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REVIEW ARTICLE

Biomedical research: guidance on how to take the first research steps

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The expanding body of regulations that affect biomedical research both in Spain and the rest of Europe have led to an increasing amount administrative work for obtaining approvals before a study can start. The complexity of the requirements will depend on the study design: clinical trials with medicines or other health care products are subject to the most highly developed regulations, whereas those affecting studies of noninvasive procedures are less complex. Between the 2 extremes, a range of requirements can complicate the clinical researcher's task. In this article we seek to provide instructions according to the type of study being planned and to explain relevant legislation.

Keywords: Clinical research. Guidelines. Legislation. Application procedures

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La investigación biomédica: algunas orientaciones sobre cómo dar el primer paso

La creciente regulación de la investigación clínica, tanto nacional como europea, ha venido a incrementar los trámites administrativos necesarios para obtener las autorizaciones pertinentes previas al inicio de cualquier estudio de investigación biomédica. En función del tipo de estudio estos requisitos son más o menos complejos: los ensayos clínicos con medicamentos e investigaciones clínicas con productos sanitarios se encuentran entre los que disponen de más desarrollo normativo, mientras que los proyectos de investigación con procedimientos no invasivos están en la situación opuesta. Entre ambos, todo un abanico de normativas puede dificultar la labor del clínico a la hora de llevar a la práctica un estudio. Con este artículo pretendemos proporcionar unas instrucciones a seguir para cada tipo de estudio, así como informar de la legislación aplicable.

Palabras clave: Investigación clínica. Guías. Legislación. Procedimientos de solicitud.

Introduction

Biomedical research is subject to legal regulation with a double objective: to ensure quality through the reliability of the results obtained and to safeguard the rights of participants. In fact, as a consequence of the results obtained, changes in routine medical practice may be introduced, clinical indications on the use of registered medicines may be expanded or reduced, or new drugs or medical devices may be marketed.

Doctors often wish to undertake their own projects without commercial support. In these cases the professionals are faced with many difficulties for the implementation of a study. Before beginning, researchers must comply with a series of procedures to obtain authorization. The procedures vary depending on the type of study and depend on both the design and the type of intervention and procedures applied:

1. Medication studies (including advanced therapies): clinical trials with drugs and observational studies with approved drugs (post-authorization studies).
2. Studies with medical devices: clinical research with health products; clinical trials with health products and observational studies with health products.
3. Other research projects: studies with invasive procedures; studies with non-invasive procedures; and studies with biological samples of human origin.

The present article aims to facilitate the implementation of a clinical trial, provide instructions to follow for each specific type of study (Table 1) and inform the researcher about the applicable legislation (Table 2).

Studies with medications

The Spanish Agency for Medicines and Health Products (AEMPS in Spanish) has created the Independent Clinical Research support office, where one can request information using the form available on its website[1].

Clinical trial with medications

A clinical trial is any investigation in human beings to determine or confirm the clinical, pharmacological and / or other pharmacodynamic effects and / or identify any adverse reactions, and / or study the absorption, distribution, metabolism and excretion of one or more investigational medicinal product or drug in order to determine their safety and / or efficacy.

An investigational drug is the pharmaceutical form of an active substance or placebo being tested or used as a

Table 1. Procedures to follow before starting a clinical trial

Type of study	Procedures	Recommendations / Requirements
Clinical trial with drugs	1st CEI Approval 2nd AEMPS authorization	Read RD 223/20043 and "Clarifications on the application of Authorization clinical trials with medicinal products for human use " Contact the AEMPS Support Office One can not start the study until one obtains the following: - Favorable decision of the reference CEI - Authorization of AEMPS - Conformity of each center's management - Specific liability insurance (hired by the developer) - Contract signed between the promoter and / the center / s.
Post-authorization study	1. Classification by AEMPS 2. CEI Approval 3. Approval by AEMPS or the com regional authority (if applicable)	Read the Order SAS / 3470/20097 Contact Support Office of AEMPS One can not start the study until one obtains: - Favourable CEI decision - Authorization of AEMPS or the CCAA (if applicable) - Conformity of each center's management - Contract signed between the promotor and the center/s - Does not require specific liability insurance
Clinical trial with health products (not CE labeled or unauthorized indication)	1.CEI Approval 2. Approval by AEMPS	Read Circular 7/20049 Contact the Department of Health Products AEMPS10 One cannot start the study until one obtains: - Favorable CEI decision at each center where the study is to be conducted (unlike clinical drug trials, there is no single CEI decision) - Authorization of AEMPS - Conformity of each center's management - Contract signed between the promoter and / the center / s - Specific liability insurance (contracted by the promotor)
Clinical trial with health products (CE labeled and with authorized indication)	1.CEI Approval	One cannot start the study until one obtains: - Favorable CEI decision at each center where the study is to be conducted (unlike clinical drug trials, there is no single CEI decision) - Authorization of AEMPS - Conformity of each center's management - Contract signed between the promoter and / the center / s - Does not require specific liability insurance, unless the CEI considers that interventions or procedures involved in the trial pose a higher risk than would apply in clinical practice. - Does not require authorization by AEMPS
Observational studies with health products	1.CEI Approval	One cannot start the study until one obtains: - Favorable decision by a single CEI - Contract signed between the promoter and / the center / s - Does not require specific liability insurance - Does not require authorization by AEMPS - In the absence of specific regulation, simply notify the center about the study after obtaining CEI approval.
Studies with invasive procedures	1.CEI Approval	One cannot start the study until one obtains: - Favorable CEI decision - Contract signed between the promoter and / the center / s - Specific liability insurance (contracted by the promotor) - Requires permission of the competent regional authority - In the case of minors and mentally incompetent subjects, authorization from the Fiscal Ministry is required. - In the absence of specific regulation, simply notify the center about the study after obtaining CEI approval.
Studies without invasive procedures	Aprobación CEI	One cannot start the study until one obtains: - Favorable CEI decision - In the absence of specific regulation, simply notify the center about the study after obtaining CEI approval.

CEI: Comité de Ética de Investigación (Research Ethics Committee); AEMPS: Spanish Agency for Medicines and Health Products; EC: European Certificate of Conformity; RD: Royal Decree. * Clinical drug trials require civil liability insurance, unless the following conditions apply: a) the trial involves medicinal products authorized in Spain; b) their use conforms to the approved conditions of use, and c) the CEI considers that the interventions involve an equivalent or lower risk for participants than would correspond to their attention in clinical practice. However, the legislation provides that in case of damage attributable to participation in the trial, the investigator, the promotor and the center assume joint liability outlined in a specific document of liability.

Table 2. Reference legislation

Type of study	Study Legislation	Development policy
Clinical trial with drugs	Law 29/2006, July 26, guarantees and rational use of medicines and health products[2]	RD 223/2004, February 6, which regulates clinical trials with medicines[3] Read the "Clarifications on the application the regulations on clinical trials with medicines for human use"[20]
Clinical trial with advanced therapies	Law 29/2006[2]	RD 223/2004[3] RD 1564/1992 which regulates the authorization of pharmaceutical companies and importers of medicinal drugs, and the quality of industrial manufacture.
Post-authorization study	Law 29/2006[2]	Order SAS 29/20062/3470/2009 of 16 December, which publishes the guidelines for post-authorization observational studies with drugs for human use[7]
Clinical research with health products	Law 29/2006[2]	RD 1591/2009 which regulates health products[22‡] RD 1616/2009 which regulates implantable medical devices[23‡] Circular 07 / 2004[9§]
Clinical trial with health products	Law 29/2006[2]	RD 1591/2009 which regulates health products[22**] RD 1616/2009 implantable medical devices[23‡]
Observational study with health products	No specific legislation	
Study with invasive procedures	Law 14/2007	No se dispone de desarrollo normativo

CEI: Ethical Research Committee; AEMPS: Spanish Agency for Medicines and Health Products; EC: European Certificate of Conformity; RD: Royal Decree. ‡ This regulation states that the ethical, methodological and protection of trial subjects principles apply, referred in the regulation of clinical drug trials. §Según information from the Department of Medical Devices of AEMPS, in the circular 07/2004 the procedure for applying AEMPS described and explained what documentation must be submitted. Despite being obsolete, the procedure and documentation are useful, since the forms and schedules to fill remain the same. ** This regulation states that the principles contained in Royal Decree 223/2004 for clinical trials with medicinal products, except that these studies do not require AEMPS approval.

reference in a clinical trial, including products already on the market when used or presented (formulated or packaged) in a form that is different from the authorized form, or when used for an unauthorized indication, or to obtain further information about authorized drug use[2].

Clinical trials with drugs are those studies that meet one or more of the following criteria:

- Experimental and control subjects assigned (randomly or not) to a given treatment, (best known form of a clinical trial).
- The study drug is under clinical development, not yet approved by the health authorities (even though there is only a single treatment group).
- The drug is registered, but is studied for an indication other than that authorized.
- The drug is registered and used for an authorized indication, but not in conditions of common use: there is amendment in the pattern, dose, route of administration or any other aspect concerning drug delivery as stated on the instruction sheet; or it is studied in combination with other drugs.
- The drug is registered, used for an authorized indication under common use conditions, but during the study tests or examinations are conducted that are not part of routine clinical practice.

Procedures to be followed and requirements

It is necessary to obtain the approval of a Clinical Research Ethics Committee (CEIC in Spanish) and authorization from AEMPS[3]. Henceforth the Research Ethics Committee will be referred to as CEI, as defined in Law 14/2007 on Biomedical Research[4].

The Ministry of Health Clinical Trials with Drugs website[5] provides detailed instructions on the steps to follow and the necessary documentation for evaluation, application and authorization, which include at least the protocol, the researcher manual and the information sheet and consent forms.

Simultaneously one can request authorization from CEI and AEMPS. The latter authority will not issue its decision until it has received CEI approval and the document of approval of at least one of the participating centers. It is recommended that the application to the CEI involved be sent a few weeks before requesting AEMPS authorization for the trial, because it will be rejected if those documents have not been received within the stipulated time period.

If the investigational medicinal product is not yet marketed or has never been used in a clinical trial in Europe, it is necessary to obtain its classification as a new investigational product (NIP) before requesting authorization for the first clinical trial. This requires further steps including, among others, a dossier documenting the chemical-pharmaceutical quality of the medication, the preclinical and clinical studies required to perform the clinical research proposed along with a clinical investigation plan which must include a comprehensive and justified description of the objectives, indications and target populations, dose range, routes of administration, maximum duration of the experimental treatment and treatments for the controls and also a detailed description of further trials to be undertaken in Spain. NIP applications should preferably be submitted with the first clinical trial of the plan for simultaneous evaluation.

In addition to the provisions of Royal Decree (RD) of 223/2004[3] on clinical drug trials, each CEI may establish their own additional requirements. It is necessary to contact each of them to know what documentation they require.

In the case of multi-center clinical trials with drugs, a single ruling is issued in Spain which is binding on all participating centers. The promotor must ask one of the CEI at one of the participating centers to act as the reference CEI and assess the views of any others involved. To coordinate all the participant CEIs, the promotor must deliver the documents to the secretariat of each one before day 6 of each month.

The complexity of all these steps, if they do not preclude the promotion of academic clinical trials, requires considerable time and effort. It is therefore advisable to enlist the help of a support unit for independent research, colloquially known as an academic CRO, usually available in hospitals with high research activity. It is advisable to consult such units before presenting the project, and one must include the cost of their services in the estimated financial cost document.

Clinical trials on advanced therapies

Advanced therapy medicinal products for human use are based on genes (gene therapy), cells (cell therapy) or tissues (tissue engineering) and include products of autologous, allogeneic or xenogenic origin[6].

Procedures to be followed and requirements

They are the same as for clinical trials with drugs, but it is also necessary to request NIP classification of the drug, or justify why that is not requested. It also requires manufacturing permission. Advanced therapy investigational medications must be developed by authorized manufacturers. When the manufacturer is located in Spain, they must have proper authorization from AEMPS (General Sub-Directorate for Inspection and Control of Medicines). When these drugs are developed wholly or partly in associated centers of the National Health System, the centers must be certified as complying with the norms of correct manufacture, issued by AEMPS General Sub-Directorate for Inspection and Control of Medicines.

We recommend consulting, before initiating proceedings, the Advanced Therapies section on the AEMPS website6 and the Office of Independent Clinical Research Support.

Observational post-authorization studies (EPA, in Spanish) for human medicines)

These are studies in which drugs are prescribed in authorized conditions.

Assigning a patient to a specific therapeutic strategy is determined by the standard of practice, and the decision to prescribe a certain drug will be clearly dissociated from the decision to include the subject in the study. Patients are not subject to any non-standard intervention, either diagnostic, therapeutic or follow-up, and epidemiological research methods are used in analyzing the data collected[7].

An EPA encompasses any observational study that includes data collection and marketed drugs. AEMPS classifies this type of study in five categories according to study design and source of funding:

- EPA-LA: set as a condition by the health authorities on approval of a new medicine, or a requirement of the competent authority to clarify safety of the drug, or form part of the risk management plan.
- EPA-AS: studies with prospective follow-up design and promoted by health authorities or publicly funded.
- EPA-SP: studies with prospective follow-up design but not promoted by health authorities or publicly funded.
- EPA-OD: studies not categorized as EPA-LA without prospective follow-up, for example, case-control, cross-sectional or retrospective cohort studies.
- Non-EPA: the factor of exposure investigated is not a drug but on collecting information on drugs, the protocol must be submitted to AEMPS for classification.

Procedures to be followed and requirements

- AEMPS classification must be obtained. Depending on the assigned category, one needs to follow one or another administrative process and authorization is required from AEMPS (EPA-LA and EPA-AS) or the corresponding regional authority (EPA-SP), as a precondition for initiating the study (after payment of the applicable fees in some communities). The categories EPA-OD and Non-EPA do not require prior authorization, only CEI approval.
- The protocol and accompanying documentation must be submitted to the CEI for approval.

Application for classification

The AEMPS website provides Instructions and the form to request classification of an observational study[8].

Studies with medical devices

A medical device is any instrument, apparatus, equipment, material or other article, used alone or in combination, including the software necessary for its proper application as intended by the manufacturer for use in humans for the purpose of: diagnosis, prevention, control, treatment or alleviation of disease, injury or disability; investigation, replacement or modification of the anatomy or of a physiological process; regulation of conception; and which does not achieve its principal action by pharmacological, immunological or metabolic means.

If the study also involves a drug, it is governed by both standards, for studies with medical devices and medical drug studies.

Clinical research with medical devices

This refers to clinical research with medical devices where: a) the product has no CE label (Certificate of European Conformity); b) the product bears the CE label but is used in a treatment or procedure which differs from that authorized; and / or c) patients are assigned to either treatment group.

Procedures to be followed and requirements

The studies described as a) and / or b) require the approval of all the CEI (not just one) and AEMPS authorization. If the medical device is CE-labeled and is to be used as authorized, AEMPS authorization is not required.

Although the necessary documentation is similar to that for clinical drug trials, the procedures to request authorization are even more complex, and there are no detailed instructions on the steps to be taken for authorization, as there are for clinical trials with drugs (Ministry of Health website). Therefore, we recommend accessing a contact point of AEMPS for clinical research with health products for information about the documentation needed and the steps to take.

Postmarketing studies with medical devices

These are studies with medical devices bearing the CE label, used as indicated and authorized, without affecting usual clinical practice or requiring patients to undergo more tests or being assigned to a group, and there is no comparison of devices. The doctor only collects data about the product in use.

Procedures to be followed and requirements

One only needs to submit the protocol and documentation to the CEI for approval (information obtained from the AEMPS Department of Health Products).

Other research projects

In studies not investigating a drug or a medical device, but a surgical technique or a diagnostic method or some other non-drug intervention, the key factor for the administrative process is whether the activities or procedures to be performed are invasive or not, regardless of the design (either a clinical trial where patients are assigned to a given treatment group, or an observational study where clinical practice is not changed).

For example, a randomized study of two different training programs for athletes would be a clinical trial without invasive procedures, while a study where a single group of subjects are subjected to the same surgical procedure would not be classified as a clinical trial, but the Biomedical Research Act[4] would apply due to the invasive nature of the procedure.

The relevant Law 17/2004 defines an invasive procedure as any intervention undertaken for research that involves a physical or psychological risk.

Studies with invasive procedures

Procedures to be followed and requirements

One must submit the protocol and documentation to the CEI and the competent regional authority for approval and authorization, respectively.

Studies with non-invasive procedures

Procedures to be followed and requirements

This type of study is not contemplated in law, but according to the Helsinki Declaration[11] all research involving humans must be adequately described in a protocol which should be evaluated and approved by a CEI.

Studies with specimens of human origin

Procedures to be followed and requirements

These studies, regulated by Law 14/2007[4] and a royal decree (RD 1716/2011)[12], may only be carried out on samples which are obtained directly from the subject for a specific project or samples stored in an authorized biobank, registered in the National Registry of Biobanks of Carlos III Health Institute, and provided they have been approved by a CEI and informed consent of the patient has been obtained. The information to be provided in the informed consent form differs for each case.

Each of the projects undertaken with samples from a collection or a biobank must be approved individually by a CEI, otherwise it will be necessary to seek consent from the subjects again.

Common requirements for all types of study

Depending on the type of study, the documents needed may vary.

All research projects must be outlined in a protocol document which describes the objectives, design, methodology, statistical considerations and overall organization of all aspects of the study. Depending on the type of study, specific sections should be included, such as those relating to the manufacture, management and safety, whether of a drug or medical device.

The protocol must be approved by a CEI and some also require AEMPS approval or regional authority approval. The study cannot be carried out without these approvals and specific authorization (Table 1).

The protocol should be accompanied by an information sheet about the participants and informed consent. Even when standard practice is not to be modified, studies involving people and / or confidential data must comply with the provisions of the Organic Act

Protection of Personal Data and RD 1720/2007[15]. It is essential to obtain written informed consent from the participants.

Clinical trials with drugs and medical devices, in ad-

dition to being governed by specific regulations, shall be conducted under the rules of Good Clinical Practice (GCP)[16]. It is essential that the researchers know and demonstrate training in GCP.

Before starting patient recruitment, the trial must be registered in a public database (See next section).

If one intends to store biological samples obtained in the course of a project for use in future studies, according to RD 1716/2011[12], these must be organized into collections or biobanks (see section on studies with biological samples of human origin).

Public register of research trials

Clinical drug trials must be registered in a European public database[17] and the Spanish clinical studies register[18]. The study is registered automatically when the promoter sends the application form to the competent authority for evaluation and authorization. Many promotors also register their trials in the American public database (www.clinical.trials.gov.)

Publication of results

According to RD 223/2004[3] on clinical trials with drugs, the promoter is obliged to publish the results of authorized clinical trials in a scientific journal (both positive and negative results).

It is important to note that the International Committee of Medical Journal Editors (ICMJE), before publishing an original article, requires that the study be registered in a public database before inclusion of the first patient (The ICMJE does not accept the Spanish register). We recommend consulting their website if in doubt[19].

Conflict of interest

The authors declare no conflicts of interest in relation to this article.

References

1 Agencia Española de Medicamentos y Productos Sanitarios. Oficina de apoyo a la investigación. (Consultado 24 Febrero 2014). Disponible en: http://www.aemps.gob.es/investigacionClinica/medicamentos/oficinApoyo.htm.

2 Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios. Boletín Oficial del Estado Núm. 178, de 27 de julio de 2006. Madrid: BOE; 2006.

3 Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. Boletín Oficial del Estado Núm. 33, de 7 de febrero de 2004. Madrid: BOE; 2004.

4 Ley 14/2007, de 3 de julio, de Investigación biomédica. Boletín Oficial del Estado Núm. 159, de 4 de julio de 2007. Madrid:BOE;2007.

5 Ministerio de Sanidad, Servicios Sociales e Igualdad. Portal ECM de Ensayos Clínicos con Medicamentos (Consultado 24 Febrero 2014). Disponible en: https://ecm.aemps.es/ecm/paginaPresentacion.do

6 Agencia Española de Medicamentos y Productos Sanitarios. Información sobre terapias avanzadas (Consultado 10 Febrero 2014). Disponible en: http://www.aemps.gob.es/investigacionClinica/terapiasAvanzadas/preg-resp_TA.htm#preg1.

7 Orden SAS/3470/2009, de 16 de diciembre, por la que se publican las directrices sobre estudios posautorización de tipo observacional para medicamentos de uso humano. Boletín Oficial del Estado Núm. 310, de 25 de diciembre de 2009. Madrid: BOE; 2009.

8 Agencia Española de Medicamentos y Productos Sanitarios. (Consultado 24 Febrero 2014). Disponible en: http://www.aemps.gob.es/investigacionClinica/medicamentos/estudiosPostautorizacion.htm.

9 Circular 7/2004. Investigaciones clínicas con productos sanitarios. (Consultado 24 Febrero 2014). Disponible en: http://www.aemps.gob.es/investigacionClinica/productosSanitarios/home.htm.

10 Punto de contacto del departamento de Productos Sanitarios de la AEMPS. (Consultado 24 Febrero 2014). Disponible en: http://www.aemps.gob.es/investigacionClinica/productosSanitarios/docs/contactos-IC-PS_mayo-2006.pdf

11 Asociación Médica Mundial. Declaración de Helsinki. Principios éticos básicos para las investigaciones médicas en seres humanos. 64ª Asamblea General, Fortaleza, Brasil, octubre 2013 (Consultado 10 Febrero 2014). Disponible en: http://www.wma.net/en/30publications/10policies/b3/index.html.

12 Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica. Boletín Oficial del Estado Núm. 290, de 2 de diciembre de 2011. Madrid: BOE; 2011.

13 Registro Nacional de Biobancos. Instituto de Salud Carlos III. Ministerio de Economía y Competitividad. (Consultado 5 Marzo 2014]. Disponible en: http://www.isciii.es/ISCIII/es/contenidos/fd-servicios-cientifico-tecnicos/registro-nacional-de-Biobancos-2.shtml

14 Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal. Boletín Oficial del Estado Núm. 298, de 14 de diciembre de 1999. Madrid: BOE; 1999.

15 Real Decreto 1720/2007, de 21 de diciembre, por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal. Boletín Oficial del Estado núm. 17, de 19 de enero de 2008. Madrid: BOE; 2008.

16 Note for guidance on good clinical practice (CPMP/ICH/135/95) 17 January 1997. Including post Step 4 errata. Status: September 1997. (Consultado 24 Febrero 2014). Disponible en: ec.europa.en/health/files/eudralex/vol-10/3cc1aen_en.pdf

17 European Medicines Agency. EU Clinical Trial Register (Consultado 24 Febrero 2014]. Disponible en: https://www.clinicaltrialsregister.eu/

18 Registro español de Ensayos clínicos. (Consultado 24 Febrero 2014). Disponible en https://reec.aemps.es

19 International Committee of Medical Journal Editors (ICJME). (Consultado 24 Febrero 2014). Disponible en http://www.icmje.org/

20 Agencia Española de Medicamentos y Productos Sanitarios. Aclaraciones sobre la aplicación de la normativa de ensayos clínicos con medicamentos de uso humano partir del 1 de mayo de 2004 (versión nº 6, Mayo de 2008). (Consultado 24 Febrero 2014). Disponible en: http://www.aemps.gob.es/investigacionClinica/medicamentos/docs/aclaraciones_normativaEC_mayo08.pdf

21 Real Decreto 1564/1992, de 18 de diciembre, por el que se desarrolla y regula el régimen de autorización de los laboratorios farmacéuticos e importadores de medicamentos y la garantía de calidad en su fabricación industrial. Madrid: BOE; 1992.

22 Real Decreto 1591/2009, de 16 de octubre, por el que se regulan los productos sanitarios. Boletín Oficial del Estado Núm. 268, de 6 de noviembre de 2009. Madrid: BOE; 2009.

23 Real Decreto 1616/2009, de 26 de octubre, por el que se regulan los productos sanitarios implantables activos. Boletín Oficial del Estado Núm. 268, de 6 de noviembre de 2009. Madrid: BOE; 1999.