HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2022; 9(3):1215-1230

UDC: 615.03

doi:10.5937/hpimj2203215K

Review Article

# Clinical Pharmacology - Developmental Path, Regulations, Education, Practical Management - Generally And in Serbia

Dragana A. Kastratović[1], Srdjan Z. Marković[1,2], Slobodan M. Janković[3,4]

[1] University Clinical Centre of Serbia, Belgrade, Serbia
[2] Center for Physical Chemistry of Biological Systems, Faculty of Physical Chemistry, University of Belgrade, Belgrade, Serbia
[3] University Clinical Center Kragujevac, Kragujevac, Serbia
[4] Faculty of medical Sciences, University of Kragujevac, Kragujevac, Serbia

## SUMMARY

**Introduction:** After searching literature, Professor of Pharmacology at Cornell University Harry Gold was the first to use the name Clinical Pharmacology in the late 1930s and early 1940s.

**Topic:** Clinical pharmacology is a medical discipline created in the middle of the 20th century, it implies the most effective application of medicine, and it could be said that it is the culmination of all therapeutic approaches in medicine, or simply in the preservation of human health. It is a field that spontaneously appeared in the medical field and from the first moment has the only perspective in the unity of practice and science.

The second half of the last century is the time of the beginning of the recognition of specialization in clinical pharmacology as an independent medical discipline, in Europe - first in Sweden, England, Switzerland, Norway in the fifties of the last century, in America also in the same period. In Serbia and Montenegro, we noted the beginning in 1981. Clinical pharmacology is a hospital medical specialization; specialists in clinical pharmacology are doctors who know the most adequate use of drugs, which achieves an optimal therapeutic effect. The basis of clinical pharmacology is pharmacokinetics and pharmacodynamics.

The development path of clinical pharmacology spans more than seven decades, and the key moments are the following: *concept of bioavailability* (Oser et all, 1945), pharmacokinetics (Friedrich Hartmut Dost, 1953), pharmacokinetics / pharmacodynamics (PK/PD) model (De Jongh and Wijnans and Van Gemert and Duyff, 1950), 1960 - 1980 explosion of pharmacokinetic studies and dramatic progress in the field. Pharmacokinetic interactions between drugs become evident and become the subject of many studies: in the 1970s, drug-level monitoring for digoxin, aminoglycosides, phenytoin, theophylline and other drugs began to be implemented in many hospitals. The 1980 - 2000 period is characterized by the advancement of technology, including liquid chromatography, liquid chromatography with a mass detector, and the development of computer technology.

What makes clinical pharmacology attractive is the concept of the connection between drug concentration and pharmacodynamic effect, which unites science and practice in achieving a therapeutic effect and more successful medical treatment patients,

**Corresponding author:**
Professor, Primarius Slobodan M. Janković, MD, PhD
Specialist in Clinical Pharmacology
Department of Pharmacology and Toxicology, Faculty of Medical Sciences, Svetozara Markovića 69, 34000 Kragujevac, Serbia
E-mail: slobnera@gmail.com

appeared in the eighties of the last century. In the mid-1980s, Yusko and Boudinot began research linking biochemical mechanisms with pharmacokinetic/pharmacodynamic techniques and leading to their refinement.

**Conclusion:** The development of pharmacology as a profession and science related to the use of drugs spontaneously moved from experimental pharmacology to clinical pharmacology to hospital pharmacology. In order for a clinical pharmacology specialist to really show and prove the useful value of this knowledge, the cooperation of all doctors in teamwork is necessary, as well as cooperation with scientists and cooperation with pharmaceutical magnates. If they find a way for a positive dialogue, the results will become a daily practice. Underline the letter to editors of journals, and alert letters via professional community, meaning be supported and informed.

The main developmental goal of hospital pharmacology is to encompass a wide vaiety of specialists and subspecialists, together with strict demands in respecting pharmacoterapy choice, clinical trials law, monitoring side effects of drugs and medical devices.

Ffrom authors's experience clinical pharmacologists' duties are clear, however, clinical pharmacology specialists and subspecialists are insufficient. Educating more colleagues is necessery for the future in order to increase presence of clinical pharmacology.

**Keywords:** Clinical Pharmacology, Hospital Pharmacology, Clinical Pharmacologist

## INTRODUCTION

Few people know about who first used the term Clinical Pharmacology. One would say after searching the works, books, correspondence as memories that it was Harry Gold, Professor of Pharmacology at Cornell University, who had carried out fundamental research on the human pharmacology of digitalis glycosides in the late 1930s and early 1940s [1].

## TOPIC

### Clinical pharmacology developmental path

Clinical pharmacology is a medical discipline created in the 20th century, it implies the most effective application of medicine, and it could be considered the culmination of all therapeutic approaches in medicine, or simply in the preservation of human health. It is a field that spontaneously appeared within the medical science and from the very beginning its unique perspective is in the unity of practice and science. In some countries, clinical pharmacology has reached a high level of development and identity. In the Republic of Serbia, development coincided with that in other European countries, but hospital units were included mainly in the 21st century [2,3].

The second half of the last century is the time of the beginning of the recognition of specialization in clinical pharmacology as an independent medical discipline, in Europe - first in Sweden, England, Switzerland, Norway in the fifties of the last century, in the USA also in the same period. In Serbia and Montenegro, we noted the beginning in 1981 [4].

Clinical pharmacology is a hospital medical specialization; specialists in clinical pharmacology are doctors who are familiar with the correct use of drugs to achieve an optimal therapeutic effect. The basis of clinical pharmacology is pharmacokinetics and pharmacodynamics.

The development path of clinical pharmacology spans more than seven decades, and the key moments are the following: The „*concept of bioavailability*" was introduced by Oser et al. in 1945, using as a model a comparison of the bioavailability of vitamins in the form of oral solution and tablets [5].

The term pharmacokinetics was first used in the chapter The Blood Level written by Friedrich Hartmut Dost in 1953 [6].

The first scientific paper on pharmacokinetics / pharmacodynamics (PK/PD) was published in 1950, written by De Jongh and Wijnans [7] and Van Gemert and Duyff and represents the first applied PK/PD model for optimizing the application of many medicines [8].

The period from 1960 to 1980 was characterized by an explosion of pharmacoki-

netic studies and dramatic progress in the field. This is related to the beginning of the application of information technologies (computers), as well as the application of much more precise analytical techniques such as gas and liquid chromatography, which enabled faster and better measurement of the concentration of drugs then in biological fluids [9], and later in all biological samples. In fact, 1965 is marked as the year when this type of research found direct application in clinical medicine with the work of Beckett and Rowland [10], which was noted by the Swiss physician Louisius Dettli [11].

Following that, pharmacokinetic interactions between drugs become evident and become the subject of many studies [12]. In the 1970s, drug-level monitoring for digoxin, aminoglycosides, phenytoin, theophylline and other drugs began to be implemented in many hospitals [13,14,15,16].

The period from 1980 to 2000 was characterized, more than ever, by the advancement of technology, including liquid chromatography, liquid chromatography with a mass detector, and the development of computer technology.

What makes clinical pharmacology attractive is the concept of the connection between drug concentration and pharmacodynamic effect [17,18,19,20], which unites science and practice in achieving a therapeutic effect and more successful medical treatmentof patients, appeared in the eighties of the last century.

We should not forget the importance of numerous specific therapeutic classifications of drugs and a large number of works in this field in those years. In the mid-1980s, Yusko and Boudinot began research linking biochemical mechanisms with pharmacokinetic/pharmacodynamic techniques and leading to their refinement [21,22].

This is followed by a period of integration of the results of preclinical and clinical research [23]. In the early 1990s, the PK/PD model as an integral part of the process of improving the use of drugs was encouraged by the initiative of Peck and associates through studies with controlled drug concentrations [24]. This also found its application in the process of industrial drug development [25]. At that time, books on pharmacokinetics and pharmacodynamics were printed [26,27,28]. In the early nineties of the last century, Population Pharmacodynamics entered the literature [29,30].

The early eighties of the last century also brought the beginning of the application of pharmacostatistical models [31,32,33]. Statistical methods provide a high valiability clinical trial data processing and the prediction possibility of the most efficient therapy options [34]. Simultaneously, interest begins in America and Europe for legal regulations on the use of medicines. In the early eighties, the expansion of generics also began [35,36,37,38].

Temple from Food and Drug Administration (FDA), organizes, under the leadership of Peck, an Agency that brings together scientists with whom it invests in drug development [39].This is how a golden base of scientific knowledge and an internal group of experts is created, which critically and expertly evaluates the improvement of work and results within pharmaceutical companies. As an urgent need of people who have contact with the drug, at any level and at any stage, a large number of professional works on clinical experiences from various medical fields are printed, which would mark the beginning of hospital pharmacology, of course not called that, but practically experiential practical pharmacology. It is interesting that then the expansion of clinical pharmacology related to pediatrics begins, e.g. Grasela initiated the analysis of the pharmacokinetics of barbiturates in neonates, which was the first demonstration of the value and importance of this technique in the most sensitive patient population, and published the results in 1985 [40]. With its population analyses, Grasela shows the possibilities of improving the application of drugs as well as the software for connecting the collected rare and scattered data, as well as the possibility of inserting important parameters [eg Apgar score] directly into the pharmacokinetic model, whereby the final analysis of the results gains quality. The PK/PD model was studied by many famous scientists, including our researchers in the field of finding the minimum effective dose of anesthetics with the help of BIS monitoring technology [41] At that pointthe current FDA guideline for population pharmacokinetics was created [42]. The most important thing is that all this provoked a dialogue between scientists, manufacturers and administration. In 1991, in Manchester, United Kingdom, there was an international meeting entitled New Strategies in Drug De-

velopment and Clinical Evaluation: The Population Approach, which was the first time that the population approach was discussed at such a meeting and in that way.

The first clinical pharmacologist was Paul Martini, professor of medicine at the University of Bonn, officially since 1932, published a monograph entitled Methodology of Therapeutic Investigation. Dr. Martini can be said to have laid the foundation for Good Clinical Practice in clinical trials [43]. Clinical pharmacology in Serbia and Montenegro was integrated into European and world guidlineses by the prominent Professor Tomislav Kazic, author of many research papers, monographs and textbooks [44]. With his systematicity and benevolence, Professor Kažic helped many doctors, including the authors of this work, develope their professional identity of doctors dealing with the administration of medicines.

**Regulations**

In the 1980s, interest in legal regulations on the use of medicines began both in America and Europe.

There are many tasks a clinical pharmacologist undertakes regarding drug regulations. These include responsibilities for the premarketing assessment of a new product's efficacy and safety, for scrutiny of the Summary of Product Characteristics, and for monitoring its performance after marketing. Furthermore, the clinical pharmacologist has a subsidiary responsibility in examining the results of preclinical pharmacological and toxicological studies. 2. Clinical pharmacologists in regulatory authorities have one further, and crucial, responsibility. From their training and experience they will (or should) know of their own scientific limitations and of the necessity for seeking help and advice from other disciplines [45].

The first directive with precisely defined rights and obligations of the principal investigator and members of the research team and implies cooperation in multinational multicenter teams with mandatory compliance with the same regulatory rules is European Parliament and the Council of the European Union [46].

This directive primarily refers to EU member states, but Serbia implemented the EU directive in its legislation, even though it was on the threshold of negotiations for EU membership at the time. This directive contains amended and supplemented articles of earlier valid laws.

One of the first laws on medicines and medical devices in Serbia was published in the Official Gazette of the RS, no. 30 of May 7, 2010. The Law was supplemented and amended through versions 107 of November 9, 2012, 105 of November 23, 2017, and 113 of December 17, 2017 [47].

The work of the Ethics Committee of Serbia is regulated by the Law on Health Care (Articles 141 and 142). The members of the ethics board are experts in the field of health care, professional ethics and humanities. A person who has been appointed to a position in a state body, a health council, a body of territorial autonomy or local self-government, a person appointed to the bodies of organizations that provide health insurance, i.e. bodies of health institutions, higher education institutions, medical chambers, cannot be elected as a member of the Ethics Committee, the Serbian Medical Association and the Association of Health Institutions (Article 137). The Ethics Committee of Serbia has its own rules of procedure. The rights and obligations of the members of the Ethics Committee of Serbia (ECS) in relation to clinical trials of drugs are defined by the Decision on appointing ECS and the Rules of Procedure of the Ethics Committee of Serbia [48,49].

On the basis of the Law on Medicines and Medical Devices, regulations were adopted to solve the current issues related to practice.

Clinical trials conducted according to the principles of Good Clinical Practice in Clinical Trials guarantee the acceptance, reproducibility and ethics of a clinical trial performed in any part of the world and on any population group. They are implemented in our Law on Medicines, the Regulation on Clinical Trials of Medicines and the Regulation on Testing Medical Devices. Their functionality is based on: *Respect for Persons*: This principle acknowledges the dignity and freedom of every person. It requires obtaining Informed consent from research subjects (or their legally authorised representatives), *Beneficence*: This principle requires that researchers maximise benefits and minimise harms associated with research. Research-related risks must be reasonable in light of the expected benefits. *Justice*: This principle requires equitable selection

and recruitment and fair treatment of research subjects [47,50,51,52].

The currently valid precise guidelines specific to clinical trials of drugs and medical devices are defined by the Regulation on clinical trials of drugs [53]. In order to exercise the right to the drug, the pharmaceutical industry must comply with the regulations of our country for the necessary documentation for clinical trials, and quality control of the drug [54].

The first regulation on medical devices appeared in the Republic of Serbia in 2011 and refers to quality control and clinical trials [54]. The following regulations refer to clinical trials of medical devices and have appeared in the RS since 2016 [55,56]. Due to frivolous advertising information about medical devices, the regulatory body (ALIMS) before others set a Regulation on how to advertise a medicine or a medical device [57].

In order for the medicine to get its rightful place in use, all the time of use, from the registration onwards, there is a legal obligation of the doctor and the legal right of the patient to report any suspicion of an unwanted effect of the medicine to ALIMS [51].

Proposing a clinical trial, conducting a clinical trial and reporting on a clinical trial of a drug is performed in accordance with the Good Clinical Practice Guidelines [58,59].

Clinical trials for children are also performed in accordance with the guidelines of good clinical practice and the Guidelines for clinical trials of drugs on children, which are part of the 2022 Regulation [53].

This Regulation introduced the existence and role of the Ethics Committee of the Republic of Serbia, and the jurisdiction of the ethics committees of health institutions where the examination is performed ceased to be valid. This denied the opportunity to the physician-researchers and especially the principal investigators to assess the real possibilities and quality of the proposed clinical trial. The role of the clinical pharmacologist, given this change, is more serious because he decides on behalf of the entire state and all research doctors. For these reasons, it is necessary that all members of the Ethics Committee of Serbia (Central Ethics Committee) for a certain period, and we suggest 2 years, renew their education in good clinical practice (GCP) [53].

**Education**

The development of education in the field of clinical pharmacology, from a student to a specialist has its own logical path, which was actually the same in all countries. Whether the task of education on this topic was successfully completed depended on all possible factors (development and stability of the school system, quality of teaching staff, economic and even political freedoms). The rapid implementation of teaching programs in accordance with European trends was achieved consistently in terms of the promptness of individual representatives of the teaching staff [44,60,61], but the number of participants was always lacking for success. Thus, countries with fewer changes in all these areas managed to provide a stable infrastructure for the application of the highest quality therapy for their residents and thus save a greater number of human lives. The country that led the drug policy most stably is certainly the UK . The realization of the increase in the number of staff was in accordance with the changes in the personnel structure of the regulatory bodies, which determinated the number of needed clinical pharmacologists [62].

Before the formation of specialist training, the seminar was considered the most suitable form of education. The leader of the first Pharmacotherapy Seminar for clinicians, held in 1929, was Prof. Radivoje A. Pavlović. By the way, a Serb, born in Čibu Bačka. In 1926, he launched the scientific journal "Medicinski pregled" and was the first assistant to Professor Arnold Holste in pharmacology at the Faculty of Medicine in Belgrade [63].

Practical work of a hospital pharmacologist requires completed specialization and/or subspecialization training. In addition, doctoral studies in clinical pharmacology are requied for the teaching staff of the faculty . Specialists and sub-specialists of clinical pharmacology are qualified by their education to participate in clinical drug trials as principal researchers and/or as part of the research team [64]. At the Faculty of Medicine in Belgrade, the basic specialization in clinical pharmacology was introduced on August 22, 1981 by the head of specialist teaching, prof. Varagić [65]. A narrower specialization in clinical pharmacology-pharmacotherapy was included in the statute of the Ministry of Health Belgrade in 1979, and the head of the specialist program

was Prof. Leposava Grbović from 1989, and the Master Degree in Clinical Pharmacology was headed by Prof. Ranka Samardžić [64]. The scientific and educational board of the Medical Faculty in Novi Sad and its Department of Pharmacology and Toxicology formally introduced the clinical pharmacology as postgraduate programme (MSc, and PhD degree) in 1975. In addition to the profession and science, clinical pharmacology also has a social responsibility, because drug prices are sometimes unaffordable for everyone, and the therapeutic effect should be available to everyone, regardless of socioeconomic status [66].

An independent medical residency programme of clinical pharmacology was established on the August 22, 1981 at the Medical Faculty in Belgrade [65,67,68,69,70,71]. A 3-year training of the graduated MDs, consisted of 13 months spent at the Institute of Basic Pharmacology, 9 months of formal lectures and 14 months of clinical training. A shorter training programme, clinical pharmacology subspecialty, lasting for 18 months, was also available for specialists in internal medicine, anaesthesiology, general surgery, paediatrics, infectious diseases and neuropsychiatry.

Within the framework of basic medical studies at medical faculties in Serbia, Pharmacology is a subject at the 3rd year and Clinical Pharmacology at the 6th year of study.

Doctoral studies in Medical Pharmacology at the MoF in Bg within the unified program of doctoral studies in medical sciences were accredited in 2011 under the name „Medical pharmacology" for unified basic and clinical pharmacology, which was used by Aronson 2010 in the article Br J Clin Pharmacology and on World Congress of Clinical Pharmacology in the same year. Doctoral studies in medical pharmacology have been supervised since 2014 by Prof. Ljiljana Gojković Bukarica. A successful professional educationa requires a high-quality, accessible textbook, validated by the length of practical application in teaching. One of such textbooks was written by Varagić & Milošević with the simple title „Pharmacology" [72].

The first formally trained clinical pharmacologist in Serbia was Prof. Milan Stanulović, who after his education in the Great Britain, Nordic countries and the United States, passed his examination at the Board of Croatia in Zagreb, in 1984 [73].

In Belgrade, Serbia, the first national center for adverse drug reactions was in Clinical Centre of Serbia (CCS) founded in 1995 and headed by Prof. Vaso Antunović, Ph.D. and Ljiljana Vučković, Ph.D. The Agency for Medicines and Medical Devices of Serbia (ALIMS) was founded on October 1, 2004. The clinical pharmacology working units took over the monitoring of adverse drug effects in clinical centers.

The authors of the first textbook of pharmacology called *The Pharmacological Basis of Therapeutics*, with the first edition from 1941 were Goodman and Gilman. The textbook represented a significant turning point in the medical profession and science, and new editions continue to be published to this day [74].

Prof. Tomislav Kažić, PhD was a rare combination of lecturer, pedagogue and scientist in Serbia who wrote many books, papers and educated numerous doctors. One of his first textbooks, which is still in use although there are no new editions, is Clinical Pharmacology [60]. Research in the field of clinical pharmacology inextricably links pre-clinical-experimental research with applied research, and realistically, there is little applied research and experimental research should be supported. What is missing in the development of hospital pharmacology is multidisciplinary multinational research, especially of an academic character [75]. For the correct direction of future research work, it is necessary that projects and research rely on methodologically correctly conducted studies, as well as the conclusions from the results correctly drawn [76,77].

Through working units adapted to the development and needs of clinical pharmacology, the following were distinguished: Drug development units with a pharmacology laboratory , Preclinical studies with safety pharmacology, Pharmacotherapeutic units, Working units for Clinical trials Monitoring and analysis of adverse drug effects, pharmacoeconomics unit Pharmacotherapy unit.

As with the entire medical science and profession, monitoring the indicators of the patient's health condition in the field requires a clinical-pharmacology laboratory with a multidisciplinary team: clinical pharmacologist, clinical transfusionist, pharmacist , molecular biologist, chemist, technicians. Analytical equipment is used from the equipment: HPLC, LM (Liquid mass) chromato-

graph, etc.

The entire clinical pharmacology is related to hospital systems and rarely has a drug development unit, and they are most often related to the pharmaceutical industry or institutes attached to faculties. Modern clinical centers call this integrative approach to drug administration hospital pharmacology, and the employed clinical pharmacologists are called hospital pharmacologists. Experienced clinical pharmacologists from around the world insist on focused education on individual areas of clinical pharmacology, which in Serbia is called subspecialization [78].

Globally, the number of doctors choosing to specialize in clinical pharmacology is declining. A large number of the authors hope to outline an alternative practice and training paradigm to potentially address the decline in physicians being trained in and practicing clinical pharmacology since the late 1970s [79]. Also, globally, hospital pharmacologists point to this problem, while departments do not react by correcting the way of education [73,80].

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project in which regulatory authorities from Europe, Japan and the United States and experts from the pharmaceutical industry of the mentioned regions participate. Since the very beginning in 1990, ICH has gradually evolved to respond to the growth of the global development of the pharmaceutical sector, so that an increasing number of regulatory bodies apply ICH guidelines. ICH's mission is to achieve the greatest possible harmonization around the world to ensure safe, effective and high-quality medicines and their development, to register and maintain the highest quality in use. All this requires high standards in work, both regulatory and personnel. The start of using the new harmonization guideline for GCP in 1997 until 2002 ICH increases the number of members to in October 2015 ICH has grown to an organization that includes 25 members and 35 observers European Union, Japan, the United States, Canada, and Switzerland [81,82]. The foundations of Good Clinical Practice were set by the FDA (Food and Drug Administration) and were quickly accepted in Europe, and at the 18th World Medical Congress, Helsinki, Finland, June 1964. Good Clinical Practice is completely accepted. GCP amendments: 29th World Medical Congress, Tokyo, Japan, October 1975, 35th World Medical Congress, Venice, Italy, October 1983, 41st World Medical Congress, Hong Kong, September 1989. The most recent revision of the Declaration of Helsinki was made at 52th The World Medical Meeting in Edinburgh, Scotland, October 2000. From the utility of such principles arose the position that only the results of clinical trials conducted in accordance with GCP are considered research valid.

Adherence to these standards ensures public confidence that the rights, safety and well-being of the subjects are protected and in accordance with the principles derived from the Declaration of Helsinki and that the data obtained in the clinical trial are reliable. The aim of these principles is to provide a single standard for Europe, Japan and the USA, in order to facilitate the mutual acceptance of clinical data from competent authorities. [81,82]

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. It also serves to protect the rights, integrity and confidentiality of trial subjects [50].

The principles of Good Clinical Practice are: 1. Conduct of clinical trials in accordance with the ethical principles derived from the Declaration of Helsinki, GCP standards and valid competent regulation/regulations. 2. Before starting the test, the foreseeable risks and consequences should be evaluated against the expected benefit for the subject and society. A clinical trial should be initiated and conducted only if the expected benefit justifies the risk. 3. The rights, safety and well-being of the subjects are the most important and should prevail over the interest of science and society. 4. The intended clinical trial should be supported by available non-clinical and clinical information on the investigational substance and drug (investigator brochure). 5. The clinical trial should be scientifically based, and clearly and thoroughly described in the protocol. 6. The clinical trial should be conducted according to the existing protocol for which approval or a favorable opinion has been obtained from the Institutional Supervisory Board / Independent Ethics Committee. 7. Medical care and medical decisions related to the subject should always be the responsibility of a qualified phy-

sician. 8. Each individual who participates in conducting the examination should have the qualifications (education, training and experience) to perform the intended task. 9. The subject's voluntary consent with full information should be obtained from each subject before inclusion in the clinical trial (the subject must sign the informed consent). 10. All clinical trial information should be recorded, managed and stored in a manner that enables accurate reporting, interpretation and verification. 11. Data that can reveal the identity of the respondents is protected, observing the rules of privacy and confidentiality, in accordance with the applicable legal regulations. 12. Investigational drugs should be manufactured, handled and stored in accordance with the applicable Good Manufacturing Practice. They should be used in accordance with an approved protocol. 13. Quality assurance procedures for all aspects of a clinical trial should be prepared and implemented in advance.

In addition to standard operating procedures, GCP includes rules on data archiving, reporting of side effects, control of deviations.

Since not a single health organization in Serbia has developed all the activities of clinical-hospital pharmacology, in the desire to work together, the Section for Clinical Pharmacology Dr. Srđan Đani Marković (SCP „Dr. Srđan Đani Marković") Serbian Medical Society (SMS) was founded on February 19, 2009 with the basic task to enable the implementation of knowledge about the use of the highest quality drugs in therapeutic and diagnostic procedures in medicine, with the final goal of providing our patients with the highest quality drugs. In order to achieve this in practice, knowledge from the regulation of clinical drug trials is necessary. Given the rapid development of this field, partial on-time education, ie short focused continuous medical education, proved to be the most practical. Since 2009, SKF Dr. Srđan Đani Marković SLD has been conducting 2x annual education in Good Clinical Practice in Clinical Trials (GCP) in clinical trials, whose certificates are recognized internationally and in our country. All clinical pharmacologists complete training in GCP, in the last 2 years only electronically due to the epidemiological situation related to COVID 19. Education in GCP is necessary for all members of the research team [83].

Guidelines for good clinical practice in the Republic of Serbia were first published in the Official Gazette in 2008 [58].

In order to achieve accepted standards, we work with colleagues from Serbia (other clinical centers in Belgrade, Novi Sad, Kragujevac, Nis, Valjevo, Sabac, Leskovac, etc.) and the world (ACCP, UPSALA, centers for clinical pharmacology from other countries) on modernization and harmonization program for specialization in Clinical Pharmacology [84]. In some countries there are centers that unite all activities - college, hospital, unit-department (example American College of Clinical Pharmacology).

**Practical management of hospital pharmacology**

Why to form special organizational units of hospital pharmacology? We are exposed to an invasion of new drugs, of which only one part is a new substance. This is our chance, a challenge, but also the possibility of confusion and omission.

We owe it to our patients to provide comfortable therapy, which enables functionality and good quality of life. Our goal is to provide the patient with the best possible quality of life through good therapy. And the inevitable question, does all this have to cost us terribly? Of course, a quality drug will not arrive on a tray from a drug factory. We make our contribution in practice by respecting the principles of good clinical practice, good scientific practice, good laboratory practice, and good prescribing practice. Simply, when we team up with colleagues from other specialties and monitor the treatment results, we get accurate information about the drug, which, further combined with many similar ones from other hospitals, cities, countries, gives the real truth about how to best use the drug.

So, clinical pharmacology is a wonderful field of medicine. After all, what is integrated into a good choice of medicine (from basic scientific research to the IV phase of the drug clinical trial, to the experience and results we get through years and decades of applying the medicine in practice) is difficult to enumerate, but clinical pharmacology is the conclusion designed for medical practitioners and clinicians.

Why clinical pharmacology is important? Clinical pharmacologist improves hospital work through rational cost-effective use of

drugs. Some calculations suggest that every £1 spent on employing a new clinical pharmacologist reduces hospital costs by around £6. This is the reason why the main asset for the development of clinical pharmacology is to keep the patient safe during the use of drugs, editorial errors have serious consequences for patients [62].

The position of hospital pharmacologist was established by Dr. Petty as a doctor who brings a perspective in the good selection of medicine for hospital treatment, in cooperation between the hospital pharmacy of the doctor and the patient. The hospital pharmacologist investigates and recommends the appropriate use of drugs in the hospital, teaching rational use to associates at all levels: medical students, medical staff, residents; works as a manager of the pharmacy and therapeutic councils, helps in finding adequate regulatory solutions; coordinates institutional supervisory boards; provides advice to doctors and feedback to the institution's pharmacy in order to correct and improve the drug procurement policy. Every management carries the question of meaning and purpose, so when preparing new work units of hospital pharmacology, we ask ourselves what the future holds. The most correct answer is we don't know. From our experience, the units from which we expected development did not survive the reverse. The factors for this situation are different and are the subject of another research [4].

Duties as a pharmacologist in a clinical setting may include things such as planning and carrying out pharmacology studies, standardizing drug doses and plans for treatment, preparing and writing research grants, developing and following safety procedures, and performing actual research on human participants [62,73,85].

A hospital clinical pharmacologist as a consultant to other specialists is most often included in cardiovascular medicine, some surgical disciplines, psychiatry, etc. In the clinical centers of Serbia, clinical pharmacologists, as needed and according to the tasks for individual clinics, go and do a consultative examinations or give short consultations by phone. Increasing the number of clinical pharmacologists is carried out according to the standards prescribed by the Republican Fund Health Ensurance (RFHE ). Good prescribing practice is our code of conduct in consulting activities, but also in planning the consumption of medicines at the level of Institutes and Centers of the University Clinical Center of Serbia. However, modern clinical pharmacology tends towards individual - individual patient-oriented therapy, which can be provided by a clinical pharmacology specialist through consultative examinations. With rare exceptions, clinical pharmacology developed in the academic hospital setting. It has proven its value in such environments (1). It is logical to assume that clinical pharmacology could contribute significantly in Primary Health Care if it is extended to this discipline. In order to make a full contribution in primary health care, not only experts in clinical pharmacology should be included, but also doctors of other practices and other specialists, because in most countries the prescribers of medicines are doctors from primary health care [86].This is particularly important in the field of psychopharmaceuticals, especially anxiolytics, which is reflected in the high consumption of drugs. As a result, patients do not use psychotherapeutic support, but only pharmaco therapy, which may lead to the development of addiction [87].

Every secondary or tertiary institution should have The Drug Information Center as a service that is included in the daily work as part of the clinical pharmacology work units. An example of this kind of work is The Johns Hopkins Medical Institutions [88].

A clinical pharmacologist participates in clinical drug trials in different ways, depending on the phase of the clinical trial and the needs of the institution where he works [46].

Clinical studies of drugs have four phases: I phase pharmacokinetic studies - absorption, distribution, biotransformation, elimination (most often on healthy volunteers), II phase - pharmacodynamic studies - effect of the drug on the body and therapeutic effects (early, initial), III phase - definitive study efficiency and safety and optimal dosage, IV phase - new aspects of the drug (post-registration phase). Hospital pharmacology units coordinate and participate in all four phases of clinical drug trials.

*Organization of all phases of clinical trials* of drugs (providing space, necessary permits for conducting clinical studies, scheduling and triage of subjects, etc.), in accordance with the regulations of GCP, ALIMS, EMEA, FDA, performed by doctors hired by Contact Research Organisation (CRO), sponsors, aca-

demic research positions.

It should be borne in mind that the main goal of practical clinical pharmacology is to improve the prescription and use of drugs. At the same time, evidence-based medicine is the basic element of improving the therapy. The methods by which this is achieved are: therapeutic mega-studies, from which changes in therapeutic protocols arise as a result, pharmacoepidemiological studies that deal with the monitoring of adverse effects and the risk/benefit ratio, as well as the monitoring of the real use of drugs and interventions. What is worrying is that pharmacoeconomic cost/benefit ratio studies are becoming one of the main criteria for accepting drugs. The text of Bora's song often fits into the situation we are facing - look at your home angel, you will see shocking scenes, you will see unhappy and sick people [89].

In developed hospital systems of the highest level, hospital pharmacology units provide:

- Compilation of a database of researchers at KCS (CVs, recommendations received from previous collaborators, references published from previous research).
- Creation / assistance in the development of protocols for clinical studies and statistical processing.
- Ensuring the quality control of the clinical study - local monitoring.
- Organization and participation in academic clinical studies of local character for the needs and at the initiative of the University Clinical Center of Serbia.
- Monitoring of drug consumption, by groups of drugs expressed through defined daily doses (DDD) with an annual report intended for colleagues and management.

***We begin the development of pharmacological doctrine*** by informing our colleagues that in teamwork we can supplement the effect of treatment with demystified information about drugs by openly discussing the possible side effects of drugs during daily practice, which are part of correct application, but that it is important to be reported. in doing so, it is important that suspected adverse effects of the drug be reported to the regulatory body of the state (in the Republic of Serbia, ALIMS). In addition, the Periodic Safety Update Report (PSUR) is done by drug manufacturers, which is very important for the industry and clinical trials of drugs. It is desirable that each health institution has a local database of adverse drug effects that enables better selection when purchasing and strengthens the development of pharmacological doctrine among colleagues.

Based on this, clinical pharmacologists can provide their colleagues with recommendations for certain drug groups or individual drugs. Certainly, it is possible and necessary to use the information obtained in cooperation with SKF Dr. Giani, with the European Association of Clinical Pharmacologists (EACPT) and the International Association of Clinical Pharmacologists (IUPHAR). Our section has been a member of EACPT and IUPHAR since its foundation, i.e. since 2009.

The clinical-pharmacological laboratory will provide therapeutic monitoring of drug concentrations in biological material, based on the results of which we will enable the combination of drug doses for KCS patients. In accordance with the development of individual therapy for individual patients, pharmacogenomic analysis, monitoring of metabolites, as well as drug and food interactions are planned.

Even at the primary health level, doctors specializing in general medicine (general practice) may find interest in cooperation with a clinical pharmacologist. namely, patients are treated by different specialists and the general practitioner has to solve the therapeutic problem of polypragmasy [73].

The clinical pharmacologist then has to take a history and examine a patient, as well as to study his or her medical documentation, in order to understand the patient's problems and give the appropriate advice [80]. Academic and health service clinical pharmacology is needed and must not be allowed to wither [78].

In order for clinical pharmacology to be used and become close to everyday practice, it is necessary for specialist clinical pharmacologists to become part of the team in routine work. As in any profession, one doctor cannot perform all activities, so for the purposes of monitoring the adverse effects of drugs, pharmacoeconomic analysis and the organization of conducting clinical trials, it is necessary to form multidisciplinary teams with a clinical pharmacologist [84]. Regardless of where a clinical pharmacologist comes from, from a more or less developed country, hospital work units are set up and developed in the same way according to the pure rule of the profession.

Unfortunately, the problems encountered by hospital pharmacologists are the same: lack of staff, painstakingly obtaining approval from regulatory and management bodies, and lack of awareness among colleagues from other specialties about the possibilities of working in a team [84, 90]. Although research and teaching are the essential roles of clinical pharmacologists, the Serbian experience shows that for further development of the discipline, they must be accompanied by hard work within the health care system [80].

Depending on the level of professional and scientific work of the health institution, clinical pharmacology work units have different levels of organization - quantitatively and qualitatively. But, from the author's experience a clinical pharmacologists' duties are clear, but the number of clinical pharmacology specialists and subspecialists are insufficient. Educating more colleagues is necessery for the future in order to increase presence of clinical pharmacology.

## CONCLUSION

The development of Pharmacology as a profession and science related to the use of drugs spontaneously moved from experimental pharmacology to clinical pharmacology to hospital pharmacology. In order for a clinical pharmacology specialist to really show and prove the useful value of this knowledge, the cooperation of all doctors in teamwork is necessary, as well as cooperation with scientists and cooperation with pharmaceutical magnates. If they find a way for a positive dialogue, the results will become a daily practice.

The main developmental goal of hospital pharmacology is to encompass a wide vaiety of specialists and subspecialists, together with strict demands in respecting pharmacoterapy choice, clinical trials law, monitoring side effects of drugs and medical devices.

Underline the letter to editors of journals, and alert letters via professional community, meaning be supported and informed.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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# Klinička farmakologija - razvojni put, propisi, obrazovanje, praktični menadžment – u svetu i u Srbiji

Dragana A. Kastratović[1], Srđan Z. Marković[1,2], Slobodan M. Janković[3,4]

[1] Univerzitetski Klinički centar Srbije, Beograd, Srbija
[2] Centar za fizičku hemiju bioloških sistema, Fakultet za fizičku hemiju, Univerzitet Beograd, Beograd, Srbija
[3] Univerzitetski klinički centar Kragujevac, Kragujevac, Srbija
[4] Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija

## KRATAK SADRŽAJ

**Uvod:** Nakon pretraživanja literature, profesor farmakologije na Univerzitetu Kornel Hari Gold je prvi upotrebio naziv Klinička farmakologija kasnih 1930-ih i ranih 1940-ih. **Tema** Klinička farmakologija je medicinska disciplina nastala sredinom 20. veka, podrazumeva najefikasniju primenu medicine, i moglo bi se reći da je vrhunac svih terapijskih pristupa u medicini, ili jednostavno u očuvanju zdravlja ljudi. To je oblast koja se spontano pojavila u oblasti medicine i od prvog trenutka ima jedinu perspektivu u jedinstvu prakse i nauke. Druga polovina prošlog veka je vreme početka priznavanja specijalizacije iz kliničke farmakologije kao samostalne medicinske discipline, u Evropi – najpre u Švedskoj, Engleskoj, Švajcarskoj, Norveškoj pedesetih godina prošlog veka, u Americi takođe u istom periodu. U Srbiji i Crnoj Gori smo zabeležili početak 1981. godine. Klinička farmakologija je bolnička medicinska specijalizacija; specijalisti kliničke farmakologije su lekari koji poznaju najadekvatniju primenu lekova, čime se postiže optimalan terapijski efekat. Osnova kliničke farmakologije je farmakokinetika i farmakodinamika. Razvojni put kliničke farmakologije obuhvata više od sedam decenija, a ključni momenti su sledeći: koncept bioraspoloživosti (Oser et al, 1945), farmakokinetika (Friedrich Hartmut Dost, 1953), model farmakokinetike/farmakodinamike (PK/PD) (De Jongh i Vijnans i Van Gemert i Duiff, 1950), 1960 - 1980 eksplozija farmakokinetičkih studija i dramatičan napredak u ovoj oblasti. Farmakokinetičke interakcije između lekova postaju očigledne i postaju predmet mnogih studija: 1970-ih, praćenje nivoa leka za digoksin, aminoglikozide, fenitoin, teofilin i druge lekove počelo je da se primenjuje u mnogim bolnicama. Period od 1980. do 2000. godine karakteriše napredak tehnologije, uključujući tečnu hromatografiju, tečnu hromatografiju sa detektorom mase i razvoj kompjuterske tehnologije. Ono što kliničku farmakologiju čini atraktivnom jeste koncept povezanosti koncentracije leka i farmakodinamičkog efekta, koji objedinjuje nauku i praksu u postizanju terapijskog efekta i uspešnijeg lečenja pacijenata, pojavio se osamdesetih godina prošlog veka. Sredinom 1980-ih, Jusko i Budino su započeli istraživanje povezivanja biohemijskih mehanizama sa farmakokinetičkim/farmakodinamskim tehnikama i dovodeći do njihovog usavršavanja.
**Zaključak:** Razvoj farmakologije kao struke i nauke u vezi sa upotrebom lekova spontano je prešao iz eksperimentalne farmakologije u kliničku farmakologiju u bolničku farmakologiju. Da bi specijalista kliničke farmakologije zaista pokazao i dokazao korisnu vrednost ovog znanja neophodna je saradnja svih lekara u timskom radu, kao i saradnja sa naučnicima i saradnja sa farmaceutskim magnatima. Ako nađu način za pozitivan dijalog, rezultati će postati svakodnevna praksa. Podvuci pismo urednicima časopisa, i pisma upozorenja preko stručne zajednice, što znači biti podržan i informisan. Glavni razvojni cilj bolničke farmakologije da obuhvati širok spektar specijalista i subspecijalista, zajedno sa strogim zahtevima u poštovanju izbora farmakoterapije, zakona o kliničkim ispitivanjima, praćenju neželjenih efekata lekova i medicinskih sredstava. Iz iskustva autora, obaveze kliničkih farmakologa su jasne, međutim, broj specijalista i subspecijalista kliničke farmakologije je nedovoljan. Obrazovanje više

kolega je neophodno za budućnost kako bi se povećalo prisustvo kliničke farmakologije.

**Ključne reči:** klinička farmakologija, bolnička farmakologija, klinički farmakolog

Received: **August** 07, 2022
Accepted: **September** 15, 2022