EXECUTIVE SUMMARY
OF THE REGULATORY IMPACT ANALYSIS REPORT OF THE DRAFT ROYAL DECREE ESTABLISHING THE CONDITIONS FOR THE PREPARATION AND DISPENSING OF STANDARDISED MAGISTRAL FORMULAS OF CANNABIS PREPARATIONS

Proposing Ministry/Body	Ministry of Health (Spanish Agency of Medicines and Medical Devices)	**Date 16/12/2024**
Title of the Regulation	Royal Decree establishing the conditions for the preparation and dispensing of standardised magistral formulas for cannabis preparations.	
Report Type	**Normal ¤ Abbreviated ☐**	
TIMELINESS OF THE PROPOSAL		
Subject	Cannabis is a plant substance that contains different pharmacological active ingredients, called cannabinoids, among which stand out—due to their well-known pharmacological activity—tetrahydrocannabinol (THC), which is the main psychoactive component, and cannabidiol (CBD), which is considered devoid of psychotropic effect. Scientific evidence has revealed a varying degree of benefit from cannabis and its extracts in some therapeutic indications. At present, the indications for which the greatest degree of evidence is available are spasticity due to multiple sclerosis, severe forms of refractory epilepsy, chemotherapy-induced nausea and vomiting, and chronic refractory pain. There are a number of authorised industrially manufactured medicinal products containing preparations obtained from cannabis for some of these indications, which have been authorised following a full assessment of their quality, safety and efficacy, including mandatory clinical trials. There are cases in which authorised treatments are not sufficiently effective, and in some cases, there is scientific evidence indicating that the administration of cannabis preparations may constitute an alternative for these patients. It is in any case necessary to ensure that the medicinal products used are of adequate quality, with a defined composition, manufactured and prepared in accordance with the appropriate technical standards.	

	This is the position expressed by the Sub-Committee for the purpose of analysing experiences in regulating cannabis for medicinal use, created at the request of the Committee on Health and Consumer Affairs of the Congress of Deputies, in its session of 13 May 2021, which calls for the adoption of the measures necessary to allow the availability of standardised cannabis preparations to respond to patients in authorised treatments that have not been effective. This Royal Decree is drafted taking into account the recommendations of the aforementioned Sub-Committee, to allow the availability of medicines containing standardised cannabis preparations, with proven quality and to be used for specific indications. In the cases in which there are no authorised industrially manufactured medicines, it is necessary to resort to the magistral formulation, the preparation of which must comply with the requirements contained in this Royal Decree.
Objectives pursed	Establish the conditions for the prescription, preparation, dispensing, and use of standardised magistral formulas of cannabis preparations. Define the standard preparation, which is the basis for the magistral formulas, establish the register for these preparations, the conditions to be met, and the information to be submitted for registration. Establish the guidelines to be followed in the manufacture of standardised cannabis extracts and standardised cannabis preparations. Establish the framework for the publication of the corresponding monographs in the National Formulary, which will be mandatory. Define the conditions for supervision and control measures applicable to cannabis and standardised cannabis preparations, depending on their status as narcotics or their content of psychotropic active substances.
Main alternatives considered	There are no non-regulatory alternatives to achieve the objectives pursued. The regulation seeks to establish the conditions for the prescription, preparation, and dispensing of magistral formulas, and to set additional requirements beyond those applicable to other magistral formulas, which must be set out in a normative text, which has not existed until now. No other alternatives have been considered, since the issues addressed by the drafted Royal Decree always require regulatory treatment.
CONTENT AND LEGAL ANALYSIS	
Type of Regulation	Royal Decree
Structure of the regulation	The draft Royal Decree consists of a preamble, ten articles, two additional provisions, three final provisions, and an annex.
	Report of the Technical General Secretariat of the Department (Article 26(5)

Reports received.	fourth paragraph of Law 50/1997 of 27 November 1997). Report of the Ministry of Agriculture, Fisheries and Food (Article 26(5) fourth paragraph of Law 50/1997 of 27 November 1997). Prior approval by the Ministry for Digital Transformation and the Civil Service (Article 26(5) fifth paragraph of Law 50/1997 of 27 November 1997). Report of the Ministry of Territorial Policy and the Democratic Memory on the compliance of the draft with the distribution of powers between the State and the Autonomous Communities (Article 26(5) sixth paragraph of Law 50/1997 of 27 November 1997). Report of the Office for Coordination and Regulatory Quality of the Prime Minister's office, Justice and Relations with Parliament (Article 26(9) of Law 50/1997 of 27 November 1997). Ministry of Social Rights, Consumer Affairs and the 2030 Agenda (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of Youth and Children (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of Economy, Trade and Enterprise (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of Industry and Tourism (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of the Interior (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of Finance (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of the Prime Minister's Office, Justice and Relations with Parliament (National Institute of Toxicology and Forensic Sciences) (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Ministry of Defence (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997). Report of the autonomous communities and the cities of Ceuta and Melilla. Spanish Council for Consumers and Users. Spanish Council on Drug Dependence and other Addictions. Notification to the European Commission pursuant to Directive (EU)

	2015/1535 of the European Parliament and of the Council of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services. Opinion of the Council of State (Articles 22(2) and 22(3) of Organic Law 3/1980 of 22 April 1980 on the Council of State).	
Prior public consultation procedures	The public consultation was carried out prior to the drafting of the text of this regulatory initiative, from 13 February 2024 to 4 March 2024, incorporating thereafter a succinct summary of the content of these contributions into this Regulatory Impact Analysis Report.	
Hearing and public information procedures	The public announcement process has been conducted via the Department's website from 30 September 2024 to 21 October 2024, targeting associations or organisations that group or represent individuals whose rights or legitimate interests are affected by the regulation and whose objectives are directly related to its purpose.	
IMPACT ANALYSIS		
COMPLIANCE WITH JURISDICTIONAL PRIORITY	The prevailing jurisdictional title is Article 149(1)(16) of the Spanish Constitution, which confers on the State exclusive competence in matters of legislation on pharmaceutical products.	
ECONOMIC AND BUDGETARY IMPACT	Overall effects on the economy.	No significant impact is expected. In Spain, there are already companies producing cannabis, as well as manufacturing extracts. Prescription and dispensing conditions do not suggest a substantial change in the activity of these companies.
	With regard to competition	☐The regulation has no significant impact on competition. ¤The regulation has positive impacts on competition. ☐The regulation has negative impacts on competition.
	With respect to administrative burdens	☐ It entails a reduction in administrative burdens. ¤ It generates new administrative burdens ☐ It does not affect the administrative burdens

	With respect to budgets, the regulation ¤ Affects State budgets ☐ Affects the budgets of other Territorial Administrations	☐ Involves an expense ¤ Involves income ☐ Involves neither income nor expense
GENDER IMPACT	The regulation has the following gender impact	Negative ☐ None ¤ Positive ☐
IMPACT ON CHILDREN AND ADOLESCENTS	The regulation does not have a specific impact on children and adolescents	
IMPACT ON THE FAMILY	The regulations have no significant impact on the family.	
IMPACT DUE TO CLIMATE CHANGE	The regulation has no impact due to climate change.	
OTHER IMPACTS CONSIDERED	The regulation has a positive impact on equal opportunities, non-discrimination and universal accessibility for persons with disabilities.	
EX-POST EVALUATION	Not considered necessary.	

REGULATORY IMPACT ANALYSIS REPORT
ON THE DRAFT

This report has been drawn up pursuant to the provisions of Royal Decree 931/2017 of 27 October 2017 regulating the Regulatory Impact Analysis Report.

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1. Economic impact.
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7. Other impacts.

VII. EX-POST EVALUATION

I. TIMELINESS OF THE PROPOSAL

1. Reasons.

Among the conclusions of the Sub-Committee's report to analyse experiences of regulating cannabis for medicinal use, which was created at the request of the Committee on Health and Consumer Affairs of the Congress of Deputies at its session of 13 May 2021, it is indicated that, despite the incomplete evidence, preparations derived from cannabis could be useful as a therapeutic option for some patients for whom the authorised medicines have not been effective. It was therefore urged to take the measures necessary to allow the availability of standardised cannabis preparations to respond to certain patients. The existence of standardised preparations, compared to other forms of presentation of cannabis, is an advantage in terms of dosage, stability and handling.

Cannabis is deemed a narcotic drug under international control treaties, signed by Spain and the other Member States of the European Union. This implies that their manufacture, export, import, distribution, trade, use, and possession should be limited to medical and scientific purposes, and any rules governing their use should take into account the specific requirements applicable to this category of substances. Cannabis contains a wide variety of components, including, for their well-known pharmacological activity, tetrahydrocannabinol (THC), which is the main psychoactive component, and cannabidiol (CBD), which is considered to have no psychotropic effect.

Scientific evidence has revealed a variable degree of benefit of cannabis and its extracts in some therapeutic indications, among which the treatment of spasticity due to multiple sclerosis, severe forms of refractory epilepsy, chemotherapy-induced nausea and vomiting, and the treatment of chronic refractory pain stand out for their greater evidence. For the first three indications, there are industrially manufactured medicinal products with cannabis extracts or cannabinoids, which have been authorised under the usual procedures applicable to industrially manufactured medicinal products, following the evaluation of studies proving their quality, safety, and efficacy in certain therapeutic indications, including the mandatory clinical trials. However, there are patients for whom the authorised medicines are not sufficiently effective, for whom cannabis, used as a magistral formula, may be an option to consider.

However, this requires assessing in which indications the evidence can be considered to support this use with a more favourable benefit/risk balance, establishing a list of indications in which this assessment is reflected and setting requirements for its prescription. In addition, given the great diversity of ways in which cannabis is presented and administered, it is necessary to regulate the quality of the extracts used, the conditions of their manufacture, the entities that can carry out the preparation and dispensing of the medicines, and the guidelines that must be complied with. Among the legally recognised types of medicinal products, magistral formulas are the most appropriate option, and it is necessary to establish specific requirements.

The use of standardised magistral formulas of cannabis preparations, registered with the Spanish Agency for Medicines and Medical Devices, ensures the quality of these formulas, their reproducibility, and homogeneity, allowing for a more predictable dosage and use. The National Formulary contains the standard magistral formulas. The inclusion of a monograph in the National Formulary addresses the need to standardise the development of these medicines and establish a series of uses and indications in which the standardised magistral formulas of cannabis preparations could be an alternative in the event that therapeutic options fail.

This draft Royal Decree establishes the conditions for the prescription, preparation, dispensing, and use of standardised magistral formulas of cannabis preparations. Likewise, it establishes a Register of standardised cannabis preparations used in the elaboration of these standard magistral formulas, in order to guarantee their quality.
In the preparation of this draft, the different normative regulations on the regulation of medical cannabis in countries of the European Union (France, the Netherlands, the Czech Republic, Croatia, Portugal, Italy, Germany…) and in third countries (Switzerland, Israel, the United Kingdom, Canada…) have been considered. The review has been carried out considering its scientific basis, based on evidence published in scientific literature, the available information on the functioning of the different systems

and their health effects, and the possibility its adaptation to the Spanish regulatory framework.

2. Objectives.

- Establish the conditions for the prescription, preparation, dispensing, and use of standardised magistral formulas of cannabis preparations.
- Define the standard preparation, which is the basis for the magistral formulas, establish the register for these preparations, the conditions to be met, and the information to be submitted for registration.
- Establish the guidelines to be followed in the manufacture of standardised cannabis extracts and standardised cannabis preparations.
- Establish the framework for the publication of the corresponding monographs in the National Formulary, which will be mandatory.
- Define the conditions for supervision and control measures applicable to cannabis and standardised cannabis preparations, depending on their status as narcotics or their content of psychotropic active substances.

3. Alternatives.

There are no non-regulatory alternatives to achieve the objectives pursued. The regulation seeks to establish the conditions for the prescription, preparation, and dispensing of magistral formulas, and to set additional requirements beyond those applicable to other magistral formulas, which must be set out in a normative text, which has not existed until now.

Article 8 of the consolidated text of the Law on guarantees and rational use of medicines and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July 2015, establishes the types of medicines legally recognised, as a closed list. Among these are industrially manufactured medicines and magistral formulas. Magistral formulas are the only means, among those established in the aforementioned consolidated text, that allow the access to medicines based on cannabis preparations to respond to patients in authorised treatments that have not been effective.

For industrially manufactured medicinal products, which have the required quality, safety and efficacy tests, there is a specific regulatory framework for their evaluation and authorisation.

No other alternatives have been considered, since the issues addressed by the drafted Royal Decree always require regulatory treatment.

4. Adherence to the principles of sound regulation.

Article 129 of Law 39/2015 of 1 October 2015 on the Common Administrative Procedure for Public Administrations, lays down the principles for sound regulation with which the exercise of legislative action and regulatory power must comply.

The draft Royal Decree complies with the principles of necessity and effectiveness, given that there is no regulation regarding standardised cannabis preparations.

With regard to compliance with the principle of proportionality, it should be noted that the draft Royal Decree establishes control measures proportional to the guarantees that this type of medicinal product must offer, in which the scientific evidence is limited and which are intended for patients who require pharmacotherapeutic monitoring.

This rule also guarantees the principle of legal certainty, as it is exercised in a manner consistent with the national and European Union legal order in force in the matter, as well as in a general manner.

Likewise, during the processing of this regulation, the principle of transparency is respected with regard to the followed procedure, by collecting the required reports and ensuring the active participation of the potential addressees of the regulation through the procedures of hearing and public consultation.

During the drafting of this standard, the study and assessment of unnecessary costs and repercussions that may arise from it have been carried out in order to comply with the principle of efficiency.

The draft Royal Decree creates the Register of standardised cannabis preparations, referring to the procedure for registration of an abbreviated medicinal product dossier. However, it does not introduce or establish additional or different procedures to those contemplated in Law 39/2015 of 1 October 2015.

5. Annual regulatory plan.

The draft Royal Decree is not included in the Annual Regulatory Plan, but its processing is justified, given the lack of specific regulations regarding the conditions for the preparation and dispensing of standardised magistral formulas of cannabis preparations.

II. Content

1. Structure.

The draft Royal Decree consists of a preamble, ten articles, a single additional provision, three final provisions, and an annex.

2. Content.

Article 1 sets out the subject matter and scope of the Royal Decree. Its purpose is to establish the conditions for the prescription, preparation, dispensing, and use of standardised magistral formulas of cannabis preparations, as well as to establish a register for these preparations, so as to guarantee their quality. This Article also states that authorised industrially manufactured medicinal products and investigational medicinal products based on cannabis, which will be governed by their respective specific regulations, and cannabinoids obtained by synthetic processes or from sources other than cannabis, are outside the scope of application.

Article 2 defines the following terms: standardised preparation of cannabis (a product that has a defined amount of THC and/or CBD, which contains one or more standardised cannabis extracts, and which has been registered by the Spanish Agency for Medicines and Medical Devices, for the purpose of being used in the preparation of a standardised magistral formula), cannabinoids (organic compounds present in cannabis and responsible for its main pharmacological effects), delta-9-tetrahydrocannabinol (THC) (cannabinoid component of cannabis, present in variable quantities, the main chemical responsible for its psychoactive effects and which has the legal status of a psychotropic, included in Schedule II of Annex 1 to RD 2829/1977), cannabidiol (CBD) (cannabinoid component of cannabis, present in variable quantities and responsible for different pharmacological effects), and standardised magistral formula (magistral formula included in the National Formulary, due to its frequent use and usefulness).

Article 3 sets out the conditions for the control of cannabis as a narcotic substance included in Schedule I annexed to the Single Convention on Narcotic Drugs of 1961, and of standardised preparations of cannabis with a THC content equal to or greater than 0.2 % by weight as psychotropic substances included in the annexed Schedule of Royal Decree 2829/1977 of 6 October 1977 regulating psychotropic medicinal substances and preparations, as well as the control and inspection of their manufacture, distribution, prescription and dispensing.

Article 4 establishes that the monograph to which the standardised magistral formulas of standardised cannabis preparations must conform will be published in the National

Formulary, and that it will also contain the legally recognised action and indications for these medicines for the purposes provided for in Article 42 of the consolidated text of the Law on guarantees and rational use of medicines and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July 2015.

Article 5 sets out the obligations of pharmaceutical laboratories manufacturing standardised cannabis preparations. Among these obligations is the requirement to carry out all manufacturing and/or control operations of these preparations in accordance with the good manufacturing practices of the European Union, to ensure compliance with the good manufacturing practices and good distribution practices by suppliers or manufacturers of starting materials used in the manufacture of the aforementioned preparations, and to document the supply chain of each starting material.

This Article also regulates the destination of standardised cannabis preparations, which will be solely for legally established hospital dispensary services, or for export.

In addition, in Paragraph 4, this Article establishes the obligation for pharmaceutical laboratories that manufacture preparations considered psychotropic to have the corresponding authorisation, according to Royal Decree 2829/1977 of 6 October 1977 which regulates psychotropic medicinal substances and preparations, and the supervision and inspection of their manufacture, distribution, prescription and dispensing, and, where appropriate, with the corresponding authorisation in accordance with the provisions of Law 17/1967 of 8 April 1967, of the United Nations.

Article 6 regulates the registration of standardised cannabis preparations, establishing the way in which the pharmaceutical laboratories responsible for the manufacture of these preparations must request registration in this registry, as well as the documentation and information that must accompany this application.

This Article lays down the time limits for the resolution of the registration procedure, the procedure for amending the conditions of the registration procedure, as well as the applicable fee.

Article 7 regulates the prescription of standardised magistral formulas of cannabis preparations, establishing the cases in which they may be prescribed, which would be in those cases where there are no authorised and marketed industrially manufactured medicines, or these do not meet the needs of a specific patient.

This Article also establishes that the prescription is limited to medical specialists who treat patients with the indications detailed in the corresponding monograph of the National Formulary, when the authorised drugs do not achieve satisfactory control of the

symptoms. Likewise, Article 7 indicates that the prescribing doctor must document in the medical record the justification for the treatment with these magistral formulas and inform the patient about the available clinical evidence, the expected benefits, and the possible risks. Additionally, the doctor must periodically evaluate the therapeutic usefulness and safety of the prescribed magistral formula and consider discontinuing the treatment if a sufficient clinical benefit is not obtained or if the benefit-risk ratio is unfavourable.

Article 8 states that the preparation of standardised magistral formulas of cannabis preparations will be limited to legally established hospital dispensary services that have the necessary means for their preparation in accordance with the requirements established in the National Formulary and in the standards of correct preparation and quality control that are established by regulation.

Article 9 regulates the dispensing of these magistral formulas by hospital dispensary services to both inpatients and outpatients, who, in collaboration with the medical team, will carry out a comprehensive follow-up of the patient.

In paragraph 2, it also states that the need to continue treatment must be evaluated, based on the clinical benefit obtained and the occurrence of adverse reactions.

Article 10 regulates drug safety monitoring, establishing the need for health professionals to report suspected adverse reactions to the aforementioned magistral formulas to the Autonomous Centre for Drug Safety Monitoring corresponding to their field of care.

The first additional provision establishes the maximum period after the entry into force of the Royal Decree for the publication in the National Formulary of the monographs of standardised magistral formulas to which these formulas must conform.

The second additional provision provides for the creation of the Register of standardised cannabis preparations for the preparation of magistral formulas typified by the Spanish Agency for Medicines and Medical Devices, as well as its maintenance.

The first final provision indicates the title of competence, and the second final provision the authorisation for the regulatory development under which this Royal Decree is issued, in particular for the development of the Register of standardised cannabis preparations, and for the amendment of the annex.

The third final provision establishes the entry into force of the provision.

The single annex contains the information to be sent to the Spanish Agency for Medicines and Medical Devices for the registration of standardised cannabis preparations. Specifically, the administrative information and the chemical and pharmaceutical information to be submitted by the applicants are collected.

3. Key developments.

The Royal Decree establishes the conditions for the prescription, preparation, dispensing, and use of standardised magistral formulas of standardised cannabis preparations; cannabis extracts that, until now, have only been part of authorised industrially manufactured medicinal products. These medicinal products are indicated for the treatment of spasticity due to multiple sclerosis and severe forms of refractory epilepsy.

Article 42 of the consolidated text of the Law on Guarantees and Rational Use of Medicines and Medical Devices establishes the requirements for magistral formulas, which include that substances with legally recognised action and indication in Spain be used in their preparation, in accordance with Article 44(1) and the guidelines of the National Formulary.

This Royal Decree establishes a regulatory framework with the conditions applicable to magistral formulas with cannabis extracts, which must be classified, comply with the published monograph, and be prepared from standardised cannabis preparations, previously evaluated and registered in the corresponding registry created for this purpose with the Spanish Agency for Medicines and Medical Devices. In addition, it lays down conditions regarding prescription, which must be limited to medical specialists in the fields corresponding to the indications contained in the monograph, and regarding its preparation and dispensing, exclusively in hospital dispensary services that allow pharmacotherapeutic monitoring in accordance with the indications.

III. Legal Analysis.

1. Legal basis and regulatory status.

Article 40 of General Health Law 14/1986 of 25 April 1986 provides that the General State Administration is to develop the regulation, authorisation and registration or approval, as appropriate, of medicinal products, as well as the regulation and authorisation of the activities of natural or legal persons engaged in manufacturing such products. By virtue of the above, it is considered that the regulatory status of the draft should be that of a Royal Decree, pursuant to the provisions of the aforementioned legal bases.

2. Consistency with the Spanish legal system.

This draft Royal Decree is consistent with Spanish law in that it is deemed to be in accordance with the provisions of Article 8 of the consolidated text of the Law on guarantees and rational use of medicines and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July 2015, establishing the types of medicines legally recognised, as a closed list. Among these are industrially manufactured medicines and magistral formulas.

Magistral formulas are the only means, among those established in the aforementioned consolidated text, that allow access to medicines based on cannabis preparations to respond to patients for whom the authorised treatments have not been effective.

For industrially manufactured medicinal products, which have the required quality, safety and efficacy tests, there is a specific regulatory framework for their evaluation and authorisation.

3. Consistency with European Union law.

The material scope addressed by this Royal Decree is not regulated by European Union law, although it complies with and does not contravene other European regulations.

4. Repeal of regulations.

This draft Royal Decree does not repeal any previous legislation.

5. Entry into force and effect.

This Royal Decree will enter into force on the day following its publication in the 'Official State Gazette'.

IV. Adaptation of the regulations to the distribution of powers.

1. Titles of competence: identification of the prevailing authorisation.

The prevailing jurisdictional title under which this Royal Decree is issued is the exclusive jurisdiction that, in matters of legislation on pharmaceutical products, Article 149(1)(16) of the Spanish Constitution confers on the State.

2. The most relevant competence issues raised by the draft.

In view of the circumscribed material scope regulated by the Royal Decree, it is considered that the jurisdictional title of Article 149(1)(16) amply empowers the State to adopt this rule within its exclusive jurisdiction.

3. Regional and local participation in the drafting of the draft.

During the processing of the draft, the Autonomous Communities and the cities of Ceuta and Melilla have been consulted.

V. Description of the procedure.

In regard to the processing of the draft, the provisions established in Article 26 of Government Law 50/1997 of 27 November 1997 have been followed.

The draft Royal Decree was subject to prior public consultation on the website of the Ministry of Health from 13 February up to and including 4 March 2024.

Likewise, in accordance with the provisions of Article 26(6) of Law 50/1997 of 27 November 1997, the process of public information has been carried out through the Department's website, from 30 September 2024 to 21 October 2024, addressed to associations or organisations that group or represent persons whose rights or legitimate interests are affected by the rule and whose purposes are directly related to its purpose.

The annex to this report contains an assessment of the contributions received during the public information procedure.

The approval of the draft also requires the following procedures:

- Report of the Technical General Secretariat of the Department (Article 26(5) fourth paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Agriculture, Fisheries and Food (Article 26(5) fourth paragraph of Law 50/1997 of 27 November 1997).

- Prior approval by the Ministry for Digital Transformation and the Civil Service (Article 26(5) fifth paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Territorial Policy and the Democratic Memory on the compliance of the draft with the distribution of powers between the State and the

Autonomous Communities (Article 26(5) sixth paragraph of Law 50/1997 of 27 November 1997).

- Report of the Office for Coordination and Regulatory Quality of the Prime Minister's office, Justice and Relations with Parliament (Article 26(9) of Law 50/1997 of 27 November 1997).

- Report by the Ministry of Social Rights, Consumer Affairs and the 2030 Agenda (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Youth and Children (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Economy, Trade and Enterprise (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Industry and Tourism (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Ministry of the Interior (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Finance (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Report of the Prime Minister's Office, Justice and Relations with Parliament (National Institute of Toxicology and Forensic Sciences) (Article 26(5) first paragraph of Law 50/1997 of 27 November 1997).

- Report of the Ministry of Defence (Article 26(5) first paragraph of Law 50/1997 of 27 November).

- Report of the autonomous communities and the cities of Ceuta and Melilla.

- Report of the Consumers and Users Council.

- Report of the Spanish Council on Drug Dependence and other Addictions.

- Notification to the European Commission in accordance with the provisions of Royal Decree 1337/1999 of 31 July 1999 regulating the transmission of information in the field of technical standards and regulations and regulations relating to information society services, and Directive (EU) 2015/1535 of the

European Parliament and of the Council of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on information society services.

- Opinion of the Council of State (Articles 22(2) and 22(3) of Organic Law 3/1980 of 22 April 1980 on the Council of State).

VI. Project impact analysis:

1. Economic impact.

a) General impact on the economy:

No significant impact is expected. In Spain, there are already companies producing cannabis, as well as manufacturing extracts. The conditions of prescription and dispensing and the indications for which their use is established do not lead to an expectation of a substantial change in the activity of these companies.

b) Impact on market competition:

The rule is expected to have positive effects on competition by opening up the sector of cultivation and manufacture of cannabis preparations to use by Spanish citizens.

c) Impact on market unity:

In relation to the possible impact this draft will have, once approved, in relation to the matters set out in Law 20/2013 of 9 December 2013 on the guarantee of market unity, it should be noted that the draft does not contain conditions or requirements that directly or indirectly discriminate based on the establishment or residence of an economic operator.

2. Budgetary impact.

1. Impact on the General State Budget.

It entails an increase in revenue derived from the application of fees in the registration of standardised preparations used in standardised magistral formulas. Estimated revenues are EUR 260 000, based on the number and types of extracts currently manufactured. However, the budget is not immediately affected, as revenues will be generated gradually.

2. Budgetary impact on Autonomous Communities or local entities

It is not expected to have an impact on the expenditure associated with medicines borne by the Autonomous Communities. The preparations are intended for patients who do not respond to marketed treatments, meaning their use can be expected to replace other prescribed medicines.

Hospital dispensary services will have to assume the preparation of standardised magistral formulas of cannabis preparations, as well as their dispensing. Being aimed at very specific patient groups, massive use is not expected; thus, no significant increase in workload is expected.

3. The impact that the development or use of the means and services of the digital Administration will have for the citizens and for the Administration

No impact is expected.

3. Analysis of administrative burdens.

Incorporates new administrative burdens Estimated quantification EUR 8 736.33 per registration, pursuant to the application of Fee I.2, entry in the register of an abbreviated dossier.

4. Gender impact.

In the pathologies for which formulas based on standardised cannabis preparations are intended, there are no significant differences in terms of gender, if considered together. Although the provisions of Article 19 of Organic Law 3/2007 of 22 March 2007 on substantive gender equality, and Article 26(3)(f) of Government Law 50/1997 of 27 November 1997, have been taken into account to analyse the gender impact, it should be noted that with regard to industrial activity, the pharmaceutical industry is the industrial sector with the best rates of gender equality, 52 % of the direct jobs generated by pharmaceutical companies based in Spain correspond to women. The entry into application of this Royal Decree does not foresee or imply, directly or indirectly, any gender impact.

5. Impact on children and adolescents.

This impact has been assessed pursuant to Article 22 *quinquies* of Organic Law 1/1996 of 15 January 1996 on the Legal Protection of Minors, partially amending the Civil Code and the Civil Procedure Act. No impact is expected whatsoever, since the purpose of the draft legislation does not specifically address these groups. No target population can be established beforehand.

It has also been taken into consideration, given the connotations of these preparations due to their composition and the risk of diversion to illicit trafficking, the special control of them, in the interest of protecting patients and possible uses by population groups – especially youth – outside the sole and main purpose, which is the treatment of certain diseases.

6. Impact on the family.

In turn, following an assessment, the impact that the regulation could have on the protection of the family, as provided for in the tenth additional provision of Law 40/2003 of 18 November 2003 on the Protection of Large Families, is considered null and void for the same reasons as set out in the previous paragraph, since the proposed regulation does not affect the subjects under the scope of Law 40/2003 of 18 November 2003.
In relation to the impact derived from the availability of new treatments, which could be effective in patients in whom other options have failed, the impact on the family could be considered positive in that these preparations are intended to address the improvement of diseases and, therefore, the quality of life of patients, resulting in family welfare when a member of the same suffers from some of the diseases for which these preparations are intended.

7. Other impacts.

This draft Royal Decree has a positive impact on equal opportunities, non-discrimination and universal accessibility for persons with disabilities since it is expected that these preparations will be prescribed by doctors and prepared in the hospital dispensary services, mostly belonging to the National Health System, guaranteeing equal access to them for all patients, including vulnerable groups and those at risk of exclusion.

VII. *Ex-post* evaluation.

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It is not deemed necessary to propose a regulatory impact assessment.

Annex.

1. Assessment of the contributions received during the prior public consultation process, by content and meaning of the proposal:

INSTITUTION	COMMENTS AND PROPOSALS RECEIVED	ASSESSMENT OF PROPOSALS AND CHANGES MADE IN THE DRAFTING
Spanish Society of Hospital Pharmacies Spanish Society of Primary Care Pharmacists (SEFAP)	Include in the Royal Decree the definition of standardised extract or preparation	The definition of a standardised preparation of cannabis has been included in the draft Royal Decree.
Spanish Society of Primary Care Pharmacists (SEFAP)	Include in the Royal Decree the consideration of cannabis as a narcotic drug included in Schedule I of the Single Convention on Narcotic Drugs of 1961. To omit as an objective of the Royal Decree: 'procedure for assessing the quality of standardised cannabis preparations as starting materials in the preparation of magistral formulas' is more typical of a monograph by the Royal Spanish Pharmacopoeia than of a high-ranking legal standard.	The definition of a standardised preparation of cannabis has been included in the draft Royal Decree. Include in the Royal Decree the consideration of cannabis as a narcotic drug included in Schedule I of the Single Convention on Narcotic Drugs of 1961. The objective of evaluating the quality of standardised cannabis preparations has been eliminated. The objectives of the Royal Decree are finally to establish the conditions for the prescription, preparation, dispensing, and use of standardised magistral formulas of cannabis preparations. Also, to establishing a register of standardised cannabis preparations used in the elaboration of these magistral formulas, in order to guarantee their quality.
Tilray (company)	Include in the Royal Decree the definition of standardised extract or preparation, herbal product, and herbal substance.	The definition of a standardised preparation of cannabis has been included in the draft Royal Decree. The rest of the proposals have not been considered necessary.
Individuals Madrid Association for Cannabis Studies (AMEC)	In the Royal Decree, regulate the recreational use of cannabis.	The draft Royal Decree does not intend to regulate the use of cannabis for recreational purposes but only establishes the conditions for the preparation and dispensing of standardised magistral formulas of cannabis preparations, exclusively for medicinal use.
Individuals	Regulate in the draft Royal Decree the penalisation of cannabis consumption in relation to roadside checks by the DGT: adjusting the current consumption limit, issuing a medical report in case of a DGT check, etc.	The Royal Decree has not provided for the regulation of roadside checks following the consumption of these products by the DGT, which are governed by its specific regulations.

Individuals	Include the possibility of self-cultivation.	The possibility of self-cultivation has not been contemplated in the draft Royal Decree, in principle because it goes against current legislation and because it is not possible to guarantee the quality of the products.
Basque Federation of Cannabis Associations European Observatory on the Consumption and Cultivation of Cannabis	Include the possibility for self-cultivation and/or collective cultivation	The possibility of self-cultivation has not been contemplated in the draft Royal Decree, in principle because it goes against current legislation and because it is not possible to guarantee the quality of the products.
Almirall Pharmaindustry	Regulate the cloning of cannabis varieties to ensure the standardisation of products	The Royal Decree does not contemplate the regulation of these aspects; the objectives are to establish the conditions of registration and medicinal use of cannabis preparations.
Almirall Pharmaindustry	Regulate Good Agricultural Practices	The Royal Decree does not contemplate the regulation of these aspects; the objectives are to establish the conditions of registration and medicinal use of cannabis preparations. The quality guidelines referred to are in any event applied through audits of manufacturing pharmaceutical laboratories, and are drawn up at European level.
Almirall Pharmaindustry Tilray (company) Medical Cannabis Business Association in Spain (AECAME)	Include the obligation of compliance with Good Manufacturing Practice by laboratories that manufacture cannabis preparations	The Royal Decree includes the requirement for manufacturing pharmaceutical laboratories to ensure compliance with good manufacturing practices.
Individuals Ministry of Agriculture, Fisheries and Food (MAPA) CTAEX (company) 'Spanish Cannabis Cluster' business association	Prioritise the use of cannabis produced in Spain for the preparation of cannabis preparations.	This possibility has not been contemplated, since it is not one of the objectives of the Royal Decree.
Neuraxpharm	Include the possibility of using cannabis obtained in Malta	This possibility is already provided for in the regulations governing the cultivation of cannabis plants and the legislation in force in this regard.
Tilray (company)	Requests that the AEMPS evaluate and approve each herbal substance and herbal preparation on the basis of its quality data before placing it on the market. Manufacturers will be required to submit to the AEMPS all relevant	The draft Royal Decree establishes a register of standardised cannabis preparations used in the preparation of these magistral formulas, in order to guarantee their quality.

	changes to their original application that may affect the final quality of their herbal substance or preparation, as performed in the variations set out in the quality section (CTD Module 3) of any other medicinal product. The AEMPS should have mechanisms in place for manufacturers to communicate the start of the marketing of their products and, most importantly, any disruption in the supply chain that may affect the continuity of treatment.	
APROFARM Spanish Society of Individualised Medicines (LASEMI) Official Board of Pharmacists of Málaga Trichome (company)	Limit the preparation by maximum dose of THC content or by maximum dose of standardised preparation	This possibility has not been contemplated in the draft Royal Decree since the magistral formulas of standardised cannabis preparations will comply with the monographs to be published for that purpose.
Spanish Society of Clinical, Family and Community Pharmacy (SEFAC)	Not limiting the elaboration of magistral formulas in relation to the national formulary, but indicating that it will be a matter of adjusting or following the indications/recommendations in the preparation of the magistral formulas to the National Formulary.	This possibility has not been contemplated in the draft Royal Decree since the magistral formulas of standardised cannabis preparations will comply with the monographs to be published for that purpose. It is deemed that limiting the preparation to what is established in the monograph offers greater guarantees of quality, safety, and efficacy to patients.
Individuals Medcann (company) MAPA CTAEX (company) 'Spanish Cannabis Cluster' business association European Observatory on the Consumption and Cultivation of Cannabis Trichome (company) Getafe Hospital	Include the possibility of the medical use of cannabis flowers	The draft Royal Decree does not consider this possibility at the present time, taking into account the conclusions of the Sub-Commission for the purpose of analysing experiences of regulation of cannabis for medicinal use, which was created at the request of the Committee on Health and Consumer Affairs at its session of 13 May 2021, preparations derived from cannabis could be useful as a therapeutic option for some patients. Consequently, the Sub-Commission's recommendations included urging for the adoption of the necessary measures to allow for the availability of standardised cannabis preparations to accommodate certain patients, for whom these medicines may entail an improvement after the authorised treatments have not been effective. They also recognised that the existence of standardised cannabis

		preparations, with a defined composition, is an advantage in terms of dosage, stability, and handling, compared to other possible modes of cannabis use. However, the generation of evidence of adequate quality may lead to reconsideration of this matter. The use of standardised magistral formulas of cannabis preparations, registered with the Spanish Agency for Medicines and Medical Devices, ensures the quality of these formulas, their reproducibility, and homogeneity, allowing for a more predictable dosage and use.
Individuals Medical Cannabis Business Association in Spain (AECAME) European Medicinal Cannabis Association European Observatory on the Consumption and Cultivation of Cannabis Getafe Hospital Council of Pharmaceutical Boards of Catalonia	Include as routes of administration, in addition to the oral route, the inhalation route and the topical route.	It is deemed that, in the proposed indications, the oral route offers greater guarantees of reproducibility and has greater support in terms of evidence. However, this issue could be reconsidered when quality evidence is generated.
Medical Cannabis Business Association in Spain (AECAME)	Define in the Royal Decree the formats that could be marketed directly from the manufacturer, in large batches and with an expiration date (AECAM).	Defining the formats is not an objective of this Royal Decree. Stability will depend on the data generated by the manufacturer, and evaluated in the register, which will determine the period of validity.
Official Board of Pharmacists of Málaga	Indicate the toxicity margin and route of administration on the labelling.	Defining labelling is not an objective of this Royal Decree; However, the registry will assess whether standardised cannabis preparations are placed on the market with the necessary information. With respect to the standardised magistral formulas, the general regulations apply in this case and ensure these issues.
Spanish Society of Hospital Pharmacies (SEFH)	Accounting for raw materials deserves special consideration in the development of regulations	Already regulated by its specific regulations, so it is not considered necessary to include it in this Royal Decree.
APROFARM Official Board of Pharmacists of Málaga	Eliminate the requirement for an Official Prescription for Narcotic Drugs for magistral formulas with a THC content below a certain limit	The Royal Decree does not include this requirement; In any case, the corresponding general rules on narcotic drugs and psychotropic substances apply, depending on the characteristics of the preparation.
'Spanish Cannabis Cluster' business association	Include the consideration of dried hemp flowers of varieties in the European Catalogue of Horticultural	Clarification of the categorisation of cannabis as a narcotic regardless of its cannabinoid content has been included. The flowering tops of the Cannabis plant are

	Species as 'non-narcotic'	narcotic regardless of whether the varieties from which they are obtained are in the European Catalogue of Horticultural Species, as established by the legislation in force in the matter.
Ministry of Agriculture, Fisheries and Food EXTREMADURA NATIONAL AGRO-FOOD TECHNOLOGICAL CENTRE – CTAEX Individuals LASEMI (SPANISH SOCIETY OF INDIVIDUALISED MEDICINAL PRODUCTS)	Regulation of cannabidiol, as a substance.	It exceeds the objective of this Royal Decree, which deals with cannabidiol as an active ingredient in standardised preparations and standardised magistral formulas. Uses other than those indicated are outside the scope of the Royal Decree.
Official Board of Physicians of Barcelona Spanish Society of Psychiatry and Mental Health (SEPSM)	Promotion of public health communication campaigns	It is not among the objectives of this Royal Decree
Individuals Medical Cannabis Business Association in Spain (AECAME) LASEMI (SPANISH SOCIETY OF INDIVIDUALISED MEDICINAL PRODUCTS) 'Spanish Cannabis Cluster' Tilray Medical (company) TRICHOME PHARMA S.L. (company)	Inclusion of any type of practitioner as a prescriber of these magistral formulas	The proposal is not considered relevant. It has been deemed that the prescription should be limited to medical specialists who treat patients with the indications detailed in the corresponding monograph of the National Formulary, when the authorised medicines do not achieve satisfactory control of the symptoms.
Individuals Spanish Society of Primary Care Pharmacists (SEFAP) Council of Pharmaceutical Boards of Catalonia General Council of Official Pharmaceutical Associations Official Board of Pharmacists of Málaga Medical Cannabis Business Association in Spain (AECAME) Independent Association of Pharmaceutical Formulators	Include the possibility of dispensing these magistral formulas in dispensing pharmacies	The draft Royal Decree does not contemplate this possibility, taking into account the conclusions of the Sub-Commission for the purpose of analysing experiences in the regulation of cannabis for medicinal use, which was created at the request of the Committee on Health and Consumer Affairs at its session of 13 May 2021. The proposed indications require pharmacotherapeutic monitoring, which is carried out mostly in hospital settings, so it is considered that limiting the preparation and dispensing to hospital dispensary services is justified.

(APROFARM) LASEMI (SPANISH SOCIETY OF INDIVIDUALISED MEDICINAL PRODUCTS) 'Spanish Cannabis Cluster' European Medicinal Cannabis Association Tilray Medical (company) TRICHOME PHARMA S.L. (company) Several dispensing pharmacies.		
Spanish Society of Psychiatry and Mental Health (SEPSM)	Limit the dispensing of these magistral formulas to the hospital environment	This limitation has been included in the draft Royal Decree.
Medical Cannabis Business Association in Spain (AECAME) Individuals European Observatory on the Consumption and Cultivation of Cannabis ICEERS Foundation (International Center for Ethnobotanical Education, Research & Service)	Creation of a patient registry to monitor the use of medical cannabis and evaluate its effectiveness and safety	The proposal was not considered necessary
Individuals 'Spanish Cannabis Cluster' European Observatory on the Consumption and Cultivation of Cannabis Tilray Medical Medical Cannabis Business Association in Spain (AECAME) Almirall	Price regulation and financing	It is not among the objectives of this Royal Decree
Council of Pharmaceutical Boards of Catalonia Independent Association of Pharmaceutical Formulators (APROFARM) Official Board of Pharmacists of Málaga	Eliminate the requirement for an Official Prescription for Narcotic Drugs for magistral formulas with a THC content below a certain limit	Standardised cannabis preparations with a THC content equal to or greater than 0.2 % by weight will be considered psychotropic, and will be subject to the control measures and restrictions derived from the 1971 Convention on Psychotropic Substances, as provided for in Royal Decree 2829/1977 of 6 October 1977 regulating psychotropic medicinal substances and preparations, as well as the control and inspection of their manufacture, distribution, prescription and

		dispensing.
Spanish Society of Hospital Pharmacies (SEFH)	Accounting for raw materials deserves special consideration in the development of regulations	Already regulated by its specific regulations, so it is not considered necessary to include it in this Royal Decree.
Individuals MEDCANN (company) LASEMI (SPANISH SOCIETY OF INDIVIDUALISED MEDICINAL PRODUCTS) European Medicinal Cannabis Association European Observatory on the Consumption and Cultivation of Cannabis Getafe Hospital	Include indications different from the proposals.	In relation to the pathologies that could benefit from the use of magistral formulas based on standardised cannabis preparations, the available data have been evaluated and those in which a favourable risk-benefit ratio is considered to exist have been selected.
Getafe Hospital Medical Cannabis Business Association in Spain (AECAME)	Do not include treatment of pathologies but treatment of symptoms	This possibility has not been contemplated in the Royal Decree; it will be detailed in the corresponding monograph.
Individuals Trichome (company ICEERS (International Centre for Ethnobotanical Education, Research & Service)	Do not limit the medical use of these magistral formulas to any pathology	In relation to the pathologies that could benefit from the use of magistral formulas based on standardised cannabis preparations, the available data have been evaluated and those in which a favourable risk-benefit ratio is considered to exist have been selected. In any case, the magistral formulas must be prepared with substances with legally recognised action and indication.
'Spanish Cannabis Cluster'	Regulate its use in homoeopathy, cosmetics and food	The proposal has not been evaluated since it is not among the objectives of the Royal Decree
Official Board of Physicians of Barcelona Pharmaceutical Service of the National Hospital for Paraplegics in Toledo Tilray (company) SEOM (Spanish Society of Medical Oncology) Spanish Society of Epilepsy (SEEP)	Limitation of indications	Pathologies that could benefit from the use of magistral formulas based on standardised cannabis preparations have been limited to those for which the available data indicate a favourable benefit-risk ratio.
Particular Spanish Epilepsy Federation	Eliminate this indication since this pathology has an approved drug that has demonstrated scientific	In this Royal Decree, it is already contemplated that only in cases where the authorised treatments do not have sufficient efficacy, using standardised magistral

	evidence for epilepsy. Also, that it is always prescribed with priority over any standardised cannabis preparation.	formulas of cannabis extracts can be an option to consider, when the authorised drug, of industrial manufacture, is not suitable for the patient.
Getafe Hospital	Proposes the inclusion of contraindications.	The inclusion of contraindications is not among the objectives of this Royal Decree. They may be included in the corresponding monograph.
Spanish Association of Laboratories for Orphan and Ultra-Orphan Medicinal Products (AELMHU) Spanish Diabetes Federation Almirall Jazz Pharmaceuticals Pharmaindustry Spanish Society of Epilepsy (SEEP)	Priority for treatment with industrially manufactured medicines over the magistral formula.	In this Royal Decree, it is already contemplated that only in cases where the authorised treatments do not have sufficient efficacy, using standardised magistral formulas of cannabis extracts can be an option to consider.
Getafe Hospital	Proposes different titles and dosages of the magistral formula	It is not among the objectives of this Royal Decree. They will be included in the corresponding monograph.
Official Board of Physicians of Barcelona	They propose strict control of the prescription.	The prescription and its control have been considered in this Royal Decree.