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THE “COMPASSIONATE EXEMPTION” IN SPAIN: NOT ASKING FOR COMPASSION

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THE “COMPASSIONATE EXEMPTION” IN SPAIN: NOT ASKING FOR COMPASSION*

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Francisco Miguel Bombillar Sáenz ♦

Abstract:

The Royal Decree 1015/2009, June 19th 2009 (RDDMSE) aims to facilitate the access to drugs –the drug in question should be subject to a marketing authorisation application or must be undergoing clinical trials– before approval, in Spain, in patients with a chronic or severely debilitating disease or one considered life threatening and who cannot be treated satisfactorily by an authorised product (*compassionate use*); as well as the access to drugs approved in countries other than Spain, when they do not comply with the definition of compassionate use of investigational drugs (*foreign drugs use*) and, finally, the access to drugs in conditions other than those stated in the authorised data sheet (*off-label use*). Traditionally, in Spain, the first and third cases were known as "compassionate use" –an unfortunate name, as it is not compassion that is sought–, being legally regulated in the same way.

The RDDMSE seeks to eliminate formal steps and speed up procedures, strengthening, in turn, guarantees of safety in these special applications, without neglecting the information and transparency that should prevail in this area. Among the innovations stated in the RDDMSE, we must highlight the fact that the access to drugs that are in research or unauthorised in Spain can be managed telematically for each patient, as well as through a temporary authorisation issued by the AEMPS (the Spanish Medicines Agency), in coordination with other European agencies, for a group of patients. In relation with the off-label use, this Decree eliminates the need to obtain an individual authorisation from the AEMPS, focusing liability on doctors.

* This article is part of the result of my PhD thesis, defended at the University of Granada (Intervención administrativa y régimen jurídico del medicamento en la Unión Europea) and the University of Bologna (Regime giuridico del farmaco negli ordinamenti italiano e spagnolo: la trasposizione del diritto farmaceutico europeo) and it has been made within the research project financed by the Andalusian Government SEJ-03266 «El derecho a la salud y al medio ambiente en la sociedad del riesgo y la innovación», lead by Professor Rafael Barranco Vela, Head of Department of Administrative Law at the University of Granada, the master of my entire university research career. In other way, we would like to remark that the quotes collected in this article have been unofficially translated from Spanish to English, with the help of the lawyer Patricia Gil.

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Key words: Availability of drugs in specific situations. Compassionate use. Foreign drugs. Off-label. Clinical trials. Authorisation. Temporary authorisation. Telematic application. Spanish Medicines Agency. Patient. Risk. Pharmacovigilance.

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Availability Of Drugs In Specific Situations: Cases

Drugs are designed as an instrument of health policy in the States through which, the right to health protection¹ becomes effective, as they help prevent, cure or relieve diseases and correct or repair the damage caused by these. Thanks to the medicine, mankind has been able to effectively fight against the diseases which have plagued us in recent years. Medicine saves lives, eases pain, provides a better quality of life, and is a hope for the future². Access to these is, therefore, an integral part of the right to health protection³, this being the reason³ why our legal system «recognises the right of all citizens to obtain medication under equal terms» (art. 88 LGURMPS⁴).

¹ See PEMÁN GAVÍN, J.: *Derecho de la salud y Administración Sanitaria*, Publicaciones del Real Colegio de España, Bolonia, 1989; APARICIO TOVAR, J.: «El derecho a la protección de la salud. El derecho a la protección sanitaria», in MONEREO PÉREZ, J. L.: *Comentario a la constitución socio-económica de España*, Comares, Granada, 2002, pp. 1553-1566; ESCRIBANO COLLADO, P.: *El derecho a la salud*, Instituto García Oviedo de la Universidad de Sevilla, Sevilla, 1976; or RIVERO LAMAS, J.: *Protección de la salud y Estado social de Derecho. Discurso leído en el acto de su recepción académica el día 30 de noviembre de 2000*, Real Academia de Medicina, Zaragoza, 2000.

² In this regard, in Spain, the Explanatory Memorandum to the Medicines Act 1990 [Ley 25/1990 of December 20th, 1990 (BOE n. 306 of December 22th, 1990)] stated the following: «*The drugs have achieved, in the past eighty years, memorable successes in the prevention of and fight against pain and disease. Old scourges afflicting humanity such as smallpox: have been wiped off the face of the earth, not to mention more than one example to which many others could be added. In fact many of the acts and medical or surgical procedures include drug treatment. The benefits of drugs are not only expressed in terms of lives saved and suffering avoided, but also in terms of disease and hospitalization shortened, and major economic savings due to the replacing role they play in relation with prior less effective therapies.*»

³ The Spanish Constitution recognises, in article 43, section one, «*the right to health protection*», and compels, in section two, «*the public powers to organise and guarantee public health through preventive measures and the necessary provisions and services*». This right is connected, in this as well as to other constitutional rules, with the respect to the person stated in articles 1.1. and 10 CE, and with the fundamental right to life and to physical and moral integrity stated in article 15 CE. See DE LA CUEVA ALEU, I.:

Several months ago, the Government adopted a significant regulatory standard to control the availability of the drugs in specific situations: the Royal Decree 1015/2009, June 19th 2009 (hereinafter RDDMSE⁵), as regulatory development of provisions stated in article 24 LGURMPS⁶. The mentioned Decree aims to facilitate the access to drugs in the clinical research stage for patients who do not have a satisfactory therapeutic alternative, suffering from diseases severely debilitating, endangering their lives, even without being part of a clinical trial (compassionate use⁷). Also, the Decree regulates access to drugs approved in other countries but not in Spain, for patients who are not in research and whose use is essential for these (foreign drugs⁸). Third, it controls access to drugs used in conditions other than those provided in their data sheet (off-label⁹). Traditionally, in Spain, the first and third cases are known as "compassionate use"¹⁰, being legally regulated in the same way. However, this is an unfortunate name, as it is not compassion that is sought.

This rule seeks to eliminate formal steps and speed up procedures, strengthening, in turn, guarantees of safety in these special applications, without neglecting the information and transparency that should prevail in this area. Among the innovations stated in the RDDMSE (innovations that will be considered in this work), we must highlight the fact that the access to drugs that are in research or unauthorised in

«El Derecho constitucional a la protección de la salud: Jurisprudencia constitucional», *Cuadernos de derecho judicial*, n. 5 (2004), *Salud pública y Derecho administrativo*, pp. 13-80.

Specially, in relation to the field of drugs, in Argentina, for instance, the Supreme Court of Justice of the Nation has recognised on several occasions that the protection of health is a consequence of the right to life and, hence, the State has the obligation to provide the population with the necessary drugs (among other issues, *vid Asociación Benghalensis y otros vs Estado Nacional*, June 1st 2000; *Campodónico de Beviacqua, Ana vs Estado Nacional*, October 24th, 2000 or *Asociación de Esclerosis Múltiple vs M.S.A.S.N.*, December 18th, 2003).

⁴ Law regarding Guarantees and Rational Use of Medicines and Health Products (*Ley 29/2006, de 26 de julio, de Garantías y Uso Racional de los Medicamentos y Productos Sanitarios*. Hereinafter, LGURMPS). BOE n. 178 of July 27th, 2006.

⁵ In Spanish, *Real Decreto 1015/2009, de 19 de junio, por el que se regula la disponibilidad de medicamentos en situaciones especiales*. BOE, n. 174 of July 20th, 2009, pp. 60904 *et seq.*

⁶ Provision which contemplates how, in exceptional circumstances, the Spanish Agency for Medicines and Medical Devices (hereinafter, AEMPS) may grant a permit subject to the requirement for the applicant to meet certain annually reviewable conditions, –concerning, particularly, the safety of the drug, the information given to the competent authorities referred to any incident related to its use, and the measures to be taken. The RDDMSE is responsible, under this protection, to establish the criteria for granting such authorisations. Specifically, those related to prescription and implementation of unapproved drugs for patients not included in a clinical trial, in order to, by compassionate use, treat the special needs of individual patients; as well as the conditions for prescribed approved drugs when used under conditions other than those authorised, being, in any case, exceptional. The LGURMPS also empowers the AEMPS to authorise the importation of drugs not approved in Spain, provided that they are legally marketed in other States, when such importation is necessary for prevention, diagnosis or treatment of specific diseases, being no other proper alternative in Spain, or due to shortage situations.

⁷ The RDDMSE understands the compassionate use of drugs in research as follows: «*the use of a drug before approval, in Spain, in patients with a chronic or severely debilitating disease or one considered life threatening and who cannot be treated satisfactorily by an authorised product. The drug in question should be subject to a marketing authorisation application, or must be undergoing clinical trials*» (article 2.1 RDDMSE).

⁸ Under the provisions of article 2.3 RDDMSE, the access to unapproved drugs in Spain is defined as «*the use of drugs approved in countries other than Spain, when they do not comply with the definition of compassionate use of investigational drugs*».

⁹ Finally, article 2.2 RDDMSE, establishes the following definition for drugs used in conditions other than those authorised: «*the use of drugs in conditions other than those stated in the authorised data sheet*» (article 2.2 RDDMSE).

¹⁰ To know the regulation of the compassionate exemption in the United States, see: MATHIEU, M.: «Accessibility programs for the desperately ill», in *New drug development: a regulatory overview* (Ed. M. MATHIEU), Columbia, Parexel International Corporation, 1987, pp. 257-274.

Spain can be managed telematically for each patient, as well as through a temporary authorisation issued by the AEMPS, the Spanish Medicines Agency (hereinafter, AEMPS)¹¹, in coordination with other European agencies, for a group of patients.

The use of the temporary authorisations mentioned above will bring forward administrative procedures, as patients who meet the requirements stated in the protocols issued by the Administration will have direct access to compassionate use without resorting to an individual authorisation. Regarding the problem of access to drugs that are used for conditions other than those authorised in Spain, and included in its data sheet, the RDDMSE establishes a specific authorisation procedure different to the one provided for compassionate use. The new regulation eliminates the need to obtain an individual authorisation prior to the AEMPS. The responsibility in this area is assumed by the doctor, who will address the recommendations issued by the AEMPS in this respect.

Compassionate Use And Rddmse: A Before And After?

A. TRADITIONAL LEGAL CONCEPT OF COMPASSIVE USE OF MEDICINE.

In connection with the specific authorisation procedures, we must consider, first of all, what is legally known as *compassionate use of drug*, being this term being the result of a poor translation –as it does not require compassion– from the English *compassionate exemption*¹². We are not referring here to an altruistic treatment, palliative, or placebo; but to the use, in individual patients not related to clinical trials, of drugs in research or drugs for indications other than those authorised. To NÚÑEZ LOZANO, compassionate use would entail «the use of a drug in a special way, different to general use, because it is not yet approved, or because it is being authorised, it is prescribed for practices other than those for which they were authorised»¹³. This would be the explanation of its special authorisation regulation.

In order to authorise the compassionate use of a drug, the following requirements must be met: patient’s informed consent, doctor’s report and compliance from the director of the centre where the drug will be obtained. The fact that our legal system has not granted an active role to those concerned – the patients¹⁴ – is striking. The legal system’s fundamental criterion for dispensing the drug is the

¹¹ Its Statutes have been approved by the Royal Decree 520/1999, March 26th, 1999 (BOE, n. 77, March 31st, 1999). See AEMPS homepage: <http://www.agemed.es/>

¹² See OLALLA, R. & TERCERO, M.J.: «Uso compasivo de medicamentos. Marco legal, tramitación y suministro», *OFFARM*, vol. 26, n. 8 (September, 2007), pp. 94-98.

¹³ See NÚÑEZ LOZANO, C.: «Régimen jurídico del uso compasivo de los medicamentos», *REDA*, n. 130 (2006), pp. 327 *et seq.*, specially, p. 328.

¹⁴ As DOMENECH expressively states, «AEMPS’ assessment prevails over the patient’s, although only the interests of the patient are at stake; the citizen considers that it is worth taking some risks to save his life, but the public authorities deprive him the possibility of salvation, trying to protect him against his freely formed will, as they consider that they know better than him what he needs, that the risks exceed the expected benefits». See DOMENECH PASCUAL, G.: *Régimen jurídico de la farmacovigilancia*, Thomson-Civitas, Madrid, Cizur Menor (Navarra), 2009, p. 173.

indispensable quality of its use at the doctor's discernment. It does not state specifically under what criteria.

Although our legal system does not mention exactly what drugs may benefit from this procedure, it is understood that the compassionate use applies basically to those who suffer from diseases which are considered serious (cancer, HIV, rare diseases...) and improves the quality of life of those suffering, especially in areas of paediatric, oncology and psychiatry.

B. ITS DIFFERENCES WITH THE LEGAL REGULATION APPLICABLE TO CLINICAL TRIAL

The legal regulation applicable to the compassionate use of drugs differs from the corresponding regulation to clinical trials. Although in both cases the patient makes use of medicines in research -that *«pharmaceutical form of an active substance or placebo that is being tested or used as a reference in a clinical trial, including products which have marketing authorisation when used or combined (in formulation or packaging) in a different way from that authorised, or when used as treatment for an unauthorised indication, or for obtaining further information regarding an authorised use»*¹⁵ - these are assumptions that are not in the same class. Although it repeatedly seems that, *de facto*, this is not so. The Health Administration keeps demanding requirements for the compassionate use that are not adequate for this¹⁶.

Therefore, the compassionate use takes place, according to its definition, on the fringes of a clinical trial with an individual (see, i.e. the Judgment of Tribunal Superior de Justicia de Catalonia, Sala de lo Social, n. 2700, 1st April 2008). Unlike in clinical research, in which it applies to a group¹⁷. While in a clinical trial multiple interests meet (those of the sponsor, the investigator, the individuals of the trial and also the society as a whole)¹⁸ -as it is to determine the safety and/or effectiveness of a drug subject to

¹⁵ Article 2.d) of Royal Decree 223/2004, of February 6th, which regulates clinical trials with drugs. On this regard, see ANTÚNEZ ESTÉVEZ, F.: «Los ensayos clínicos», RIVAS VALLEJO, P. & GARCÍA VALVERDE, M^a D. (dirs.): *Derecho y Medicina. Cuestiones jurídicas para profesionales de la salud*, Thomson-Aranzadi, Cizur Menor (Navarra), 2009, pp. 619-668.

¹⁶ In this sense, the words of M^a A. MONEDERO MATEO, Head of the Pharmaceutical Assistance Service to the Department of Pharmacy and Health Products in Madrid, are illustrative, stating that «the compassionate use of a drug should be based on ethical assumptions and evidence of effectiveness as strong as those required for approval of a clinical trial»; «the absence of “something better” does not justify the use in clinical practice of uncontrasted emerging technologies». See MONEDERO MATEO, M^a A. «Uso compasivo», *Formación continuada para farmacéuticos de hospital 2.5*, pp. 114 and 115; searchable online at: www.ub.es/legmh/capitols/monedero.pdf

¹⁷ In Andalusia, we can mention the prohibition, by the Andalusian Health Service (*Servicio Andaluz de Salud, SAS*), in May 2010, of the prescription of *aprepitant* as antitumor. The drug, used to alleviate nausea and vomiting from chemotherapy, was administered in the *Virgen del Rocío* Hospital, in Seville, to some patients as a last attempt to stop the cancer. The Andalusian Ombudsman's complaint of an alleged preferential treatment for drug use, administered only to those patients who were relatives of hospital doctors, uncovered inappropriate and unsafe use of the compassionate procedure. Indeed, in a context of utter arbitrariness and total lack of methodological rigor, rashly and in haste, patients were used as "guinea pigs" in order to test the anticancer drug effect, resulting high mortality (seven of ten patients died). In fact, what was carried out was a clinical trial, transgressing basic ethical principles that should be observed in the field of medical and health care.

¹⁸ The regulation and practice of the Administration in this field leaves a lot to be desired: it links the authorisation of the treatment to the risks that it entails. In the words of the chemists OLALLA and TERCERO: «The main advantage of compassionate use is that it allows certain patients, due to the type of disease they have or the seriousness of their condition,

research— here, the only possible remedy existing for a patient who has no other therapy is being sought. This is why there are no specific rules for those cases in which the patients that will benefit from the compassionate use are minors or disabled adults, such as occurs in the field of clinical trials. No specific precautions are contemplated because, by definition, compassionate use seeks the benefit of the patient, therapeutic benefit¹⁹.

The authorisation procedure for compassionate use has been considered in the Spanish legal system – until the arrival of RDDMSE— as a procedure planned for exceptional cases, under the sole responsibility of the doctor who suggests and justifies its need, having the informed and express consent of the individual patient who accepts it, with the agreement of the director of the centre where the treatment is to be administered²⁰, and after administrative approval of AEMPS, through its Directorate General for Medicinal Products for Human Use. Once the compassionate use has been authorised, the specific drug will only be administered to the individual patient and used to treat the disease approved for. Now, however, there will be certain cases where access to the drug will be allowed for compassionate use without prior individual authorisation.

Without any doubt, the Spanish legislation in this area is now more advanced than, for example, the Italian one. The D.M. May 8th, 2003²¹, regulates compassionate use in Italy, addressing the legal regime of *«uso terapeutico di medicinale sottoposto a sperimentazione clinica»*. In that country, compassionate use will always require a prior individual authorisation, not contemplating the possibility of collective ones, as it happens in Spain.

C. THE PATIENT AS A MINOR PLAYER IN THE PROCESS

to benefit from the latest drug developments, even before passing all necessary administrative procedures for marketing, whenever there is scientific proof that supports its efficacy and safety for the indication for use that is requested. However, the compassionate use should be limited only to patients, for which clinical benefit can be obtained, not fulfilling the inclusion criteria of the clinical trial. It is not recommended to use this as an alternative to clinical trials, as the compassionate use is not a means for evaluating a drug, does not provide data on its effectiveness». See OLALLA, R. & TERCERO, M. J.: «Uso compasivo de medicamentos...», *op. cit.*, p. 97.

¹⁹ See NÚÑEZ LOZANO, C.: «Régimen jurídico del uso compasivo de los medicamentos», *op. cit.*; specially, p. 333.

²⁰ In Extremadura, the Compassionate Use Committee deals with this approval, regulated in Order of February 13th 2006, as a collegiate body, attached to the Directorate General of Health Care of the Health Service of Extremadura. In the case of granting its assent, the Directorate General of Health Service of Extremadura will transfer the proceedings to the AEMPS, which will authorise the use of drugs under the conditions for compassionate use. The Commission must verify the existence of informed consent, as well as study the clinical report in which the doctor justifies the need for treatment, granting or denying such approval for compassionate use of the drug in question.

²¹ GU n. 173, July 28th, 2003. In relation to article 25 of D. Lgs. n. 178, May 29th, 1991, *Norme di recepimento delle direttive della comunità economica europea in materia di specialità di medicinali per uso umano*, D.L. n. 536, October 21st, 1996, *Misure per il contenimento della spesa farmaceutica e la rideterminazione del tetto di spesa per l'anno 1996* (transformed into Law by art. 1 Law n. 648, December 23rd, 1996), D.L. n. 23, February 17th, 1998, *Disposizioni urgenti in materia di sperimentazioni cliniche in campo oncologico e altre misure in materia sanitaria* (transformed into Law with modifications by art. 1.1 Law n. 94, April 8th, 1998); D.M. February 11th, 1997, *Modalità di importazione di specialità medicinali registrate all'estero*, and D.M. March 18th, 1998, *Modalità per l'esenzione dagli accertamenti sui medicinali utilizzati nelle sperimentazioni cliniche*. See SILANO, V. & SILANO, M.: *Medicinali di uso umano. II Edizione. Aspetti amministrativi, economici, legislativi, normativi e tecnici connessi alla sperimentazione, alla produzione, al commercio, ai prezzi e all'uso dei medicinali industriali e galenici e delle relative materie prime*, Tecniche Nuove, Milano, 2001, pp. 272 and 273.

The traditional regulation of compassionate use in Spain has pushed the role of the patient into the background, as we have previously said. Everything is subject to the doctor's opinion, which opens or closes the doors to compassionate use. Worse than this, although the doctor's opinion is "vital" in this procedure, there have not existed –nor exist today, until, perhaps, the future approval of "protocols" and "recommendations" of the AEMPS– clear evaluation parameters which would function as a reference in order to examine their performance when analyzing the feasibility of the treatment that the patient intends to benefit from²². Moreover, it is presumed that the patient has a lack of knowledge to declare about the subject, even when what is at stake is his/her own life. Thus, the doctor's refusal to meet the patient's request of compassionate use leaves the patient an only solution, which is to trek around other hospitals looking for another doctor –perhaps in private practice– who is willing to undertake the patient's request.

This is despite the fact that the patient consenting to the treatment is the one taking the risk²³, not the doctor who evaluates its viability. The doctor will be as liable for the above as for ordinary prescriptions. It is not required to sign any specific document to assume liability, nor have to address the potential risks of the treatment with a financial guarantee (such as an insurance policy, established for clinical trials). As a general rule, it will be enough for the doctor to practice according to *lex artis*. He/she does not take, therefore, greater responsibility than the one incurred when drugs are prescribed and used as usual. The doctor will be liable, however, when prescribing a drug for an indication not approved by our health authorities without being under the protection of a compassionate use (case *Iloprost*)²⁴.

Therefore, the fact that the only role that the patient has historically played in this process is, of course, giving informed consent to the treatment on the terms contemplated in the patient's autonomy regulation, is very striking. The Centre Director must also consent to the treatment. This

²² The author of these lines is unaware of any pronouncement in this regard from the Spanish Constitutional Court, nor in relation, due to obvious temporary reasons, to RDDMSE, nor to the previous rules contained in Royal Decree 223/2004, February 6th.

²³ See RECUERDA GIRELA, M. A.: «Dangerous Interpretations of the Precautionary Principle and the Foundational Values of European Union Food Law: Risk versus Risk», *Journal of Food Law & Policy*, vol. 4 (2008), pp. 1 to 43.

²⁴ In this case, a patient diagnosed with primary pulmonary hypertension died as a result of her doctor changing her treatment. The doctor replaced the *Flolan*, *postaciclina* medication, with intravenous *Iloprost*, *prostaglandin*, the use of intravenous *Iloprost* not being authorised in this disease, only approved by inhalation, as there was not enough clinical experience or doctrinal or scientific studies to substantiate its safety. Therefore, this patient was administered a drug that was not authorised for her disease. Moreover, on account of its vasodilator effect, it was damaging to the patient due to the congestive heart failure that she suffered. This treatment could only have been justified if the procedure for compassionate use of the former article 28 RD 223/2004 had been correctly followed.

The Court Juzgado de lo Contencioso n. 1 in Seville (Judgement of February 6th, 2006) understood, however, that a case for compassionate use could not be argued here. Firstly, because the change of medication was not seeking the absolute necessity of a cure, instead it was expecting an improvement in the quality of life of the patient and a development of scientific research in this field, and, secondly, because the authorisation of the Directorate General of Pharmacies was subsequent to the initiation of the treatment, and the patient's consent was provided when the drug had been already changed. See ABELLÁN, F. & SÁNCHEZ-CARO, J.: *Responsabilidad médica por la información del medicamento*, Comares, Granada, 2007, pp. 55 and 56.

does not mean that the compassionate use can only take place within a health facility with regard to hospitalized patients or those who depend on their treatment, but also the obligation to access these drugs through pharmacy services in health centres. Although the regulation does not clarify what evidence is to be considered by the Centre Director in order to provide compliance or not, NÚÑEZ LOZANO supports the idea that «what is expected from the Director is a control of the rational use of the drug, this is, a decision valuing the cost that the drug prescription may entail, on the basis of the effectiveness expected from the treatment», a positive assessment of the economic aspect²⁵. Do not let yourself be deceived: this is the great "Trojan horse" from which all objections that are made regarding to compassionate use derive.

After this, the AEMPS always intervene, being competent to approve or refuse the compassionate use for each case. This is a new step in this obstacle race against the clock, fighting against administrative bureaucracy; at stake, a person's life. To this mentioned author (and time has proved her right) it was a mistake that the AEMPS had to deal with evaluating, case by case, the benefit/risk connection of a given treatment; and, further, that the access to compassionate use had to be subject to the existing scientific evidence, refusing to subject patients to "unnecessary" risks²⁶. Here we can deal with some logical bioethical issues that may emerge in some tragic choices, as the one of the recent judgment of Tribunal Supremo –Sala Tercera de lo Contencioso-Administrativo– 7th July 2009²⁷.

It is contradictory to base this relationship on the denial of authorisation, as the prevailing approach in order to undertake the decision cannot be other than the patient's will, who wants healing, who wants the improvement of quality of life and, in many cases, just to live. Unless the AEMPS has available data supporting the uselessness of compassionate use (in connection with the provisions of article 3.4 RD 223/2004 with regard to clinical trials: «*In order to ensure optimal protection of the health and rights of individuals, obsolete or repetitive research may not be conducted*»), it should not be refused on the basis of possible existing risks to the patient.

²⁵ See NÚÑEZ LOZANO, C.: «Régimen jurídico del uso compasivo de los medicamentos», *op. cit.*, pp. 327 *et seq.*, *passim*; specially, p. 337.

²⁶ Written reply of the Ministry of Health to a parliamentary question based on the therapy against cancer suggested by Dr. Brú (BOCG, Chamber of Deputies, Serie D, n. 371 of April 17th, 2006, p. 261). The Government refused to accept the compassionate use in this case, arguing that there was no data that would justify the extensive use of this treatment proposed by the physicist-mathematician, not considering «appropriate to subject patients to risks from the use of drugs, of which there is no evidence to suggest a potential efficacy».

²⁷ In the application of thrombolytic therapy, consisting of installation of a pharmaceutical agent in order to dissolve the existing clot or thrombus inside the artery, the Court recognises that this therapy is not exempt from complications, mainly bleeding, being the worse cerebral haemorrhage. For this reason, the Court understood that: «it cannot be said that [...] it was possible to apply the abovementioned therapy, or that the same could have prevented or lessened the effects (suffered by the patient), given the nature and complications presented by the application of the therapy [...] due to the risk and special characteristics of the therapy (intraarterial thrombolysis), the family would have to be informed as of a "heroic" treatment [...]».

The patient has already considered and accepted these, giving his/her informed consent and, therefore, the treatment can be interrupted or ceased only by the patient's own will.²⁸ The refusal of authorisation cannot be based on the absence of scientific certainty, as, not in vain, it is on precisely this uncertainty that the factual element of the regime is founded²⁹. Unfortunately, as we shall see below, not now (with both RDDMSE and LGURMPS regulations) nor during our recent past (with RD 223/2004), the legal system of compassionate use has established the substantive parameters on which doctors and AEMPS take their decisions; nor has been regulated the proceedings in view of the suspension, revocation or modification of any authorisations issued in this field.

D. RDDMS GESTATION. BACKGROUND TO THE ANDALUSIAN REGIONAL MINISTRY OF HEALTH RESOLUTION, FEBRUARY 2008

The slowness of a process fraught with red tape –mostly unknown to health professionals- and the Centre Directors' reluctance to give their approval to these treatments (not wanting to pay the high costs that these directly generate in their budgets) are just some of the main problems that historically the patients who wanted access to this medication in the specific situations outlined above had to deal with³⁰. A few years ago, and in order to address these and other identified problems, the Government raised a reform of the legal framework of compassionate use. In the struggle for this reform, associations of patients affected by rare diseases (BARRANCO³¹) integrating into FEDER spoke on several occasions³².

Consequently, it is in the area of rare diseases where there is a greater number of applications for compassionate use. Most of these requests are for drugs used in cancer diseases, or neurological, ophthalmologist and dermatological cases. In Spain, the access to these drugs in specific situations, in year 2008, according to the Ministry of Health, lead to the processing of 60,000 applications before the

²⁸ See NÚÑEZ LOZANO, C.: «Régimen jurídico del uso compasivo de los medicamentos», *op. cit.*, pp. 327 *et seq.*, *passim*; specially, p. 343.

²⁹ For the journalist A. MURO, we can see the absurdity of protecting forests, animals or coastlines with more eagerness than human beings. Not surprisingly, the Rio Declaration of year 1992 states that «*When the threat of serious or irreversible damage exists, the lack of definitive scientific evidence should not be used to justify measures directed to prevent environmental degradation and to protect ecosystems*». In this sense, MURO wonders: «Is there further environmental degradation for a human being than to helplessly contemplate how cancer is going to consume his health? Is there any other ecosystem to be protected by our administrators understood more delicate than human life?». See MURO, A.: «Caso Bio-Bac: el principio de precaución y el uso compasivo», *Dsalud*, on line at: http://www.dsalud.com/numero47_3.htm

³⁰ Conclusions drawn by Dr. MONTERO COROMINAS, Coordinator of Compassionate Medicinal products Area for the AEMPS, within the framework of the *V Conference on Rare Diseases of Andalusia*, Granada, November 14th and 15th, 2008.

³¹ See BARRANCO VELA, R.: «El estatuto jurídico de los medicamentos huérfanos en la Unión Europea: el derecho a la salud de los pacientes con enfermedades raras», in *El acceso al medicamento. Retos jurídicos actuales, intervención pública y su vinculación al derecho a la salud* (dir. R. BARRANCO VELA; coord. F. M. BOMBILLAR SÁENZ), Comares, Granada, 2009.

³² The Spanish Federation for Rare Diseases (FEDER), established in Seville in year 1999, brings together more than 170 associations and non-profit organizations that deal, in Spain, with the care of diseases of low incidence. Website: <http://www.enfermedadesraras.org>

AEMPS (50% related to foreign drugs, 35% related to drugs in conditions other than those stated in its data sheet and 15% related to drugs in research).

After the LGURMPS come into effect, the Government proceeded to repeal (via RD1345/2007) the regulatory source that previously dealt with this issue: article 28³³ of the mentioned RD223/2004, regarding clinical trials³⁴. This allowed the Government to continue with a new regulation for compassionate use, adapted to the demands of society, aiming for a reduction in waiting times for patients. In order to achieve this significant goal, considered the Decree’s guiding cross, a “temporary authorisation for use” has been created and the administrative procedures so far available have been speeded up. Specifically, we must mention the unification of applications and the use of new information technologies, establishing telematic procedures.

The momentary and apparent regulatory gap that occurred between the repeal of the regulation and the approval of the new Decree 1015/2009, was seized with striking precipitation by the Andalusian Administration, approving a Resolution in February of 2008³⁵ (clearly invading the exclusive area of competence reserved for the Spanish Government according to article 149.1.16° Spanish Constitution: legislation on drug products³⁶) regulating the administrative procedure to be followed by the Andalusian Health Service staff in order to use a drug under conditions other than those specified in its data sheet;

³³ Article 28 of Royal Decree 223/2004 of February 6th, defines compassionate use as *«the use in individual patients and outside a clinical trial, of investigational drugs, including medicinal products for indications other than those authorised, when the doctor on his own responsibility considers its use essential»* (Section one), requiring for this *«informed consent from the patient or his legal representative, a clinical report in which the doctor justifies the need for such treatment, the compliance of the director of the centre where the treatment is to be implemented, and the approval of the Spanish Agency for Medicines and Health Products»* (Section two), adding that *«the doctor will inform the Spanish Agency for Medicines and Health Products about the treatment’s results, as well as any suspected adverse reactions which may be due to it»* (Section three).

³⁴ Previously, this issue had been addressed in article 23 of Royal Decree 561/1993 of April 16th, which laid down the requirements for conducting clinical trials with drugs, in force until May 1st, 2004. article 23 stated, as would occur later, that: *«The use of a drug under compassionate use conditions will require written informed consent from the patient or his legal representative, a clinical report in which the doctor justifies the need of such treatment, the agreement of the Director of the centre where it is to be implemented, and the approval of the Department of Pharmacy and Health Products for each particular case»*.

³⁵ Resolution of the Ministry of Health of Andalusia (*Consejería de Salud de Andalucía*), February 21st, 2008, on Harmonisation of criteria for use of drugs in the Andalusian Health Service (SAS). See SUÁREZ, J.: «Resolución del Servicio Andaluz de Salud y uso compasivo», *Cuadernos de Derecho Farmacéutico*, n. 25 (2008), pp. 6-12. Also in Andalusia, we should bear in mind the mentioned prohibition of the drug *aprepitant* as antitumor in the footnote n. 17.

³⁶ In observance to Community guidelines, the Spanish Government has exclusive power of legislation on pharmaceutical products, allowing the establishment of «plans of drugs as “substances” whose manufacture and marketing is under [...] the control of public authorities, in order to guarantee the rights of patients and users who use them» (see SSTC 98/2004, of May 25th, FJ 5, and 152/2003 of July 17th, FJ 7). Together with mentioned art. 149.1.16° CE, the Spanish Government also asserts here other evidence of exclusive jurisdiction stated in our Constitution: basis and general coordination of health (art. 149.1.1 and 16 CE), economic regulation of Social Security (art. 149.1 17 CE), Procedure law (art. 149.1.6 CE), General Taxation (art. 149.1.14 CE) or industrial property (art. 149.1.9 CE). See GARRIDO CUENCA, N. M.: «Sanidad, salud y farmacia», in *Reformas estatutarias y distribución de competencias* [F. BALAGUER CALLEJÓN (dir.); L. ORTEGA ÁLVAREZ, G. CÁMARA VILLAR & J. A. MONTILLA MARTOS (coords.)], Instituto Andaluz de Administración Pública, Sevilla, 2007, pp. 549 *et seq.*; and VIDA FERNÁNDEZ, J.: «La redistribución de competencias entre el Estado y las Comunidades Autónomas en materia de medicamentos», *Revista Española de Derecho Administrativo*, n. 117 (2003), pp. 67 *et seq.*

in clear disagreement with the objective criteria on the matter at a Community and National level, without observing the exceptionality³⁷ quality or the protective rules of our legal system.

In particular, a request for authorisation would be submitted to the SAS General Secretary. This management centre would make the final decision after advisement from a committee set up for this purpose, consisting primarily of medical specialists that belong to the SAS. This administrative body manifestly incompetent, as the Law 22/2007 of Pharmacy in Andalusia³⁸, as it could not be otherwise, did not give any powers to the mentioned Regional Ministry to perform this task. The Autonomous Communities have competence in the area of pharmacy, not in the world of medicine³⁹. This administrative Ministry could not authorise the use of drugs under conditions other than those approved. No medication can be made available to the public without the authorisation of the relevant health authorities of the Member States (in Spain, the AEMPS) or, at a European Community level, the European Commission, following the scientific opinion of the European Medicines Agency (EMA), in compliance with the established procedures.

Apart from the relevant patient's informed consent, this Order –nowadays repealed- stated that, in order to request authorisation from the Ministry of Health of Andalusia, the doctors would issue, without any other requirements, a report which would specify the reason for the request and would support, with bibliographical documentation, the drug's usefulness⁴⁰, along with the proposal to this effect of the Multidisciplinary Committee for the Rational Use of Drugs of the referred Hospital⁴¹. It

³⁷ Moreover, if we take into account the fact that this Resolution was focused on medicines registered in the past five years – more innovative and, therefore, more expensive from the perspective of its funding- it was said by some professionals of this field that we might find ourselves before a unique use of this mechanism due to purely economic criteria. See SUÁREZ, J.: «Resolución del Servicio Andaluz de Salud y uso compasivo», *op. cit.*, p. 9.

³⁸ Law 22/2007 of December 18th, of Pharmacy in Andalusia, regulates the planning and management of pharmaceutical services in this Community, trying to ensure quality access to the drug and greater transparency in the allocation of the pharmaceutical offices. The rule includes a policy of rational use of the drug that has been carried out in Andalusia for many years, such as prescription by active principle, and reinforces the role of the pharmacist as a health agent. See GÁLVEZ PÉREZ, J.F.: «El futuro de la ordenación farmacéutica en Andalucía», *Revista Andaluza de Administración Pública*, n. extra 2 (2003), pp. 495-534.

³⁹ In Spain, the Autonomous Communities have competence to develop and implement health issues, meeting general basis and coordination in this regard established by the Spanish Government, but it is the Spanish Government, as noted, who is exclusively responsible of the configuration and development of those measures addressed to ensure the security and safety of drugs, being the CCAA competent to implement. The State Government has taken into consideration the demands of the principle *market unity*, stated in article 139.2 of the Constitution: well above the territorial scope of an autonomous community of the phenomenon under competition, the Spanish Government has argued that public activity exerted on it is not susceptible of division, requiring an amount of homogeneity that can only be ensured through the assignment of executive powers to a single authority, the Spanish Government itself (STC 243/1994 of July 21st, FJ 6). On the other hand no one misses, as evidenced by DOMÉNECH, that leaving to the Autonomous Communities the decision to grant or deny a permit could cause an irrational fragmentation of the market, raising the costs supported by pharmaceutical companies. See DOMÉNECH PASCUAL, G.: *Régimen jurídico de la farmacovigilancia*, *op. cit.*, *passim*, specially, pp. 125 to 130.

⁴⁰ It is worth recalling that, if a doctor, outside both a clinical trial and the established legal procedure, prescribes a drug for a different indication (based, for instance, on scientific publications), the potential adverse effects that might occur to the patient will have no legal coverage and, therefore, the doctor himself will be responsible for these.

⁴¹ Each of these Committees, based on scientific evidence criteria, evaluates the efficacy, safety and efficiency of new drugs, in comparison with the available therapeutic alternatives, deciding whether the drug is included or not in the Hospital's Pharmaceutical Guide in question and, if so, under which use conditions. About the economic evaluation of drugs, should bear in mind the important role, in the United Kingdom, of the NICE (National Institute for Health and Clinical Excellence), The recommendations of this independent organisation, can help the NHS to save millions of pounds, whilst

was enough if the doctor understood necessary off-label uses of the drug, in the event that the drug's usefulness was justified. Therefore, other objective conditions related to the patient's situation and especially the fact of not having any other drugs approved for the treatment of disease were dispensed. In any case, the Andalusian Regional Government led the way and, shortly after, the Spanish Government would follow, adopting the RDDMSE in year 2009.

In this sense, the Director of any SAS hospital was able to directly authorise a request similar to another one which the Government had already provided a positive response, whenever the clinical circumstances described in both cases would meet; extending, thus, automatically the SAS authorisation of other “similar” situations, without the supervision of an independent administrative entity. As stated above, the RDDMSE does not include the need for an application and authorisation individualized for each patient. Access to drugs in research or that are unauthorised in Spain may be managed through a *temporary authorisation* issued by the AEMPS, in coordination with other European agencies, for a group of patients.

Related to this issue, we must mention that the request of some Autonomous Regions, such as Madrid, to participate in the decision of authorising these drugs, was left out of the oral hearing stage. They had a strong interest in participating in such proceedings, due to the drug being a very high cost product, and they would then have to pay through the integrated hospitals in their Health Services. For them, the application of such a rule was especially concerning in a period of economic recession, taking into consideration the pharmaceutical spending bill growing exponentially year after year⁴². An economic impact that we cannot rule out, although what it stands for is precisely the rationalisation of these types of procedures –which, in any case, would be justified by the fact that these procedures seek only to reach patients with seriously debilitating or life threatening diseases, possibly meaning their salvation.

maintaining or improving the quality of care. See: <http://www.nice.org.uk/> and the report written by J. ESPÍN & J. ROVIRA: «Analysis of differences and commonalities in pricing and reimbursement systems in Europe», EASP Final Report, June 2007.

⁴² In order to avoid the "discrepancies" produced in recent years among the various doctors within the Andalusian Public Health System when prescribing drugs having a special health, social and, of course, economic impact, Resolution of the Andalusian Health, August 7th, 2009, entrusts the SAS Head Management, at the new Advisory Commission's proposal for harmonisation of standards for the use of such drugs, and in view of reports of the Andalusian Sanitary Technologies Evaluation Agency, to decide, based on these criteria, which drugs will be included in the Hospital's Pharmaceutical Guide in the SAS organisation. Moreover, a unified procedure for prior authorisation for prescribing and dispensing drugs with prescriptions subjected to control is established. It is used when, exceptionally, due to lack of therapeutic alternatives, it is necessary to conduct an off-label use of these drugs. Such authorisation may be requested only by doctors assigned to a hospital. This will be accompanied by a doctor's report stating the non existence of alternative therapies, as well as providing scientific documentation. This will be referred to the relevant Branch, who will seek, from the Advisory Commission, a report harmonising the criteria for use of drugs in different conditions to those stated in its data sheet, containing the proposed terms of use in order to grant permission or the reasons for its refusal. The above without losing sight of the recommendations issued by the AEMPS in this regard. In case of disagreement among the members of this Commission, the procedure for high-impact medication will be attended. In this case, provided that the application is invoked the circumstances of urgency of treatment, SAS Branch may propose to the Head Management to issue an interim decision applicable only to the individual case concerned. In other cases that do not have such complications, the head Management will make a decision, extended to all patients who attend the same circumstances.

E. A NEW REGULATION FOR AUTHORISATIONS

The AEMPS may allow the compassionate drugs used for investigational drugs. For this purpose, there are two available procedures: individual access authorisation and temporary use permits. It is no longer necessary, as it was before, the express permission of the AEMPS for each case. Patients who meet the requirements set out in the corresponding protocol, approved by the AEMPS, shall have access to compassionate use without resorting to an individual authorisation issued by the mentioned authority.

In the first case, referred to in article 8 RDDMSE, the hospital in question will submit a request to the AEMPS for access to investigational drugs on an individual basis⁴³, subject to approval by Centre Management. In its application, the Centre will enclose a clinical report issued by the corresponding doctor stating, on the one hand, the need for medication for that specific patient, including dosage and expected duration; on the other, the reason that justifies that the patient is not able to be treated by a drug that has already been approved in our country⁴⁴; also proof and data supporting its use in the patient; and, finally, the explanation of this why drug is not appropriate to be included in a clinical trial. Although the patient's consent (or his/her representative's) –previously informed of the drug's relevance, implications and risks of treatment– will be essential prior to the administration of the drug, this will not be part of the authorisation application before the AEMPS. This Spanish Agency will enable a formal system so as to facilitate access of the Autonomous Communities' Competent Authorities to the individual authorisations.

Second, we must pay special attention, as already pointed out, to the temporary authorisation to use investigational drugs outside a clinical trial⁴⁵ (article 9 RDDMSE). Such authorisations, considered a great innovation of the Decree 1015/2009, may be issued *«in cases of drugs that are at an advanced stage of clinical research designed to support a marketing authorisation, whenever it is planned to be used on a significant group of patients»*. The resolution, which will include the requirements and conditions under which the drug may be used out of clinical trial, will exonerate the centres from the need to apply for authorisation to individualised access for each patient.

In the European Union, the Regulation (EC) 726/2004⁴⁶ contemplates *–acquis communautaire* which is now embraced by our internal rules⁴⁷ – a query procedure before the Committee for Medicinal Products

⁴³ Obviously, prior to this fact, the sponsor of the clinical trial or the applicant for marketing authorisation must state their willingness to provide that product to the AEMPS (article 7.1, second paragraph, RDDMSE).

⁴⁴ In the case of patients with rare diseases, it is difficult to find an alternative treatment available. Therefore, it is among this group of diseases where the largest numbers of requests for compassionate use are submitted.

⁴⁵ The AEMPS will encourage and facilitate the inclusion of these patients in clinical trials, promoted in relation to investigational medicinal products for which the compassionate use was applied for.

⁴⁶ Regulation (EC) n. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

for Human Use (CHMV) in EMEA towards the development of protocols for use with the objective of ensuring equity in the access to compassionate use drugs⁴⁸. These protocols are called, by the RDDMSE, *temporary use permits*. These tools streamline administrative procedures, this being something to treasure in a field in which human lives are at stake.

The AEMPS will develop and give these temporary authorisations, and will amend, suspend or revoke them when new scientific evidence indicates so, for the sake of the patient’s safety and the proper use of the product. In order to do so, work teams will be formed, according to different pathologies, composed by physicians, pharmacists, pharmaceutical companies, research groups, scientific societies, patient associations and the AEMPS itself. They will set the criteria to be reflected in those protocols. Protocols or temporary use permits that which we believe will fit into the category of plurality or general administrative acts, as will be discussed later.

The AEMPS will also notify such temporary use authorisations to the EMEA⁴⁹ and report them, as well as the security problems detected in relation to them, to the competent authorities of the Autonomous Communities (Spain it is an extraordinarily decentralised country) and the clinical trial sponsor or the applicants for the marketing authorisation. The applicants will also be informed within 15 days from notification, of suspected serious adverse reactions. Obviously, the doctor should also notify the AEMPS immediately of the severe reactions suspected according to his knowledge, as well as any other information related to the requested treatment. The sponsor of clinical trials or the applicant for marketing authorisation will cooperate with the AEMPS, in order to lay down the requirements of its use, and will notify the AEMPS at once of any significant information in relation to product’s safety. Each and every one of these agents is involved in the activity of pharmacovigilance, having the obligation to continuously provide the best possible information on drug safety.

⁴⁷ As in the 33rd initial consideration it has been said: *«In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions. In the field of medicinal products for human use, a common approach should also be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislations».*

⁴⁸ Article 83.2 Regulation (EC) 726/2004 provides the following definition of compassionate use *«to give, for compassionate reasons, a drug belonging to the categories mentioned in paragraphs 1 and 2 of Article 3, to a group of patients suffering from chronic or serious debilitating illnesses, or considered to be life threatening and cannot be satisfactorily treated by an authorised drug. This drug should be subject to an application for marketing authorisation pursuant to Article 6, or to clinical trials».* The drugs in question should be those subject to a centralized procedure (orphans, biotechnology, paediatric...), along with others which contain a new active substance not authorised in the Community on the date the regulation coming into force, those which constitute a significant innovation from a therapeutic, scientific or technical point of view, and those whose consent would present a concern for patients at a community level.

⁴⁹ Art. 83 Regulation (EC) 726/2004 states that, when a Member State grants an authorisation for compassionate use, the Agency shall be notified. The Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on conditions of use, distribution conditions and the patient’s necessity of the above. These opinions will be updated regularly, published on the website of the Agency, and will be taken into consideration by Member States. In any case, these opinions will not affect the civil or criminal liability of the manufacturer or the applicant for marketing authorisation.

Concerning the Hospital Management, after approving the implementation of such authorisation in its centre it will ensure, that the patients who are proposed to use these drugs meet the conditions set out in temporary permits, and that they have given their written informed consent to the medicine administration.

The Use Of Drugs In Different Conditions To The Approved

The RDDMSE also raises the problem of access to drugs used in conditions other than those authorised in Spain and included in its data sheet⁵⁰. The RDDMSE states a separate authorisation procedure for such cases, differing from the established procedure for compassionate use. This particular situation occurs when there is clinical data on a particular therapeutic use, but it does not appear on the drug's data sheet (or on the product's characteristics summary). This sometimes happens in therapeutic areas in which research activity is very intense –not allowing the existing scientific knowledge at a given time to incorporate such uses in the data sheet– on drugs that are used with a specific population (such as paediatrics), as well as on “classic” drugs, that can have established conditions of its use in clinical practice, but not mentioned in the authorisation, as it is not economically viable to undertake the necessary studies to obtain its approval.

The RDDMSE leaves no doubt: this is an exceptional use of the drug, limited to those situations in which there are no authorised therapeutic alternatives. It is framed within a clinical practice area and subjected to a special procedure before the AEMPS, differing from the corresponding procedure for compassionate use. This new procedure focuses liability on doctors⁵¹. These must justify the need for using drugs in different conditions from those provided in the data sheet, and properly inform the patient of all the details related to this practice, obtaining the patient's consent after explaining risks and benefits of this use. A different question would be the patient having to know how to act against doctors who do not approve the access to medication in different conditions than those stated in the data sheet, if these are protected by *lex artis*. This question is left unanswered by the RDDMSE.

Although the new legislation eliminates the need to obtain an individual permit from the AEMPS, it keeps its ability to issue such use recommendations as it deems appropriate in the following cases listed in article 13 RDDMSE, namely: when a health risk due to a drug used in conditions other than those

⁵⁰ For instance, the use of antidepressants to treat obesity problems. See OLALLA, R. & TERCERO, M. J.: «Uso compasivo de medicamentos...», *op. cit.*, p. 95.

⁵¹ The prescription is a document that ensures the establishment of a treatment with drugs under the instructions of a doctor, a dental surgeon or a chiropodist. Now, after the reform of article 77 LGURMPS on December 2009, nurses can also to prescribe certain drugs, through a dispensing order from the hospital.

authorised can be reasonably foreseen, in the case of drugs subject to restricted medical prescription⁵², or finally when the use of a drug in such conditions «entails a significant health care impact», meaning, substantially increases public pharmaceutical expenditure⁵³ (i.e. the Judgment of Tribunal Superior de Justicia of Madrid, Sala de lo Contencioso Administrativo, n. 1810/2009, September 30th, 2009⁵⁴). These recommendations are to be considered by health care facilities when developing the appropriate treatment protocols replacing individual permits. The AEMPS will share this information with the competent authorities of the Autonomous Communities.

These recommendations for use prepared by the AEMPS will be revised, depending on the efficacy and safety data available. The AEMPS may request information not only from the authorisation holder – who will be informed of these recommendations as well as notified of the suspected adverse reactions – but will also have its own group of experts. The holder of the marketing authorisation is obliged to notify, in turn, the possible adverse reactions of his knowledge, not to advertise⁵⁵ the use of the drug in different conditions to those approved, and to provide the AEMPS with all the information concerning the product in question that could affect it. The treating doctor will also notify the AEMPS of the adverse reactions he suspects according to his knowledge, and also inform the patient, in a comprehensive way, of the treatment, of its implications and of its risks.

Use Of Foreign Drugs

In relation to foreign drugs, the regulation updates the procedure towards its acquisition, allowing patients to access to them through an individual application in accordance with a protocol supported by the AEMPS, provided that these drugs have been legally authorised in other countries and are essential to the prevention, diagnosis or treatment of specific diseases, there being, in our country, no other

⁵² The drugs subject to treatments that can only be followed in the hospital (due to their pharmacological properties, novelty or reasons of public health); those used for the treatment of diseases which must be diagnosed in a hospital or an other appropriate centre, although the administration and monitoring can be carried out outside this centre; and those intended for outpatients, whose action can produce very serious adverse reactions, shall be subject to the subcategory of medicinal products reserved to restricted prescription, requiring such documents as issued by a specialist and a specific monitoring during the treatment. In the Spanish legal system, Title II, Chapter II, LGURMPS, the Order of May 13th, 1985, on medicinal products under special medical supervision in its prescription and use, or the Royal Decree 618/2007 of May 11th, which regulates the procedure for the establishment, by a specific permission (*visado*), of a unique procedure for prescribing and dispensing drugs.

⁵³ The resources that the States have are limited, being the right to health shaped by *economic considerations*. The State must not only preserve the health of the citizens, but also of public funds, which must face many other needs of its population. Although limited to the Italian context, a particular referenced work on this issue is the doctrinal article developed by Profs. CASSESE, S.; PARDOLESI, R. & CARAVITA DI TORITO, B.: «La disciplina dei prezzi dei farmaci», *Il Foro amministrativo T.A.R.*, 2003, pp. 3117 *et seq.*

⁵⁴ In this judgment the Court understood that a patient had no right to receive the medical assistance consisting of infiltration of BOTOX, in order to treat chronic headache and cervical dystonia, under ASISA insurance company, together with ISFAS (Social Institute of Armed Forces), as such treatment had not taken place in a hospital stay regime.

⁵⁵ See DE LA QUADRA SALCEDO, T.: «La regulación de la publicidad de los medicamentos de uso humano», in *Derecho de la sanidad y los medicamentos: seis estudios*, Ministerio de Sanidad y Consumo, Madrid, 1999, pp. 15 to 61; or SUÑÉ ARBUSSÁ, J. M. y BEL PRIETO, E.: «El Real Decreto 1416/1994, por el que se regula la publicidad de los medicamentos de uso humano», *Cuadernos de Derecho Europeo Farmacéutico*, n. 3 (1996), pp. 57-91.

suitable alternative approved for this indication, or in a situation of shortages. Logically, we will only be in the presence of this alleged case when the definition of compassionate use of investigational drugs is not being observed.

Given the above, two requirements are, therefore, included in the RDMSE in order to allow, in exceptional circumstances, access to unapproved drugs in Spain: that there is no other drug with the same composition already authorised in our country –or being so, it must be in a pharmaceutical form that does not allow the patient's treatment– or, second, that there is no other licensed drug in our country as an alternative to it. As in the field of compassionate use, here there are also two established procedures for authorising public access to such drugs: individual access and collective access through a protocol of use.

As for individual access, the corresponding request will be submitted to the AEMPS through the Health Ministries of the Autonomous Communities (or specific departments designated by them) or through the Hospital Management. The application must be attached to a medical prescription and a clinical report which justifies the need of such treatment, its duration and the number of containers required, as well as scientific data that can justify the use of such medication for the specific therapeutic indication when, exceptionally, it differs from that mentioned in the data sheet of the country of origin (also, and if required, the laboratory's consent will be attached) It will not be necessary to enclose the mentioned documents, if the AEMPS understands so, when the product in question is necessary in our country as a result of shortages of the alternative approved drug in Spain. The patient's informed consent will not be part of the application for authorisation, although it will be essential in order to administrate the drug.

Secondly, access to these drugs is provided through a protocol of use, which makes it unnecessary to request an individual permit. The AEMPS, via these protocols -which may be nominated by the competent authorities of the Autonomous Communities- will set the conditions for the use of a “foreign drug” when its need is foreseen for a significant subset of patients. The AEMPS will review these protocols when necessary, based on scientific data or new drug approvals of its knowledge, informing the owner of the drug. The AEMPS will also inform the competent authorities of the Autonomous Communities about these protocols –as individual licenses– in order to then spread the documents among the health centres located in their own region. According to these protocols of use, the ministries of health (or centres designated by them), or the management of health facilities will request the needed amount of drug from the AEMPS, provided that the patient in question complies with the protocol of use established by the AEMPS.

The treating doctor will prescribe the drug and draft a medical report justifying the need for the specific treatment, he will then notify the suspected adverse reactions of his knowledge informing the patient of all the details related to the treatment, in order to obtain his/her informed consent. At the same time he

will ensure that the patients meet the conditions required in the approved use protocols. As for the holder of the marketing authorisation, he is subject to a number of obligations, namely: he must provide the documentation requested by the AEMPS, he must notify all suspected adverse reactions to the AEMPS or confirm the availability of the drug and to ensure its supply. Given the exceptional nature of the procedure that we are addressing, the holder of the authorisation for the foreign drug has the obligation not to promote the use of the drug and ensure that it will be used solely and exclusively by the applicant institutions.

Along with the aforementioned unauthorised access to drugs in Spain and the drugs intended to be used in our country, referred to in article 4.24 LGURMPS and regulated in Chapter IV of RDDMSE, we must mention a special case in which, provided that there is a health emergency, the legal system includes an exception in terms of import and export of drugs. In this sense, article 24.5 LGURMPS, along with article 5 D2001/83⁵⁶ empowers the AEMPS to *«temporarily allow distribution of unauthorised drugs in response to the suspected or confirmed spread of a pathogen or a chemical toxin, or nuclear radiation capable of causing harm»*. Such a permit is temporary. During this period of time, lasting as long as the health emergency, the holder of the authorisation and health professionals are exempt from civil liability for the use of the referred drug or the unauthorised signs⁵⁷.

Administrative Simplification And Use Of Icts

The RDDMSE seeks that all requests under its coverage are submitted to the AEMPS, except in specific cases, such as telematic uses (GAMERO)⁵⁸, as provided in article 27.6 of Law 11/2007, June 22nd, regarding electronic access of citizens to Public Services⁵⁹, stating that *«the Civil Service may make it compulsory to communicate with them via electronic means only, when persons concerned are legal persons or groups of individuals who, due to economic or technical capacity, professional dedication or other accredited reasons, have guaranteed*

⁵⁶ Directive 2001/83/EC of the European Parliament and Council of November 6th 2001, which establishes a Community Code on Medicinal Products for Human Use; subject to several reforms up to the current date, one of the most important being that operated by Directive 2004/27/EC.

⁵⁷ See OLIVERA MASSÓ, P.: «Fabricación, distribución, importación y exportación de medicamentos en el marco de la Ley 29/2006, de garantías y uso racional de los medicamentos», *Noticias de la Unión Europea*, n. 288 (2009), pp. 33-45; specially, p. 45.

⁵⁸ In connection with telematic notifications, we must mention the work of GAMERO CASADO. Among others, the following monographs: *Los medios de notificación en el procedimiento administrativo común*, Instituto Andaluz de Administración Pública, 2001; y *Notificaciones telemáticas y otros medios de notificación administrativa en el procedimiento común*, Bosch, 2005.

⁵⁹ All this in connection with the guarantees of transparency stated in article 3 RDDMSE: the AEMPS *«will ensure access to its decisions and recommendations in this Royal Decree to health facilities, to the competent authorities of the autonomous communities, to the holder of the marketing authorisation of the drug or his representative, to the applicant of the marketing authorisation or the sponsor of the investigational product»*; and under the provisions of Organic Law 15/1999, of December 13th, on Protection of Personal Data; in Law 41/2002 of November 14th, regulating the patient's autonomy and rights and obligations regarding information and clinical documentation; and, of course, the Law 30/1992 of November 26th, on the Legal Regime of Public Administration and Common Administrative Procedure (LRJAP).

access and availability of precise technological means». The above is related to the *Plan for the Reduction of Administrative Burdens and Regulation Improvement*, i.e., administrative simplification work (CIERCO)⁶⁰.

Moreover, the transitory disposition of RDDMSE anticipates that, during the period of one year from coming into effect the mentioned regulation, it will be possible to submit the applications here given by any of the means listed in article 38.4 LRJAP⁶¹. However, after such period, the applications must be submitted by telematic means. In our opinion, the patient would not be helpless due to this new rule. The citizen himself is not who directly processes the compassionate use request to the AEMPS⁶². A hospital (a legal person to which it is guaranteed access and availability of precise technological means) will do so meaning that the application would not be here exempted under article 27.1 of Law 11/2007⁶³.

Under this new legal framework, it is expected that a telematic application will be installed in the AEMPS site, now running as a pilot project, allowing the hospital pharmacy teams send requests for compassionate use from their own terminals, leaving behind years of long and cumbersome administrative processes used under the previous regulation. Thus, it is expected that practitioners have more time to invest fully in the monitoring of patients and the safety of drugs. Not surprisingly, more than 60,000 applications processed through the AEMPS in year 2008 entailed between two hours and a month's work per request. Therefore, the Health Ministry and the AEMPS have a special interest in the RDDMSE beginning to deploy its effects as soon as possible. In any case, until the summer of 2010, the AEMPS will continue processing requests via paper format.

⁶⁰ In compliance with First Additional Provision of Law 4/1999 of January 13th, amending Law 30/92, the Royal Decree 670/1999 of April 23rd was approved, creating the Interministerial Commission of Administrative Simplification. In this respect, the thoughts of César CIERCO, included in his articles, are very interesting: «Algunas reflexiones sobre la simplificación de los procedimientos administrativos a la luz de los avances de la Administración electrónica», *Revista General de Derecho Administrativo*, n. 19 (2008); «Simplificación administrativa y principio de precaución: ¿Objetivos incompatibles? (Reflexiones a propósito del asunto Monsanto, STJCE de 9 de septiembre de 2003)», *Revista española de derecho europeo*, n. 13 (2005), pp. 111-155; «La tramitación integrada de los procedimientos administrativos conexos», *Revista Vasca de Administración Pública*, n. 65, 1, 2003, pp. 11-50; or «La reducción de la carga de presentación de documentos ante la Administración Pública», *Revista Andaluza de Administración Pública*, n. 48 (2002), pp. 389-436.

⁶¹ Under this provision of the LRJAP, the requests directed by the citizens to the bodies of the Public Administration may be submitted: in the Registers of the Administrative centres where they are addressed, in the Registers of any Administrative centre belonging to the government (in the case of entities of the Local Government, only if they have signed the appropriate agreement), in post offices or diplomatic or consular offices of Spain abroad. Specific cooperation agreements signed between the different public administrations will establish intercommunication systems and coordination of registries to ensure their technological compatibility, as well as the data transmission of registration entries and requests.

⁶² See TEDESCO, M. R.: *L'integrazione europea e l'influenza delle nuove tecnologie sui diritti di partecipazione ai processi decisionali delle Istituzioni*, PhD thesis, defended at the Seconda Università degli Studi di Napoli, 2009.

⁶³ In the mentioned article, it is stated that: «The citizens may choose at any time how to communicate with the Administrations, by electronic means or not, except in those cases where a legal regulation establishes the use of a non-electronic means. The option to communicate by different means is not binding for the citizen, who may, at any time, may choose a mean other than the one initially appointed».

Challenge Of The Denial Of Approval

Due to the legal problems that this issue may raise, we want to highlight in its own chapter the procedures provided to challenge the denial of approval by the AEMPS of the procedures for access to drugs in special situations. The variety of cases in which the patient can request access to the drug in special situations –from those involving a deadly serious risk to the applicants (“situations of eviction”) to those which “only” affect certain conditions of the enjoyment of their lives– results in a broad *technical discretion*⁶⁴. Discretion meaning that, in the case of refusal by the Administration to accept such use, the patient will not have effective feedback mechanisms. In any case, to NÚÑEZ LOZANO, the criterion understood here should not be purely technical, it will be necessary to weigh the different interests at stake⁶⁵. To do otherwise would, once again, wrongly attribute compassionate use requirements that are characteristic of clinical trials.

The RDDMSE provides in articles 8 and 18, in both cases in paragraphs 3 and 4, the procedure to follow in order to challenge the authorisation of individual access to compassionate use of drugs to be authorised and of unauthorised drugs in Spain, respectively.

If the application does not meet the requirements stated in our existing legal regulation, in the opinion of the AEMPS, it will be required that the applicant corrects the deficiencies within 10 days. If this is not done correctly, it will be understood that the applicant will withdraw its application. Similarly, if the AEMPS considers that individual access to the drug in question cannot be allowed, the applicant will be informed and will have a period of 10 days for allegations and to provide the documentation deemed appropriate. The problem is that neither LGURMPS nor RDDMSE expressly establish the substantive parameters under which the AEMPS shall grant or refuse such approval.

The denial of approval is a final administrative act, that is capable of challenging the appropriate appeal for reversal (*recurso de reposición*) or judicial review (*recurso contencioso-administrativo*). The authorised person who has the right to bring forward the action is the patient, who is considered to be “the interested party” in the procedure, although he cannot initiate it, as the application is processed through the hospital. Even conceiving the authorisation as a singular administrative act, in this case the subjective element of the authorisation is the patient himself, as an authorised individual to use the drug in a

⁶⁴ Regarding legal authority and administrative discretion, SÁNCHEZ MORÓN, M.: *Derecho Administrativo. Parte General*, Tecnos, Madrid, 2008 (4th Edition), pp. 87-98; specially pp. 90 and 91. According to this author, this would be a case of technical discretion «when the legal system states in favour of managers, an area of their own decision to issue an argument based on purely technical assessments or characteristics of a professional knowledge». The decision has an objective basis, being able to contrast and, if necessary, withdraw, citing contradictory evidence or technical analysis to show the “error” of the Administration. See also IGARTUA SALAVERRIA, J.: *Discrecionalidad técnica, motivación y control jurisdiccional*, Civitas, Madrid, 1998.

⁶⁵ According to this author, this technical discretion «cannot ignore the interest of the patient; and the decision taken on the request for compassionate use must be sufficiently motivated, with appropriate consideration between what the current state of Science dictates the doctor, the potential profit that could be obtained by compassionate use and the risk that the patient –not the doctor- is willing to take». See NÚÑEZ LOZANO, C.: «Régimen jurídico del uso compasivo de los medicamentos», *op. cit.*, specially, p. 337.

special situation⁶⁶. Obviously, in such cases, the logical response would be to request a discretionary appeal and immediately ask for, as a precautionary measure, the suspension of the denial, which would mean precautionary receiving authorisation for the drug⁶⁷. This measure would have its full meaning, as the dismissal of the petition could have irreparable consequences for the patient's health or life.

But is there any way to challenge the decisions of temporary authorisation of use of investigational drugs, apart from a clinical trial, or protocols developed by the AEMPS stating the conditions for access to unapproved drugs in Spain? Moreover, what legal status do these “protocols” developed by the Administration have? There are many questions which the RDDMSE gives no answer to.

We understand that these protocols could be considered administrative acts, described by doctrine as plural or general (THOMA⁶⁸): those with a general subjective scope, presenting a plural or indefinite receiver (MARTÍN-RETORTILLO⁶⁹). This act relates Administration, hospitals and doctors –in short, the National Health System– and, of course, patients themselves who demand access to these drugs through compassionate use. Citizens that would be entitled to challenge such “protocols” –first, through an administrative appeal and then, if necessary, before the administrative courts– would be covered by their *legitimate interest* in this regard. A qualified interest, not just an objective interest in the enforcement of the law or a hypothetical interest, i.e., an interest resulting from an administrative action that leads to a particular subject (own, real, actual or potential).

Although these citizens will not be able to object to the protocol claiming an their own right, a subjective right of substantive nature, they may, however, claim that the decision of the Administration (the protocol) is taken by the competent authority, following the established procedure, without arbitrariness, meeting all requirements and conditions stated in the legal system. In order to do so, they have a reactional right to defend their interests and rights of participation in the procedure dealing with that decision (article 31.2 LJCA⁷⁰). The challenge will be precisely identifying and specifying the requirements and conditions on the basis of which these citizens could claim the annulment of the

⁶⁶ See LAGUNA DE PAZ, J. C.: *La autorización administrativa*, Civitas, Madrid, 2006, p. 196.

⁶⁷ Although this measure is rarely taken, we can find an exception to this rule in the Judgment of the Sala de lo Contencioso-Administrativo of Seville, TSJA, of October 19th, 2004.

⁶⁸ From a doctrinal point of view, the concept of “*allgemeine Verfügung*” was thought of by the German author THOMA, being the first to notice the existence of general orders, focused on a plurality of persons which were lacking legal status so they should be considered as administrative acts. Several examples can be mentioned: the determination of the date of an exam, the announcement of an official examination. See THOMA: *Der Polizeibefehl im Badischen Recht*, I, Tübingen, 1906, pp. 63 *et seq.*

⁶⁹ See GARCÍA DE ENTERRÍA, E.: «Recurso contencioso directo contra disposiciones reglamentarias y recurso previo de reposición», *RAP*, n. 29 (1959), pp. 161 *et seq.*; MARTÍN-RETORTILLO BAQUER, L.: «Actos administrativos generales y reglamentos», *Revista de administración pública*, n. 40 (1963), pp. 225-250; or LEGUINA, J.: «Legitimación, actos administrativos generales y reglamentos», *RAP*, n. 49 (1966), pp. 193-224.

⁷⁰ Law 29/1998 of July 13th, regulating the Administrative Procedure (in Spanish, *Jurisdicción Contencioso Administrativa*), its article 31.2, states that the claimant «*may claim the recognition of a particular legal situation and the adoption of appropriate measures for the full restoration of the same, including compensation for damages, when appropriate*».

decision taken in breach of law. It would be more difficult, given the field in which we are, to see compensation for “damages” suffered as a result of that action⁷¹.

These citizens could also act through groups of patients or persons affected by a particular disease, as our legal system also considers it worth protecting the *collective interests* –interests that do not affect, or at least not exclusively– a person individually, but a group or category of people (i.e., those affected by the *brittle bone* disease, grouped within the association AHUCE). This is a collective interest that goes beyond mere compliance with law. Thus, these kinds of associations are given the right of their holders to intervene in administrative proceedings (article 31 LRJAP), to be party in judicial proceedings (article 7.4 LOPJ) and, in short, to defend through these their rights as a collective.

Not much more can be said until we have knowledge of the effects that this Decree RDDMSE will have. In any case, it is a promising standard for the millions of patients who have been struggling for years against their own disease and against a procedure that is slow, cumbersome and bureaucratic in the extreme. An obstacle race against time to reach a drug that allows them to save or considerably improve their greatest asset: life. We hope for that.

⁷¹ See SÁNCHEZ MORÓN, M.: *Derecho Administrativo. Parte General*, Tecnos, Madrid, 2008 (4th Edition), pp. 87-98.

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