REVIEW

by Prof. Kancho Trifonov Chamov, MD, PhD, member of a scientific jury according to an order

No. RK 38 - 116 / 08.02.2023 of the Rector of Sofia University "St. Kliment Ohridski"

Regarding: procedure for the obtaining the scientific-educational degree "Doctor of Pharmacy" after the defense of the PhD Thesis of master pharmacist **Emanuil Plamenov Yordanov**, a full-time PhD student in Professional field - 7.3 Pharmacy, Scientific specialty "Social Medicine and the Organization of Health Care and Pharmacy" of the Faculty of Chemistry and Pharmacy at Sofia University "St. Kliment Ohridski" on the topic: **"Retrospective study on drug utilization, availability and affordability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria".**

Scientific supervisor: Prof. Emil Hristov, MD, PhD

1. Biographical data and career development of the PhD student

Emanuil Plamenov Yordanov was born on June 30, 1992 in the city of Sofia. In the period 2012 - 2017, he completed his higher education at the Faculty of Chemistry and Pharmacy of Sofia University "St. Kliment Ohridski" with professional qualification Master of Pharmacy. Since 2018, he has worked successively as an expert on "Medicine regulation, pricing and reimbursement of medicinal products" and as "Deputy for quality assurance" at PharmAdvice LTD. In 2020, he won a competition for a full-time PhD student at the Faculty of Chemistry and Pharmacy of the University of St. Kliment Ohridski" by Professional field - 7.3 Pharmacy, Scientific specialty "Social Medicine and the Organization of Health Care and Pharmacy". MPharm Emanuil Yordanov completed his PhD studies on time, presenting a completed dissertation entitled "Retrospective study on drug utilization, availability and affordability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria."

2. Dissertation data

The PhD Thesis presented for discussion of MPharm Emanuil Plamenov Yordanov is in a volume of 129 standard pages. The text of the development is illustrated with 48 figures, 15 tables and 1 appendix. The literature reference contains 126 sources, of which 7 are printed in Bulgarian and 119 in international scientific publications. Most of the scientific sources used were published in the last 10 years. The dissertation is written in accordance with the accepted requirements and contains: introduction (4 pages), literature review (35 pages); goals, tasks, material and methods (6 pages); analysis of results (58 pages); discussion of results (4 pages); conclusions, references and appendix. The separate chapters of the work are chronologically connected and meet the structural and content requirements for a similar scientific work.

The PhD student presented a list of 11 publications made in connection with the dissertation, which include 3 articles printed in scientific publications referenced and indexed in world-renowned scientific information databases and 8 published in non-refereed journals with scientific review or published in edited collective volumes. MPharm E. Yordanov is the winner of the following two scientific awards: For "Best oral report of a PhD student or young scientist" at the Seventh Congress of Pharmacy with international participation, November 21 - 24, 2019, Borovets, Bulgaria; and "Alma Mater" for the academic year 2019/2020 by order of the Rector of SU "St. Kliment Ohridski" No. RD -27-1596 of 20.11.2020

3. Relevance of the PhD Thesis

Biosimilar medicinal products (BSMPs) are biological medicines that have a certain similarity to others produced by a different manufacturer than the one producing the original product, called the "reference biological medicinal product". The term "biosimilar" refers to a biologic drug that is very similar to an already approved reference biologic drug product. It is for this reason that the EU has created a legal framework and a separate regulatory pathway for such biosimilar medicinal products. The main objective of the European regulatory framework is to determine the similarity of a given biological product compared to a similar reference biological medicinal product. A biosimilar medicinal product approved by the EMA should have the same quality, safety and efficacy profile as the reference medicinal product and be used for the treatment of the same diseases. If a biosimilar medicine is of proven similarity and has comparable safety and efficacy in a therapeutic indication, they they can to be extrapolated for all other indications already approved for the reference medicinal product. Extrapolation must be supported by scientific evidence obtained during preclinical and clinical trials. Research results have found that biosimilars are much more affordable than the original product, resulting in lower costs for the payer.

In this context, presented by MPharm Emanuil Yordanov PhD Thesis treats an actual, but unstudied medical-therapeutic problem in the country, related to the medicinal use, availability and accessibility of BSMP containing monoclonal antibodies. The relevance of the presented study is also supported by the need for modern knowledge and experience on: the regulation of BSMP; the use, substitutability, interchangeability and switching of biologics and biosimilars; the availability, affordability and cost of treatment with such products; need for evidence-based drug interchangeability models regulated by national competent authorities.

4. Awareness of the issue

The literature overview in a volume of 35 pages synthesizes the scientific information from 126 literary sources, (7 in Bulgarian and 119 in international editions), the majority of which were published in the last ten years. The analysis of scientific publications is structured in two sections - methodical and analytical. The first methodically uses a modified version of the "Guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines)". The second includes an overview analysis of the results of studies on the use of biological medicinal products (BMPs) and biosimilar medicinal products (BSMPs) containing monoclonal antibodies in rheumatological diseases (Rheumatoid arthritis) and

gastroenterological diseases (Inflammatory bowel diseases - ulcerative colitis, Crohn's disease and undifferentiated colitis).

The PhD student demonstrates good literature awareness and analytical abilities for the synthesis of current problems related to the obtained results of the applied therapeutic approaches in Rheumatoid Arthritis and Inflammatory Bowel Diseases (Ulcerative Colitis, Crohn's Disease and Undifferentiated Colitis). The synthesis of literary sources shows a thorough knowledge of the problem, high professional and terminological competence. The conclusions formulated within the separate sections are focused on essential medical and therapeutic details, which synthesize opportunities for their use in the methodological toolkit of the research conducted by the PhD student.

5. Purpose, tasks and methodology of the study

The purpose and tasks of the dissertation development are clearly formulated, specific and justified. The objects and units of observation are correctly defined. For the realization of the study, the PhD student has formulated two goals and six tasks, which are clearly formulated, specific and justified. Objective No. 1 includes a study of medicinal use, availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria at a macro level. Objective #2 includes determining the medicinal use of biosimilar medicinal products containing monoclonal antibodies in specific therapeutic areas such as rheumatology and gastroenterology by analyzing the medicinal usability of two major socially significant diseases - Rheumatoid arthritis and Inflammatory bowel diseases (ulcerative colitis, Crohn's disease and undifferentiated colitis).

The tasks related to the implementation of objective No. 1 successively include: determining the availability of BSMPs containing monoclonal antibodies in Bulgaria by assessing their registration status; determination of the availability of BSMP containing monoclonal antibodies in Bulgaria by assessing the availability of registered prices; determining the availability of BSMP in Bulgaria with an assessment of their inclusion in the reimbursement systems; determining the accessibility of BSMP in Bulgaria by evaluating the costs of treatment with this type of medicinal products with the measurement of absolute and relative market shares and macro-level budgetary parameters for medicinal usability. Tasks related to Objective No. 2 include: conducting a comparative analysis of drug use and usability between BMP and BSMPs containing monoclonal antibodies in the treatment of Rheumatoid Arthritis and Inflammatory Bowel Diseases; assessment of the knowledge and readiness of medical specialists to prescribe BMP and BSMPs containing monoclonal antibodies in Bulgaria.

The sources of information include data from public registers of statutory institutions such as the EMA, European Commission - Register of Medicinal Products, National Health Insurance Fund (NHIF), National Council on Prices and Reimbursement of Medicinal Products (NCPRM) and the Law on Medicinal Products in Human Medicine (LMPHM). In order to assess the level of knowledge and willingness of specialists to prescribe biological and biosimilar medicinal products containing monoclonal antibodies in Bulgaria, a survey was conducted among medical specialists in Rheumatology and Gastroenterology.

The chosen research methodology allows to successfully achieve the set goal by adequately solving the tasks in the PhD Thesis. Research methods are successfully selected and comprehensively described, including comparative analysis, financial analysis, statistical and sociological methods. A high degree of correspondence was achieved between the 6 tasks set, the number of scientific interventions undertaken and the results obtained from the study.

6. Evaluation of the results

The results of the MPharm Emanuil Yordanov own studies are presented in Chapter III of the dissertation, being grouped into 6 thematic sections, following the chronology of the assigned tasks.

In fulfillment of task No. 1, the medicinal use, availability and accessibility of biosimilar medicinal products containing monoclonal antibodies in Bulgaria at the macro level were determined. The data for the authorizations for the use of 67 biosimilar medicinal products registered by the EMA in Bulgaria as of December 31, 2019 were analyzed, of which 14 contain monoclonal antibodies. The share of BSMP containing monoclonal antibodies is 1/5 of the total number or 20.89%. The approved BSMPs are divided into the following 6 International Nonproprietary Names (INN) - Adalimumab, Infliximab, Rituximab, Bevacizumab, Trastuzumab and Trastuzumab emtansine. A comparative analysis of the distribution of the reference and biosimilar medicinal products by INN, as well as the authorization periods for use in the EU and in Bulgaria, was made.

The results obtained from the implementation of task No. 2 have a historical and analytically informative character, synthesizing the regulatory mechanisms and the characteristic features of international practice and national specificity in the regulation, registration and pricing in the EU, EMA and national health care systems. The advantages and disadvantages of the two options available for the purpose – imported and self-developed models, as well as a block diagram are analyzed for procedures and conditions for registration of the BSMP price.

The comparative analysis that the PhD student makes of the chronology in the evolutionary development of EU Directives and Regulations and their procedural implementation in Bulgaria establishes: that the procedures for registering the price of BMP in the EU member states are one of the shortest; in what periods after marketing authorization reference BMPs and their BSMPs become available for Bulgarian patients after the availability of MA and registered price; the prices of BMP and BSMP and the price of one conducted therapeutic course in our country significantly exceed the average income of Bulgarian citizens, i.e. they become available only after they are included in the reimbursement system.

Within the framework of task No. 3, when reviewing the registers of the NCPRM, the PhD student found that all BMP and BSMP are included in the reimbursement system, and none of the products presented in Table 8 has registered a price only for the free market in Bulgaria. The reference BMPs in Bulgaria were included in the reimbursement system relatively late compared to other EU member states, due to the later acceptance of our country as a member of the EU (01 January 2007), after which the centralized MAs became directly valid for

Bulgaria. The first BMPs containing monoclonal antibodies appear on the Bulgarian market with an average delay of 5.5 years, compared to EU member states. 12 BSMPs are included in the PDL, with the significantly longer average term for inclusion in the reimbursement system in Bulgaria of BSMPs after the issuance of the MA - 6.3 months established by the dissertation. Presented in a series of graphs are the reference BMPs and their BSMPs containing monoclonal antibodies included in the PDL with their respective registered prices as proof of their availability in our laboratory.

When analyzing the public data on drug usability at the macro level for the period 2015-2019, the PhD student found: the total costs of treatment with BMP and BSMP, distributed also by international non-proprietary names (INN), the sum of which amounts to BGN 716,360,871; the share of reference BMPs amounts to 95.25% of them, while that of BSMP is only 4.75%. A comparative analysis of the costs of the NHIF for BMP and BSMP was made for the period 2015-2019. The analyzes made established the preferential prescription of reference products, with the exception of the product with the INN Infliximab. When researching the ratio of the costs of the studied international non-proprietary names (Adalimumab, Infliximab, Rituximab, Bevacizumab, Trastuzumab and Trastuzumab emtansine (reference and biosimilar)) to the total costs of medicinal products for the period 2015-2019, it is found that the share of BSMP is only 4.75% of the total amount in the distribution by INN in BGN. This proves the low usability of biosimilar medicinal products in Bulgaria. Analyzes with the application of BSMP and Reference BMP for the following INN products are presented in graphic form: Adalimumab, Infliximab, Rituximab, Adalimumab, Infliximab for Rheumatoid Arthritis; Rituximab for M05.8 for Other Seropositive Rheumatoid Arthritis; and comparative distribution of BMP and BSMPs costs for INN Adalimumab, Infliximab, Rituximab for ICD - M05.8 - Other Seropositive Rheumatoid Arthritis.

To study the degree of knowledge and the willingness of specialists to prescribe biological and biosimilar medicinal products containing monoclonal antibodies in Bulgaria, the PhD student conducted a survey among 40 medical specialists in Rheumatology (37) and Gastroenterology (3) with a questionnaire developed by him with 17 questions. The readiness of rheumatologists to prescribe biosimilar medicinal products was analyzed according to the length of their working experience. 44.8% of respondents preferred to prescribe BSMP as a first line of therapy, while 41.2% preferred prescribing BMP. The survey was also conducted among doctors specializing in Gastroenterology, but only 3 of them or 1.2% of all doctors specializing in "Gastroenterology" responded. The results of the study show that the prescription and dispensing of biosimilar medicinal products among rheumatologists is at a very low level – only 4.75% of the total prescription, estimated through the budgetary costs of the NHIF. The reasons for this are also analyzed, related to: the lack of national standards for substitutability /interchangeability of BMP and BSMP; prescribing by trade names, conservatism and mistrust of prescribers to the so-called replacement therapies; aggressive drug promotion to medical specialists, etc. Pathognomonic is the example of the availability, accessibility and medicinal usability of Infliximab, which is preferred due to the lack of a reference biological medicinal product on the Bulgarian market. The study among rheumatologists found that the main reasons for the low level of prescription and limited dispensing of BSMP in our country are related to

their lack of knowledge and confidence in prescribing these medicinal products. There is concern and uncertainty among professionals about the use of BSMP, especially among patients who have not previously been treated with BSMP. The results of the study prove the need for more training courses, materials and resources to support specialists in our country to increase their knowledge and confidence in prescribing BSMP, to achieve more rational drug use for the benefit of patients.

7. Evaluation of the contributions of the PhD Thesis

- For the first time, a survey of medicinal use and availability was conducted in our country and the availability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria.

- The conclusions from the rich literature review have a high scientific and informative value, placing precise emphasis on existing medical-therapeutic, regulatory and financial facts related to the use of BSMPs containing monoclonal antibodies and the presence or absence of established rules for their prescription, use, pricing and reimbursement.

- The results of the study of the total costs of treatment with BMP and BSMP for a five-year period, as well as their availability, accessibility, usability, interchangeability on the example of two socially significant diseases, have a scientific and applied contribution.

- The results of the conducted survey on the level of knowledge and readiness of two groups of specialists to prescribe BMP and BSMP containing monoclonal antibodies in real practice have a scientific-theoretical and applied contribution.

The main conclusions in 13 thematic directions to a significant extent reflect the obtained results and correspond to the purpose and tasks of the PhD Thesis. An additional effort by the PhD student, including the formulation of recommendations for which there is sufficient substrate in the work presented, would enrich the contribution nature of the PhD Thesis.

The content and quality of the author's reference meets the requirements of the Regulations of the SU "St. Kliment Ohridski", faithfully reflecting the main results of the study.

In conclusion, I believe that the one presented by MPharm Emanuil Plamenov Yordanov's PhD Thesis on the topic "Retrospective study on drug utilization, availability and affordability of biosimilar medicinal products containing monoclonal antibodies in Bulgaria" contains scientific and scientific-applied results that represent an original contribution and meet the requirements of the Law on the Development of Scientific composition in the Republic of Bulgaria (LDSRB) and the Regulations for the implementation of LDSRB. The results obtained and the presented dissertation materials correspond to the requirements of the Regulations for the Development of the Academic Staff of SU "St. Kliment Ohridski". The dissertation shows

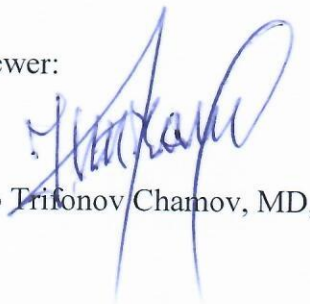
that the PhD student MPharm Emanuil Plamenov Yordanov possesses theoretical knowledge and professional skills for independent conduct of scientific research.

In this regard, I will vote positively, recommending the members of the respected Scientific Jury to award MPharm Emanuil Plamenov Yordanov the scientific-educational degree "Doctor of Pharmacy" in Professional field - 7.3 Pharmacy, Scientific specialty "Social Medicine and the Organization of Health Care and Pharmacy".

14/05/2023

Sofia

Reviewer:



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