Review

By Prof. Zlatka Dimitrova Dimitrova, D.Sci, Head of ESL on Social Pharmacy, Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at SU "St. Kl. Ohridski"-Sofia, appointed as a Member of a Scientific Jury by Order No. RD-38-116/08.02.2023 of Prof. Anastas Gerdjikov, Rector of Sofia University“ St. Kliment Ohridski ”.

Subject: procedure for the defense of the dissertation on the topic: "Retrospective study of medicinal use, availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria" for the acquisition of ESD "Doctor" of mag. pharm. Emanuil Plamenov Yordanov, full-time doctoral student at the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy 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” with supervisor Prof. Emil Ivanov Hristov,MD, Ph.D.

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 new Regulations on the terms and conditions for acquiring scientific degrees and occupying academic positions at SU "St. Kliment Ohridski", Chapter II. Acquisition of the ESD "Doctor" and the scientific degree "Doctor of Sciences", Section III. Conditions and procedure for acquiring the ESD "Doctor", as well as on the basis of my designation as a reviewer(protocol № 1 / 12.04.2023)

Procedure data. By Order No RD-20-118/2.01.2020 mag. pharm. Emanuil Plamenov Yordanov is enrolled as a full-time doctoral student in the field of higher education 7. Health care and sports, Professional direction 7.3 Pharmacy, in the doctoral program "Social medicine and organization of health care and pharmacy" in the Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at SU "St. Kliment Ohridski", considered from 22.01.2020 to 22.01.2023.

The doctoral student's report on performance of the educational and scientific plan for the time of the regular doctoral studies was presented, as well as Order No. РД-20-359 /7.02.2023 for his deduction due to the expiration of the deadline with the right to defend his dissertation after its discussion by the Department council and a decision on his readiness to be referred for public defense. The doctoral student's document folder contains all required documents for the defense of a dissertation.

At the first meeting of the Scientific Jury, which was held on 12.04.2023 at 2 p.m. were elected: chairman of the scientific jury - prof. Zlatka Dimitrova and two reviewers: Prof. Zlatka Dimitrova, DSci and Prof. Dr. Kancho Chamov,D.Sci/external member of the Scienific Jury/, and the other members of the scientific jury to present opinions. The deadline for submitting reviews and opinions is 07/06/2023. Based on the submitted documents, incl. the certificate of fulfillment of the minimum requirements, the Scienific Jury decided to admit the candidate to the evaluation and set a date for the defense June 28, 2023/Wednesday/, at 1 p.m. in the Faculty of Chemistry and Pharmacy.

Biographical data and career development of the candidate: M. Pharm. Emanuil Plamenov Yordanov, was born on 30.06.1992. He graduated and obtained a master's degree in pharmacy on 01.01.2017 at the Faculty of Pharmacy at SU-Sofia. After graduation, he started working at PharmAdvice ltd, BG as a pharmacist in the following areas: drug regulation, pricing of medicinal products and preparation of pharmaco-economic and budget impact analyses.

I believe that the dissertation of mag. pharm. Emanuil Plamenov Yordanov, a full-time doctoral student in the doctoral program "Social medicine and organization of health care and pharmacy" has a significant and practical topic, as he analyzes and evaluates the availability, accessibility and usability of new BMPs and biosimilars(BSMPs), containing monoclonal antibodies on the Bulgarian market before and after the accession of our country to the EU on a macro level and proves that the time for their

entry has been reduced from several years/5.5 years on average/, when Bulgaria was a third country for the EU to 6.3 months when our country is already an EU member state.
This ensures timely treatment of patients in need of such therapy. But on the other hand, the use of BMPs and BSMPs is associated with very high costs - their price is several times higher than the price of conventional MPs and the price for a therapeutic course significantly exceeds the average income of Bulgarian citizens, which is why this type of MPs are considered to be accessible only after they are included in the positive list and their costs are paid from public funds.
And here a new problem appears - prescribers are reluctant to treat their patients with BSMPs, which have the same efficacy and safety as BMPs and their price cannot exceed 80% of that of the reference product, i.e. costs can be saved to go towards therapy for other patients in need.
The problem is not only related to patients and doctors, but above all to the lack of an adequate national drug policy, to the lack of independent drug information for doctors and patients, and much more factors because replacement and switching from one BMP to its BSMP or vice versa is a matter for the competent authorities at national level, who must make decisions based on the information on the evaluation of these products by the Committee for MP in Human Medicine, but this is outside the competence of the EMA.
The dissertation, dedicated to a significant problem for public health care, is up-to-date and original, since such a comprehensive study has not been conducted in our country, and in other EU countries, the number of scientific reports on the problem is limited /a total of 17 over a 12-year period/. The dissertation submitted for review has a volume of 116 pages and one appendix and is illustrated with 14 tables and 44 figures. The bibliography includes 125 sources, of which 6 are in Cyrillic and 119 in Latin.
Characteristic of the candidate's research and applied scientific activity.
The dissertation was discussed, accepted and referred for defense by the department council of the Department of Physical chemistry at the Faculty of Chemistry and Pharmacy of SU "St. Kliment Ohridski". It is structured according to the requirements and written in clear, professional and accessible language. The literature review is presented in two parts: in the first part, an analysis of 17 publications related to the topic of the dissertation was performed. Many obstacles to the market entry of biosimilar medicinal products containing monoclonal antibodies have been identified in other EU countries as well, the most important of which are: lack of trust on the part of doctors in BSMPs, lack of established rules for making decisions on "substitutability/interchangeability/switching" of biological and biosimilar medicines by national competent authorities, lack of reforms in reimbursement and pricing systems, lack of financial incentives for doctors and patients, aggressive promotion policies, etc. All studies report the use of biosimilar medicinal products as too low, and although the quality, safety and efficacy of biosimilar medicinal products are clearly established, their market penetration is still unsatisfactory. The second part of the literature review briefly describes the epidemiology, etiology, clinical picture and therapeutic approaches for two socially significant diseases - rheumatoid arthritis and chronic inflammatory bowel diseases - in which BMPs and BSMPs containing monoclonal antibodies are used.
The overview clearly shows the good professional awareness of the doctoral student on the discussed issues, since during his short professional path until now he has worked as an expert in a relatively new field for the professional realization of a master's degree pharmacists in our country, he graduated recently before winning the competition for a full-time doctoral student and as such teaches classes in pharmacoeconomics and social pharmacy.
A good knowledge of the unresolved serious problems in the implementation of BSMPs determine the purpose and tasks of his dissertation work. They are well substantiated and an adequate methodology has been chosen for the realization of the research.
The doctoral student sets himself a significant goal: "To determine the medicinal use, availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria at the macro level and in two specific therapeutic areas - rheumatology and gastroenterology by analyzing their

medicinal usability for the treatment of two socially significant diseases - Rheumatoid arthritis and Inflammatory bowel diseases (ulcerative colitis, Crohn's disease and undifferentiated colitis).
Achieving these 2 goals becomes possible by solving 6 specific tasks, with detailed descriptions of the methods and materials used for each of them. I am impressed by the evaluation of the results and their competent discussion on the basis of publicly available data from the EMA and EC, NDA, NHIF and NCPRLP registers and officially provided data by the NHIF on the number of patients and on the costs of the study period for BMP and for BSMP per 6 INNs requested through an Application for Access to Public Information. The relative share of biological products is 17%, which shows excellent availability, accessibility and usability at the macro level, evaluated through the budgetary indicators for the researched 5-years period. Although they fall into a higher price range, reference medicinal products are a preferred means of prescription, dispensing and treatment in our country.
Prescription and dispensing of biosimilar medicinal products is at a negligible low level – only 4.75% of the total prescription estimated through the budget expenditures of the NHIF. The case of the availability, accessibility and medicinal usability of Infliximab shows that the lack of a reference biological medicinal product on the Bulgarian market leads to the prescription and dispensing of biosimilar medicinal products
Competent analysis of the data obtained from the respondents/rheumatologists and gastroenterologists/ in the two surveys, processed with descriptive statistical methods, convincingly substantiates the need to overcome some weaknesses in the current practice of prescribing and irrational use of BPLP containing monoclonal antibodies at the macro level and specifically for the treatment of the two main socially significant diseases - Rheumatoid arthritis and Inflammatory bowel diseases. The obtained results for each task are presented separately and are illustrated with a large number of figures, diagrams and graphs that facilitate their perception. Diametrically opposite answers to similar questions are observed. Bulgarian practice lacks national standards for substitutability and interchangeability of biological and biosimilar medicinal products.
The conclusions in the dissertation result from the analyzes conducted and the results obtained and are clearly and accurately formulated. I accept the reference for the contributions of the doctoral student.
Basic scientific and scientific-applied contributions. In the most generalized form, in my opinion, the main scientific and applied contributions in the dissertation of mag. Pharm. Emanuil Plamenov Yordanov can be summarized as follows: Contributions of an original nature:
● The design and purpose of the study is original. For the first time, a systematic review of scientific publications under the PRISMA standard was conducted to assess the medicinal utility of biosimilar medicinal products containing monoclonal antibodies, and a survey of medicinal use at the national level was conducted and the availability and affordability of biosimilar medicinal products containing monoclonal antibodies were analyzed in Bulgaria
● A methodical contribution is the developed original protocol and design of a questionnaire survey for the assessment of scientific knowledge among doctors of various specialties regarding new medicinal products - BMPs and BSMPs.
Scientific-applied and confirmatory contributions:
● The study reveals the impact of biosimilar medicinal products containing monoclonal antibodies on pricing and reimbursement systems and enriches the knowledge of medical professionals regarding the practical application and medicinal use of biosimilar medicinal products containing monoclonal antibodies worldwide.
● A mandatory element of the national drug policy is the introduction of the criteria for rational drug use in clinical practice
The dissertation enriches the Bulgarian pharmaceutical literature and gives rise to ideas for new similar future studies on the subject. The doctoral student presents a well-formed dissertation, which is structured correctly and synthetically reflects the most important results of studies in accordance with

the set goals and objectives. 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, 3 publications are presented in the Journal of Generic Medicines, which is referenced and indexed in world-famous databases with scientific information, 1 participation with a report at the Seventh Congress of Pharmacy with international participation, November 21-24, 2019, Hotel "Rila", Borovets resort complex, Bulgaria, received the award "Best oral presentation of a doctoral student or young scientist" and 6 more participations with reports at scientific student conferences at SU"St. Cl. Ohridski" and Faculty of Pharmacy at MU-Sofia.

The doctoral student, together with his supervisor Prof. Dr. E. Hristov, PhD, participated in project 3717/2022 on the topic "Comparative analysis of the pricing and reimbursement systems between Italy and Bulgaria", purpose-financed by the state budget through the Scientific Research Fund of the University "St. Kliment Ohridski" in Sofia. .The doctoral student's report card includes 138.50 points.

Conclusion. The doctoral student M. Pharm. Emanuil Plamenov Yordanov presents a dissertation work dedicated to a current and significant problem for our health care. The results of the research published in the specialized literature and reported on pharmaceutical scientific forums.

The dissertation fulfills all the requirements of LDASRB,RALDASRB and the Regulations for the terms and conditions for acquiring scientific degrees and occupying academic positions in SU "St. Kliment Ohridski" for the acquisition of the ESD "doctor". I give my positive assessment of the dissertation and fully convinced that I will support the awarding of the ESD "Doctor" in Pharmacy to Emanuil Plamenov Yordanov, Ph.D. in the doctoral program "Social Medicine and Organization of Health Care and Pharmacy" by voting "Yes".

29.05.2023r.
Sofia

Reviewer:.....

/prof. ZL. Dimitrova, DSc./