Medicinal Products for Human Use - SERBIA

Competent authority

Contact Details	**Contact Name 1** Medicines and Medical Devices Agency of Serbia ALIMS (Agencija za lekove i medicinska sredstva Srbije) **Phone** +381 11 3951-169; +381 11 3951-163 **Fax** +381 11 3951-131 **Email Department** hygia@alims.gov.rs **Address** 458, Vojvode Stepe Street **ZIP/City** 11221 Belgrade **Country** Serbia (RS) **Web address** http://www.alims.gov.rs/eng/medicinal-products/ **Additional Information** No local CA.
Trial Authorisation / Registration / Notification	**Regulatory and ethics bodies involved in approval process** Competent Authority/-ies (CA) Ethics committee(s) **CA - Submission for authorisation mandatory for** Clinical IMP trials Clinical ATMP trials **CA - Registration/ notification without approval required for** – **CA - Submission required to** National CA **Applicable national legal framework/ Reference** Art 78 Law on MP & MD 2010
Submission of Application	**Responsible for study submission** Sponsor Legal representative **Entitled to study submission** –

	Prerequisites for submission Positive opinion by relevant EC(s) **Guidance on submission of application** Details on the application procedure, along with the required documentation, are provided in Art 4-10 and Annex 1&2 of the Rulebook on Application 2011. **Applicable national legal framework/ Reference** Art 4-10 and Annex 1&2 of the Rulebook on Application 2011
Submission Format	**Format option(s)** Paper form (or electronically + hard copy); in the script in official use in the RS **Preferred format** – **Standard application form available** Yes **Standard application form** The standard application form (Form 1) to be used is available (in Serbian and Cyrillic script only) on the ALIMS website in section Regulativa » Humani Lekovi » Obrasci (Obrasci vezani za klinička ispitivanja lekova)
Language of Submission	**Language(s) of application** Serbian English **Preferred language of application** – **English accepted** Protocol, CRF Investigator’s Brochure, etc **Documents mandatory to be in official national language** Protocol Summary Information material, Documents and Forms intended for study participants and patient information **Applicable national legal framework/ Reference** Art 6&7 Rulebook on Application 2011
Submission Fees	**Fees for trial submission mandatory** Yes **Fees** Authorisation of Clinical trials: Phase I-III: 114 000 RSD (approx. 920€) Phase IV: 20 000 RSD (approx 163€) Amendments: 57 000 RSD (approx. 460€) **Waiver for academic (non-commercial) studies possible** Not specified **Official guidance on required fees** Applicable fees for authorization of clinical trials is provided in a document on the ALIMS website in section: Regulativa » Cenovnik usluga (Price list) **Applicable national legal framework/ Reference** Art 11 Law on MP & MD 2010

Timelines Authorisation	**General timespan (max nr days)** 60 **Mode of approval (General)** – **ATMP/GMO trials (max nr days)** 90 **Mode of approval (ATMP/GMO trials)** – **External expert advice required (max nr days)** + 90 **Xenogeneic cell therapy (max nr days)** No time limit **Mode of approval (Xenogeneic cell therapy)** – **Clock-stop possible if complementary information requested** Yes **Timespan counted from** Date of submission of valid application **Applicable national legal framework/ Reference** Art 80-82 Law on MP & MD 2010 **Additional Information** In case of incompleteness of the application dossier the sponsor has 30 days to submit the missing information/ documentation. Submission to the national CA is anytime possible. NB! There is no parallel application process to CA and EC(s) in Serbia. A positive vote of the EC is a prerequisite for CA application and approval.
Amendments/ Substantial Amendments (SA)	**Notification mandatory for** – **Authorisation mandatory for** Any substantial amendments **Responsible for submission of SA** Sponsor **Standard notification form available** Yes **Standard notification form** The standard form for submission of substantial amendments (Form 2) to be used is available (in Serbian and Cyrillic script only) on the ALIMS website in section Regulativa » Humani Lekovi » Obrasci (Obrasci vezani za klinička ispitivanja lekova).

Timeline for approval of SA (max nr days)

30
From date of submission
One clock stop possible if complementary information requested
Positive EC vote is prerequisite for CA approval

Guidance on submission of SA

Details on types and definitions of substantial amendments as well as on the application procedure, along with the required documentation, are provided in Art 13-22 of the Rulebook Application 2011.

Applicable national legal framework/ Reference

Art 85 Law on MP & MD 2010
Art 13-23 of Rulebook Application 2011

Additional Information

NB! Positive vote of the EC is prerequisite for CA approval: No prior EC opinion is required, if the substantial amendment is related to the quality of the investigational medicine and/or changes to the bearer of the authorization for the implementation of clinical trials for the medicine (pursuant to Art 22 Rulebook Application 2011

Safety Reporting

Responsible for AE reporting to CA

Sponsor

Sponsor must declare reportable events to

National CA
Relevant EC(s)
All investigators

Reportable AEs

SAE (Serious Adverse Event)
SUSAR (Suspected Unexpected Serious Adverse Reaction) in combination studies only

SUSAR being life-thereatening or leading to death must be reported

Immediately
Within a max of 7d upon first knowledge (+ 8d for additional information)

All other SUSARs

Immediately
Within a max of 15d upon first knowledge

SAE /SADE must be reported

–

National standard reporting form available

No, European standard SUSAR reporting form CIOMS-I recommended

Standard Reporting Form

The standardized international form CIOMS-I, used for SUSAR reporting to the Agency, is presented in Attachment 7 of the Rulebook on AR reporting 2011

Reporting format - Options

–

Preferred format

–

Provision of Annual safety report mandatory

Yes

Annual safety report shall be provided by sponsor to

National CA

Guidance on AE reporting procedure

The reporting procedures are specified in Art 43-52 of the Rulebook on AR reporting 2011

Applicable national legal framework/ Reference

Art 87 & 92 Law on MP & MD 2010

Additional Information

Sponsor is required to report quarterly to the national CA and the EC about the conduct of the clinical trial, pursuant to Art 92 Law on MP & MD 2010. The tri-monthly report encompasses the number of subjects involved per site, the occurrence of adverse reactions as well as other relevant data related to the implementation of the clinical trial.

Annual safety report on all adverse reactions must be submitted by the sponsor to the national CA. Attachment 6 of the Rulebook Rulebook AR reporting 2011 prescribes in detail the required contents of the safety report.

AE reporting timelines are in accordance with Directive 2011/20/EC.

Investigator shall report SAE to

–

Reporting timeline

–

End of Trial

End of trial declaration mandatory for

All clinical trials requiring authorisation by CA

Responsible for End of trial declaration

Sponsor

Regular Termination - Declaration timespan (max nr days)

90

Timespan counted from

–

Early/premature Termination - Declaration timespan (max nr days)

15

Standard Declaration form available

Yes

Standard Declaration form

The standard End of trial declaration form (Form 3) to be used is available (in Serbian and Cyrillic script only) on the ALIMS website in section Regulativa » Humani Lekovi » Obrasci (Obrasci vezani za klinička ispitivanja lekova » Obaveštenje o završetku kliničkog ispitivanja).

Applicable national legal framework/ Reference

Art 92 Law on MP & MD 2010

Additional Information

Final report shall be submitted to the Agency within one year.

Ethics committee

Contact Details	**Contact Name 1** There are approximately 30 local ECs in Serbia: **Contact Name 2** Hospitals, health care institutions, clinical centres and the Serbian Medical Society have their own ECs for review of CT applications **Contact Name 3** (1) Serbian Medical Society - Ethics Committee **Address** Dzordza Vasingtona 19 **ZIP/City** 11000 Belgrade **Country** Serbia (RS) **E-Mail** sld@bvcom.net **Web address** http://www.sld.org.rs **Additional Information** (2) Clinical Centres (with websites) are: • Clinical Centre Serbia: www.klinicki-centar.rs • Clinical centre Vojvodina www.kcv.rs • Clinical centre Kragujevac www.kc-kg.co.rs • Clinical Centre Nis • Clinical-Hospital Centre Zemun • Clinica-Hospital Centre Zvezdara • Clinical-Hospital Centre Bezanijska kosa There is no central EC. For ECRIN CEC is ECSMS.
Ethical Review – General	**Submission for Ethical review mandatory for** Clinical IMP trials Clinical ATMP trials **Submission to CA and EC to be performed in the following order** EC first Positive EC opinion required for CA application/approval **Procedural interaction - Additional information** A favourable opinion is a prerequisite for the trial evaluation and authorization by the national CA. The EC is obliged to inform the sponsor and the national Agency within 15 days after the decision has been reached! **Regulatory and ethics bodies involved in approval process** –
Single-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) to be obtained from** Local EC

	Additional Information The local EC of the respective trial site reviews the CT application and issues a reasonable opinion. There are approximately 30 local ECs in Serbia (Hospitals, health care institutions, clinical centers, Serbian Medical Society).
Multi-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) required from** All local ECs of participating sites **Submission of application required to** All local ECs of participating sites **Additional Information** There is no central EC for the evaluation of multi-centre trials (MCT). MCT must be submitted for approval to the local ECs of the trial sites where the clinical trials are being performed. The Local ECs assess the clinical trial and issue their opinion on the applications independently. There is no single opinion procedure! (Art 42 Rulebook Application 2011). Multi-centre clinical trials are conducted in accordance with the provisions pursuant to Art 93 of the Law on MP & MD 2010 . _____ For ECRIN research: Lead EC will be Serbian Medical Society Ethic Committee (SMS EC), for application submission. The final decision will be given from SMS EC after local EC approval.
Submission of Application	**Responsible for study submission** Sponsor Legal representative **Entitled to study submission** – **Prerequisites for submission / approval** – **Guidance on study submission available** Yes **Guidance on study submission** The documentation to be submitted in accordance with the CA application documentation, pursuant to Art 40 Rulebook Application 2011.
Submission Format	**Format option(s)** Paper form or electronic format (depending on the specifications of the EC concerned) **Preferred format** –
Language of Submission	**Language(s) of application** Serbian English **Preferred language of application** – **English accepted** Partly, not for all documents

	Documents mandatory to be in official national language Information material, Documents and Forms intended for study participants and patient information
Submission Fees	**Fees for Ethical review mandatory** Yes **Fees for Ethical review** Evaluation fees charged from the sponsor depend on the EC concerned, e.g.: EC Clinical Centre of Serbia: € 1200.- (for commercial studies) EC Clinical centre of Kragujevac: € 1200.- EC Clinical Centre of Vojvodina: € 800.- For ECRIN research: Applications to SMS (Serbian Medical Society) are free of charge
Timelines Ethical Review	**General timespan for single-centre studies (max nr days)** 60 **General timespan for multi-centre studies (max nr days)** 60 **ATMP/GMO trials (max nr days)** 90 **External expert advice required: Timespan (max nr days)** + 90 **Xenogeneic cell therapy: Timespan (max nr days)** No time limit **Clock-stop possible if complementary information requested** Yes **Timespan counted from** Date of submission of valid application **Applicable national legal framework/ Reference** Art 74-77 Law on MP & MD 2010 Art 40 Rulebook Application 2011 **Additional Information** In case of incompleteness of the application, the sponsor has 30 days to submit the missing information/ documentation. Some ECs have shorter internal timelines. The EC is obliged to inform the sponsor and the national Agency within 15 days after the decision has been reached!
Amendments/ Substantial Amendments (SA)	**Ethical review mandatory for** Any substantial amendments (except related to quality of investigational medicine) **Responsible for notification of SA** Sponsor **Timeline Ethical review of SA (max nr days)** –

	Applicable national legal framework/ Reference Art 20-22 Rulebook Application 2011 **Additional Information** A positive vote of the relevant EC(s) is a prerequisite for approval by the CA. NB! Assessment by the EC(s) is not required if the substantial amendments are related to the quality of the IMP or changes to the bearer of the authorization for the implementation of clinical trials.
Safety Reporting	**Reportable AEs** – **Investigator shall report SAE to** Sponsor **Reporting timeline** Immediately **Responsible for AE reporting to relevant EC(s)** – **SUSAR being life-thereatening or leading to death must be reported** – **All other SUSAR must be reported** – **SAE/SADE must be reported** – **National Standard Reporting form available** – **Reporting format - Options** – **Preferred reporting format** –
End of Trial	**End of trial Declaration mandatory** Yes **Responsible for End of trial Declaration** Sponsor **Regular Termination - Declaration timespan (max nr days)** 90 **Timespan counted from** – **Early/premature Termination - Declaration timespan (max nr days)** 15 **Applicable national legal framework/ Reference** Art 92 Law on MP & MD 2010

Study specific Requirements

Sponsor	**Sponsor - Definition available in national law** Yes **Sponsor - Definition (pursuant to national law)** Clinical trial sponsor is an individual or a legal entity that takes responsibility for commencing, conducting, and/or financing a clinical trial (Art 2 Law on MP & MD 2010) Clinical trial sponsor can be a manufacturer, legal or physical entity, who is responsible for the initiation, management, quality and financing of the clinical trial conduct. (Art 71 Law on MP & MD 2010) **Sponsorship mandatory** Yes **Co-Sponsor - Definition available in national law** No **Co-sponsorship allowed** No **Additional Information** Sponsor can transfer a part or all of its obligations in relation to clinical trials conduct to a contract research organization based in the Republic of Serbia, which is responsible for the activities the sponsor has transferred onto them, in the procedures for approval and conduct of clinical trials on the territory of the Republic of Serbia. Sponsors who are not based in the Republic of Serbia can have a legal entity as a representative, or an agent based in the Republic of Serbia. (Art 71 Law on MP & MD 2010)
Investigator	**Entitled to be principal investigator** – **Additional Information** Training/ Qualification of Prinicipal Investigator: Qualification of the investigator shall be according to Art 30 of Rulebook Application 2011. GCP training for investigators is required (Section for Clinical pharmacology of Serbian Medical Society accredited in Serbian Medical Chamber Continious Medical Education: Good Clinical Practice in clinical investigation)
Study Participants - Informed Consent (IC)	**Standard IC form (ICF) available** Not specified **Informed Consent - Definition/ Requirements** The definition for “Informed subject consent” resp. “willing informed consent” is provided in Art 2 (9) of Rulebook Application 2011. Informed consent must be obtained from the study participants in written form (in verbal form under special provisions) and in Serbian language according Art 61 of Law on MP & MD 2010 **Applicable national legal framework/ Reference** Art 2 (9) of Rulebook Application 2001 At 61, 63-67 Law on MP & MD 2010

	Additional Information There are specific requirements to be considered for vulnerable populations such as children, pregnant and lactating women, prisoners and adults who are not able to give written consent for trial participation (according to Art 63-67 of Law on MP & MD 2010).
Study Participants - Vulnerable Population	**Minors / Children - Studies allowed** Yes Special provisions apply **Legal framework/Reference (Minors/Children)** Art 63-65 Law on MP & MD 2010 **Incapacitated persons - Studies allowed** Yes Special provisions apply **Legal framework / Reference (Incapacitated persons)** Art 66 Law on MP & MD 2010 **Emergency situations - Studies allowed** Yes Special provisions apply **Emergency situation without prior consent of patient or proxy - Studies allowed** No **Legal framework / Reference (Emergency Situation)** Art 66 Law on MP & MD 2010 **Pregnant or breastfeeding women - Studies allowed** Yes With limitations Special provisions apply **Specific provisions** Clinical trials on healthy pregnant or lactating women are prohibited. **Legal framework / Reference (Pregnant or breastfeeding women)** Art 63 Law on MP & MD 2010 **National legal framework for protection of vulnerable populations in place** Yes **Applicable legal framework / Reference (Vulnerable Population)** Art 63-67 Law on MP & MD 2010
Data Protection	**Notification to DP Authority/ Ombudsmann is mandatory** No **Approval/ authorisation required** No **Specific notification timelines before operations start** –

Language of notification

–

Notification format

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Data Protection Authority/ Agency - Contact Details

Commissioner for Information of Public Importance and Personal Data Protection/ Poverenik za informacije od javnog značaja i zaštitu podataka o ličnosti (sr)

Phone

+381 11 3408 900

Fax

+381 11 3343 379

E-Mail

office@poverenik.rs

Web address

http://www.poverenik.rs/en.html

Address

15, Bulevar kralja Aleksandra str

ZIP/City

11000 Belgrade

Country

Serbia (RS)

Additional Information

The Serbian Law on Personal Data Protection_en (Official Gazette of the RoS, no. 97/2008 and 104/2009) regulates the collection, processing and use of personal data such as patient data etc.

Inadequate data processing and non-compliance with the Law results in liability for an offence and the prescribed sanction is a monetary fine in the amount of up to RSD 1,000,000.00 (approximately EUR 10,824.00).
In addition, unauthorized collecting of personal data is prescribed as a criminal offence by the Criminal Code of the Republic of Serbia. It is stipulated that the person who collects, announces to others or uses for the purpose for which personal data are not intended to be used, shall be punished with a monetary fine or a prison for up to a year, i.e. up to three years if stated actions are undertaken by an official in performing its duties.

Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)

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Insurance

Liability insurance or alternative arrangements for damages mandatory for

Study participants

Responsible for covering insurance

Sponsor

Applicable national legal framework/ Reference

Prior to the commencement of a clinical trial, the sponsor is obliged to contract insurance for study subjects in the event of health damage caused by the clinical trial (according to Art 72 Law on MP & MD 2010 and Art 6 (18) of Rulebook Application 2011).

Quality Assurance/ Quality Control (QA/QC)

Monitoring

Compulsory

Audit by sponsor

Compulsory

Standard Operating Procedures (SOPs)

Compulsory

National legislation

General Information: Applicable Legislation & Conventions

Official website providing relevant national legislation

Website of the National CA (ALIMS) provides the national legislation in Serbian and English.

Clinical Trials on IMPs in Humans

Applicable national regulations

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Transposition of (CT) Directive 2001/20/EC (or comparable national legal framework)

Law on Medicines and Medical Devices/ Zakon o lekovima i medicinskim sredstvima ("Sl. glasnik RS" br. 30/2010 i 107/2012)published in the "Official Gazette of the Republic of Serbia" No. 30/2010 dated 7th May 2010 (hereinafter referred to as Law on MP & MD 2010)

This law determines the performance of the national CA (ALIMS) in Serbia and all significant issues related to medicinal products and medical devices, such as clinical trials, marketing authorization procedure, entry of MP into the registers etc.

Applicable to ATMP/ GMO trials

Yes

Transposition of (GCP) Directive 2005/28/EC

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Other applicable regulations/ implementing provisions (Acts, laws, decrees, ordinances, circulars, etc)

Pursuant to Art 78 (par 3), Art 199 (par 3) and Art 161 (par 8) of Law on Medicines and Medical Devices, the Minister of Health implemented this law by adopting the following regulations:

(1) Rulebook on the Contents of the Application, and/or Documentation on the Approval of Clinical Trials for Medicines and Medical Devices, as well as the Method of Implementation for Clinical Trials of Medicines and Medical Devices (hereinafter referred to as "Rulebook Application 2011")
(Published in the „Official Gazette of the RS", nr. 64/2011 of 31 August 2011)
It prescribes the content, and/or documentation for the approval of clinical trials for medicines and medical devices, as well as the method of implementation for clinical trials of medicines and medical devices in human medicine.

(2) Rulebook on the method of reporting, collecting and monitoring adverse reactions to medicines (hereinafter referred to as "Rulebook AR reporting 2011")
The Rulebook was published in the "Official Gazette of RS", No. 64/2011 of 31 August 2011

Radiation & Radiotherapy	**Use of radiation or radioactive compounds - Specific requirements** Yes **Applicable legal framework** The use of radiopharmaceuticals, as defined by Art 19, is covered by Law on MP & MD 2010. For trial authorization, additional requirements for medicines with specific characteristics such as radiopharmaceuticals must be met (pursuant to Art 6 the Rulebook Application 2011).
Blood & Tissue Samples	**Specific requirements** Yes **Applicable legal framework** Organ Transplantation: Law on Organ Transplantation, Official Gazette No. 72/2009 (Serbian)
Data Protection	**Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)** National Data Protection Act **National DP act** The Serbian Law on Personal Data Protection (Official Gazette of the RoS, no. 97/2008 and 104/2009) regulates the collection, processing and use of personal data such as patient data etc.

Definition

IMP/IMP Study	**IMP - Definition** Investigational Medicinal Product (pursuant to Art Rulebook Application 2011): 'is the pharmaceutical form of the active substance being tested, or the placebo used for comparison with the tested substance, as well as the medicine with an authorization for placement on the market of its form or packaging is changed, and/or if it is used in a way different to the approved method of use as per the authorization for placing the medicine on the market, when the medicine is tested for application for new indications and when the medicine is used to provide new information on its approved use' Definition of a MP and the various types (e.g. ATMP) are specified in Art 14-24 Law on MP & MD 2010

IMP Study - Definition

Clinical trial (pursuant to Art 59 Law on MP 6 MD 2010):
'a medicinal product examination performed on humans there to be determined or confirmed clinical, pharmacological or pharmacodynamic effects of one or more investigational medicinal products, and/or to be identified any adverse reactions to one or more investigational medicinal products, and to be examined the absorption, distribution, metabolism and excretion of one or more medicinal products, in order their safety and efficacy to be determined'

Interventional post-marketing clinical trial (pursuant to Art Law on MP & MD 2010):
'a trial that implies the medicinal product application in respect to the conditions prescribed in the marketing authorisation, and that requires additional diagnostic procedures, as well as the monitoring procedures defined by the clinical trial protocol'

Non-interventional post-marketing clinical trial (pharmacoepidemiological testing) (pursuant to Art 2 Law on MP & MD 2010):
'a trial that implies the medicinal product application in respect to the conditions prescribed in the marketing authorisation and where the election of the patient is not predetermined by the clinical trial protocol but is a part of a ongoing practice of the usual type of treatment; in addition, the medicinal product prescription is clearly separated from the decision to involve the patient into the trial'