Royal Decree establishing the conditions for the preparation and dispensing of specified magistral formulas for standardised cannabis preparations.

I

Cannabis is considered a narcotic drug under the international control treaties, signed by Spain and the rest of the Member States of the European Union, as it is included in Schedule I of the Annex to the Single Convention on Narcotic Drugs of 1961. This implies that its manufacture, export, import, distribution, trade, use, and possession should be limited to medical and scientific purposes.

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 shown varying degrees of benefit from cannabis, and its extracts, in some therapeutic indications. At present, the indications for which there is more evidence and consensus in the scientific community are spasticity due to multiple sclerosis, severe forms of refractory epilepsy, chemotherapy-induced nausea and vomiting, and refractory chronic pain. For the first three indications, industrially manufactured medicinal products containing either cannabis extracts with the active ingredients THC and/or CBD, or synthetic cannabinoids have been authorised. These medicinal products have been authorised according to the usual procedures applicable to industrially manufactured medicinal products, after a full evaluation of the studies proving their quality, safety, and efficacy in certain therapeutic indications, including the mandatory clinical trials. The authorisation of these medicinal products by the European national authorities, the European Commission, or regulatory authorities with equivalent requirements ensures a favourable benefit-risk balance for the indications and conditions of use included in their product leaflet. For the indication of refractory chronic pain, there are no authorised medicines in Spain based on cannabis. Although a wide range of medicines and therapeutic strategies are available to treat all types of pain, sometimes sufficient pain control is not achieved for patients. In cases where authorised treatments are not sufficiently effective, using standard magistral formulas for standardised cannabis extracts may be an option to consider.

At the request of the Health and Consumer Affairs Committee of the Congress of Deputies, in its session on 13 May 2021, and in order to analyse experiences of regulating cannabis for medicinal use, a Sub-Commission was created, whose conclusions indicate that cannabis-derived preparations 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 preparations with a defined composition is an advantage in terms of dosage, stability, and handling, compared to other possible types of cannabis use.

The use of specified magistral formulas for standardised 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. These formulas are prepared after the issuing of a medical prescription and, under the direction of a

pharmaceutical professional, by hospital dispensaries, complying with the applicable Rules for Correct Preparation.

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 specified magistral formulas for standardised cannabis preparations could be an alternative in the event that therapeutic options fail.

In order to guarantee their quality, this Royal Decree establishes the conditions for the prescription, preparation, dispensing, and use of specified magistral formulas for standardised cannabis preparations, as well as a Register of standardised cannabis preparations used in the preparation of these magistral formulas.

II

This royal decree is structured into ten articles, two additional provisions, three final provisions and an annex.

Articles 1 and 2 establish the purpose of the Decree, the conditions for the prescription, preparation, and dispensing of standardised cannabis preparations, and the establishment of a register for these preparations. A list of definitions used in this Decree is also drawn up.

Article 3 regulates the inspection conditions applicable to the preparations covered by this Decree.

Article 4 concerns the need for, and regulations applicable to, the publication in the National Formulary of the corresponding monograph of the specified magistral formulas for standardised cannabis preparations.

Articles 5 and 6 lay down the obligations of pharmaceutical laboratories manufacturing standardised cannabis preparations, with regard to compliance with the rules for good manufacturing practices and good distribution practices, as well as the obligation of pharmaceutical laboratories to apply to the Spanish Agency for Medicines and Medical Devices to register in the Register of standardised cannabis preparations.

Articles 7, 8, and 9 establish the conditions for prescription by medical specialists, and their obligation to justify the treatment with specified magistral formulas for standardised cannabis preparations through the required documentation, as well as the conditions for preparation by legally established hospital dispensaries, in accordance with the requirements of the National Formulary. The Decree also covers the conditions for dispensing and pharmacotherapeutic monitoring by hospital dispensaries and the medical team.

Finally, Article 10 establishes the need for health professionals to report suspected adverse reactions to the standard magistral formulas to the corresponding Autonomous Centre for Drug Safety Monitoring.

This Royal Decree is in accordance with the principles for sound regulation referred to in article 129 of Law 39/2015 of 1 October on the common administrative procedure for Public

Administration, particularly the principles of necessity, effectiveness, proportionality, legal certainty, transparency and efficiency.

It complies with the principles of necessity and effectiveness as it is justified by the reasons of general interest described in the preceding paragraphs, and is the most appropriate instrument to ensure the achievement of the proposed targets.

As regards compliance with the principle of proportionality, this rule contains the regulations necessary to meet the identified needs, so that in order to achieve the objectives set, there are no other measures which are less restrictive of rights or impose fewer obligations on the addressees. Likewise, the possible limitations of rights comply with the provisions of Law 14/1986 of April 25, and the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices.

This Royal Decree does not introduce or establish procedures additional to or other than those provided for in Law 39/2015 of 1 October. However, specialities of the specific procedure are maintained on account of the matter, relating to time-limits and reports to be obtained, already present in the procedures governed by the previous legislation.

Likewise, during the drafting procedure, the active participation of potential addressees of the standard has been promoted through the procedures of prior public consultation and public hearing and information, taking their observations into account.

This Royal Decree has been the subject of a prior report by the Advisory Committee and the entire Interterritorial Council of the National Health System. In the process of drafting this standard, the Autonomous Communities, the cities of Ceuta and Melilla, and the affected sectors have been consulted, among others.

This Royal Decree has also been subject to the procedure for the provision of information on technical standards and regulations and on regulations relating to the information society, regulated by Royal Decree 1337/1999 of 31 July regulating the transmission of information in the field of technical standards and regulations and rules on Information Society services, in order to comply with 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.

In compliance with the provisions of Article 149.1.16 of the Spanish Constitution, this Royal Decree is issued in accordance with the exclusive competence of the State in matters of legislation on pharmaceutical products, and by virtue the provisions of the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July, in particular its Chapter IV, on health guarantees for standard magistral formulas, and its second final provision, which authorizes the Government, within the scope of its powers, to approve regulations and rules for the application and development of said law.

Accordingly, on the proposal from the Minister for Health, with the prior approval of the Minister for Digital Transformation and the Civil Service, in agreement with the Council of State, and after deliberation by the Council of Ministers, at its meeting on XX XXXXXXX 202X

THE FOLLOWING IS DECREED:

Article 1. *Aim and scope of application*.

1. This Royal Decree establishes the conditions for the prescription, preparation, dispensing, and use of specified magistral formulas for standardised 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.
2. Authorised industrially manufactured medicinal products, and cannabis-based medicinal products under investigation, which shall be governed by the respective specific regulations, fall outside the scope of this Royal Decree. Cannabinoids obtained by synthetic processes, or from sources other than cannabis, also fall outside the scope of this Royal Decree.

Article 2. *Definitions.*

For the purpose of this Royal Decree, the following definitions shall apply:

a) Standardised cannabis preparation: a product with a defined amount of THC and/or CBD, containing one or more standardised cannabis extracts, registered by the Spanish Agency for Medicines and Medical Devices, for use in the preparation of a standard magistral formula.

b) Cannabinoids: organic compounds, belonging to the group terpenophenols, present in cannabis and responsible for its main pharmacological effects.

c) Delta-9-tetrahydrocannabinol (THC): cannabinoid component of cannabis, present in variable quantities, the main chemical substance responsible for its psychoactive effects and which has the legal status of psychotropic substance, included in Schedule II of Annex 1 to Royal Decree 2829/1977 of 6 October regulating psychotropic medicinal substances and preparations, as well as the control and inspection of its manufacture, distribution, prescription, and dispensing.

d) Cannabidiol (CBD): cannabinoid component of cannabis, present in varying quantities, a chemical responsible for various pharmacological effects.

e) Standard magistral formula: the standard magistral formula included in the National Form, due to its frequent use and usefulness.

Article 3. *Conditions for the control of standardised cannabis preparations.*

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, provided for in Royal Decree 2829/1977 of 6 October regulating psychotropic medicinal substances and preparations, as well as the control and inspection of its manufacture, distribution, prescription and dispensing.

Article 4. *Monograph of the National Formulary of standard magistral formulas for cannabis preparations*.

1. The Spanish Agency for Medicines and Medical Devices will publish in the National Formulary the corresponding monograph to which the specified magistral formulas for standardised cannabis preparations must conform.
2. The monograph shall also contain the legally recognised action and indications for these medicinal products for the purposes laid down in Article 42 of the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July.

Article 5. *Obligations of pharmaceutical laboratories manufacturing standardised cannabis preparations*.

1. Pharmaceutical laboratories that manufacture standardised cannabis preparations must carry out all manufacturing and/or control operations in accordance with the European Union rules on good manufacturing practice for medicinal products.

2. Pharmaceutical laboratories are obliged to ensure compliance with good manufacturing practices and good distribution practices by suppliers or manufacturers of starting materials used in the manufacture of standardised preparations. To this end, the suppliers or manufacturers shall be audited at regular intervals. They shall also document the supply chain of each starting material, which shall be of lawful origin and comply with the legislation applicable to narcotic and/or psychotropic substances, as appropriate.

3. Pharmaceutical laboratories producing standardised cannabis preparations may only supply such preparations to legally established hospital dispensaries or for export.

4. If these preparations are considered psychotropic due to their THC content, in accordance with Article 3, the manufacturing pharmaceutical laboratories must have the corresponding authorization, in accordance with the provisions of Royal Decree 2829/1977 of 6 October.
5. Likewise, when these manufacturers have obtained psychotropic preparations from narcotic substances (cannabis), they must have the corresponding authorization in accordance with the provisions of Law 17/1967 of 8 April.

Article 6. *Register of standardised cannabis preparations*.

1. Standardised cannabis preparations used in the preparation of standard magistral formulas must be registered in the Register of standardised cannabis preparations, under the responsibility and management of the Spanish Agency for Medicines and Medical Devices, which shall be public.
2. In order to be entered in the register, the pharmaceutical laboratories responsible for the manufacture and placing on the market of the referred preparations must submit the corresponding application to the Spanish Agency for Medicinal Products and Medical Devices, accompanied by the information on the preparations included in the Annex. These laboratories must be established in the European Union.
3. The maximum period for notification of the decision of the procedure shall be six months from the day following the date of submission of a valid application.

Otherwise, the application shall be deemed to have been rejected, and any appropriate appeals may be brought.

4. If the application does not meet the requirements, the applicant concerned shall be required to, within ten days, remedy the mistakes or submit the required documents, being informed that if he or she does not do so, he or she shall be deemed to have withdrawn their application once a decision has been made.

   The application for registration shall be rejected if the data and information contained in the documentation of the application for authorisation are inaccurate or do not comply with the relevant implementing legislation.

5. Any changes to the conditions for registration shall be notified to the Spanish Agency for Medicinal Products and Medical Devices, and the general principles laid down in Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products shall apply. Based on its scope, and the impact on the quality of the preparation, it may require re-registration as referred to in paragraph 2 of this Article.

6. The application for registration of standardised cannabis preparations shall be subject to the fee set out in heading 1.2 of Group I: medicinal products for human use, of Article 123 of the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices.

Article 7. *Prescription of specified magistral formulas for standardised cannabis preparations.*

1. The specified magistral formulas for standardised cannabis preparations shall be used for the indications set out in the corresponding monograph of the National Formulary in cases where there are no industrially manufactured medicinal products authorized and marketed, or where these do not allow for the satisfactory treatment of a specific patient.
2. Prescription is limited to medical specialists, within the scope of hospital care, who treat patients with the indications detailed in the corresponding monograph of the National Formulary, when the authorised and marketed medicines do not achieve satisfactory control of the symptoms, in the cases described in paragraph 1 of this article.
3. The justification for treatment with standard magistral formulas of cannabis preparations, in relation to other treatments received by the patient, shall be documented in the medical record. The patient should also be informed of the available clinical evidence, expected benefits and possible risks. All this in accordance with Basic Law 41/2002 of 14 November regulating the autonomy of the patient, and rights and obligations regarding information and clinical documentation.
4. The prescribing physician shall periodically assess the therapeutic utility and safety of the prescribed standard magistral formula and consider discontinuation of treatment if sufficient clinical benefit is not obtained or if the benefit-risk balance is unfavourable.

Article 8. *Production of specified magistral formulas for standardised cannabis preparations by hospital dispensaries.*

1. The production of the standard magistral formulas will be limited to legally established hospital dispensaries, which have the necessary means for their preparation in accordance with the requirements established in the National Formulary and in the regulatory established standards for correct preparation and quality control.

2. Standardised preparations that are considered psychotropic, due to their THC content, as well as the standard magistral formulas that are produced with them, will be governed by their specific regulations.

Article 9. *Conditions for pharmacotherapeutic dispensing and monitoring*.

1. The dispensation will be carried out by the hospital dispensaries, which will provide pharmaceutical care and, in collaboration with the medical team, will conduct a comprehensive follow-up of the patient.
2. The need for continued treatment shall be evaluated periodically, based on the clinical benefit obtained and the occurrence of adverse reactions, in accordance with Article 7(4).
3. When the clinical situation of dependence, vulnerability, risk, or physical distance of the patient to the centres referred to in paragraph 1 of this Article arises, the competent bodies or authorities of the Autonomous Communities may establish the distance dispensing measures provided for in paragraph 8 of Article 3 of the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July.

Article 10. *Pharmacovigilance*.

Healthcare professionals are obliged to report suspected adverse reactions to specified magistral formulas for standardised cannabis preparations to the Autonomous Centre for Pharmacovigilance corresponding to their field of care, with this notification being optional for users.

First additional provision. *Establishing of the Register of standardised cannabis preparations.*

In accordance with the provisions of Article 6, the Register of standardised cannabis preparations is established for the preparation of magistral formulas specified by the Spanish Agency for Medicines and Medical Devices.

Second additional provision. *Effects of the publication of the monographs of specified magistral cannabis formulas.*

No later than three months after the entry into force of this Royal Decree, the monographs of specified magistral formulas to which the formulas must conform shall be published.

Third additional provision. ***Production and dispensing of specified magistral formulas for cannabis preparations by dispensing pharmacies.***

The preparation and dispensing of specified magistral formulas for standardised cannabis preparations by dispensing pharmacies may be subject to specific regulation, without prejudice to their exceptional participation as third-party processors for hospital dispensaries, pursuant to of the provisions of Article 66 of the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices, approved by Royal Legislative Decree 1/2015 of 24 July.

First final provision. *Attribution of powers.*

This Royal Decree is issued under Article 149.1.16 of the Spanish Constitution, which confers on the State exclusive competence in matters of legislation on pharmaceutical products.

Second final provision. *Legislative development.*

The head of the Ministry of Health is authorised to make all necessary provisions for the implementation and development of this Royal Decree, in particular to make the provisions for the development of the Register of standardised cannabis preparations referred to in Article 6, as well as to update its annex in accordance with the progress of scientific and technical knowledge, in accordance with the guidance and guidelines of the European Union.

Third final provision. *Entry into force.*

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

ANNEX

Information to be sent to the Spanish Agency for Medicines and Medical Devices for the registration of standardised cannabis preparations

The data and documents to accompany an application for registration pursuant to Article 6 shall be submitted in accordance with the requirements set out in this Annex.

When compiling the registration application dossier, applicants shall also take into account the general chapters and monographs of the European Pharmacopoeia applicable to them, as well as the specific guidelines for herbal substances and preparations published by the European Medicines Agency.

For the purposes of this Annex, the Spanish term 'extracto' shall be considered equivalent to the English term 'herbal drug extracts' as defined in the European Pharmacopoeia.

Module 1: Administrative information

1.1. The Registration Form shall include:

- Identification of the standardised cannabis preparation by its name, the name of the herbal substance (according to the European Pharmacopoeia), and the definition of the extract(s) (including the physical state and the extraction solvent(s); for standardised extracts, the content of THC and/or CBD and excipients, if any, shall be indicated; the equivalent amount of genuine herbal preparation shall also be indicated, as a range, if applicable).
- The name and address of the applicant, the name and address of the suppliers of the herbal substance, as well as the name and address of the manufacturers and the places where the various stages of manufacture of the standardised extract(s) and of the standardised preparation of cannabis are carried out and their control.

1.2. The application shall be accompanied by the Manufacturing and Import Authorisation of the manufacturer(s) of the standardised cannabis preparation. The latest certificate of Good Manufacturing Practice (GMP) or other proof of compliance with the GMP (reference number in the EudraGDMP database) shall also be attached.

1.3. The proposed text for the label for the immediate packaging to be supplied to hospital dispensaries shall be provided. The labelling of such packaging shall contain at least the following information:

- Name of the standardised cannabis preparation, as well as the name of the herbal substance (according to the European Pharmacopoeia), and the definition of the extract(s) (including the physical state and extraction solvent(s); for standardised extracts, the THC and/or CBD content and excipients, if any, shall be indicated; the equivalent amount of genuine herbal preparation shall also be indicated, as a range, if applicable).
- For the excipients that have recognised action or effect and that are subject to mandatory reporting, in accordance with the applicable guidelines of the European Commission, the amount present in the standardised cannabis preparation shall be indicated.
- Expiry date.
- Storage conditions.

Module 2: Chemical and pharmaceutical information

2.1. Standardised cannabis extract

2.1.1. General information:

- *Plant substance:* Must comply with the provisions of the monograph of the European Pharmacopoeia of *Cannabis flos* (3028). The chemotype shall be indicated.
- *Excerpt:* For the nomenclature of the extract, the binomial scientific name of the plant shall be included (*Cannabis sativa* L.), as well as its chemotype, the parts of the plant used, the definition of the extract, the ratio of the plant substance to the extract, the extraction solvent(s).
  The physical form shall be indicated.
  The content of components with known therapeutic activity (THC and CBD), and other component(s), shall be indicated. Where applicable, the excipients used shall be indicated.

2.1.2. Manufacture:

2.1.2.1. Manufacturers:

- *Plant substance:* The name, address, and responsibility of each supplier, including contractors and each proposed place or facility for the production/collection and control of the herbal substance, shall be indicated. It must be confirmed that the herbal substance complies with good agricultural and collection practices for starting materials of plant origin.
- *Excerpt:* The name, address, and responsibility of each manufacturer, including contractors, and each proposed place of manufacture or installation for the manufacture and testing of the extract shall be indicated.

2.1.2.2. Description of the manufacturing process and process controls:

- *Plant substance:* For each producer, information shall be provided to adequately describe the production and harvesting of the plants, including their geographical origin and growing conditions, pre- and post-harvest treatments, drying and storage conditions, as well as lot size.
- *Excerpt:* A detailed description of each stage of the manufacturing process, including a flowchart, shall be presented. It shall be indicated how the extract is standardised to the declared THC/CBD content and, if excipients are used for the standardisation of the extract, the amount that can be added. The batch size shall be indicated.

2.1.2.3. Control of starting materials:

- *Plant substance:* Not applicable.
- *Excerpt:* A list of all materials used in the manufacture of the extract (herbal substance, solvents and reagents, as well as excipients, if used) shall be provided, identifying the stage of the process at which each of them is used. Information on the quality and control of these materials shall also be provided, and must comply with the requirements established in the monographs of the European Pharmacopoeia applicable to them.

2.1.2.4. Control of critical and intermediate steps

- *Plant substance:* Not applicable.

- *Excerpt:* Information on critical steps will be presented. Information on the quality and control of intermediate process steps, if any, shall be provided.

2.1.2.5. Manufacturing process validation and/or evaluation.

- *Plant substance:* Not applicable.
- *Excerpt:* Validation data of the manufacturing process shall be submitted.

2.1.2.6. Development of the manufacturing process. A brief summary will be provided.

2.1.3. Characterisation:

2.1.3.1. Structural elucidation and other characteristics:

- *Herbal substance:* information on botanical, macroscopical, microscopical, and phytochemical characterisation shall be provided.
- *Extract:* information on the phytochemical and physicochemical characterization shall be provided.

2.1.3.2. Impurities:

- *Herbal substance:* the potential contaminants/impurities arising from the cultivation of the herbal substance and post-harvest treatments (residues of pesticides and fumigants, toxic metals, aflatoxins etc.) shall be indicated, and their origin described.
- *Extract:* the potential contaminants/impurities of the extract shall be indicated, and their origin described.

2.1.4. Control of the active substance:

2.1.4.1. Specifications.

- *Plant substance:* Detailed information on the specifications used for the control of the herbal substance shall be provided and shall comply with the provisions of the monograph of the European Pharmacopoeia of *Cannabis flos (3028)*, as well as with the general application monograph (*Herbal drugs*, 1433).
- *Excerpt:* Detailed information on the specifications used for the control of the extract shall be provided. Those specifications shall be established in accordance with the European application guidelines or the specific monograph of the European Pharmacopoeia, if any.

2.1.4.2. Analytical procedures. The analytical procedures used for the control of both the herbal substance and the extract shall be described in sufficient detail so that they can be reproduced in tests carried out at the request of the competent authority. In the case of test procedures included in the European Pharmacopoeia, this description may be replaced by the corresponding reference to the monograph(s) and general chapter(s).

2.1.4.3. Validation of analytical procedures. Validation results of the analytical procedures used for the control of the herbal substance and extract shall be provided, where appropriate.

2.1.4.4. Batch analysis: For both the herbal substance and the extract, results of analyses of representative batches shall be submitted.

2.1.4.5. Justification of specifications. The specifications of the herbal substance, where relevant, and those of the extract shall be justified.

2.1.5. Standards or reference materials: The standards and reference materials used in the control of both the herbal substance and the extract shall be identified and described in detail. Where available, the European Pharmacopoeia reference standards shall be used.

2.1.6. Container and closure system: For both the herbal substance and the extract, the description of the container and the closure system and its specifications shall be provided. They must comply with European legislation on plastic materials and articles intended to come into contact with food, or with the general chapters of the European Pharmacopoeia applicable to them.

2.1.7. Stability: Information on the stability studies carried out, and their conclusions (retest period or shelf life and storage conditions), shall be presented. In the absence of such studies and, thus, where no retest period or shelf life has been established for the herbal substance and/or extract, these shall comply with the specifications immediately prior to use.

2.2. Standardised cannabis preparation

If the standardised cannabis preparation contains more than one standardised extract, the above-mentioned information shall be presented for each of them.

Where the manufacturing process of the standardised cannabis preparation includes the mixing of different standardised extracts and/or their dilutions, the following information shall also be provided:

2.2.1. Description and composition of the mixture of standardised extracts and/or their dilutions.

2.2.2. Manufacture of the mixture of standardised extracts and/or their dilutions:
- Manufacturers involved in the process.
- Batch formula: The detailed batch formula of the proposed size shall be provided.
- Description of the manufacture process and process controls.

2.2.3. Excipient control: Information should be provided on the quality and control thereof, if necessary.

2.2.4. Control of the mixture of standardised extracts and/or their dilutions:

2.2.4.1. Specifications: Detailed information on the specifications used for its control shall be provided.

2.2.4.2. Analytical procedures: The analytical procedures used for the control shall be described in sufficient detail so that they can be reproduced in tests carried out at the request of the competent authority. In the case of test procedures included in the European Pharmacopoeia, this description may be replaced by the corresponding reference to the monograph(s) and general chapter(s).

2.2.4.3. Validation of analytical procedures: The validation results of the analytical procedures used for their control shall be provided.

2.2.4.4. Batch analysis: Results of analyses of representative batches shall be submitted.

2.2.4.5. Justification of specifications: The proposed specifications shall be justified.

2.2.5. Standards or reference materials: The standards and reference materials used in its control shall be identified and described in detail, in case they do not coincide with those used for the control of the extract.

2.2.6. Packaging material: The description of the container and the closure system and its specifications shall be provided. They must comply with European legislation on plastic materials and articles intended to come into contact with food, or with the general chapters of the European Pharmacopoeia applicable to them.

2.2.7. Stability: Information on the studies carried out and their conclusions (validity period and storage conditions) shall be included.