



MINISTRY OF DEFENCE  
REPUBLIC OF SERBIA



# **Centre for Clinical Pharmacology Military Medical Academy Belgrade, Serbia**



# Basic Information



- Clinical trials on new medicinal products have been conducted in the Military Medical Academy (MMA) since 1973, when the approval from Federal Secretariat for Health and Social Policy was obtained;
- Ethics Committee of the MMA approves on average 50 new clinical trials per year;
- Since 1995 more than 100 bioavailability & bioequivalence studies (BA/BE) have been performed in the MMA;
- Centre for Clinical Pharmacology (CCP) was established in 2005.



# CCP Staff



- Head of the CCP, Full Professor of Pharmacology and Toxicology, Clinical pharmacology specialist;
- Clinical pharmacology specialists;
- Medical Doctor with PhD diploma, Assistant Research Professor;
- Clinical pharmacology resident, M.D.;
- Pharmacy Specialist in Pharmaceutical Technology and Pharmacoeconomy, Assistant Professor;
- Highly trained medical technician with GCP diploma;
- Administration support;
- All other healthcare professionals, employees of the other MMA clinics and laboratories can also be engaged during the study.



# CCP Activity



- Members of the CCP give expertise and regulatory support to the entire realization of the clinical trials in the MMA by participating in the activities of the Expert Team for Clinical Trials, Drug and Therapeutics Committee as well as Ethics Committee of the MMA,



# CCP Activity



- Drug and Therapeutics Committee of the MMA was established in 1980;
- MMA Ethics Committee was established in 1991;
- SOPs of the MMA Ethics Committee is available both in Serbian and English language;
- Following documents can be obtained from official MMA web-site as well as from Ethics Committee Secretariat:
  - Directions for conducting clinical trial in MMA,
  - Clinical trial approval form,
  - List of documents needed for the submission and conduction of clinical trial required by the MMA Ethics Committee.



# CCP Activity

- CCP participate in all activities concerning adverse drug reactions, including the assignment of the Head of the Centre as Pharmacovigilance Coordinator on behalf of the MMA for cooperation with National Pharmacovigilance Centre of the Medicine and Medical Devices Agency of Serbia;
- Participation in a consensus building in the context of consultations concerning unlicensed and reserve antimicrobial drugs;
- CCP is involved in decision-making processes regarding the introduction of new methods for therapeutic drug monitoring (TDM) in biological samples;



# CCP Activity



- Members of the CCP ensure providing valid information concerning drugs through participation in the activities related to application of knowledge in the field of pharmacotherapy concerning concrete clinical problems;
- Pharmacoeconomic evaluation methods are performed on MMA management demands;
- Statistical analyses of data concerning academic and commercial clinical trials;



# CCP Activity



- CCP employees are teaching personnel in Pharmacology and Clinical Pharmacology in graduate and postgraduate level of education at the Medical Faculty of the MMA, University of Defence, Belgrade, Serbia.
- CCP employees participate in academic and commercial clinical studies, evidenced by large number of published papers.





# CCP activity in BR/BE studies



- Study design and clinical trial protocol development;
- Conducting the clinical part of the study at the CCP;
- Pharmacokinetic analyses (PK) and calculations;
- Final clinical study report;
- Realization of the laboratory part of the BR/BE study in cooperation with the Department for Toxicological Chemistry, MMA as well as other accredited laboratories in Serbia and foreign ones.



# Education, Licences



- All investigators and nurses have years of experience, working licences and GCP certificates;
- **Serbian Medical Society - Clinical Pharmacology Section - Course: Good Clinical Practice in Clinical Trials, 2016;**
- **CRA Academy: ICH E6 GCP Training for Investigators and Site Personnel Version 1.0, Februar 2015.**



# Educations



## ➤ **TAIEX, Twinning European Commission:**

1. TAIEX Workshop on the **Implementation of EU Pharmacovigilance Legislation, 2015**, Belgrade, Reference code: INT MARKT 59928;
2. TAIEX Workshop on **Challenges of Bioequivalence Assessment of Generic Medicinal Products, 2016**, Belgrade, Reference code: INT MARKT 62596.



# MMA Integrated Management System (IMS) of Quality



- Since 2008 CCP as an organizational unit of the MMA fulfills requirements and owns certificates for:
  - A. Quality Management System (QMS) - **ISO 9001:2008**,
  - B. Environment Managing System (EMS) - **ISO 14001**,
  - C. Occupational Health and Safety Management System - **OHSAS 18001**,
  - D. Food Safety Management System - **ISO 22000**,
  - E. General requirements for the competence of laboratory for testing and calibration laboratories - **ISO/IEC 17025** and **ISO 15189**.



# MMA IMS - sorts of documents

- Internal Rules (SOPs)
- Policies
- Procedures
- Directives
- Forms
- Records



# CCP working process



- Complete activities of the CCP is regulated by adequate procedure
  - CCP procedures:
    1. Planning of the CCP activities,
    2. Organizational activities of the CCP (procedures related to clinical trials, related to giving services concerning rational pharmacotherapy, educational and publishing activities etc.),
    3. Supportive procedures,
    4. CCP work analysis,
    5. Taking corrective measures in order to improve further activities of the CCP.



# CCP Standard operative procedures - SOPs:



- No. 1 - Subject Informed Consent Form,
- No. 2 - Maintaining study participant confidentiality,
- No. 3 - Document completion,
- No. 4 - Source document library,
- No. 5 - Recording source data in case report forms (CRF's),
- No. 6 - Sample handling,
- No. 7 - Patient safety and comfort,
- No. 8 - Screening history and physical exam,
- No. 9 - Obtaining vital signs,
- No. 10 - Electrocardiogram Interpretation Guidelines,
- No. 11 - Collection of blood samples,
- No. 12 - Documentation and document handling,
- No. 13 - Informed consent documentation,



# CCP Standard operational procedures - SOPs:



- No. 14 - Ethics Committee protocol approval,
- No. 15 - Storage, Distribution, and Accountability of Investigational Drugs,
- No. 16 - Suspension or Premature Termination of a Study,
- No. 17 - Clock synchronization,
- No. 18 - Admission and discharge from the hospital,
- No. 19 - Biochemical evaluation of study participants,
- No. 20 - Blood sample centrifugation,
- No. 21 - Labelling tubes for blood sample collection,
- No. 22 - Investigational product administration,
- No. 23 - Monitoring of adverse events related to the application of  
the investigational medicinal product,
- No. 24 - Food intake during a clinical study,
- No. 25 - Frozen plasma/serum sample transport.





# Relation to other documents



- Direct connection with numerous procedures in the MMA:
  1. Scientific and research process in the MMA,
  2. Professional qualification of medical staff (nurses and technicians),
  3. Provision of Institutes and Clinics of the MMA with drugs, medical devices and medical supplies,
  4. Hazardous waste management,
  5. Non-hazardous waste management,
  6. Accidents awareness and response,
  7. Preparation and distribution of diet food,
  8. Laboratory equipment malfunction procedures,
  9. General and specific objectives of environmental, occupational health and safety protection,

And many others .....



# CCP connection with other organisational units of MMA



Department for prevention and control of nosocomial infections

Center for hyperbaric medicine

Department for quality management, planning and analysis



Specialist Polyclinic

Clinic for Dental Medicine

Neuropsychiatry clinics:

- Psychiatry
- Neurology

Pharmacy Sector

Internal diseases clinics:

- Physiotherapy and rehabilitation
- Clinic for skin and venereal diseases
- Pulmonology
- Clinic for infective and tropical diseases
- Gastroenterology and hepatology
- Endocrinology
- Haematology
- Emergency Internal Medicine
- Nephrology
- Rheumatology
- Cardiology

Institutes:

- Medical biochemistry (ISO 17025)
- Pathology and legal medicine
- Nuclear medicine
- Transfusiology i haemobiology
- Radiology

Sektor for preventive medicine:

- Hygiene
- Epidemiology
- Occupational medicine
- Microbiology

Emergency Center

National Poison Control Center,  
Department for Toxicological  
Chemistry  
(ISO 17025)

Surgery clinics:

- General surgery
- Vascular and endovascular surgery
- Orthopedic surgery and traumatology
- Neurosurgery
- Plastic surgery (including burn treatments)
- Cardiac surgery
- Thoracic surgery
- Urology
- Maxillofacial surgery
- Otorhinolaryngology
- Ophtalmology
- Anesthesiology and intensive therapy
- Operational unit with central sterilisation



# GCP and GLP - preclinical trials



**MMA**



**Sector for Treatment**



**Center for Clinical Pharmacology -**

**Clinical part of the trial -  
in compliance with GCP**

**Department for Toxicological Chemistry -**

**a part for Drug analytics**

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**Laboratory for sample preparation -  
in compliance with GCP**

**Department for Experimental  
Toxicology and Pharmacology -  
*In vivo***

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**Preclinical Trial Laboratory -  
in compliance with GLP**



# Interconnection of CCP with other MMA organisational units



- In 2015, according to Republic Ministry of Health decision, laboratories of CCP, Department for Toxicologist Chemistry (DTC) and Department for Experimental Toxicology and Pharmacology (DETP) were enrolled in National Registry of Laboratories for following activities:
  - Bioavailability and/or bioequivalence,
  - Preclinical trials of drugs used in human and veterinary medicine,
  - Testing the safety of substances which compose drug substances, pesticides, biocides, cosmetic products, food additives, animal food additives, industry chemicals and nanoparticles.
- Person responsible for Quality Assurance and Quality Control of above mentioned activities is nominated from DETF - (GLP certificates, 2014 and Advisor for Chemicals, 2014, etc.).



# CCP ability and capacity for realisation of BA/BE trials



- Healthy volunteers and patients database - fast recruitment of subjects.
- Good working conditions for clinical trial monitors, audits and inspections.
- Using services and possibility of including staff from all institutes, clinics and laboratories in MMA.
- Clinic for Emergency Internal Medicine is stationed nearby CCP.
- Fast communication lines (internally provided) with reanimation team from Clinic for Anaesthesiology.



# CCP Equipment



- Separate department with digital entrance code and video surveillance.
- Limited access to trial documents.
- 12 beds for trial subjects with full hospital signaling.
- Free-time activity space for trial subjects.
- Dining room with TV and internet connection.
- Bathrooms and toilets with adequate hospital signaling.



# CCP Equipment



- Own library - with contemporary literature.
- Comfortable space for staff, including overnight stay.
- Computers with limited access (code).
- Actual version of Kinetica 5<sup>®</sup> programme for PK.  
parameters and SPSS for statistic data analysis.



# CCP Equipment



- Outpatient room.
- Drug storage room under controlled temperature conditions.
- Fireproof locker for keeping drugs.
- Blood sampling space.
- Centrifuge for sample preparation (-10° to +40°C).
- Freezer (-20°C and also the one available for sample storage at -70°C).





# CCP Equipment



- Biological samples: processing and storage in compliance with GCP guidelines.
- Electrocardiograph.
- Laryngoscope.
- Cart with antishock therapy and defibrillator.
- Analytic scale.
- Height and weight scale.



# CCP Equipment



- Vital function monitors.
- Equipment which enables subject emergency calls for medical staff in all facilities (rooms for volunteers, toilets).
- Detection of emergency calls within the space of the staff unit.
- Centralized kitchen.
- Possibility for preparing and distribution of specially prepared meals according to trial protocol.



# Limited access to CCP with digital entrance code



ЦЕНТАР ЗА КЛИНИЧКУ  
ФАРМАКОЛОГИЈУ

Ulaz u Centar za kliničku farmakologiju  
Molimo pozovite!  
Centre for Clinical Pharmacology entrance  
Please, ring the bell!





# Room for trial subjects with hospital signaling





# Central area of the CCP







# Vital function monitor





# Free-time activity space for trial subjects





# Digital clocks in the CCP







# Centrifuge for sample preparation





# Cart with defibrillator and electrocardiograph





# CCP staff

