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CMS Life Sciences Monograph Clinical Trials

Implementation of Directive 2001/20: an overview of national variations

Introduction

For the European Union, a number of legal and ethical issues concerning clinical research on human subjects have been harmonised in Directive 2001/20. In the Directive a set of minimum requirements is given, which recently has been transposed into legislation of the member states. However, some room is given to the member states to implement certain rules at their own discretion.

Further to our monograph on Clinical Trial Liability Insurance, in this monograph we give an overview of the most important variations in the local laws of the EU member states and of countries that are not (yet) EU member states, but in which we have CMS offices.

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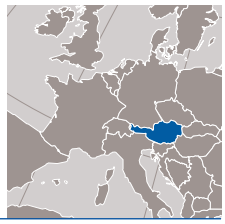
Austria



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Directive 2001/20 has been implemented through a revision of the AMG (*Arzneimittelgesetz* – 'pharmaceutical law') in 2004 (BGBl I 35/2004). This revision is in large part a translation of the Directive and incorporates the principle of Good Clinical Practice.

Approval of the protocol

According to section 40 AMG a clinical trial may only be initiated if the competent Austrian authority ('*Bundesamt für Sicherheit im Gesundheitswesen*') and the Ethics Committee consider that the risks have been weighed against the anticipated benefit for the individual trial subject and other present and future patients and the anticipated therapeutic and public health benefits justify the risks. Also, the risk of disturbance of the patient's health must not be extensive.

Prior to starting a clinical trial, the sponsor has to obtain:

a) an approval of the '*Bundesamt für Sicherheit im Gesundheitswesen*' and
b) a statement of the Ethics Committee.

The Austrian legislature did not make use of the possibility of Article 6.4 of the Directive regarding a member state's possibility to decide that the competent authority it has designated for the purpose of Article 9 shall be responsible for the consideration of, and the giving of an opinion on, the matters referred to in paragraph 3 (h), (i) and (j) of the Directive. The Austrian legislature also did not make use of the possibility contained in Article 9.5 of the Directive regarding the necessary explicit consent of the competent authorities for investigations involving biotechnological products.

As stated in the Directive 2001/20, a written authorisation has to be obtained from the '*Bundesamt für Sicherheit im Gesundheitswesen*' for somatic cellular therapy and for pharmaceuticals that contain genetically modified organisms.

According to Article 7 of the Directive section 41b AMG establishes that for multi-centre clinical trials that are limited to the Austrian territory, a single

opinion of one Ethics Committee is sufficient.

Minors and individuals not able to give informed legal consent

According to Article 4 of the Directive, the Austrian legislature establishes in section 42 AMG that a minor's participation in a clinical trial requires consent of the minor's legal representatives and of the minor if he or she has received information according to his or her capacity of understanding regarding the trial, the risks and the benefits. The research must either relate directly to a clinical condition from which the minor concerned suffers or be of such nature that it can only be carried out on minors. The consent may be revoked at any time. Incentives or financial inducements are not admissible except compensation. The clinical trials have to be designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage. The interests of the patient always prevail over those of science and society.

The same conditions have to be fulfilled if clinical trials are accomplished on incapacitated adults who are not able to give informed legal consent.

Timelines

Section 40 AMG establishes the period of 35 days for the examination of the application by the '*Bundesamt für Sicherheit im Gesundheitwesen*' otherwise the application is considered to be authorised. According to paragraph 41a AMG the Ethics Commission has to give its statement within 35 days. The consideration of a valid request for authorisation by '*Bundesamt für Sicherheit im Gesundeswesen*' has to be carried out as rapidly as possible and may not exceed 60 days. These time periods may be extended up to 90 days if the clinical trial refers to somatic cellular therapies.

These periods are as stated in the Directive.

EudraCT database

In Austria the '*Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH*' (AGES) and the '*Bundesamt für Sicherheit im Gesundheitswesen*' are entrusted with the inclusion of details with respect to any clinical trial conducted in Austria into the European database ('EudraCT'), as provided for in Article 11 of the Directive. The AGES receives such information from the 'Bundesamt für Sicherheit im Gesundheitswesen' and the Minister of Health.

Notification of adverse events

Sections 41d and 41e AMG are a translation of Article 16 and 17 of the Directive. Therefore the sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life threatening is reported as soon as possible to the competent authorities in all the member states and to the Ethics Committee. In Austria the '*Bundesamt für Sicherheit im Gesundheitswesen*', the 'Bundesminister für Gesundheit und Frauen' and the Ethics Committee have to be informed.

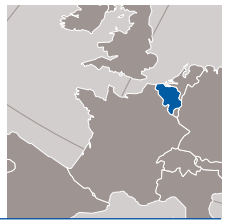
Study medication and devices free of charge

According to the Directive section 32 paragraph 3 AMG establishes that the investigational medicinal products and the devices for their administration shall be made available free of charge by the sponsor.

Supervision of clinical trials

According to section 47 AMG the '*Bundesamt für Sicherheit im Gesundheitswesen*' is authorised to control and ensure the clinical compliance with Good Clinical Practice.

Belgium



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The European Directive 2001/20/EC has been implemented through the Act of 7 May 2004 on clinical trials on human beings. This Clinical Trials Act (CTA) almost literally transposes the text of the EU Directive and incorporates the principles of Good Clinical Practice (GLP).

Approval of the protocol

According to the Belgian Clinical Trials Act, a clinical trial may be initiated only if the Ethics Committee has issued a favourable opinion and if the competent authority has not informed the sponsor of any ground for non-acceptance. A sponsor should thus, prior to starting a clinical trial, obtain:

a) the approval of an ethics committee and, in addition,
b) a declaration of non-objection by the Belgian competent authority. In most cases, the '*Direction Générale Médecine*' (DGM) of the Ministry of Public Health shall be the competent authority according to the Royal Decree of 30 June 2004 (Art. 1).

The Belgian legislature did not make use of the possibility foreseen in Article 6.4 of the Directive to make this authority responsible for the consideration of or the giving of an opinion on the provision for indemnity or compensation in the event of injury or death attributable to a clinical trial, any insurance or indemnity to cover the liability of the investigator and sponsor, the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects.

According to Article 7 of the Directive the Belgian Clinical Trials Act provides that the sponsor can choose the ethics committee, which shall give the single opinion for Belgium (Art. 11, § 2). All participating centres have to provide a certificate of feasibility to the ethics committee.

Minors and individuals not able to give informed legal consent

With regard to the protection of minors or incapacitated adults, the Belgian Clinical Trials Act provides the same degree of protection as the Directive and almost literally transposes Articles 4 and 5 of the Directive.

Timelines

The period in which the competent authority '*Direction Générale Médecine*' can file its objections to a planned single-centre non-therapeutic trial is 15 days from the date of submission of the request by the sponsor. For other trials, this period is a maximum of 28 days (Art. 13 Clinical Trials Act). These time periods may be extended by a maximum of 30 days in case of trials involving gene therapy, somatic cell therapy or medicines containing genetically modified organisms. This period may be extended by 90 days when the '*Bio Security Council*' must be involved, for example when genetically modified organisms are being put on the market.

The Belgian Act provides that there is no time limit for the xenogenic cell therapy trials.

The objection procedure as set out above is to be distinguished from the approval procedure by the Ethics Committee. Such approval should be granted within 15 days as from the date of submission of the request by the sponsor in case of single-centre non-therapeutic trial, and 28 days in the case of other trials (Art. 11, § 5 Clinical Trials Act), which period can be extended by a further 30 days when the trial involves gene therapy, somatic cell therapy, or medicines containing genetically modified organisms.

The Belgian Act provides that there is no time limit for the xenogenic cell therapy trials.

For medicines containing genetically modified organisms, this period may be extended by 90 days when the Bio Security Council must be involved as set out above.

Finally, in case of a proposed amendment to the protocol, the Ethics Committee and the competent authority '*Direction Générale Médecine*' shall give their opinion within the above mentioned time frames after receipt of the proposed amendment in good and due form (Art. 19).

EudraCT database

In Belgium, the competent authority '*Direction Générale Médecine*' is entrusted with the inclusion of details with respect to any clinical trial conducted in Belgium into the European database ('EudraCT'), as provided for in Article 11 of the Directive (Art. 32, § 4).

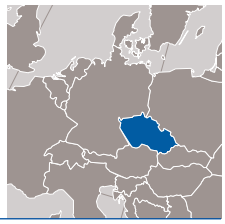
Notification of adverse events

With respect to unexpected serious adverse events in relation to a clinical trial in Belgium, the sponsor is obliged to inform the '*Direction Générale Médecine*' and the competent Ethics Committee, or, as the case may be, the Minister of Health, and (only in case of a multi country trial) the competent authorities in other member states. This notification must occur within a compulsory time schedule laid down in the Belgian Clinical Trials Act (Art. 28). The '*Direction Générale Médecine*' must send such information into the relevant European database (Art. 28, § 3).

Study medication and devices free of charge

According to the Directive, the sponsor should make investigational medicinal products and the devices used for their administration available to the subjects free of charge. This provision has been implemented in Article 24, § 7 of the Belgian Clinical Trials Act.

Czech Republic



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The Directive 2001/20 has been implemented into Czech law by the Act on Pharmaceuticals, no. 79/1997 Coll., as amended (in this respect in particular by its harmonization amendment no. 129/2003 Coll.) (the 'Act'), and its implementing Decree no. 473/2000 Coll., on Clinical Practice and Details of Conditions of Clinical Trials of Pharmaceuticals, as amended (in particular by its harmonization amendment no. 301/2003 Coll.).

Approval of the protocol

The Act, in line with Article 9 of the Directive, sets out that a clinical trial can commence if two parallel authorisations are obtained:

a) The favourable opinion of the relevant ethics committee;
b) The authorisation to be granted by the Czech '*Státní ústav pro kontrolu léčiv*' (State Institute for Drug Control, 'SÚKL', the Czech 'competent authority' in the sense of the Directive). The Act sets out:

- Cases where lack of disapproval (objections) by SÚKL to a notified trial constitutes the (tacit) authorisation (this approach is a rule, in line with Article 9, § 2 of the Directive): clinical trials in which the used investigational pharmaceuticals are exclusively products authorised in the Czech Republic or member states or such products not authorised in the Czech Republic or member states which are not obtained by biotechnological processing or where products not containing substances of human or animal origin are concerned;
- Cases where express written approval of SÚKL is required – other than listed in the previous indent (where lack of objections is a sufficient authorisation), including clinical trials in which the investigational medicinal products are of the nature of a gene therapy, somatic cell therapy including xenogenic cell therapy or contain genetically modified organisms (compare Article 9, § 5 and 6 of the Directive).

The Czech legislature has not made use of the possibility foreseen in Article 6, § 4 of the Directive.

Minors and individuals not able to give informed legal consent

The relevant provisions of the Act are basically a literal translation of Articles 4 and 5 of the Directive, i.e. are not more comprehensive. There are two minor deviations only:

- The condition of 'the interests of the patient always prevails over those of science and society', appearing in both lists of Articles 4 and 5 of the Directive, is made a general principle of undertaking clinical trials, i.e. is a more general requirement applying to all clinical trials;
- The Act makes a reference to relevant guidelines of SÚKL instead to those of the Agency (see Article 4 (f) of the Directive).

Timelines

The individual timelines set out by the Act basically fully correspond to those set out by the Directive, i.e.:

- Generally 60 days for consent of an ethics committee and for consent of SÚKL (either no objections or of an explicit consent) – no reduction of this period as allowed by Article 9, § 4, second sentence;
- Suspension effect of a call to the applicant in respect of an incomplete or defective application;
- Extension of the period for certain classes of pharmaceuticals to 90 days, possibility of an additional extension, no time limit in respect of xenogenic cells therapy;
- 35-day period for consent of an ethics committee with an amendment of the protocol.

Eudra CT Database

It is SÚKL (according to Article 38, § 8 of the Act) that is authorised and obliged to provide all relevant data regarding the clinical trial in question to the European Clinical Trial Database.

Notification of adverse events

Adverse events should generally be reported by the investigator to the sponsor (with the exception of those less serious ones which are set out in the protocol as not requiring notification). The sponsor shall keep relevant records regarding adverse events. Further, rules and timelines for the reporting of adverse events and suspected adverse events by the sponsor to SÚKL and relevant ethics committee exist.

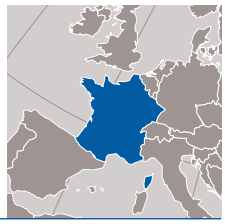
Study medication and devices free of charge

Pursuant to Article 38b, § 14 of the Act, the sponsor is obliged to provide the participants of clinical trials with trial pharmaceuticals under investigation and any devices necessary for the administration of the products free of charge. Where the sponsor is the investigator, healthcare facility, a university or the state via its organisational unit, and the investigational medicinal products are authorised in the Czech Republic, the free-of-charge provision of the investigational medicinal products shall not be obligatory.

Supervision of clinical trials

The competent Czech authority for inspection and supervision of clinical trials is SÚKL.

France



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In France, Directive 2001/20 has been implemented through the Law governing Public Health Policy, adopted on 9 August 2004, a decree dated 26 April 2006 and orders dated 25 and 27 April 2006 have been adopted for its application.

Approval of the protocol

Article L. 1121-4 of the Public Health Code (PHC) provides that a clinical trial can only be developed if the Regional Ethics Committee (Committee for the Protection of People: 'CPP') has given its favourable opinion and the AFSSAPS (hereinafter 'French Drugs Agency') has given its authorisation having considered the benefits and risks to the patient. In this sense, there are two parallel authorisations to be obtained:

a) The favourable opinion of the CPP, which is in charge of evaluating the protocol, the investigator's guide and the rest of the information provided.

b) The authorisation granted by the French Drugs Agency. The Agency verifies all the formal conditions required by law and if the Agency has no objections to the clinical trial, the authorisation shall be deemed granted. Exceptions to this tacit authorisation are also provided for (see below).

This procedure applies to an application for an initial project of clinical trial and to any application for a substantial modification of the trial thereafter.

The Decree of April 2006 states that an express authorisation must be obtained from the authorities in the following cases:

- clinical trials to which the Agency has previously made objections;
- clinical trials with gene therapy drugs, somatic cellular therapy, drugs that contain genetically modified organisms, products that contain biological components of human or animal origin, and labile blood product.

Minors and individuals not able to give informed legal consent

The minors can be requested to submit to biomedical research only if research of a comparable effectiveness cannot be carried out

on people over the age of consent and under the following conditions:

- the importance of the benefit to the minors submitting to the biomedical research is likely to justify the foreseeable risks;
- or there is evidence that the trial will profit other minors. In this latter case, the foreseeable risks and the constraints of the clinical trial must present a minimal character.

The Article L. 1122-2 of the PHC sets specific provisions for minors and incapacitated adults who are unable to give informed legal consent. There is a double degree of protection in the case of research that involves a serious risk to the integrity of the human body or of invasion of privacy.

Timelines

The Decree dated April 2006 has established the period of 60 days for authorisation of the French Agency; after this timeline there is a tacit authorisation. In case of a proposed amendment of the protocol, the French Drugs Agency authorisation is required to decide whether to grant authorisation within 35 days.

Where an express authorisation is required (gene therapy drugs, somatic cellular therapy, drugs that contain genetically modified organisms, products that contain biological components of human or animal origin, and labile blood product), the French Drugs Agency has 90 days in which to make a decision. If additional information is required by the French Drugs Agency, it can have a further 90 days in which to make its decision.

Meanwhile, the CPP has 35 days in which to give its opinion. This period can be extended once only to a maximum of 60 days when the CPP has specific questions.

EudraCT database

The French Drugs Agency is in charge of including clinical data in the EudraCT database. The French order dated 27 April 2006 specifies the type of data that had to be included in this database according to Article 11 of the Directive.

In addition, the French Drugs Agency is in charge of the national clinical trials record. The sponsor can oppose the inclusion of the data in this record. Patients Groups can now request access to this record. If after 15 days, the sponsor has not responded, this is taken as tacit acceptance.

Notification of adverse events

Article R. 1123-47 of the PHC establishes timelines for the declaration of adverse events in the case of suspected serious unexpected adverse events.

The sponsor submits an annual safety report to the French Drugs Agency and to the CPP including the list of all suspected serious unexpected adverse events. Twice a year, the sponsor informs the CPP of any adverse effects and events which have occurred in France and in other countries.

Study medication and devices free of charge

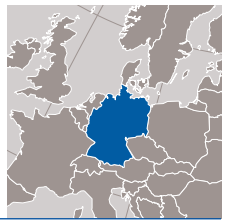
According to the Directive, French provisions provide that investigational medicinal products and the devices used for their administration should be made available to the subjects by the sponsor free of charge, except in specific cases provided by law – not defined yet (Article R 5121-17 of PHC).

The Decree dated 27 April 2006 provides also that for biomedical research relating to products other than drugs, these products are provided free of charge, except in specific cases that will have to be determined by law (Article R 1121-4 PHC).

Supervision of clinical trials

Inspectors of the French Drugs Agency are appointed for all clinical trials audits, and generally for the control of compliance with the provisions of the PHC.

Germany



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In Germany, Directive 2001/20 has been implemented by the 12th Amending Law of the Pharmaceuticals Act (12. *Gesetz zur Änderung des Arzneimittelgesetzes*) which came into force on 6 August 2004. Specific provisions concerning the approval of the protocol have been laid down in the Ordinance on the Implementation of Good Clinical Practice during the Execution of Clinical Trials with Pharmaceuticals for the Use on Humans (*Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen – GCP-Verordnung*).

Approval of the protocol

Section 40 (1) Pharmaceuticals Act AMG provides that a clinical trial of a pharmaceutical on humans may only be started if the competent Ethics Committee has favourably assessed it and the competent Superior Federal Authority has permitted it. Thus two parallel authorisations must be obtained:

a) The favourable assessment of the Ethics Committee competent under State Law;
b) The authorisation granted by the competent Superior Federal Authority, which according to section 77 AMG in principle is the Federal Institute for Pharmaceuticals and Medicinal Products (*Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM*). Authorisation by the Superior Federal Authority is deemed to have been granted if the Superior Federal Authority does not communicate any substantiated objections to the sponsor within 30 days after receipt of the request documents (section 42 (2) AMG), unless there is an exception to this implicit authorisation (see below).

The German legislature has made use of the option in Article 9 (5) of Directive 2001/20 by requiring written authorisation by the Superior Federal Authority before the commencement of clinical trials for all pharmaceuticals mentioned in Article 9 (5) of Directive 2001/20 (section 42 (2.5) AMG).

In line with Article 7 of Directive 2001/20, section 42 (1.2) AMG provides that the request for a favourable assessment of the Ethics Committee has to be addressed to the Ethics Committee competent for the main investigator of the clinical trial for multi-centre clinical trials within Germany. This Ethics Committee is responsible for the handling of the request (section 7 (1) *GCP-Verordnung*).

Minors and individuals not able to give informed legal consent

Following the implementation of Article 4 of Directive 2001/20, section 41 (2) of the Pharmaceuticals Act (AMG) for the first time allows for clinical trials on minors where benefit is obtained only for the group of patients suffering under the same kind of clinical condition as the minor but not for the individual minor itself. However, German law still is stricter than Article 4 of Directive 2001/20 in only allowing for clinical trials on minors, if the research relates directly to a clinical condition from which the minor suffers. If the reason for carrying out the clinical trial on minors would be that the research is of such a nature that it can only be carried out on minors (Article 4 (e) third option of Directive 2001/20), such a trial is not allowed in Germany.

Regarding individuals not able to give informed legal consent, section 41 (3) AMG is not more comprehensive than Article 5 of Directive 2001/20.

Timelines

Section 42 AMG establishes a deadline for the assessment of the Ethics Committee of up to 60 days after receipt of all the relevant documentation by the sponsor.

The authorisation by the Superior Federal Authority is deemed to have been granted if the Superior Federal Authority does not communicate any substantiated objections to the sponsor within 30 days after receipt of the request documents. For clinical trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms or medicinal products whose active agent is a biological product of human or animal origin or contains parts of human or animal origin or requires such parts for their production, no implicit authorisation can be obtained. For these clinical trials the Superior Federal Authority has to grant an express authorisation within a period of 60 days after receipt of all the relevant documentation by the sponsor.

Both the deadline for the favourable assessment of the Ethics Committee and the deadline for the authorisation by the Superior Federal Authority are extended to a maximum of 90 days in the case of clinical trials involving medicinal products for somatic cell therapy or medicinal products containing genetically modified organisms.

The deadline is further extended to 180 days if the Ethics Committee or the Superior Federal Authority consults experts or expert opinions. For trials concerning xenogenic cell therapy there are no time limits to the assessment and authorisation periods.

The time limit for the assessment of the Ethics Committee is shortened to 30 days if only one trial centre within Germany is involved in the clinical trial. The time limit is further shortened to 14 days for both the Ethics Committee and the Superior Federal Authority in the case of clinical trials in Phase I based on another clinical trial, which was already agreed to by the same Ethics Committee or Superior Federal Authority, if both trials are part of the same programme of clinical trials.

EudraCT database

In Germany the Superior Federal Authority is entrusted with communicating the relevant information on clinical trials to the EudraCT database (section 14 (3) *GCP-Verordnung*).

Notification of adverse events

By the investigator

In accordance with Article 16 (1) and (2) of the Directive, section 12 (4) *GCP-Verordnung* states the investigator has to immediately inform the sponsor and subsequently file a written report about the occurrence of a serious adverse

event except for those events that the protocol or investigator's brochure identifies as not requiring immediate reporting. Section 12 (5) *GCP-Verordnung* obliges the investigator to report to the sponsor on adverse events and laboratory abnormalities identified in the protocol as critical to the assessment of the clinical trial within the time periods laid down in the protocol. In the event of the death of a concerned person, the investigator has to submit any additional information required for the fulfilment of their respective duties to the competent Ethics Committee, the Superior Federal Authority and the sponsor. In the case of multi-centre clinical trials, the investigator has to submit this information to the involved Ethics Committee as well.

By the sponsor

According to section 15 (1) *GCP-Verordnung* the sponsor has to provide documentation of all adverse effects reported to him by the investigators. This documentation is conveyed upon request to the competent Superior Federal Authority and to the competent authorities in those other member countries of the European Union and the European Economic Area, on whose territory the clinical trial is executed.

With regard to suspected untoward serious adverse effects the sponsor has to report these immediately, at the latest within 15 days after first knowledge, to the competent Ethics Committee, to the Superior Federal Authority, to the investigators taking part in the clinical trial and to the competent authorities in other member countries of the European Union and the European Economic Area, on whose territory the clinical trial is executed (section 15 (2) *GCP-Verordnung*). If one of these suspected untoward serious adverse effects is fatal or life threatening, the time limit is up to 7 days for the reporting of all information important for the assessment and up to a further 8 days for all other relevant information (section 15 (3) *GCP-Verordnung*).

Study medication and devices free of charge

Germany has not established any conditions deviating from Article 19 (2) of Directive 2001/20.

Supervision of clinical trials

According to section 15 (1) *GCP-Verordnung* inspections in the context of the supervision of ongoing or finished clinical trials are conducted by those authorities of the German states which are competent for inspecting pharmaceutical businesses under the Pharmaceuticals Act (AMG). Inspections to evaluate the compliance of the clinical trial with the information provided by the sponsor in the application are conducted by the competent Superior Federal Authority. Both kinds of inspections are carried out on behalf of the European Union.

The competent authority has to draw up a report on the inspection that is conveyed to the inspected facility and the sponsor. The report contains a request to take corrective action against deficiencies and objections.

Hungary

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Directive 2001/20/EC ('Directive') has been implemented by the following new legislations in Hungary: (i) Act XCV of 2005 on the Medicines for Human Use ('Medicine Act'); and Decree 35/2005 (VIII.26) on the Clinical Trials of Investigational Substances for Human Use and the Good Clinical Practice ('Clinical Trial Decree').

Approval of the protocol

In Hungary the National Institute of Pharmacy (in Hungarian: *Országos Gyógyszerészeti Intézet*; 'OGYI') is the competent authority for the approval of clinical trials. OGYI makes the decision after obtaining the opinion of the Clinical Pharmacology Ethics Committee of the Health Care Scientific Council ('ETT KFEB'). If the ETT KFEB has an unfavourable opinion in relation to the given trial OGYI is not entitled to approve it.

With regard to paragraph 4 of Article 6 of the Directive, the Clinical Trial Decree stipulates that the ETT KFEB has to examine the matters referred to in paragraphs 3(h), (i) and (j) of the same Article and the OGYI does not have the possibility to do so.

The ETT KFEB is obliged to send its opinion only to the OGYI, and OGYI will forward a copy to the sponsor together with its resolution containing the decision.

In case of a multi-centre clinical trial the ETT KFEB takes into consideration the report already issued by an ethics committee of any member state of the EEA.

Minors and individuals not able to give informed legal consent

In general the respective provisions of the Clinical Trial Decree are the pure translation of the relevant Article of the Directive, however, there are some rules which seem to make the Hungarian legal framework stricter.

A minor may be the participant of a clinical trial, in addition to the requirements laid down in the relevant Articles of the Directive, if no other procedure that is as effective as the clinical trial exists and the trial would not have similar effectiveness on adults. These are general rules in connection with the medical scientific researches stipulated in the Act CLIV of 1997 on Health Care.

Articles 4(i) and 5(h) apply not only to minors and individuals not able to give informed legal consent but also to all patients that are subjects of a clinical trial. In addition, Article 4(e) applies not only to the 'group of patients' but to the individuals themselves, which means that the direct benefit from the clinical trial has to be obtained for the minors and the individuals not able to give informed legal consent (an assumption is not enough).

Timelines

The deadline for the approval of the clinical trial is 60 days from the date of submission of the application, within which period the ETT KFEB's process shall take not more than 42 days, counted from the date when the committee receives the application. This latter timeline is only 35 days – in line with the relevant provision of the Directive – if a significant modification to the protocol is necessary and therefore the opinion of the ETT KFEB was requested.

The authorisation period for clinical trials involving investigational medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms shall be 90 days, within which the ethics process shall be completed within not more than 72 days.

In case the clinical trial involves investigational products for xenogenic cell therapy, the procedure is 12 months and the ethics process should not be more than 11 months.

EudraCT database

OGYI is the responsible authority, which provides the information on the Hungarian clinical trials to the European database.

Notification of adverse events

The investigator must report serious adverse events not only to the sponsor but also to the ethics committee of the respective institution. The deadlines of the reporting system for the adverse reactions are in full compliance with the Directive.

Study medication and devices free of charge

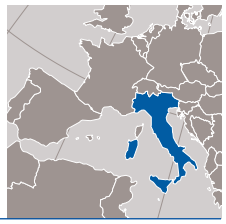
This rule shall also apply in Hungary without any exemptions.

Supervision of clinical trials

The Clinical Trial Decree prescribes the compulsory requirements (university degree or equivalent diploma, certificate on the attendance of GCP course within five years, special ID card issued by the OGYI) regarding the pharmacists or doctors appointed as inspectors by the OGYI.

The inspection may be carried out before, during and/or after the clinical trial. The OGYI provides the ETT KFEB, an EEA member state and/or the EMEA with the report on the inspection upon their request.

Italy



By Antonella Mameli
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In Italy, Directive 2001/20 (hereinafter the 'Directive') has been implemented by Legislative Decree no. 211 dated 24 June 2003 (hereinafter the 'Decree'). This Decree has been in force in Italy since 1 January 2004.

Approval of the protocol

According to the Decree, before commencing any clinical trial it is necessary for the sponsor to obtain the approval of the competent Ethics Committee, and it is also necessary to submit a request for authorisation to the Competent Authority.

The **'Competent Authority'** – which must approve clinical trials of medical products together with the competent Ethics Committee – is

1) as a general rule, the general director or the person legally in charge of the public medical facilities, or equivalent medical facilities where the clinical trial is carried out;
2) the Ministry of Health in case of clinical trials involving a) medical products which do not have a marketing authorisation, b) medical products that contain biological components of human or animal origin or c) medical products for gene therapy, somatic cellular therapy or medical products containing genetically modified organisms. The Ministry of Health must authorise in **writing** the carrying out of the trial;
3) the *Istituto Superiore della Sanità* (hereinafter 'ISS') – which is a technical and scientific public body related to the Italian National Health Service – in case of medical products included in Decree of the President of the Republic no. 43 dated 21 September 2001, (i.e. products never used before on human beings).

If the Ethics Committee gives its approval and if the Competent Authority does not raise any objection, the sponsor can start the clinical trial.

Therefore, before starting any clinical trial the sponsor should obtain:

a) the approval by the competent Ethics Committee which is in charge of evaluating the application and the protocol submitted by the sponsor. In

particular, the Ethics Committee must guarantee the rights, safety and health of the subjects involved in the clinical trial and verify whether the possible benefits justify the risks involved in the trial.

The Decree has also established that in case of mono-centre clinical trial the Ethics Committee must notify its opinion to the sponsor, to the Italian Ministry of Health and also to the Competent Authority.

b) the non-objection of the competent authority. In the event of objections from local authorities the clinical trial cannot be carried out in the local medical facility, while if the objections come from the Ministry of Health or from the ISS the clinical trial cannot be carried out in any medical facility in Italy.

Article 7 of the Decree states that in case of multi-centre clinical trials carried out only in Italy, or in Italy and in other countries, the clinical trials must be approved by the Ethics Committee of the Italian medical facility to which the coordinating investigator for Italy is connected. In this case the Ethics Committee must notify its opinion to the sponsor, to the other Ethics Committees involved in the trial, and to the Ministry of Health. The approval of the Ethics Committee can be accepted or rejected by the other Ethics Committees involved in the trial and the acceptance or the rejection by one of them must be notified to the sponsor, to the other Ethics Committees involved and to the Competent Authorities. Each of the Ethics Committees involved in the trial is also entitled 1) to modify the contents of the 'informed consent' to be signed by the subjects taking part in the trials to be carried out in their medical facilities, and 2) to judge all the aspects of the protocol.

Minors and individuals not able to give informed legal consent

As far as the clinical trials on minors are concerned, Article 4 of the Decree sets forth the same requirements represented in Article 4 of the Directive.

However, there is one difference: the (d) requirement of the Directive, where it is stated that clinical trials may be undertaken only if no incentives or financial inducements are given except compensation, has not been implemented in the Italian Decree.

Article 5 of the Decree refers to the clinical trials on incapacitated adults not able to give informed legal consent.

The only difference on this matter between the Decree and the Directive is that the Italian Decree provides, like the Directive, that no incentives or financial inducements are given except compensation, but it also adds that compensation can be granted only within the budget limits already decided if the sponsor is a public entity.

Timelines

The Ethics Committee shall notify its opinion to the sponsor, the Italian Ministry of Health and the Competent Authority within 60 days from receipt of the sponsor's application.

These terms can be extended up to 30 days if the clinical trials involve medical products for gene therapy, somatic cellular therapy or medical products that contain genetically modified organisms. For said products this 90-day period can be extended to a further 90-day period waiting for the authorisation of the Ministry of Health. In case of xenogenic cell therapy there is no time limit to the authorisation period.

The examination by the Competent Authorities of the request of authorisation shall be carried out within 60 days. However, the Competent Authority may notify the sponsor with its consent within a shorter period than 60 days if there are no objections.

In case of clinical trials that involve medical products for gene therapy, somatic cell therapy, xenogenic cell therapy or medicines that contain genetically modified organisms the

period for the authorisation can be extended up to 30 days and then up to a maximum of a further 90 days if necessary.

If the Competent Authority notifies the sponsor with some objections, the sponsor has only one possibility to amend the request and if he/she does not amend the request within 30 days, the request shall be considered rejected and the clinical trial may not commence.

EudraCT database

The Ethics Committees and the sponsors shall communicate all the data to include in the national and European database to the Italian Drugs Agency, to the regional authorities where the clinical trials are carried out, and to the Ministry of Health. The Ministry of Health is then in charge of including the clinical data in the EudraCT database.

Notification of adverse events

The provisions of the Decree concerning the notification of adverse events are in line with the provisions of Article 16 of the Directive. Therefore, the sponsor shall keep detailed records of all the adverse events that are reported to him/her by the investigator. All these records, if requested, shall be submitted to the Italian Ministry of Health.

Study medication and devices free of charge

The Italian Decree provides that the investigational medicinal products and the devices used for their administration shall be made available free of charge by the sponsor.

Supervision of clinical trials

The Italian Ministry of Health appoints the inspectors who must inspect the sites where the clinical trials are conducted. Reports of these inspections shall be notified by the Italian Ministry of Health to the EMEA.

The Netherlands

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Directive 2001/20 has been implemented through a revision of the WMO (*Wet Medisch Wetenschappelijk Onderzoek*). The new WMO is for the greater part a translation of the Directive and incorporates the principles of Good Clinical Practice (GLP).

Approval of the protocol

According to the WMO a clinical trial may be initiated only if the Ethics Committee and the competent authority come to the conclusion that the anticipated therapeutic and public health benefits justify the risks. A sponsor should, prior to starting a clinical trial obtain:

a) the approval of an ethics committee and, in addition,
b) a declaration of non-objection by the Dutch competent authorities. In most cases, the *Centrale Commissie Mensgebonden Onderzoek* (CCMO) shall be the competent authority. However, in case the CCMO is designated as the appropriate ethics committee, the Dutch Minister of Health shall be the competent authority. The Dutch legislator has made use of the possibility foreseen in Article 6.4 of the Directive. In case the trial involves gene therapy or xenogenic cell therapy the CCMO is designated as the appropriate ethics committee.

The Dutch legislature has not made use of the possibility to implement a rule under which it is mandatory for a sponsor to obtain the explicit written consent from the competent authorities in case of trials that involve products that fall under the centralised procedure or other biological medicines.

According Article 7 of the Directive member states have to establish for multi-centre clinical trials a procedure providing for the adoption of a single opinion for that member state. Under the WMO this procedure implies that the sponsor can choose the ethics committee that shall give the single opinion for the Netherlands. All participating centres have to provide a certificate of feasibility to said ethics committee.

Minors and individuals not able to give informed legal consent

In addition to Articles 4 and 5 of the Directive, member states have the possibility to make their provisions on the protection of clinical trial subjects more comprehensive than the one mentioned in the Directive. The Dutch legislature has not made use of this possibility. The new WMO contains in greater part a translation of Articles 4 and 5 of the Directive.

Timelines

The period in which either the CCMO or the Minister of Health can file its objections to a planned trial is 14 days as from the date of submission of the request by the sponsor. In case the CCMO or the Minister does not object within this period, the trial may commence. However, in case of trials that involve gene therapy, somatic cell therapy, xenogenic cell therapy or medicines containing genetically modified organisms, the sponsor should obtain the explicit (written) authorisation from the Minister of Health. In such cases, the period in which the authorisation should be given can be extended by 30 days at the maximum. These periods are considerably less than the maximum periods as included in the Directive (60 days and 90 days respectively).

The objection procedure as set out above should be distinguished from the obtainment by the sponsor of an approval by the relevant ethics committee. Such approval should be granted within 60 days as from the date of submission of the request by the sponsor, which period can be extended with a further 30 days if the trial involves gene therapy, somatic cell therapy, xenogenic cell therapy or medicines containing genetically modified organisms. In case of trials that relate to xenogenic cell therapy, no maximum applies to the period in which the ethics committee should give its approval. These periods are in line with the periods as set out in the Directive.

Finally, in case of a proposed amendment of the protocol, the Ethics Committee shall give an opinion within 35 days after receipt of the proposed amendment in good and due form. This period is in line with the period as set out in the Directive.

EudraCT database

In the Netherlands the *College ter Beoordeling van Geneesmiddelen*, the Dutch Medicines Evaluation Board (MEB), is entrusted with the inclusion of details with respect to any clinical trial conducted in the Netherlands into the European database ('EudraCT'), as provided for in Article 11 of the Directive. The MEB should receive such information from the CCMO or, as the case may be, the Minister of Health.

Notification of adverse events

With respect to unexpected serious adverse events in relation to a clinical trial in the Netherlands, the sponsor is obliged to inform the MEB, the CCMO or, as the case may be, the Minister of Health, the relevant ethics committee and (only in case of a multi-country trial) the competent authorities in other member states. The MEB should include such information in the relevant European database.

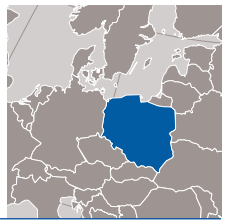
Study medication and devices free of charge

According to the Directive, investigational medicinal products and the devices used for their administration should be made available to the subjects by the sponsor free of charge. In the WMO an exception is made for registered medicines, even if they are administrated in a trial for another indication.

Supervision of clinical trials

To verify compliance with the provisions of GLP and GMP, the inspectors of the Health Care Inspectorate of the Ministry of Health, Welfare and Sport are appointed. The inspection reports will be made available to the sponsor of a study while safeguarding the confidential aspects and privacy of the subjects. The inspection reports will also be made available to the accredited ethics committees of other member states and to the EMEA at their reasoned request.

Poland



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The Directive 2001/20 has been implemented into Polish law by the Pharmaceutical Law dated 6 September 2001, the Act on the professions of doctor and dentist dated 5 December 1996, the Minister of Health's Regulation on the requirements of Good Clinical Practice dated 11 March 2005, and the Minister of Health's Regulation on carrying out clinical trials with the participation of minors dated 30 April 2004.

Approval of the protocol

According to Article 37(l) of the Pharmaceutical Law, clinical trials can only be carried out if a bioethical commission has given a favourable opinion on the conduct of the clinical trial and if the Minister of Health has not requested additional information by a specified time.

The Minister of Health will refuse a permit if: the application or documentation does not fulfil requirements defined in the Pharmaceutical Law; the trial's assumptions are inconsistent with the principles of social co-existence or threaten public order; or the trial's assumptions do not meet the requirements of Good Clinical Practice.

After obtaining a favourable decision from the bioethical commission and a permit from the Minister of Health (or no summons for supplementary information), the Chairman of the Medicinal Products, Medical Devices and Biocide Products Registration Office (hereinafter the Chairman of the Registration Office) is obliged to register the clinical trial within the Central Clinical Trial Register.

Minors and individuals not able to give informed legal consent

A clinical trial with the participation of minors can only be carried out upon the fulfilment of the conditions enumerated in Article 37(h) of the Pharmaceutical Law. A minor's participation in a clinical trial requires the consent of the minor and his legal representative. The clear and complete information regarding the clinical trial shall be provided to the minor and his legal representative. The trial may only be carried out with the participation of minors if it concerns a disease that the minor suffers from or because the trial

can only be performed with the participation of a minor. The pain, suffering and fear to which the minors may be exposed during the clinical trial must be reduced to a minimum. Moreover, pursuant to Article 25 point 3 of the Act on the professions of doctor and dentist, the participation of a minor in a clinical trial is possible only if the anticipated advantages are of direct significance for the minor's health and the risk is small and commensurate to the possible positive results.

A clinical trial with the participation of individuals not able to give informed legal consent can only be carried out upon the fulfilment of the conditions enumerated in Article 37 (i) of the Pharmaceutical Law. If the individual is legally incapacitated, the participation in the clinical trial of such an individual requires the informed legal consent of the individual's legal representative, and, if the individual is capable to grant the conscious consent, then his or her consent is also required. The individual and legal representative have to be provided with clear and complete information regarding the clinical trial. If the individual is not legally incapacitated but is not able to give conscious consent, the consent of the guardianship court is required. The trial may only be carried out if the following conditions are met jointly: (i) it concerns a disease that the individual suffers from, (ii) it is necessary to confirm the data obtained from clinical trials conducted with individuals who had granted the informed legal consent, (iii) it may be assumed that the individual will benefit from its participation in the clinical trial, (iv) it does not cause any risk to the individual. The pain, fear and potential risk to which the individual may be exposed during the clinical trial must be reduced to a minimum.

Timelines

On the basis of Article 37(p) of the Pharmaceutical Law, the Minister of Health shall review the application within 60 days of the submission of the complete application. The aforementioned period may be prolonged by up to 30 days if an expert's opinion is required, and by up to 90 days if the clinical trials concern gene or cell therapy, or if the investigated products include genetically modified organisms. The review timeline may be suspended for 90 days if the documentation enclosed with the application needs to be completed. The competent bioethical commission shall issue its opinion on the clinical trial within 60 days of the request for the opinion being submitted. The sponsor of the clinical trial is obliged to inform the bioethical commission and the Minister of Health at the end of the clinical trial, and no later than 90 days after the date the clinical trial is finished.

Eudra CT Database

According to Article 37(ad) of the Pharmaceutical Law, the Chairman of the Registration Office is authorised to publish any data regarding the clinical trial in the European Clinical Trial Database.

Notification of adverse events

According to Article 37(aa) of the Pharmaceutical Law, whenever any suspected unexpected serious adverse reaction occurs during a clinical trial it must be reported by the sponsor to the Chairman of the Registration Office and bioethical commission which has given an opinion on the clinical trial and must be transmitted via an electronic reporting system to the community database of adverse reactions. Additionally, under Article 37 (z) of the Pharmaceutical Law the investigator is obliged to report any serious adverse events to the sponsor.

Study medication and devices free of charge

Pursuant to Article 37(k) of the Pharmaceutical Law, a sponsor is obliged to provide the participants of clinical trials with the medicinal products under investigation and any devices necessary for the administration of the products free of charge.

Supervision of clinical trials

The Inspection of Clinical Trials is authorised to ensure the clinical trials' compliance with Good Clinical Practice. Inspections can also be carried out at the request of the European Commission.

Romania

By Valentina David,
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Directive 2001/20 (the 'Directive') has been implemented through the Minister of Health Order no. 615/2004 and the Minister of Health Order no.904/2006 regarding the approving of the regulations and, respectively, of the norms, for the implementation of the good clinical practice rules in the conduct of clinical trials on medicinal products for human use (collectively referred to as the 'Relevant legislation').

These provisions are in large part a translation of the Directive and incorporate the principles of Good Clinical Practice.

Approval of the protocol

According to the Relevant Legislation a clinical trial may be initiated only if the Ethics Committee has issued a favourable opinion and if the competent authority i.e. National Medicines Agency ('NMA'), has not notified the sponsor about any ground for non-acceptance. Before initiating any clinical trial, the sponsor has to present to the NMA a correct and valid request, expressing his intention of conducting a clinical trial. If NMA informs the sponsor that there are grounds for non-acceptance, the sponsor is allowed, only once, to modify the content of the request considering the mentioned grounds.

Romania did not make use of the possibility granted by Article 6.4 of the Directive with respect to a member state's possibility to decide if NMA is responsible for the consideration of the matters referred to in paragraph 3 (h), (i) and (j) of the Directive.

However, with respect to Article 9.5 of the Directive regarding the necessary explicit consent of the competent authorities for investigations involving products that do not have a marketing authorisation and other medicinal products with special characteristics, the Romanian legislator did include the possibility of this consent having to be requested.

As stated in the Relevant Legislation, a written authorisation is necessary before starting a clinic trial that involves medicines used for gene therapy, somatic cell therapy including xenogenic cells

therapy and all medicinal products containing genetically modified organisms.

According to Article 7 of the Directive, the Relevant Legislation provides that in case of multi-centre clinical trials limited to the Romanian territory, NMA has to establish a procedure with the purpose of expressing a single opinion. In case of multi-centre clinical trials conducted in more than one state, an opinion for every one of these states should be expressed.

Minors and individuals not able to give informed legal consent

With respect to the protection of minors or incapacitated adults, the Minister of Health Order no. 904/2006 provides the same degree of protection as the Directive and literally transposes Articles 4 and 5 of the Directive.

Timelines

Timelines are as stated in the Directive

Consideration of a valid request for authorisation by NMA will be carried out as rapidly as possible and may not exceed 60 days. NMA may inform the sponsor before the period expires that there is no ground for non-acceptance. No further extensions of this term are allowed except in case of trials involving medicinal products used for gene therapy, somatic cell therapy including xenogenic cells therapy and all medicinal products containing genetically modified organisms, for which an extension of a maximum of 30 days is permitted. For these products, the 90-day period may be extended by a further 90-day period in the event of consultation of an expert group or committee. In the case of xenogenic cell therapy there is no time limit to the authorisation period.

EudraCT database

In Romania NMA is entrusted with the inclusion of details with respect to any clinical trial conducted in Romania into the European database as provided for in Article 11 of the Directive.

Notification of adverse events

Chapters 17 and 18 of the Minister of Health Order no.904/2006 are a translation of Articles 16 and 17 of the Directive.

As such the investigator must inform immediately the sponsor of any serious unexpected event. In case of severe adverse reactions the sponsor has to ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal and/or life threatening is recorded and reported as soon as possible to competent authorities in all member states concerned, and to the Ethics Committee, and in any case no later than 7 days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8-day period.

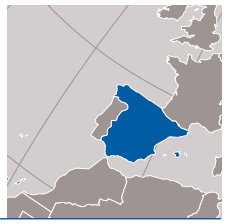
Study medication and devices free of charge

The Relevant Legislation clearly states that the investigational medicinal products and, when needed, the devices for their administration or the devices necessary according to the clinic trial protocol, are always made available free of charge by the sponsor.

Supervision of clinical trials

For controlling the compliance with the provisions regarding Good Clinical Practice, NMA assigns inspectors to control the sites involved in conducting clinical trials and especially the sites where the clinical trial is conducted, the place where the medicine is produced and any analysis laboratory used for the clinical trial.

Spain



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In Spain, Directive 2001/20 has been implemented through the Royal Decree 223/2004.

Approval of the protocol

Article 3.1. of the Royal Decree foresees that a clinical trial could only be developed if the Ethics Committee and the *Agencia Espanola del Medicamento*, the Spanish Agency on Drugs (SDA) consider that the benefits expected justify the risks assumed. In this sense, there are two parallel authorisations to be obtained:

a) The favourable report of the Ethics Committee, which would evaluate the protocol, the investigator´s guide and the rest of the information provided.

b) The authorisation granted by the Spanish Agency on Drugs. The Agency will verify all the formal requirements requested by law and if the Agency does not communicate any objections to the clinical trial, the authorisation shall be deemed granted. Exceptions to this tacit authorisation are also foreseen (see below).

The Spanish legislature has not made use of the possibility foreseen in Article 6.4 of the Directive.

Also, the Spanish legislature has not made use of the option contained in Article 9.5 of the Directive regarding the necessary explicit consent of the competent authorities for investigations that involve biotechnological products. Nevertheless, an express authorisation (instead of the usually tacit authorisation mentioned above under b)) must be obtained from the authorities in the following cases: a) clinical trials to which the Agency has made objections; b) clinical trials with drugs that require the qualification of product under clinical investigation; and c) clinical trials with drugs of gene therapy, somatic cellular therapy and drugs that contain genetically modified organisms.

According to Article 7 of the Directive, member states have to establish for multi-centre clinical trials a procedure providing, notwithstanding the number of Ethics Committees, for the

adoption of a single opinion for that member state. In Spanish law, this procedure implies the need for a report from each Ethics Committee involved in the clinical trial and the compilation by the Ethics Committee of reference of a single report that shall be the effective report duly grounded especially in those cases in which a different opinion from another Ethics Committee has been issued.

Minors and individuals not able to give informed legal consent

Article 7 of the Royal Decree regulates the so-called informed consent. In particular this Article regulates the procedure for obtaining the informed consent of minor age and disabled persons.

The Department of Public Prosecution Fiscal Ministry shall be informed about the authorisations for clinical trials involving minors.

Timelines

The Royal Decree has established the maximum period of 60 days for both the issuance of the Ethics Committee report and the authorisation of the Spanish Agency. These terms could be extended up to 90 days if the clinical trial involves drugs of gene therapy, somatic cellular therapy and drugs that contain genetically modified organisms. If an expert report is necessary, this term could be again extended up to 90 days.

The Spanish Agency would verify in a ten-day term if the application has all the formal requirements requested by law and once this is verified, a new period of 60 days would be opened for granting the authorisation, provided that the Agency has been duly notified of the favourable report issued by the Ethics Committee. If in the term of 60 days from the notification of the admission of an application the Agency does not communicate any objections, the authorisation shall be granted. In case of an express authorisation these terms could be extended up to 90 days and then for a new period of 90 days.

Finally, in case of a proposed amendment of the protocol, the Ethics Committee shall give an opinion within 35 days after receipt of the proposed amendment in good and due form. This period is in line with the period as set out in the Directive.

EudraCT database

According to section 41 of the Spanish Royal Decree, the Spanish Agency for Medicines and Sanitary Products (Agencia Española del Medicamento y Productos Sanitarios) is responsible for the inclusion within the European database of clinical trials (EUDRACT) of all those trials performed within the Spanish territory.

Notification of adverse events

Article 44.6 of the Royal Decree establishes that the SAD shall maintain a website for the data process for the registration of all suspicions of serious and unexpected adverse events.

Study medication and devices free of charge

Regarding the obligation of providing the investigational products free of charge the Royal Decree foresees, among the obligations of the sponsor, said concrete obligation without exceptions.

Supervision of clinical trials

According to section 40 of the Spanish Royal Decree, the Spanish Agency for Medicines and Sanitary Products (*Agencia Española del Medicamento y Productos Sanitarios*) and the competent authorities of the autonomous communities, shall verify the correct enforcement of such royal decree, of good clinical practice rules and of those rules regarding the correct fabrication of appliances to be used in clinical trials carried out in Spain, through diligent inspections. Additionally, said provision sets forth that the Spanish Agency for Medicines and Sanitary Products should inform the European Agency of Medicines Assessment about the inspections that were carried out and their outcome. It is also responsible for bringing the data referring to those inspections in the EUDRACT database.

Switzerland

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In Switzerland, the rules for clinical trials are set forth in the Federal Act on Drugs and Pharmaceutical Products of 15 December2000 and the Federal Ordinance on Clinical Trials of 17 October 2001, in force since 1 January 2002. The Directive 2001/20 has no direct impact on Swiss legislation since Switzerland is not a member state of the European Union. As a consequence, Directive 2001/20 has not been formally adopted in Switzerland, nor will it be adopted in the foreseeable future. Nonetheless, in the area of clinical trials, Swiss law and EU law harmonise to a large extent. The following paragraphs provide an overview on how the salient topics of Directive 2001/20 are dealt with under Swiss law.

Approval of the protocol

For clinical trials governed by Swiss law, the competent ethics committee has to give its favourable opinion. It is the investigator's responsibility to obtain such opinion from the ethics committee in charge. The sponsor must then submit the committee's favourable opinion together with a notification of the planned trial to Swissmedic, the Swiss Agency for Therapeutic Products, for the conduct of a clearing process. Generally speaking, Swissmedic grants clearance once it has determined that the sponsor's files are complete and that there are no obvious reasons to question compliance with existing laws and regulations. For clinical trials involving genetic somatic therapy or genetically modified micro-organisms, an explicit written authorisation needs to be obtained from Swissmedic. This rule is in line with Directive 2001/20.

Minors and individuals not able to give informed legal consent

Clinical trials on minors, persons under legal guardianship or persons incapable of judgement may only be carried out if trials on persons of adult age and who are capable of judgement would not produce comparable insights and if the legal representatives of the trial subjects have given their informed consent. Furthermore, persons capable of judgment, but who are minors or persons under legal guardianship, have to give their consent. Finally, clinical trials involving the aforementioned categories of

individuals may only be carried out if there is no indication suggesting that persons incapable of judgement would refuse to participate in the respective trial.

Exceptionally, clinical trials not bringing a direct benefit to the trial subjects may be carried out on minors, persons under legal guardianship or persons incapable of judgement if, in addition to the conditions specified in the preceding paragraph, (i) the trials are expected to produce important knowledge concerning the status, illness or suffering of the trial subjects, and if this knowledge would bring long-term benefits for the trial subjects concerned or for persons of the same age group, or for persons suffering from the same illness or presenting the same characteristics, and (ii) the risks and the unpleasantness that the trial subjects must endure are minor.

Timelines

The ethics committee will generally render its opinion within 30 days after having received all relevant and required documents and information. In case of radiopharmaceuticals the opinion shall be rendered within 60 days.

The period during which Swissmedic can make its objections in the ordinary clearing process is 30 days, or 60 days in case of radiopharmaceuticals. In case of somatic cell therapy or clinical trials with medicines containing genetically modified micro-organisms, an explicit written authorisation of Swissmedic needs to be obtained. In these cases, Swissmedic might be required to obtain additional consent of further Federal authorities. Swissmedic usually decides on the authorisation within a 90-day period after having received the complete application.

EudraCT data

Since Switzerland is not a member country of the European Union, data on clinical trials conducted in Switzerland are not recorded in the European database ('EudraCT'). By virtue of Swissmedic's observership status with the EMEA (European Agency for the Evaluation of Medicinal Products), it has access to the EudraCT database, but there is no data input from the Swiss end due to the aforementioned reasons.

Notification of adverse events

The Swiss regulation regarding the notification of adverse events corresponds essentially to Article 16 of the Directive 2001/20. Swiss law sets forth three types of reporting obligations: from the investigator to the sponsor, from the sponsor to Swissmedic and from the investigator to the respective ethics committee.

Study medication and devices free of charge

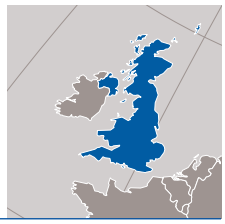
Swiss law does not explicitly prohibit the sponsor or investigator from charging trial subjects for the investigational drug. In practice, however, it is rather unusual to request trial subjects to pay for the application of unapproved study drugs, in particular in phase I to III trials.

While Swissmedic would not be expected to intervene in cases where trial subjects pay for the study drug, it cannot be excluded that ethics committees could withhold their favourable opinion since such a charge upon the trial subject could be viewed as unethical. In this respect, Swiss law appears to be more flexible than the Directive 2001/20, which bars the sponsor from charging for the investigational product.

Supervision of clinical trials

Swissmedic may at any time inspect sponsor, investigator as well as the trial site, premises and laboratories. It may inspect all documents and data relating to the clinical trial. Swissmedic may suspend or stop the clinical trial or make it subject to additional terms and conditions if Swissmedic has objective reasons to believe (i) that the conditions of its authorisation are no longer satisfied, or (ii) that the sponsor's file has been modified without prior notification, or (iii) if the trial is not carried out in compliance with the trial documentation, or if new findings regarding the innocuousness or the scientific fundamentals of the clinical trial require it.

United Kingdom



By Shuna Mason
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Directive 2001/20 has been implemented through The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) (the Clinical Trials Regulations). They include the requirement to adhere to the principles of good clinical practice (GCP) in the conduct of a clinical trial. The Clinical Trials Regulations have already been amended, mainly by The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928) which principally implement Commission Directive 2005/28/EC (the Good Clinical Practice (GCP) Directive) but which also include additional changes to the Clinical Trial Regulations which do not arise out of the GCP Directive.

The Clinical Trials Regulations contain much detail not present in the Directive. For example, the Clinical Trials Regulations introduce a number of definitions not contained in the Directive with a view to clarifying legal meaning and effect. In particular, the Clinical Trial Regulations extend the Directive's definition of a 'sponsor' to include persons who take responsibility for 'arranging the financing' of a clinical trial.

Approval of the protocol

Under Regulation 12 of the Clinical Trial Regulations, no person may start or cause a clinical trial to be started or conduct a clinical trial without an Ethics Committee approval and authorisation by the Competent Authority, which is the Medicines and Healthcare products Regulatory Agency (MHRA).

Recruitment of trial subjects and advertising for recruitment may take place before regulatory approval is received from the MHRA provided that a favourable Ethics Committee opinion has been obtained.

Regulation 14 of the Clinical Trials Regulations requires a single application for ethical approval to be made by the Chief Investigator for a clinical trial to a single Ethics Committee (irrespective of the number of trial sites in the UK). The Ethics Committee must be established or recognised for: (i) the entire United Kingdom; or (ii) for the area where the Chief Investigator is professionally based; and (iii) be responsible for assessing

the description or class of clinical trial into which the proposed clinical trial falls.

In practice electronic applications must be made via the Central Office Research Ethics Committee (COREC) Central Allocation System with an additional site-specific assessment being made to individual trial site Ethics Committees by Site Principal Investigators.

Applications for the ethical approval of gene therapy clinical trials must be submitted to the Gene Therapy Advisory Committee (GTAC).

The United Kingdom does not require review by the MHRA of the matters specified in Article 6 (4) of the Directive (i.e. the matters specified at Article 6 (3) (h)-(j)). These matters are reviewed solely by the responsible Ethics Committee.

'Negative' regulatory approval by the MHRA is the norm for Competent Authority authorisation of clinical trials in the UK.
As required by the Directive, Regulation 19 requires positive (written) authorisation to be given by the MHRA for clinical trials into the following classes of investigational medicinal products: (i) gene therapy; (ii) somatic cell therapy; (iii) xenogenic cell therapy; (iv) those containing genetically modified organisms (GMO).

The United Kingdom has also exercised its option under Article 9(5) of the Directive to require positive written authorisation for products which do not fall within the above categories (i)–(iv) and which are unauthorised biotechnology products; and products with human/animal-derived active(s), components of active(s) or whose active(s) require(s) such components to be used for manufacture, if the MHRA notifies the applicant of this requirement within 7 days of receipt of a valid application for regulatory approval.

Minors and Individuals not able to give informed legal consent

The Clinical Trials Regulations reproduce the requirements of Article 4 of the Clinical Trials Directive. Schedule 1, Part 4 of the Clinical Trial Regulations sets out the conditions and principles, which apply in relation to a minor participating in a clinical trial. A 'legal representative' for the minor must give informed consent to the minor's participation in the trial. Consent must be written (or oral, if the representative is unable to sign or to mark a document so as to indicate his consent, in which case it must be given in the presence of at least one witness and recorded in writing). For the purposes of the Clinical Trials Regulations a minor is a child of up to 16 years of age. The Clinical Trials Regulations introduce the notion of personal and professional legal representatives. (There are slightly different provisions and definitions in relation to Scotland and Northern Ireland and these are set out in Schedule 1, Part 1 of the Clinical Trials Regulations). Broadly, a 'personal legal representative' in relation to a minor or an incapacitated adult is somebody who is suitable to act as their legal representative for the purposes of the trial by virtue of their relationship with that adult or that minor and who is available and willing to act for these purposes. In relation to a minor this will be a person with parental responsibility (as defined in the Children Act 1989).

The United Kingdom has implemented the requirements of Article 5 of the Directive at Schedule 1, Part 5 of the Clinical Trials Regulations. Broadly similar conditions must be fulfilled as in relation to minors if clinical trials are carried out on incapacitated adults. Incapacitated adults who have refused to participate in a clinical trial prior to the onset of their incapacity cannot be included as clinical trial subjects.

Timelines

Under Regulation 18, the norm for 'negative' regulatory approval for a clinical trial is 30 days from the date of receipt of the valid request for regulatory authorisation. In relation to gene therapy, somatic cell therapy or products containing GMO, the period may be extended by a further 90 days where the MHRA consults with a relevant

committee, being the Commission on Human Medicines or other appropriate committee or body. There are no time limits for the MHRA to consider an application for authorisation of a trial involving xenogenic cell therapy products (Regulation 19). The period of approval for unauthorised biotechnology products or products with human/animal-derived active(s), components or manufacture is 30 days (Regulation 20).

Pursuant to Regulation 15 of the Clinical Trials Regulations an Ethics Committee must give an opinion within 60 days of receipt of a valid application. In the case of clinical trials involving a gene therapy or somatic cell therapy medicinal product or a product containing GMO where the Ethics Committee consults with a specialist group or committee in relation to the use of such therapies in the treatment of humans (gene or somatic cell therapy products) or the administration of such products to humans (GMO products) the period is extended to 180 days or, where there is no such consultation, 90 days. There are no time limits for the issuing of an Ethics Committee opinion for medicinal products for xenogenic cell therapy.

EudraCT Database

In the United Kingdom the MHRA, as the Competent Authority of the United Kingdom for the purposes of the Directive (and the GCP Directive) performs all the functions of the member state under the Directive (and the GCP Directive). The MHRA is therefore responsible for entering the information required by Article 11 of the Directive.

Notification of Adverse Events

The sponsor must keep detailed records of all adverse events that are reported to it by the investigators for a trial. Under Regulation 33 of the Clinical Trials Regulations expedited reporting is required by the sponsor as soon as possible (and in any event not later than 7 days after first knowledge on the part of the sponsor) of all suspected unexpected serious adverse reactions that are serious or life threatening to (i) MHRA, (ii) other member states hosting the clinical trial and (iii) relevant Ethics Committee.

Other suspected unexpected serious adverse reactions must be reported to each of the above entities no later than 15 days from the sponsor's first awareness.

Sponsors may fulfil their requirements to notify the MHRA or other member states' competent authorities by reporting electronically via the EudraVigilance database. UK investigators must also be notified by the sponsor of any suspected unexpected serious adverse reaction that occurs in relation to the investigational medicinal product used in the trial irrespective of whether such a reaction occurs in the course of that trial or another trial.

'Serious adverse event', 'serious adverse reaction' or 'unexpected serious adverse reaction' are defined as any adverse event, adverse reaction or unexpected adverse reaction, respectively that results in death; is life threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

Study Medication and Devices Free of Charge

Pursuant to Regulation 28(3) of the Clinical Trials Regulations the sponsor must ensure that investigational medicinal products used in the trial and any devices used for the administration of such products are made available to trial subjects free of charge. This excludes National Health Service prescription charges.

Supervision of Clinical Trials

By virtue of Regulation 4 of the Clinical Trials Regulations the MHRA is responsible for performing the United Kingdom's Competent Authority's supervisory functions

under the Directive, including in relation to GCP and GMP compliance. Regulation 47 of the Clinical Trials Regulations expressly applies many of the enforcement provisions of the *Medicines Act 1968* for the purpose of enforcing the Clinical Trials Regulations. The MHRA is specifically empowered to inspect, take samples and seize goods and documents pursuant to section 112 of the Act for the purposes (amongst other matters) of ascertaining whether there is or has been a contravention of the Clinical Trials Regulations, which therefore includes the requirements of the Directive to comply with GCP and GMP.

Since 29 August 2006 the Clinical Trials Regulations impose an additional obligation upon a sponsor to notify the MHRA of 'serious breaches' of the clinical trial protocol or GCP within 7 days of first awareness on the part of the sponsor. A 'serious breach' must be reported if the breach is likely to significantly affect: the safety or physical integrity of clinical trial subjects or the scientific value of the clinical trial. The relevant provision is Regulation 29A of the Clinical Trials Regulations.

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