Question 3

What is the process for achieving clinical trial authorisation from the competent authority in the country?
Austria

The sponsor of the Clinical Trial submits the application to the competent ethics committee (EC) and the competent authority (CA).

The CA reviews only the justification for and the relevance of the Clinical Trial.

The EC acts as the “expert reviewer” for the CA and decides within 35 days, with only one “clockstop” possible to obtain supplementary information.

If the EC vote is negative, the CA issues a legal document (“Bescheid”) prohibiting the clinical trial.

The website for the CA is at http://www.ages.at.

Belgium

The sponsor submits the application to the competent authority (the Federal Agency for Medicines and Health Products: FAMHP). The authority has in principle 28 days (with the possibility of one clock-stop of maximum one month for questions), 15 (fifteen) days for phase 1 trials.

The approval by the competent authority is a silent one: if there is no answer within the 28 days, the experiment can start. The website for the authority is at www.fagg-afmps.be.

Bulgaria

An application form is submitted to the competent authority, accompanied by the required documentation. Initial validation of the application is carried out at the Bulgarian Drug Agency. If deficiencies are noted a deficiency letter is sent to the applicant – usually in about 10 days. The review period stops with the issue of a deficiency letter. If there are no deficiencies, or after deficiencies are cleared, the documentation is transferred to the Specialized Committee for Authorization of Performance of Clinical Trials (SCAPCT). The SCAPCT assesses the protocol and accompanying documentation and issues a decision – Authorization to perform a clinical trial.

The committee can request amendments to the protocol or supporting documentation as a condition of issuing an authorization. The authorization decision is issued in as many copies as there are trial sites and they are transferred to the sites. From that moment on the trial can proceed.

Croatia

The sponsor submits a clinical trial application request and all required documentations to a) the Ministry of Health, which is the regulatory competent authority and b) the Central Ethics Committee. No clinical trial can be started without an approval from the
Minister of Health, which is issued after a positive approval from the Central Ethics Committee. The list of requirements for trial approval is available on the web site of the Ministry of Health (http://www.mzss.hr/hr/zdravstvo_i_socijalna_skrb/zdravstvo/likovni/klinicka_ispitivana_likovne_i_medicinskih_proizvoda), and the Agency for Medicinal Products and Medical Devices of Croatia (HALMED) http://www.almp.hr/?ln=en.

These requirements are:

- A request form in Croatian language, with the names of investigators and institutions for the conduct of clinical trial.
- Signed trial protocol(s)/amendment(s).
- Investigator’s brochure (IB).
- Case report form (CRF).
- Informed consent form in the Croatian and original language.
- Investigator’s current curriculum vitae.
- Monitor’s current curriculum vitae.
- Positive opinion of the Paediatric Committee of the Ministry of Health and the National Ombudsman of Parents or a positive opinion of the Psychiatry Committee of the Ministry of Health (for clinical investigations of medicinal products in the paediatric or psychiatric patients population, respectively).
- List of sites or centres for multicentre trials.
- List of sites or centres with already achieved positive or negative approval.
- Recruitment procedures (e.g. advertisements for subject recruitment if used).
- Financial aspects of the trial to document the financial agreement between the investigator/institution and the sponsor for the trial.
- Information about payments and compensation available to subjects.
- Subject’s insurance statement.
- Proofs of paid fees required for the review process.

Cyprus

The Competent Authority for clinical trial authorisation is the Drugs´ Council.

For more information the interested person may contact the Pharmaceutical Services of the Ministry of Health of the Republic of Cyprus.

For more information you may contact the Pharmaceutical Services at:
Tel: + 357 22 407107
Fax: +357 22 407149
E-mail: phscentral@phs.moh.gov.cy
Website: www.moh.gov.cy/phs

Czech Republic

Authorisation from SUKL (http://www.sukl.cz) is requested only for study drugs that are prepared by biotechnology (GMOs) and/or containing human or animal tissues. Clinical trials with other drugs (registered/non registered) are notified using the EU Clinical Trial Application form.

Question 3 - 3
Denmark

An application is made by the sponsor to the Danish Medicines Agency (Lægemiddelstyrelsen) on the EudraCT application form available at http://www.eudract.emea.eu.int.

The website for Lægemiddelstyrelsen is: http://www.dkma.dk.

Estonia

Notification of the clinical trial needs to be submitted to the State Agency using the EudraCT format 60 days before the planned commencement of the trial at latest. A formal letter of ‘no objection’ is given, often earlier than the legally stipulated 60 days. The time taken by the Agency depends directly on the quality and completeness of the documentation submitted. Together with the notification, a signed declaration by the head of the health-care institution study centre) has to be submitted. Where applicable, after that the import certificate for the study medications can be applied for.

The EudraCT application form is available at http://www.eudract.emea.eu.int.

The website for the State Agency of Medicines is at http://www.sam.ee.

Finland

Application is made to the National Agency for Medicines (Lääkelaitos) using a form that can be downloaded from its website (http://www.fimea.fi/healthcare_professionals/clinical_drug_trials) or from the EMA website (https://eudract.ema.europa.eu/eudract/index.do). The form can be completed in English, Finnish or Swedish.

France

Clinical trial sponsors have to submit their protocols both to the competent regional ethics committee (CPP), and to the competent authority. These submissions can be either simultaneous or one after the other.

The authorisation to conduct a trial requires both the E.C. (CPP) approval and the competent authority authorization.

No clinical trial will ever start without a CPP approval. This committee evaluates the different parts of the protocol, in line with the requirements set out in the Directive.

The CPP sends its written and argued advice within 35 days to the sponsor. This advice is also sent for information to the competent authority.
The CPP has 35 days from the reception of the protocol to give a written argued advice. Lack of advice after the deadline is considered as a refusal. If the CPP needs more information about the research, it can ask the sponsor only on time, the delay for advice is 60 days.

The competent authority acknowledges receipt of the protocol and informs the sponsor of the date after which in the absence of any remark, the trial can begin (silent approval).

The competent authority is allowed to ask sponsors additional information or to have reservations. These questions are transmitted to the CPP.

The list of CPP is available at http://www.recherche-biomedicale.sante.gouv.fr.

The French licensing authority is the Agence Française de Sécurité Sanitaire des Produits de Santé. Its website is at http://www.afssaps.fr.

**Germany**

The sponsor submits a CTA request to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) or the PEI (Paul-Ehrlich-Institut) (both are federal competent regulatory authorities responsible for CTAs for different types of IMPs), containing the elements required by the GCP Decree (GCP-Verordnung, for trials with pharmaceutical drugs) or the MPKP Decree (for trials with medical devices) respectively; for clinical trials involving radiation the competent authority is the Bundesamt für Strahlenschutz (BfS).

**Greece**

*NB For Greece questions 3 and 4 are most appropriately answered together.*

In order to conduct a clinical trial in Greece the application must be submitted to the Competent Authority (EOF) and a separate application must also be submitted to the National Ethics Committee (NEC). EOF issues an authorisation for the conduct of the clinical trial, provided that NEC has given a positive opinion.

The website of the Greek Competent Authority (EOF) is at http://www.eof.gr.

**Hungary**

The authorisation and approval procedure of clinical trials with IMPs is as follows:

The main rule is that applications should be submitted to the National Institute of Pharmacy (NIP, the competent regulatory authority for human medicinal products). The NIP starts its assessment and, within 8 days, sends the copy of the relevant parts of the application to the KFEB. The KFEB has an independent review and issues an independent decision. The ethical approval/rejection must be sent, within 42 calendar days starting from receiving the documentation from the NIP, back to the NIP. The whole authorisation plus approval procedure may last for 60 calendar days (as required by the Medicines Act. However, in case of a deficiency letter the clock stops).
Meeting this deadline, the NIP sends the applicant the authorisation/rejection, the first Annex of that is the KFEB opinion.

In case when the KFEB (as co-authority) is consulted first, its (positive) opinion is appended to the application to the NIP. However, the NIP’s approval time is still 60 calendar days in this case.

In case of clinical trials with immunological medicinal products, there is a second co-authority: the National Centre of Epidemiology. It has 10 work days to express its opinion.

It should be noted that non-interventional trials with IMPs also need authorisation in Hungary. The authority (also acting as ethics committee) is the TUKEB. The procedure may last 45 working days.

**Clinical trials with medical devices**

Applications should be sent to the Office for Health Administration and Authorisation (Hungarian abbreviation is EEKH) that sends its relevant parts to the TUKEB. TUKEB has 35 working days, the whole procedure should last for 45 working days.

In case when the TUKEB (as co-authority) is consulted first, its (positive) opinion is appended to the application to the EEKHP. However, the EEKHP’s approval time is still 45 working days in this case.

When the medical device contains also IMP, there is also a second co-authority: the NIP. It has 10 working days to express its opinion. (Please note that this 10 working days interval starts when NIP receives the application and EEKH re-starts its procedure when the co-authority opinion arrives).

**General biomedical research**

The authorisation is given by the Regional Office of the National Public Health Service, on the basis of the ethics committee opinion. The whole procedure is 45 work days within which the ethical approval may last for 35 work days.

In case when the trial is not directly the subject’s interest (but may serve the interest of similar group of patients), the authorisation is given by the Minister of Health (the same ethics committees apply as indicated above). The time-frame is also the same.

**Iceland**

See Reg. 443/2004: An application for a clinical trial of a medicinal product shall be sent to the Icelandic Medicines Control Agency (IMCA) and to the National Bioethics Committee (NBC). See further guidelines on NBC’s homepage (under revision). ([http://www.visindasidanefnd.is/English](http://www.visindasidanefnd.is/English)).
Ireland

The sponsor must apply for clinical trial authorization to the Irish Medicines Board which is the competent authority for Ireland.

The website for the Irish Medicines Board is at http://www.imb.ie.

Italy

In Italy, following the first step that consists in the submission to the local REC, in most cases to obtain an authorisation to conduct a clinical trial with medicines, the sponsor must apply to the local competent Authority, the legal Officer of each clinical site (e.g.: director general of the health facility). The competent Authority can authorise the trial within 60 days. If the competent Authority has not informed the sponsor of any grounds for non-acceptance within 60 days, the trial is considered authorised.

Only for clinical trials with gene therapy, somatic cells therapy and medicines containing OGM (phase II, III, IV, Bioequivalence/Bioavailability) and, for first-in-man use trials the authorisation is granted by a central competent Authority is required. In the first case, the competent authority is the Agenzia Italiana del Farmaco – AIFA (Italian Medicines Agency); in the second case, (first-in-man use, in general phase I studies) the authorisation is granted by the National Institute of Health (Istituto Superiore di Sanità). Information is available at the following site: http://www.iss.it/scf1/.

In any case, in order to start a clinical trial, a sponsor must enter the data into web-based database of the "Osservatorio Nazionale per la Sperimentazione Clinica" (National Monitoring Centre for Clinical Trials) established at. At the end of the electronic procedure, it is possible to print the data entered into the OsSC and the result will be a Clinical Trial Application (CTA) form in Italian language, to submit to the competent Authority and Ethics Committee, respectively for authorization and opinion.

Latvia

The sponsor should submit an application both to the ethics committee and to competent authority (State Agency of Medicines). A clinical trial cannot be started without a positive decision from an ethics committee and without authorization from the State Agency of Medicines.

The website for the State Agency of Medicines is at http://www.zaale.vza.gov.lv.
Lithuania

The sponsor must apply for clinical trial authorization to the State Medicines Control Agency (SMCA), which is the competent authority for Lithuania. More information about the procedure can be found at [http://www.vvkt.lt/index.php?3327723903](http://www.vvkt.lt/index.php?3327723903).

Luxemburg

Submission of a file containing:

- Confirmation of EudraCT number.
- Clinical Trial Application form.
- List of competent authorities in the EU to which an authorisation request has already been submitted for the study.
- Copy of the CNER opinion if it is already available when the file is submitted to the CA.
- Study protocol with all the previous amendments (and their dates) if applicable.
- Peer review of the trial if available.
- Patient information sheet and informed consent form in French and German.
- Investigator brochure with all information regarding the safety and pharmaceutical quality of the product.
- IMPD or simplified IMPD for the known products.
- SmPC for the products which have already received a market authorization within the EU.
- A list of all ongoing clinical trials with the same experimental product.
- A copy of the manufacturing authorisation following the article 13 of the 2001 EU Directive.
- A recent curriculum vitae of the principal investigator.
- Other documents specifically demanded for a study by the Division de la Pharmacie et des Médicaments (Competent Authority in Luxembourg).

Malta

In order to conduct a clinical trial in Malta the application must be submitted to the Medicines Authority and a separate application must also be submitted to the HEC (clarifications may be sought by the sponsor before an application is formally submitted). Following successful validation, each body generally has a 60 day period to assess the application (excluding clock-stops). A clinical trial may start if both the Health Ethics Committee and the Medicines Authority have separately issued an authorisation.


The website of the Maltese Medicines Authority is at: [http://www.medicinesauthority.gov.mt/](http://www.medicinesauthority.gov.mt/).
The EFGCP Report on
The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe
(Update: April 2012)


Netherlands

A research protocol concerning a study with medicinal products is submitted to the Central Committee on Research Involving Human Subjects (CCMO). The website for CCMO is at http://ccmo-online.nl. It is this body that acts as the competent authority for research with medicinal products involving human subjects in The Netherlands. The licensing authority is not involved until it evaluates the outcome of submitted research for a request for marketing authorisation.

The Dutch licensing authority is College ter Beoordeling van Geneesmiddelen (CBG). The website for CBG is at http://www.cbg-meb.nl.

Norway

Application is made to the Norwegian Medicines Agency (Legemiddelverk) using a form that can be downloaded from its website (http://www.legemiddelverket.no) An English translation is available.

Poland

The sponsor must apply for an authorisation to conduct a clinical trial on an IMP to the competent authority in Poland, which is the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, one department of which is responsible for GCP assessment and maintains the Central Register of Clinical Trials (http://www.urpl.gov.pl).

Portugal

The sponsor must apply for a clinical trial authorisation to the Medicines Evaluation Agency (INFARMED).

Romania

NMA SCD No. 11/2009 on approval of Regulations concerning authorisation by the National Medicines Agency of clinical trials/notification to the National Medicines Agency of non-interventional clinical trials conducted with medicinal products for human use in Romania – provides procedure steps for assessment and approval of an Application for Clinical Trial.

- Validation of the CTA dossier; if the documentation is complete, the application is accepted and it shall receive a NMA registration number.
- The authorisation tariff for admission, established through the NMA Administrative Council Decision, shall be paid after having accepted the application for authorisation.
- After the money enters into the NMA account, the evaluation procedure of the documentation needed in clinical trial authorisation shall start. The deadlines are those mentioned in Minister of Health Order (MHO) No. 904/2006.

- If, following evaluation of documentation, additional information is needed, the NMA shall thereof inform the applicant in writing.

- The authorisation/rejection of the clinical trial authorisation is extended compared to the deadline mentioned in Minister of Health Order (MHO) No. 904/2006 with the duration of time elapsed as of admission of the application letters containing applications issued by the applicant and until the NMA receipt of the solicited information.

**Russia**

The sponsor should submit an application both to the Competent Authority (Scientific Centre for the Evaluation of Products for Medical Use) and the Council on Ethics of Ministry of Health and Social Development. A clinical trial cannot be started without a positive decision from both of these bodies.

The sponsor is responsible for submitting the request to the Council on Ethics of Ministry of Health and Social Development and the principal investigator is responsible for submitting the request to the local research ethics committee.

**Serbia**

The sponsor/CRO of the clinical trial submits an application, with documentation, to the Medicines and Medical Devices Agency of Serbia, [http://www.alims.sr.gov.yu](http://www.alims.sr.gov.yu). The Agency (CA) reviews and assesses the application as the “expert reviewer” and decides within 60 days, with a possible “clockstop” to obtain supplementary documentation. If the LEC makes a negative decision, the CA will not approve the clinical trial.

**Slovakia**

For single-site clinical trials in Phases I to III, an authorization from SIDC is necessary, and for Phase IV studies notification to SIDC is required. Additionally, for all single-site clinical trials, an authorization should be sought at the “local level” – if a CT is to be conducted in a health care facility or research institution, the authorization is given by the director of that facility/institution. For CTs done in outpatient physicians’ offices, an authorization from the “state physician” of the regional state authority should be sought.

For multi-site clinical trials the authorization/notification process is similar to the one described above. If a CT is conducted in outpatient physicians’ offices located at the territory of different regional authorities, the authorization should be sought from all “state physicians” of the authorities concerned. (The territory of Slovakia is divided into 8 such regions.)

Slovenia

The application is made by the applicant to the competent authority, the JAZMP. The *authorisation* is required for clinical trials involving advanced therapy medicinal products; for all other clinical trials *notification* is required. The website of the JAZMP is [http://www.jazmp.si](http://www.jazmp.si).

Approval of the NMEC is one of the required documents before an application is granted.

Spain

The sponsor submits the application to the competent authority, the Spanish Agency for Medicines and Medical Devices (Subdirección General de Medicamentos de Uso Humano. Área de Ensayos Clínicos. Agencia Española de Medicamentos y Productos Sanitarios - AEMPS). Within 10 days of receiving the CT application, the sponsor gets a letter indicating the validity of it and the assessment schedule, or a letter indicating the reasons why the application is not valid. The maximum assessment periods in the AEMPS are 60 days in general, and 90 days for those clinical trials referring to cell or gene therapy and GMO medicinal products.

The AEMPS needs a favourable opinion from the appropriate CEIC and the letter of conformity by the management board of at least one site stated in the opinion by the CEIC before the authorisation can take place. In addition, the CEIC, but not the AEMPS, has a clock stop in the assessment period starting when clarifications are requested, until the sponsor answer is received. Taking into account all this, it is recommendable that the CT is submitted to the CEIC 2 or 3 weeks in advance of the date of submission to the AEMPS.

Once a CT is authorised, the sponsor must notify the AEMPS that the management board of the site approves starting the trial in that site.

Sweden

Application is made to the Medical Products Agency (Lakemedelsverket) using a form that can be downloaded from its website ([http://www.mpa.se](http://www.mpa.se)). An English translation is available.

Switzerland

Approval of all clinical projects by a REC is mandatory, subsequently the projects dealing with investigational medicinal products are submitted for authorisation to the Swiss Agency for Therapeutic Products, known as Swissmedic, on forms only available in German or French. These forms are available on-line on the Swissmedic website: [http://www.swissmedic.ch](http://www.swissmedic.ch).
Turkey

Questions 3 and 4 are most appropriately answered together for Turkey.

1) The application dossier for a clinical trial will be prepared according to the Guideline for Good Clinical Practice and other applicable guidelines, using the application form and its relevant annexes posted on the Ministry’s website, and will be reviewed for Ministry permission and ethics committee approval according to this Regulation and the guidelines to be issued by the Ministry.

2) In multi-center clinical trials, the scientific and ethical approval will be obtained of the ethics committee in the locality where the coordinating center is located. Notifications will be made to ethics committees in places where the other sites are located.

3) The application for a clinical trial will be made to the relevant ethics committee or general directorate by the sponsor, consisting of natural/juristic person(s), or by a contract research organization domiciled in Turkey appointed by the sponsor. If the sponsor has no representative domiciled in Turkey, the application for a clinical trial must be submitted through a contract research organization domiciled in Turkey.

4) Applications to obtain Ministry approval for conducting clinical trials that have been granted ethical and scientific approval with any substances or products which and which may involve investigation in human beings, including clinical trials with medical devices, BA/BE trials, comparability studies for biosimilar products, Phase I, Phase II, Phase III and Phase IV drug clinical trials, clinical trials with advanced therapy medicinal products, observational studies with drugs, observational studies with medical devices, clinical trials with traditional herbal medicinal products and cosmetic products or raw materials, will be made to the General Directorate of Pharmaceuticals and Pharmacy. a) For clinical trials with Class III medical devices or with implants or long-term invasive devices in Class IIa or Class IIb, the study sponsor or a contract research organization delegated by the sponsor will, upon the approval of the ethics committee concerned, make an application to the General Directorate of Pharmaceuticals and Pharmacy, and the application will be evaluated within sixty days after the notification date. b) For all clinical trials with medical devices, excluding the ones mentioned in subparagraph (a), and all other drug clinical trials will be evaluated within not more than thirty days by the relevant general directorate.

5) Applications to obtain Ministry approval for conducting clinical trials with industrial advanced medicinal products or non-industrial advanced medicinal products, gene therapy clinical trials, stem cell transplantation trials, organ or tissue transplantation trials and clinical trials with a novel surgical procedure which have been given scientific and ethical approval will be made to the General Directorate of Health Services. These applications will be evaluated within not more than sixty days.

6) If the general directorate concerned adopts an unfavorable decision regarding the request for conducting the clinical trial, this decision will be notified to the applicant, together with the rationale for the decision. The sponsor will be granted a single opportunity to resubmit the application after making amendments to address the issues raised in the decision, or to file a reasoned objection against the decision. If the requested changes are not fulfilled or an acceptable justification cannot be offered, the general directorate concerned may reject the clinical trial.

7) In the case of clinical trials with cellular therapies using products containing genetically modified organisms or products involving gene therapy, the thirty days specified for Ministry approval may be extended for an additional thirty days.
However, in cases where it becomes necessary to hold detailed deliberations or to consult non-Ministerial third party experts, the timeline may be extended further by an additional ninety days, depending on the subject matter of the study.

United Kingdom

The sponsor must apply for CTA to the Medicines and Healthcare products Regulatory Authority (MHRA), which is the Competent Authority for the whole of the UK.

April 2012

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