliximab, which is undoubtedly due to the absence of a reference biological medicinal product on the Bulgarian market.

Also of concern is the absence of uniform and adequate (ie evidence-based and health technology assessment) national standards for substitutability and interchangeability of biologics and biosimilar medicinal products with biologics and/or biosimilars in targeted therapeutic areas. At the same time, the analysis of pharmacotherapeutic guidelines for the treatment of rheumatological diseases and diseases in the field of gastroenterology shows reciprocity in the attitudes towards the interpretation of data on the quality, safety and efficacy of biosimilar products between the two studied class groups. The conducted survey shows an unacceptable level of knowledge about biosimilar products and, respectively, a lack of confidence in their quality and efficacy

I fully accept the conclusions and contributions of M.Sci Yordanov and I believe that they correctly outline the main characteristics of work in the areas of the scientific research program.

Questions, recommendations and remarks:

The dissertation is very well written and the interpretation of the obtained results is convincing. *I have one main remark, which does not detract from the importance of the work and is technical in nature - in a significant part of the tables the text is in English, which could easily be avoided.*

Scientific-metric indicators related to the dissertation

The results described in the dissertation are reflected in three publications in refereed and indexed in Scopus and/or Web of Science journals and also in 8 papers published in non-refereed peer-reviewed journals or published in edited collective volumes. The results of the dissertation work have also been reported at numerous national scientific forums. The doctoral student participated in a scientific project. The quality of the doctoral student's research is also evidenced by the "Alma Mater" award he received for the academic year 2019/2020.

Dissertation summary

The dissertation summary reflects very accurately and clearly the results and contributions of the dissertation.

CONCLUSION:

The dissertation thesis of PhD student Emanuil Yordanov "*Retrospective study of medicinal use, availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria*" is a high-quality and in many ways innovative study for our country with multiple contributions with potential translation into practice. The data from the study and their interpretation outline some problems specific to Bulgaria, leading to suboptimal treatment with biosimilar medicinal products, regardless of the provided access, giving potential solutions for their optimization. I believe that this thesis deserves to be disseminated to a wider audience in the form of a monograph. The quality of the dissertation and the scientometric characteristics of the publications show that the doctoral student has in-depth theoretical knowledge and professional skills in the field of the

scientific specialty "Social Medicine and Organization of Healthcare and Pharmacy". Emanuil Yordanov has the necessary theoretical knowledge and experience to independently conduct scientific research and correctly summarize and interpret the obtained results, which is the main goal of the third degree of study. The dissertation fully meets the requirements laid down in the ŽRASRB and the Regulations for its application for the awarding of the educational and scientific degree "Doctor".

Based on the above, **I confidently give my positive assessment of the dissertation and recommend the esteemed members of the scientific jury to vote positively for awarding the educational and scientific degree "Doctor" to Emanuil Plamenov Yordanov in the scientific specialty "Social Medicine and Organization of Healthcare and Pharmacy"**

Sofia, May 28, 2023 Reviewer:…….....

/prof. Denitsa Momekova, PhD/