MINISTRY OF HEALTH

Decree-Law no. 20/2013

of February 14th

Directive no. 2010/84/UE, of the European Parliament and the Council, of 15th December 2010, introduced various amendments, as to pharmacovigilance, to Directive no. 2001/83/CE, of the European Parliament and the Council, of 6th November 2001, amended several times already and which is transposed into national law by Decree-Law o. 176/2006, of 30th August, which established the legal system of the medicinal products for human use usually referred to as Medicinal Products Statute, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June and 106-A/2010, of 1st October, and laws nos. 25/2011, of 16th June, 62/2011, of 12th December and 11/2012of 8th March.

Therefore it is important to carry out the transposition and reformulation of the National System of Pharmacovigilance, so as to incorporate the new provided requirements to ensure a better capacity for detection, monitoring and supervision and risks detection when using medicinal products within the European level. This way, the safe use of medicinal products in our country is reinforced, enabling patients, healthcare professionals and the society to increase their trust in the medicinal product as the most used health technology in modern health systems. On the other hand, as a consequence of the application, since about six years, of Decree-Law no. 176/2006, of 30th August, several adjustments and improvements take place aiming at readjusting procedures and meeting needs for regulation resulting from the evolution of the medicinal product sector, clarifying provisions regarding allergen and homeopathic medicinal products, making the wholesale distribution of medicinal products system more flexible, procedures regarding the granting and expiration of marketing authorization of medicinal products, aspects related with advertisement and the update of the administrative offence liability.

This way flexibility, transparency and adjustment measures are introduced, making the Medicinal Product Statute more suitable to the growing regulation requirements and improve the intervention capacity of INFARMED – *Autoridade Nacional do Medicamento e Produtos de Saúde*, I.P. (National Authority for Medicinal and Health Products).

The matters governed by the new legal instrument include, among others, the mentioned transparency rules applying to the issue of comments, analysis and studies

disclosed by entities sponsored by operators within the scope of the medicinal product economics. Furthermore, it is important to take care of the transparency of the public manifestations of the civil society groups. The aim is also to disclose the allocation and reception, among any entities, the economic advantages with impact on the activity within the medicinal product policy, from patients associations to clinical studies societies as well as the healthcare professionals.

Pharmacists' Association, Portuguese Dental Association, Nurses Association, National Association of Pharmacies, Portuguese Association of Pharmaceutical Industry, Portuguese Association of Generic Medicinal Products, and *Plataforma Saúde em Diálogo* (health forum platform) – Association for the Promotion of Health and Protection against Disease and the Portuguese Federation for Rare Diseases were heard on an optional basis.

The hearing of Physicians' Association, Association of Pharmacies in Portugal and Portuguese Association of Advertising, Marketing and Communication Companies was promoted.

Therefore:

Within the development of the legal system established by Basic Law on Health, approved by Law no. 48/90, of 24th August, and according to the provisions of subparagraph c) of no. 1 of article 198 of the Constitution, the Government decrees the following:

Article 1

Object

This legal instrument introduces the seventh amendment to Decree-Law no. 176/2006, of 30th August, establishing the legal system for medicinal products of human use, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October, and Laws nos. 25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March, transposing to national law Directive no. 2010/84/UE, of the European Parliament and the Council, of 15th December 2010, which amends, as to pharmacovigilance, the Directive no. 2001/83/CE, which establishes a community code regarding medicinal products for human use.

Article 2

Amendment to Decree-Law no. 176/2006, of 30th August

Articles 1, 2, 3, 9, 14, 15, 16, 18, 24, 26, 27, 28, 29, 30, 45, 46, 52, 53, 54, 68, 75, 76, 77, 79, 87, 92, 93, 95, 96, 97, 100, 103, 104, 106, 120-A, 124, 137, 147, 152, 153, 154, 158,

159, 162, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 179, 181, 182, 189 and 202 of Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October, and by Laws nos. 25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March, have the following wording from now on:

«Article 1

[…]

1 - […].

2 - […]:

a) […];

b) […];

c) […];

d) […];

e) […];

f) […];

g) Directive no. 2008/29/CE, of the European Parliament and the Council, of 11th March 2008, which amends Directive no. 2001/83/CE, establishing a community code regarding medicinal products for human use, as far as implementing powers conferred to the Commission are concerned;

h) Directive no. 2009/120/EC, of the Commission, of 14th September 2009, which amends Directive no. 2001/83/EC, of the European Parliament and the Council, establishing a community code regarding medicinal products for human use, as far as advanced therapy medicinal products are concerned;

i) Directive no. 2010/84/UE, of the European Parliament and the Council, of 15th December 2010, which amends, in what regards pharmacovigilance, Directive no. 2001/83/CE, establishing a community code regarding medicinal products for human use.

3 - […].

Article 2

[…]

1 - […].

2 - […].

3 - […].

4 - [...].

5 – The provisions of chapter X apply to experimental medicinal products.

Article 3

[...]

1 - [...]:

a) [...];

b) [...];

c) [...];

d) [...];

e) [...];

f) [...];

g) [...];

h) [...];

i) [...];

j) [...];

k) «Actual marketing», provision of medicinal products in public dispensing places, or to entities authorized to purchase medicinal products directly, documented by bill of sale submitted to INFARMED – *Autoridade Nacional do Medicamento e Produtos de Saúde*, I.P., (National Authority for Medicinal and Health Products) hereinafter referred to as INFARMED, I.P.;

l) «Common name», international non-proprietary name recommended by the World Health Organization for active substances of medicinal products (INN), according to rules established and which may not be the subject of registration of a trade mark or name, or in the absence of the latter, the usual common name or generic name of an active substance of a medicinal product, under the terms suitable for Portugal or defined periodically by INFARMED, I.P.;

m) [Former subparagraph n)];

n) [Former subparagraph o)];

o) «The master file of the pharmacovigilance system», a detailed description of the pharmacovigilance system used by the holder of the marketing authorization in regard with one or various authorized medicinal products;

p) [...];

q) «Post-authorization safety study», a study on an authorized medicinal product aiming at identifying, characterizing or quantify a safety risk, confirming the safety

profile of the medicinal product or measuring the efficacy of the risks management measures;

r) […];

s) […];

t) […];

u) […];

v) […];

w) [Former subparagraph x)];

x) [Former subparagraph z)];

y) [Former subparagraph aa)];

z) [Former subparagraph bb)];

aa) [Former subparagraph cc)];

bb) [Former subparagraph dd)];

cc) [Former subparagraph ee)];

dd) [Former subparagraph ff)];

ee) «Allergenic medicinal product», the medicinal product aiming at identifying or inducing a specific acquired change in the immunological response to an allergen;

ff) [Former subparagraph gg)];

gg) [Former subparagraph hh)];

hh) [Former subparagraph ii)];

ii) «Advanced therapy medicinal product», product defined in article 2 of Regulation (EC) n º 1394/2007,of the European Parliament and the Council, of 13th November 2007, and in no. 2 of parte IV of annex I of this decree-law;

jj) […];

kk) [Former subparagraph ll)];

ll) [Former subparagraph mm)];

mm) [Former subparagraph nn)];

nn) [Former subparagraph oo)];

oo) [Former subparagraph pp)];

pp) [Former subparagraph qq)];

qq) [Former subparagraph rr)];

rr) [Former subparagraph ss)];

ss) «Urgent safety measure», a transient change of information on the medicinal product, based on new data regarding the safety of the use of the medicinal product, which concerns, namely, one or more of the following particulars listed in the

summary of the product characteristics: therapeutic indications, dosage, contraindications and warnings;

tt) «Name of the medicinal product», name of the medicinal product which may include a brand, or an invented name, unlikely to be mistaken for the common name; the common name with a trade mark, or an invented name; or the common name with the applicant's name, or the holder of the marketing authorization, provided, in any case, there is no misunderstanding with the therapeutic properties and the nature of the medicinal product;

uu) [Former subparagraph vv)];

vv) [Former subparagraph zz)];

ww) [Former subparagraph xx)];

xx) «Risk management plan», a detailed description of the risk management system;

yy) [Former subparagraph aaa)];

zz) [Former subparagraph bbb)];

aaa) «Healthcare professional », the person legally qualified to prescribe, dispense or administrate medicinal products, namely physicians, dentists, veterinary practitioners, dental surgeons, pharmacists or nurses;

bbb) [Former subparagraph ddd)];

ccc) « Adverse Reaction », a harmful and non-intentional reaction to a medicinal product;

ddd) [Former subparagraph fff)];

eee) [Former subparagraph ggg)];

fff) [Former subparagraph hhh)];

ggg) [Former subparagraph iii)];

hhh) [Former subparagraph jjj)];

iii) «[Former subparagraph lll)];

jjj) [Former subparagraph mmm)];

kkk) «Pharmacovigilance system», a system used by the holder of the marketing authorization and the Member States, in order to comply with the tasks and responsibilities included in chapter X, aiming at following up the safety of the authorized medicinal products and the detection of changes in the respective benefit-risk ratio;

lll) «Risk management system», a group of activities and pharmacovigilance measures aiming at identifying characterizing, preventing or minimizing the risks associated to

a medicinal product, including the assessment of the efficacy of those activities and measures;

mmm) [Former subparagraph nnn)];

nnn) [Former subparagraph ooo)];

ooo) «Transference», change of the holder of the authorization, or registration of the marketing authorization of a medicinal product, provided it is not only the change of the holder's name, which should be the same;

ppp) [Revoked].

2 – In case of doubt and when, according to all its characteristics, a certain product may be covered by the definition of the medicinal product, under the provisions of subparagraph cc) of the previous number, the provisions of this decree-law shall apply.

3 – For the purposes of the provisions of subparagraph zz) of no. 1, any pharmacopoeia or formulary recognised in Portugal is accepted, including official approved pharmacopoeias and formularies or if recognised by the maximum body of INFARMED, I.P.

4 – The definitions included in no. 1 should be interpreted in the light of the guidelines of the European Commission and adopted by regulation of INFARMED, I.P.

Article 9

[...]

1 - [...].

2 - The manufacturers, holders of authorizations or registrations, wholesale distributors and entities legally authorized to purchase directly or to dispense medicinal products to the public should provide INFARMED, I.P., with any information they have, within the scopes covered by this decree-law, in the cases and terms provided for in regulation of this National Authority.

Article 14

[...]

1 - [...].

2 – The decision to grant the marketing authorization to a medicinal product should be based exclusively on objective scientific criteria of therapeutic quality, safety and efficacy of the concerned medicinal product, aiming primarily at the protection of public health, regardless of any considerations of economic nature or other.

3 - [Former no. 2].

4 – All authorizations mentioned in the previous number are part of the same marketing authorization, and do not grant, namely, the right to any further period of time for data protection.

5 - [Former no. 4].

Article 15

[…]

1 - […].

2 – The application is accompanied by the following details and documents, in Portuguese or English or in both languages:

a) […];

b) […];

c) […];

d) […];

e) […];

f) […];

g) […];

h) […];

i) […];

j) […];

k) Summary of the pharmacovigilance system, showing that the applicant has the necessary means to comply with the tasks and responsibilities provided for in chapter X and has appointed a qualified person responsible for pharmacovigilance, as well the statement of the Member States where that person lives and runs his business, the respective contacts and the place where the master file of the pharmacovigilance system is kept;

l) Risk management plan describing the risk management system to be applied by the applicant and a summary of that plan;

m) […];

n) A copy of the marketing authorizations of the medicinal product in other Member states, as well as the decisions for refusing the authorization, including the respective reasons, and a summary of the safety-related data, including if it is the case, the ones included in periodic safety reports and the suspected adverse reaction reports;

o) A copy of the marketing authorizations of the medicinal product in third countries as well as the decisions for refusing the authorization, including the respective reasons,

and a summary of the safety-related data, including if it is the case, the ones included in the periodic safety reports and the suspected adverse reaction reports;

p) Specification of the Member states where a marketing authorization for the concerned medicinal product has been submitted, including copies of the summaries of the medicinal products characteristics and the proposed or authorized package leaflets;

q) […];

r) [Revoked];

s) […];

t) […].

3 - […].

4 - […].

5 - […].

6 - […].

7 - […].

8 – The risk management system mentioned in subparagraph l) of no. 2 is proportional to the identified and potential risks of the medicinal product and to the need of obtaining the post-authorization safety-related data, and should include all conditions and injunctions established according to the provisions of article 24 and 26-A.

9 – All information mentioned in number 5 is kept permanently updated.

Article 16

[…]

1 - […].

2 - […].

3 - […].

4 – All information provided with the application is permanently updated by the applicant, as to safety-related data of the medicinal product and in what concerns the elements mentioned in subparagraphs n), o) and p) of no. 2 of article 15.

5 - […].

6 - […].

7 - […].

8 - […].

9 - […].

Article 18

[…]

1 - […].

2 - […].

3 - […].

4 - […].

5 – The summary of the characteristics of the medicinal products included in the list mentioned in article 23 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004, should include the statement «Medicinal product subject to additional monitoring», preceded by the black symbol mentioned in the same article and a standard explanatory sentence to be set up by INFARMED, I.P.

6 – Each medicinal product is accompanied with a standard text where the healthcare professionals are expressly requested to report all suspicions of adverse reactions, in compliance with national spontaneous reporting system mentioned in article no. 1 of article 172, through the means provided for in no. 3 of the same article.

Article 24

[…]

1 – The authorization may be granted under the condition of the development of subsequent complementary studies or the compliance with special rules.

2 – In exceptional cases and provided the applicant shows, through objective and verifiable reasons, that he cannot provide the full data on the efficacy and safety of the medicinal product in normal conditions of use, the authorization may be subject to certain conditions, namely with regards to safety and the reporting of all incidents associated with its use and the measures to be taken, in the cases and according to the provisions of annex I.

3 - The implementation of the previous number is preceded by the hearing of the applicant, and INFARMED, I.P. disclosing suitably and immediately the conditions, deadlines and dates for implementation.

4 – The authorization granted under the provisions of nos. 2 and 3 is reassessed annually, and the holder should request for its reassessment, duly justified, up to 90 days before the authorization expires, subject to revocation.

5 – In addition to the provisions of no. 6 of article 16, article 17 and no. 2 of article 23, a marketing authorization may be granted for a medicinal product, provided the respective applicant, or holder, meet one of the following conditions:

a) To include in the risk management system measures, to be set out by INFARMED, I.P., according to criteria of need, suitability and proportionality, aiming at guaranteeing the safe use of the medicinal product;
b) To carry out post-authorization safety study;
c) To comply with the obligations regarding registration or suspected adverse events reporting, to be set out by INFARMED, I.P., according to criteria of need, suitability and proportionality, which must be more demanding than the ones provided for under chapter X;
d) To meet any other conditions or restrictions, to be set out by INFARMED, I.P., according to criteria of need, suitability and proportionality, regarding the safe and efficient use of the medicinal product;
e) To have a suitable pharmacovigilance system;
f) To carry out post-authorization efficacy studies, in case there are doubts regarding the efficacy of the medicinal product, which may be clarified only after the medicinal product has been marketed, taking into account the guidelines of the European Commission, if any.
6 – If necessary, the marketing authorization establishes deadlines for the fulfilment of the conditions mentioned in the previous number.

Article 26

[…]

1 - […].
2 – In case of successful application:
a) The applicant is notified of the authorization decision certificate, including the number of the marketing authorization registration number of the medicinal product and the contents of the labelling according to the approved terms;
b) The approved summary of the medicinal product characteristics and the package leaflet are published on the webpage of INFARMED, I.P..
3 - […].
4 - […].
5 - INFARMED, I.P., informs the Agency of the marketing authorizations granted under conditions or injunctions, according to the provisions of article 24 and 26-A.

Article 27

[…]

1 - Notwithstanding the provisions of article 77, the marketing authorization is valid for five years, renewable according to the provisions of the following article.
2 – After the first renewal, the authorization is valid indefinitely, unless INFARMED, I.P., for justified reasons related to pharmacovigilance, namely the exposure of an insufficient number of patients to the concerned medicinal product, requires the renewal for an additional period of five years.

Article 28

[…]

1 - […].
2 - The application for renewal is submitted, at least, nine months before the expiry date of the authorization.
3 - […]:
a) It is accompanied by a consolidated and updated version of the process as to the quality, safety and efficacy of the medicinal product, including the assessment of the data included in suspected adverse reactions reporting and the periodic safety reports submitted according to chapter X, as well as information on all the amendments made since the marketing authorization has been granted;
b) […];
c) […].
4 - […].
5 - Notwithstanding the provisions of the final part of no 1 of article 16, the application which does not comply with the provisions of nos. 2 and 3 is deemed invalid and returned to the applicant stating the grounds for invalidation.
6 – The non filling of the application for renewal within the established deadline, the invalidation of that application or its refusal, involve the expiry of the authorization, at the time of the deadlines mentioned in the previous number or within the period of time established by the decision.
7 – The decision on the application for renewal is notified to the applicant and when, unfavourable, it should include the respective grounds.

Article 29

[…]

1 - […]:
a) […];

b) […];

c) […];

d) […];

e) […];

f) […];

g) […];

h) […];

i) […];

j) Conveys precisely and promptly to INFARMED, I.P. the pharmacovigilance data, or others, which prove that the risk-benefit ratio is still favourable, whenever the National Authority requests them;

k) [Former subparagraph l)];

l) [Former subparagraph m)];

m) Ensures that the information on the medicinal product is updated in respect of the most recent scientific developments and include the assessment conclusions and the recommendations published at the European portal of medicinal products, mentioned in article 26 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004;

n) Submits to INFARMED, I.P., upon request and within a maximum period of time of seven days, a copy of the master file of the pharmacovigilance system;

o) [Former subparagraph n)].

2 - […].

3 - […].

4 – For the purposes of subparagraph f) of no. 1, and upon a request by INFARMED, I.P., the holder of the marketing authorization is under the obligation to submit, within the period of time established for this purpose, a consolidated and updated version of the process as to the quality, safety and efficacy of the medicinal product, including all the amendments made since the initial granting of the authorization.

5 – The information provided for in subparagraph i) of no. 1 include the positive and negative results of the clinical trials or other studies regarding all indications and populations, irrespective of their inclusion in the marketing authorization, as well as the data on the use of the medicinal product, when this use is outside the terms of the marketing authorization.

Article 30

[…]

1 - […].

2 - […].

3 - […].

4 - Notwithstanding the approved regulation adopted by INFARMED, I.P., the National Authority:

a) Makes publicly available, namely on its webpage, the assessment report mentioned in the following subparagraph, the marketing authorization, the package leaflet, the summary of the characteristics of the medicinal product and all conditions and injunctions provided for in nos. 2 and 5 of article 24 and nos. 1 to 5 of article 26-A, as well as the deadlines for compliance with those conditions;

b) Draws up an assessment report and remarks regarding the results of the pre-clinical and clinical pharmaceutical trials of the medicinal product, as well as the respective risk management and pharmacovigilance systems and the report should be updated whenever there is new information deemed important for the assessment of the quality, safety and efficacy of the medicinal product and include an autonomous justification regarding each one of the indications required for the medicinal product.

5 – The public disclosure of the assessment report, accompanied by the respective reasoning should be carried out, separately, for each required indication and avoiding any confidential commercial information.

6 – The report mentioned in the previous number should include a written summary, comprehensible to the public, which should include, namely, a section regarding the conditions of use of the medicinal product

Article 45

[…]

1 – Notwithstanding the provisions of no. 6, Committee for Human Use Medicinal Products of the Agency (CHMP) may be requested to intervene whenever one of the following situations occurs:

a) Following the opinion provided for in the previous number, the agreement among the involved member States is not reached within the Coordination Group provided for in article 27 of Directive no. 2001/83/EC, of the European Parliament and the Council, of 6th November 2001, according to the wording given by Directive no. 2010/84/EU, of the European Parliament and the Council, of 15th December 2010, within 60 days;

b) The Community interest so justifies and INFARMED, I.P., proposes to make a decision to amend the terms of a marketing authorization or its suspension or revocation;

c) [Revoked].

2 - […].

3 - […].

4 – The issue to submit to CHMP should be clearly defined, duly notifying the applicant and the holder of the marketing authorization, when CHMP intervention has not been required by them, if applicable.

5 - INFARMED, I.P., and the applicant or the holder of the marketing authorization should send to CHMP all available information regarding the matter concerned.

6 – If turning to arbitration result from the assessment of the data regarding pharmacovigilance of an authorized medicinal product, the issue is submitted to PRAC and the procedure provided for in no. 2 of article 175-A may apply.

7 – The governing and procedure rules applicable to CHMP and PRAC are set out under European Union law.

Article 46

[…]

1 - […].

2 - [Revoked].

3 - [Revoked].

4 - [Revoked].

Article 52

[…]

1 - Notwithstanding the provisions of no. 6, CHMP intervention may be requested whenever one of the following situations occurs:

a) Following the opinion provided for in the previous article, the agreement among the involved Member States is not reached within the Coordination Group provided within 60 days;

b) The Community interest so justifies and INFARMED, I.P., proposes to make a decision of amending the terms of a marketing authorization or its suspension or revocation;

c) [Revoked].

2 – The intervention of CHMP may also be requested in case the Member States take diverging decisions regarding the authorization, suspension or revocation of the marketing authorization regarding a medicinal product, or before any decision to amend the terms of a marketing authorization is made, namely for pharmacovigiliance reasons.

3 - [...].

4 – The issue of submitting to CHMP should be clearly set out, duly notifying the applicant and the holder of the marketing authorization, when CHMP intervention has not been required by them, if applicable.

5 - INFARMED, I.P., and the applicant or the holder of the marketing authorization should send to CHMP all available information regarding the subject concerned.

6 - If turning to arbitration result from the assessment of the data regarding pharmacovigilance of an authorized medicinal product, the issue is submitted to PRAC and the procedure provided for in no 2 of article 175-A may apply.

7 - The governing and procedure rules applicable to CHMP and PRAC are set out under European Union law.

Article 53

[...]

1 - [...].

2 - [Revoked].

3 - [Revoked].

4 - [Revoked].

Article 54

[...]

1 - [...].

2 – The holders of a marketing authorization granted under the laws mentioned in the previous number request INFARMED, I.P., to be ascribed a registration number of the marketing authorization of the medicinal product, according to the terms to be set out by regulation of the mentioned National Authority.

Article 68

[...]

1 - [...].

2 - [...].

3 - [...].

4 - [...].

5 – The documents provided for in this article are at the disposal of the employees, officers or agents of INFARMED, I.P., and of other competent authorities, during the periods of time provided for in nos. 2 and 3.

Article 75

[...]

1 - [...].

2 - [...].

3 - [...].

4 - INFARMED, I.P., may be required to issue a scientific opinion on the assessment of medicinal products intended exclusively to be exported.

Article 76

[...]

1 - [...].

2 - [...].

3 - [...].

4 – If the manufacturer is not the holder of a marketing authorization, it should, for the purposes of no. 1, provide INFARMED, I.P., with a declaration detailing the reasons why it has not been granted such a marketing authorization.

5 - [...].

Article 77

[...]

1 - [...].

2 - [...].

3 – The actual non-marketing of the medicinal product for three consecutive years, for any reason, provided not imposed by law or court decision ascribable to INFARMED, I.P., involves the expiry of the respective authorization or registration.

4 – As soon as the expiry is detected, the latter is the subject of publication on the webpage of INFARMED, I.P., and the medicinal product goes under disposal regime within 90 business days, counting from the mentioned publication.

5 – The holder of the marketing authorization or registration has 10 business days counting from the publication mentioned in the previous number to claim and prove the facts that prevent the forfeiture.

6 - If INFARMED, I.P., considers the claim to be relevant, the authorization or registration does not expire for three years and is deemed as valid in the medicinal products database.

7 – In addition to the grounds provided for in no. 3, INFARMED, I.P. may not declare the forfeiture of the authorization or registration, only under the following circumstances:

a) Medicinal product with no alternative therapy or for which there are no alternative manufacturers;

b) Vaccine or medicinal product to be used exclusively in the hospital which has not been selected within the scope of public tender for supply;

c) Medicinal product which can be used in situations of disaster or pandemic situations;

d) Medicinal product for which Portugal acts as a reference Member State and the maintenance of the respective authorization is necessary to ensure the continuity of the supply of the medicinal product in the involved State or States;

e) Medicinal product intended to be exported;

f) Medicinal product with a reimbursement request not yet granted.

Article 79

[...]

1 - [...].

2 - [...].

3 – The authorization mentioned in subparagraph e) of no.1 is granted for a single operation of direct purchase of medicinal products and is compliant with the requirements and conditions laid down by INFARMED, I.P., on the respective authorization or regulation.

4 – Except for the provisions of subparagraph c) of no. 1 of article 92, the pharmacies and entities authorized to purchase directly medicinal products may only purchase them from entities authorized by INFARMED, I.P.

Article 87

[...]

1 - [...].

2 – The price of the medicinal product which is the subject of parallel imports is governed by special regulation.

Article 92

[...]

1 - INFARMED, I.P., may authorize the use of a medicinal product in Portugal with none of the remaining authorizations provided for in this Decree-Law, or in Decree-Law no. 195/2006, of 3rd October, amended by Decree-Law no. 48-A/2010, of 13th May, or which, having been granted one of those authorizations, is not actually marketed, under one of the following conditions:

a) [...];

b) [...];

c) [...].

2 - [...].

Article 93

[...]

1 - [...].

2 - [...].

a) [...];

b) It may request the competent authority of the mentioned Member State an updated copy of the assessment report and the marketing authorization in force for the concerned medicinal product.

3 - [...].

4 - [...].

5 – The holder of the marketing authorization granted under this article should ensure the compliance with the provisions of this decree-law, namely as to advertisement and pharmacovigilance, except for regulations of INFARMED, I.P., adopted for the cases provided for in no. 1 of the previous article or for labelling and package leaflet.

6 - [...].

7 - [...].

8 - [...].

Article 95

[…]

1 - […].

2 - [Revoked].

3 – The provisions of no. 1 do not exempt the respective holder from the compliance with the remaining provisions of this decree-law.

Article 96

[…]

1 - […].

2 - […]

a) […];

b) […];

c) […];

d) […];

e) Evidence of the compliance with legal requirements with respect to prevention of fire risk;

f) Copy of the contracts signed with the person in charge with technical directorate and, when necessary, with the wholesale distributor ensuring the storage of the medicinal products;

g) [Former subparagraph f)].

3 - […].

Article 97

[…]

1 - […]:

a) Technical directorate which ensure efficiently and permanently, the quality of the activities carried out at the site for which the marketing authorization is granted, according to the provisions set out by regulation of INFARMED, I.P.;

b) […].

2 - […].

3 - […].

4 - […].

5 – When there is a request for a wholesale distribution authorization for a site located in the same building or complex where other facilities included under the same

wholesale distribution authorization are already installed, the technical director, for the purposes of the already granted authorization, may combine these duties with those of technical director for the purposes of the new authorization, provided such combination is included in a written contract signed by the applicant, the holder of the authorization and the technical director.

6 – The mentioned technical director may not combine duties, according to the provisions of the previous number, regarding more than five different sites.

Article 100

[…]

1 - […]:

a) To comply with the good practices of distribution, namely with respect to the conditions of preservation, storage, transport and recall of medicinal products;

b) […];

c) […];

d) […];

e) […];

f) […];

g) […];

h) […];

i) […].

2 - […].

3 - […].

4 - […].

5 - […].

Article 103

[…]

1 - […].

2 - [Revoked].

3 – Notwithstanding the provisions of this decree-law, the State's reimbursement system for the medicinal products and of the assessment prior to the purchase of the medicinal products by the hospitals of National Health Service (NHS) are subject to special legislation and the regulation complied with when applying these systems.

4 - […].

Article 104

General principles

1 - [*Former body of the article*].

2 – If the medicinal product is intended to be administered to the patient by a healthcare professional, or if there are serious problems regarding the availability of the medicinal product, INFARMED, I.P., may by regulation and provided the conditions required for the safeguard of human life are ensured, exempt the inclusion, on the labelling or the package leaflet of certain medicinal products, of some of the statements required by the following articles, as well as the wording in Portuguese of the labelling and the package leaflet.

Article 106

[…]

1 - […].

2 - […].

3 - […]:

a) […];

b) […];

c) […];

d) […].

e) […].

f) […]:

g) Description of the adverse reactions which may occur with the normal use of the medicinal product, as well as, if necessary, of the measures to take;

h) […]:

i) […];

j) […].

4 - […].

5 - […].

6 - […].

7 – In the case of medicinal products included in the list mentioned in article 23 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004, the additional statement is included: «Medicinal product subject to additional monitoring», which should be preceded by a black coloured symbol

mentioned in the same article followed by a suitable and standardized explanatory sentence.

8 – All medicinal products are accompanied with a standard text where the users are expressly requested to report all suspected adverse reactions to their physician, pharmacist or healthcare professional, or directly to the spontaneous national reporting system mentioned in no. 1 of article 172, by the means provided for in no. 3 of the same article.

Article 120-A

[…]

1 – When dispensing a medicinal product, the pharmacist, or his duly qualified assistant, should inform the patient of other medicinal products, available at the pharmacy, with the same active substance, pharmaceutical form, package and dosage of the prescribed medicinal product, as well as on those reimbursed by NHS and the one with the lowest price available in the market.

2 - […].

3 - […].

4 - […].

Article 124

[…]

1 - […].

2 – The marketing and use, within the Portuguese territory, of allergen medicinal products are subject to simplified authorization by the higher body of INFARMED, I.P., provided they comply with all the following conditions:

a) They do not have a marketing authorization;

b) They are manufactured according to the provisions of no.1 of article 2;

c) They are intended for a specific patient.

3 – The authorization, manufacture, distribution and dispensing of allergen medicinal products complying with the conditions mentioned in the previous number are subject to special law, set out by regulation of INFARMED, I.P.

4 – Allergen medicinal products complying with the conditions mentioned in no. 2 are subject, with due adjustments, to this decree-law and the provisions of the legislation regarding good practices of manufacture, notwithstanding the provisions of the regulation adopted under the previous number.

5 - [Former no. 3].

6 - [Former no. 4]

Article 137

[…]

1 - […]:

a) […];

b) Show a degree of dilution guaranteeing the harmlessness of the medicinal product;

c) […].

2 – For the purposes of subparagraph b) of the previous number, the medicinal product is considered not showing a degree of dilution which guarantees its harmlessness when any of these situations occur:

a) The medicinal product contains more than one part per 10 000 of mother tincture;

b) The medicinal product contains more than 1/100 of the smallest dose used in allopathy, with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

3 - [Former no. 2].

4 - [Former no. 3].

Article 147

[…]

In addition to the provisions of the previous articles, to the registration of traditional use provided for in this section is still applicable, mutatis mutandis, the provisions of subparagraph b) of no. 2 and in subparagraph c) do no. 3 of article 2, in nos. 1 and 5 of article 14, in no. 5 of article 15, no. 1 of article 16, no article 17, no. 1 of article 23, in articles 27 and 28, in subparagraph b) of no. 1 and no. 2 of article 29, in articles 55 to 76, in articles 94 to 102, in articles 113 to 120, in articles 166 a 179, in no. 1 of article 180, in articles 181 to 185 and in no. 2 of article 196.

Article 152

[…]

1 - […].

2 - […]:

a) […];

b) […];

c) Reimbursed by NHS.

3 - [...].

4 - [...].

5 - [...].

Article 153

[...]

1 - [...].

2 - [...].

3 – Advertising to the general public includes, at least, and in a legible way, in the advertisement itself, the following information:

a) [...];

b) [...];

c) [...].

4 - [...].

5 - [...].

6 - [...].

7 – The holder of a marketing authorization or registration, the company responsible for the information or promotion of a medicinal product or the wholesale distributor cannot give or promise directly or indirectly, to the general public, prizes, gifts, bonuses or benefits whether in money or in kind.

Article 154

[...]

1 - [...].

2 – The advertising of a medicinal product among healthcare professionals includes, in a legible way, in the advertisement itself:

a) [...];

b) [...];

c) [...];

d) [...].

3 - [...].

4 - [...]:

a) [Revoked];

b) [...].

5 – All and every advertisement of medicinal products in computer applications of electronic medical prescription, as well as in other applications or computer programs in connection with the former is forbidden.

Article 158

[…]

1 – The holder of a marketing authorization or registration, the company responsible for the information or promotion of a medicinal product or the wholesale distributor cannot give or promise directly or indirectly, to healthcare professionals or their patients prizes, gifts, bonuses or benefits whether in money or in kind, unless they are inexpensive and relevant for the practice of medicine or the pharmacy.

2 - […].

3 - […].

4 - [The payment of fees to healthcare professionals for their active participation, namely by means of the presentation of scientific papers in events of this nature or in training courses and promotion sessions of medicinal products does not violate the provisions of no. 1 and 2, provided that, in any case, the mentioned payment does not depend or is the compensation for the prescription or dispensing of medicinal products.

5 - […].

Article 159

[…]

1 - […].

2 - […].

3 - […].

4 - […].

5 – Any entity covered by this decree-law, directly or through an intermediary, which grants or delivers any subsidy, sponsorship, subvention or any other sum, money-convertible asset or right, to an association or any other type of entity, regardless of its nature or form, representing a specific patients' group, or else the company, association or medical society of scientific or clinical studies nature, undertakes the obligation to communicate such fact, within 30 days, to INFARMED, I.P., using a suitable section of the webpage of this National Authority.

6 - All and every association, or any other type of entity, regardless of its nature or form representing a specific patients' group, association or medical society of scientific

or clinical studies nature, or else all and any entity, corporate body or individual, which receives subsidy, sponsorship, subvention or any other sum, money-convertible asset or right, according to the provisions of the previous number, undertake the obligation to communicate such fact, within 30 days, to INFARMED, I.P., using a suitable section of the webpage of this National Authority, as well as to mention such fact in all documents intended for public disclosure it issues within the scope of its activity.

7 - INFARMED, I.P., makes the information provided for in the previous numbers available on its webpage.

Article 162

[...]

1 - [...].

2 – The limit provided for in subparagraph a) of the previous number may be included in the marketing authorization of the medicinal product or be defined in general terms by INFARMED, I.P., and cannot be, each year, greater than 12 units.

3 - [...].

4 - [...].

5 - [...].

Article 166

[...]

1 – National Pharmacovigilance System of Medicinal Products of Human Use is created, and shall be hereinafter referred to as System, comprising an articulated set of rules and material and human resources to achieve the following objectives:

a) Systematic collection of information on the risks of the medicinal products for patients and public health, mainly with regard to adverse reactions:

i) In the human being, resulting from the use of the medicinal product according to the terms of the marketing authorization or outside those terms, including overdose, misuse, abuse and medication errors;

ii) Associated with occupational exposure.

b) Scientific assessment of all information mentioned in the previous subparagraph;

c) Weighting of safety measures suitable for the prevention or minimization of risks;

d) Adoption of necessary regulatory measures, regarding the marketing authorization;

e) Handling and processing the information, under the terms resulting from the national and the European Union standards and guidelines, namely by conveying it to

the other Member States and the Agency, as well as the participation, upon request of the European Commission, in the harmonization and standardization of technical measures of pharmacovigilance at an international level, coordinated by that Agency;

f) Communication and dissemination of other information relevant for the healthcare professionals, the patients and the general public.

2 - [...].

3 - [...].

Article 167

Supervision and operation of the System

1 - INFARMED, I.P., should audit periodically the System and communicate the results of those audits to the European Commission twice a year.

2 – Within the scope of the System, INFARMED, I.P.:

a) Takes all suitable measures to encourage the suspected adverse reactions reporting by the patients and the healthcare professionals, separately or as far as it is necessary, with the participation of the organizations representing the consumers, patients and healthcare professionals;

b) Provides the patients with the means, namely electronic ones, to facilitate the reporting of the suspicions mentioned in the previous subparagraph;

c) Takes the suitable measures to retrieve precise and verifiable data for the scientific assessment of the suspected adverse reactions reporting;

d) Publishes, in useful time, on its webpage and, if necessary, in the media, the relevant information for the use of a certain medicinal product, with regard to pharmacovigilance;

e) Ensures, through methods of information collection and, if necessary, through the follow-up of the suspected adverse reactions reporting, that the reports of these suspicions regarding biological medicinal products prescribed, distributed or sold in Portugal, identify these medicinal products through their name and batch number.

3 - INFARMED, I.P., may delegate in the competent national authority of another Member State its competences as for pharmacovigilance provided for in this chapter, by means of the written agreement of the mentioned authority and provided the latter does not represent another Member State simultaneously.

4 - INFARMED, I.P., should communicate the delegation provided for in the previous number to the European Commission, the Agency and the competent national authorities of the other Member States, and carry out the respective publication on its webpage.

Article 168

System structure

1 – The System structure ensures the integration of the competent services, so as to pursue the objectives provided for in no. 1 of article 166 and the full participation of the public or private health care units and facilities.

2 - [...].

Article 169

[...]

1 - [...].

2 - [...].

3 – In the case of biological medicinal products reporting, the reports should include the name of the medicinal product and the number of the respective batch.

4 – The reporting shall be carried out according to the provisions of no. 3 of article 172.

Article 170

General obligations of the holder of the marketing authorization

1 - To comply with their pharmacovigilance obligations, the holders of the marketing authorizations or registration should adopt and keep a pharmacovigilance system equivalent to the system provided for in articles 166 to 168.

2 – Based on the pharmacovigilance system mentioned in the previous number, the holders of marketing authorizations, or registration, carry out the scientific assessment of all information, consider options to minimise and prevent risks and take the necessary regulatory measures.

3 – The holders of marketing authorizations, or registration, should audit periodically their pharmacovigilance systems and within that scope:

a) Record, in the master file of the pharmacovigilance system, the main conclusions of that audit;

b) To ensure, based on the conclusions mentioned in the previous subparagraph, the preparation and application of the suitable corrective measures;

c) To withdraw all recorded statements, after all corrective measures have been implemented.

4 – Within the scope of pharmacovigilance system, the holder of the marketing authorization, or registration should:

a) Have, permanently and continuously, available the services of a suitably qualified person responsible for pharmacovigilance;

b) To manage and provide, upon request of INFARMED, I.P., the pharmacovigilance system master file;

c) Apply a risk management system for each medicinal product;

d) Monitor the results of the measures to minimize risks provided for in the risks management plan or set out as conditions for the granting of the marketing authorization, or registration, according to the provisions of nos. 2 and 5 of article 24 or of nos. 1 to 5 of article 26-A;

e) To update the risk management system and monitor the results of pharmacovigilance to establish whether there are new risks or if the risks have changed, or if there are changes with the risk-benefit ratio of the medicinal products.

5 – The qualified person mentioned in subparagraph a) of the previous number should live and exercise his/her activity within the European Union, and is responsible for the creation and management of the pharmacovigilance system.

6 – The holder of the marketing authorization should appoint at INFARMED, I.P., a contact person on pharmacovigilance issues at a national level, who lives in Portugal, reporting to the qualified person mentioned in the previous number.

7 - The holder of the marketing authorization should communicate and keep updated:

a) The name, usual residence, business head office, telephone and fax numbers and email address of the qualified person mentioned in no. 5, with INFARMED, I.P., and the Agency;

b) The name, usual residence, business head office, telephone and fax numbers and email address of the contact person for pharmacovigilance issues provided for in no. 6, with INFARMED, I.P.

Article 171

Specific obligations

1 - The holders of the marketing authorization should:

a) Record all suspected adverse reactions they are aware of within the European Union or in third countries, irrespective of the latter having been spontaneously reported by patients, healthcare professionals, or having occurred within the scope of post-authorization studies, except for the provisions of no. 2;

b) Guarantee that the reports mentioned in the previous subparagraph are available in a single point within the Union;
c) Convey by electronic means to the database and the data-processing network mentioned in article 24 of Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004 (Eudravigilance database), information on all the serious suspected adverse reactions occurred within the European Union and in third countries within 15 days, counting from the day after the one the concerned holder of the marketing authorization became aware of the event;
d) Convey by electronic means to the *Eudravigilance* database information on all the non-serious suspected adverse reactions occurred within the European Union within 90 days, counting from the day after the one the holder of the marketing authorization became aware of the event, notwithstanding the provisions of no. 3;
e) Adopt procedures intended to obtain precise and verifiable data for the scientific assessment of the suspected adverse reactions reports;
f) Gather information received within the follow-up of the reports and to communicate the updates to *Eudravigilance* database;
g) Cooperate with the Agency and INFARMED, I.P., for the detection and duplication of suspected adverse reactions reports;
h) Take into consideration all suspected adverse reactions reports sent by patients or healthcare professionals, irrespective of being done by electronic means or any other means.
2 – The suspected adverse reactions occurred within the scope of clinical trials are recorded and reported under the terms of Law no. 46/2004, of 19th August.
3 – In the case of medicinal products containing active substances mentioned in the publication list monitored by the Agency under the terms of article 27 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st of March 2004, the holders of the marketing authorization:
a) Are exempted from reporting to the Eudravigilance database the suspected adverse reactions included in the scheduled medical literature;
b) Should follow the other medical literature and report any suspected adverse reaction.

Article 172

Spontaneous reports

1 - INFARMED, I.P., records all suspected adverse reactions occurred in the Portuguese territory, which have been reported by patients and healthcare professionals, notwithstanding the provisions of the following number.

2 – If suitable, INFARMED, I.P., may request the cooperation of patients and healthcare professionals to follow-up the received reports, according to the provisions of subparagraphs c) and e) of no. 2 of article 167.

3 – The reports provided for in the previous numbers should be sent electronically by means off the portal provided for in article 170-A or any other means, namely by mail or email.

4 - The reports provided for in the previous numbers, when regarding biological medicinal products, should include the name of the medicinal product and the number of the respective batch.

5 – If the suspected adverse reactions report is submitted by the holder of the marketing authorization and occurred within the Portuguese territory, INFARMED, I.P., may request the cooperation of the mentioned entity to follow-up that report.

6 - INFARMED, I.P., cooperates with the Agency and the holders of the marketing authorization to detect duplications of the suspected adverse reactions reports.

7 - INFARMED, I.P., sends, by electronic means, to the Eudravigilance database, the reports of suspected adverse reactions mentioned in no. 1:

a) Within 15 days, counting from its reception, as for serious suspicions;

b) Within 90 days, counting from its reception, as for non-serious suspicions.

8 – The holders of a marketing authorization may access the reports mentioned in the previous number through the *Eudravigilance* database.

9 – Directorate-General for Health and other authorities, bodies or entities, as well as the public or private healthcare units and facilities, and the healthcare professionals should report, in a specific form, to INFARMED, I.P., all suspected adverse reactions resulting from errors associated to the use of a medicinal product they are aware of, in compliance with the provisions of no. 3 of article 170.

Article 173

[…]

1 – Notwithstanding the provisions of no. 3, the holder of the marketing authorization submits to the Agency, by electronic means, periodic safety reports, which should include:

a) A summary of all relevant data for the assessment of the risk-benefit ratio of the medicinal product, including the results of all the studies and their potential impact on the marketing authorization;
b) A scientific assessment of the risk-benefit ratio of the medicinal product;
c) All data regarding the sales volume of the medicinal product and all available data on the volume of medical prescriptions, including an estimate of the population exposed to the medicinal product.
2 – The assessment mentioned in the subparagraph b) of the previous number is based on all available data, including the data of clinical trials for non-authorized indications and populations.
3 – In the case of medicinal products mentioned in no. 1 of article 19, article 20, no. 1 of article 137 or no. 1 of article 141, the holders of the marketing authorization, or registration, may only submit periodic safety reports on any of the following situations:
a) If that is a condition of the marketing authorization, under the provisions of no. 2 or no. 5 of article 24;
b) If INFARMED, I.P., so requests, grounded on issues related to data regarding pharmacovigilance or regarding the failure to submit periodic safety reports on an active substance after the marketing authorization has been granted.
4 - [Revoked].

Article 174

Initiation of procedure

1 - INFARMED, I.P., initiates the procedure provided for in this section, informing the competent national authorities of the other Member States, the Agency and the European Commission, if, following an assessment of the data resulting from pharmacovigilance activities, it deems necessary to take urgent measures, and in case:
a) It intends to suspend or revoke a marketing authorization;
b) It intends to prohibit the supply of a medicinal product;
c) It intends to refuse the renewal of a marketing authorization;
d) It has been informed by the holder of a marketing authorization that, based on safety issues, the latter has interrupted the marketing of a medicinal product or has taken measures to withdraw the marketing authorization, or intends to do so;
e) It deems to be necessary to enter a new contraindication, to reduce the recommended dose or restrict the indications.

2 – If the Agency establishes that the medicinal product is not authorized in any other Member State the safety issue is settled by INFARMED, I.P.

3 - INFARMED, I.P., informs the holder of a marketing authorization that the procedure has been initiated.

4 – The information mentioned in this article may apply to individual medicinal products, a class of medicinal products or a pharmacotherapeutic group.

Article 175

Provisional and temporary measures

1 – Notwithstanding the provisions of no.1 of the previous article, the following article and article 175-B, when an urgent action is deemed to be necessary to protect public health, INFARMED, I.P., may suspend the marketing authorization of the concerned medicinal product and the use of the medicinal product within the Portuguese territory until a final decision is made and should notify the European Commission, the Agency and the competent national authorities of the other Member States, at the latest, the following business day, on the grounds for taking that measure.

2 – At any stage of the procedure established in the following article and in article 175-B, INFARMED, I.P., may take, immediately, and upon request of the European Commission, temporary measures.

3 – Along with the communication of the information mentioned in no 1 of the previous article, INFARMED, I.P., should provide the Agency with all pertinent scientific information it has, as well as of all assessments carried out by it.

4 - [Revoked].

Article 176

[…]

1 - […]:

a) […];

b) […];

c) Check the facilities, registrations, documents and pharmacovigilance systems of the holder of the marketing authorization or any company entrusted by the holder of the marketing authorization with carrying out the activities described in chapter X;

d) […];

e) […];

f) […];

g) […];

h) […];

i) […];

j) […];

k) [Former subparagraph l)];

l) [Revoked].

2 - […].

3 - […].

4 - […].

5 - […].

6 - […].

7 - INFARMED, I.P. exercises the inspection powers mentioned in the previous numbers in cooperation with the Agency, and should, within that scope, share information on planned and carried out inspections and cooperate in the coordination of the inspections in third countries.

8 – If necessary, the inspections provided in no. 1 are carried out without prior notice.

Article 177

[…]

1 – The inspectors prepare and submit up to 60 days after the inspection is completed, a detailed report on the compliance with the good practices of manufacture and distribution, pharmacovigilance legislation and the compliance with the other legal provisions, whose project is conveyed to the inspected entities and, upon substantiated request, to the competent authority of another Member State, by electronic means.

2 – The inspected entity has 10 days to lodge written observations on the contents of the draft report.

3 – Within a period of time of 90 days, counting from the date of the inspection, INFARMED, I.P., should approve the report, taking into account the indictment provided for in the previous number, and issues on behalf of the manufacturer a certificate of good practices of manufacture, whenever the inspection concludes that the manufacturer complies with the law and other guidelines, in respect of good practices of manufacture and distribution, or the compliance, by the holder of the marketing authorization, with the obligations provided for in chapter X.

4 - [Former no. 3].

5 – If from the inspection mentioned in subparagraphs a), b), e) and f) of no. 1 of the previous article or the inspection by a distributor of medicinal products or active substances, or the inspection by a manufacturer of excipients used as raw material, it is concluded that the inspected entity does not comply with the legal requirements or principles and guidelines of good practices of manufacture or good distribution provided for in the European Union legislation, this information should be recorded in the database mentioned in no. 4 of article 57.

6 - If from the inspection mentioned in subparagraph c) of no. 1 of the previous article it is concluded that the holder of the marketing authorization does not comply with the pharmacovigilance system described in the pharmacovigilance system master file, nor the provisions of chapter X, INFARMED, I.P., brings the gaps to the knowledge of the holder of the marketing authorization, giving the latter the opportunity to deliver an opinion according to the provisions of no. 2, and informs the competent national authorities of the other Member States, the Agency and the European Commission.

7 - [Former no. 5].

8 - [Former no. 6].

Article 179

[…]

1 - […]:

a) […];

b) That the medicinal product is harmful;

c) That the risk-benefit ratio is unfavourable;

d) [Former subparagraph b)];

e) [Former subparagraph c)];

f) [Former subparagraph d)];

g) [Former subparagraph e)];

h) [Former subparagraph f)].

2 - […].

3 - […].

4 - […].

5 - […].

6 - […].

7 - […].

8 – In case the supply of a medicinal product has been prohibited or the medicinal product has been recalled from the market according to the provisions of no. 1, INFARMED, I.P. may, under exceptional circumstances, and during a transition period, authorize the supply of that medicinal product to patients who are already being treated with such medicinal product.

Article 181

[…]

1 - […].

2 - […]:

a) […];

b) […];

c) […];

d) […];

e) […];

f) […];

g) […];

h) […];

i) The violation of the provisions of articles 6, 9, in subparagraphs a) to n) of no. 1 and nos. 2, 4 and 5 of article 29, in nos. 1 to 4 of article 78, in article 85, in no. 5 of article 93, in article 94, in nos. 1 and 3 to 5 of article 100 and in articles 169 to 171, as well as the use of the same authorization more than once, in violation of no. 4 of article 79 or the purchase of medicinal products to entities non-authorized by INFARMED, I.P., in violation of no. 5 of the same article;

j) The violation of the provisions of this decree-law on labelling and package leaflet, as well as the non-compliance of no. 8 of article 106;

k) The non-compliance of the provisions of no. 3 of article 150, in nos. 1, 2, 4 e 5 of article 152, in nos. 3, 4, 5 e 6 of article 153, in nos.1 and 2 of article 154, in articles 155 and 156, in nos. 2 and 3 of article 157, in nos.1, 2, 4 and 5 of article 158, in articles 159 to 161, ins nos.1, 3 and 4 of article 162 and in no. 4 of article 164, or the duties of cooperation or notification by the hospitals and the healthcare professionals, provided in article 172, as well as the non-compliance with the provisions of article 173, on the duties that fall on the holder of the marketing authorization, or registration, under the terms of nos.1 and 2 of article 170-B, of no. 2 of article 173-E, of no. 2 of article 175-G or of no. 2 of article 175-H, or the post-authorization safety studies in violation with the provisions of articles 175-C, 175-E, 175F or 175-G, of this decree-law;

l) [Former subparagraph m)];

m) [Former subparagraph n)];

n) [Former subparagraph o)];

o) The storage, keeping or possession of medicinal products in facilities with no suitable licences issued by INFARMED, I.P.

3 - [...]:

a) [...];

b) [...];

c) [...];

d) [...];

e) [...];

f) [...];

g) [...];

h) The non-authorized access by medical sales representatives to NHS units and facilities;

i) [...];

4 - [Former no. 5].

5 – The provision of this article applies, notwithstanding the provisions of no 3 of article 84 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004.

6 - [Revoked].

Article 182

[...]

1 – The advertiser, the advertising agency or any other entity engaged in advertising activities or advertising dissemination, the holder of the advertising medium or the respective agent are punished as authors or co-authors of the administrative offences provided for in this decree-law, with regard to the violation of the duties provided for in chapter IX.

2 - [...].

3 - [...].

4 - [...].

Article 189

[...]

1 - [...].

2 - [...].

3 - [...].

4 - [...].

5 – For the purposes of the provisions of the previous numbers, a conflict of interests is deemed to exist, whenever there is any cause considered as such by Law no. 12-A/2008, of 27th February.

6 - [...].

Article 202

[...]

1 - [...]:

a) [...];

b) [...];

c) [...];

d) [...];

e) [...];

f) [...];

g) [...];

h) [...];

i) [...];

j) Definition of deadlines and other conditions for the recall of medicinal products from the market;

k) Definition of the acts to be carried out electronically by the applicants, the holders of the marketing authorizations provided for in this decree-law, as well as by other entities, individuals of corporate bodies, subject to the respective provisions, and the formats such acts should adopt;

l) [Former subparagraph j)].

2 - [...].

3 - [...].

4 - [...].

5 - [...].

6 - [...].

7 – Until the regulation provided for in subparagraph j) of no. 1 comes into force, the provisions of Order no. 1/88 of the Secretary of State of Health Administration, of 12th

May 1988, published in the Official Gazette, II series, no. 128, of 3rd June, with the wording resulting from Order no. 13/93, of 23rd of May 1993, published in the Official Gazette, II series, no. 162, of 13th July, apply, provisionally, to the recall of medicinal product, the selling deadline being, in all other cases, corresponding to the deadline established in the decision about the recall or, if this has not been established, the shelf-life of the medicinal product.

8 - [...].

9 - [...].

10 - [...].»

Article 3

Amendment to annexes I and II of Decree-Law no. 176/2006, of 30th August

Part I of annex I and annex II of Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos.182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st of October, and by Laws nos.25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March, have now the wording included in annex I of this legal instrument, of which it is an integral part.

Article 4

Addition to Decree-Law no. 176/2006, of 30th August

Articles 26-A, 149-A, 170-A, 170-B, 173-A, 173-B, 173-C, 173-D, 173-E, 175-A, 175-B, 175-C, 175-D, 175-E, 175-F, 175-G, 175-H and 181-A, are added to Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos.182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October, and by Laws nos.25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March, with the following wording:

«Article 26-A

Post-authorization Injunction

1 – After a marketing authorization is granted, INFARMED, I.P., taking into account the guidelines of the European Commission, if any, may subject the respective holder to the injunction of carrying out a post-authorization safety study, in any of the following cases:

a) If there are doubts as to the risks of the authorized medicinal product;

b) If the knowledge about the disease or the clinical methodology indicates that the former evaluations of efficacy may have to be significantly reviewed.

2 – The imposition of an injunction under the previous number is substantiated and notified to the holder of the marketing authorization, and should also include the objectives, as well as the deadlines to carry out and submit the studies.

3 – In case the holder of the marketing authorization so requests, within the 30 days following the reception of the notification provided in the previous number, INFARMED, I.P., should grant it the opportunity, within a period of time established by it, to deliver its written opinion on the injunction.

4 – Based on the observations submitted in writing by the holder of the marketing authorization, INFARMED, I.P., revokes or confirms the injunction.

5 - If INFARMED, I.P., confirms the injunction, the marketing authorization is changed, so as to include the condition for its granting, and the risk management system is updated accordingly.

6 – In case the doubts provided for in subparagraph a) of no. 1 relates to more than one medicinal product, INFARMED, I.P., in cooperation with Pharmacovigilance Risk Assessment Committee (PRAC), tries to mobilize the holders of the concerned marketing authorizations to carry out a post-authorization joint safety study.

7 – The obligation to carry out the post-authorization efficacy study provided for in no. 1 takes into account the delegated acts, and the scientific guidelines, to be adopted by the European Commission.

Article 149-A

Advanced therapy medicinal products

1 – Advanced therapy medicinal products are not subject to marketing authorization when meeting all the following requirements:

a) They are used in hospital setting under the professional responsibility of a medical practitioner;

b) They are prescribed by a medical practitioner with individual preparation for a specific patient;

c) They are prepared on a non-routine base, according to specific quality patterns.

2 – For the purposes of the previous number, medicinal products produced in small amounts for specific patients are deemed as having been prepared on a non-routine base.

3 – The manufacture and use of advanced therapy medicinal products meeting the requirements mentioned in no. 1 are subject to authorization by INFARMED, I.P., in terms to be defined by Ministerial order of the member of the Government in charge with health.

4 - The ordinance mentioned in the previous number sets out the traceability and pharmacovigilance requirements, as well as the quality standards advanced therapy medicinal products, meeting the requirements mentioned in no. 1., should comply with

Article 170-A

National web-portal of the medicinal product

INFARMED, I.P., establishes and manages, on its webpage, a national web-portal for medicinal products, which should be connected with the European web-portal for medicinal products, established under the terms of article 26 of Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004, in which, at least, the following information should be published:

a) Public assessment reports and respective summaries;

b) Summary of medicinal products characteristics and package leaflets;

c) Summaries of risk management plans for authorized medicinal products in compliance with this decree-law;

d) The list of medicinal products subject to additional monitoring mentioned in article 23 of the Regulation do (EC) no. 726/2004, of the European Parliament and the Council of 31st March 2004;

e) Information on the different ways of reporting suspected adverse reactions to medicinal products to the competent national authorities by the healthcare professionals and patients, including the standard forms accessible online, mentioned in article 25 of the Regulation do (EC) no. 726/2004, of the European Parliament and the Council of 31st March 2004.

Article 170-B

Disclosing information on pharmacovigilance

1 – When decision is made to disclose information on pharmacovigilance issues to the general public with regard to the use of a medicinal product, the holder of the marketing authorization should, prior to that disclosure or simultaneously with it, notify INFARMED, I.P., the Agency and the European Commission.

2 – The holder of the marketing authorization should ensure all information intended for the general public is presented objectively and is not misleading.

3 – Except for the cases where the protection of public health requires urgent public information, INFARMED, I.P., should inform the competent authorities of the other Member States, the Agency and the European Commission, within a minimum of 24

hours in advance, prior to the disclosure of the information on pharmacovigilance issues to the general public.

4 – With regard to active substances contained in medicinal products authorized in more than one Member State, the following should be complied with:

a) It is incumbent on the Agency to coordinate the activities of INFARMED, I.P., as to the safety announcements and their respective timetables for information distribution;

b) INFARMED, I.P., under the coordination of the Agency, should take all possible steps to reach an agreement with the competent national authorities of the other Member States about joint announcements related to the safety of the concerned medicinal product and the respective timetables for information distribution;

c) The Agency may ask PRAC for advice on the concerned safety announcements.

5 - All information of a personal or commercially confidential nature should be deleted from the announcements provided for in nos.3 or 4, by INFARMED, I.P., or another Agency, as the case may be, unless its public disclosure is necessary for the protection of public health.

Article 173-A

Frequency and submission dates

1 – The marketing authorization establishes the frequency to submit the periodic safety reports, counting from the date of that same authorization, to establish the submission dates.

2 – The periodic safety reports of medicinal products authorized only in Portugal and not covered by the provisions of the previous number, are delivered to INFARMED, I.P., within the period of time established by it, as well as, at least, in the following conditions:

a) While the medicinal product is still not actually marketed, every six months, counting from the marketing authorization is granted and until its actual marketing;

b) If the medicinal product is actually marketed, every six months, during the first two years counting from the beginning of the mentioned marketing, every year in the two following years and, after this, every three years.

3 – In the case of medicinal products subject to different marketing authorizations and which contain the same active substance or the same combination of active substances, the frequency and dates to submit the periodic safety reports, resulting from the provisions of the previous numbers, may be changed and harmonized for the purpose

of a single assessment, as well as for the purpose of establishing a reference date of the European Union based on which the submission dates are established.

4 – The amendment and harmonization provided for in the previous number are in compliance with the provisions of the European Union law, namely with regard to:

a) The request itself, as well as the respective grounds and form;

b) The single assessment, particularly as to the procedure of sharing the tasks with regard to the periodic safety reports;

c) The establishment of the harmonized frequency to submit the reports and the reference date for the European Union, which is incumbent on CHMP or the Coordination Group, according to any of the marketing authorizations with regard to the medicinal product containing the concerned active substance whether or not it has been granted according to the centralized procedure;

d) The criterion to establish the reference date for the European Union for medicinal products containing the same active substance or the same combination of substances;

e) The publication, on the European web-portal of medicinal products, of the list of reference dates for the European Union and the frequency to submit the safety reports, as well of any changes to that frequency or those dates;

f) The production, six months after the publication, of the effects of any change on the dates for submitting and the frequency of the safety reports included in the marketing authorization.

Article 173-B

Assessment

Notwithstanding the provisions of the following article, INFARMED, I.P. assesses the periodic safety reports in order to establish:

a) If there are new risks;

b) If the risks have changed;

c) If there are changes on the risk-benefit ratio of the medicinal products.

Article 173-C

Single assessment

1 – The periodic safety reports with regard to medicinal products authorized in more than one Member State, for which a reference date for the European Union and the frequency for submitting those reports have been established, under the terms of nos. 2

and 3 of article 173-A, are subject to a single assessment according to the European Union law.

2 - The single assessment is carried out by INFARMED, I.P., when appointed by the Coordination Group, in the case none of the marketing authorizations has been granted according to the centralized procedure.

3 – When appointed according to the previous number, INFARMED, I.P., prepares, within 60 days, counting from the reception of the periodic safety report, an assessment report to be sent to the Agency and the competent national authorities of the concerned Member States. It is incumbent on the Agency to send the report to the holder of the marketing authorization.

4 – INFARMED, I.P. when not appointed according to no. 2, as well as, in any case, the holder of the marketing authorization, may submit, within 30 days, after the reception of the assessment report, their remarks on the latter to the Agency and the entity which has prepared it.

5 – After the reception of the remarks mentioned in the previous number, INFARMED, I.P., when not appointed according to no. 2, updates the assessment report, within 15 days, taking into account the submitted remarks and conveys the former to PRAC, complying afterwards with the provisions of the European Union law.

Article 173-D

Measures to be taken

1 - Following the assessment of the updated periodic safety report, INFARMED, I.P., considers the need to take measures with regards to the marketing authorization of the concerned medicinal product and, as appropriate, keeps, amends, suspends or revokes the marketing authorization in compliance with the provisions of article 179.

2 – In the case the single assessment of the periodic safety reports recommends measures with regard to more than one marketing authorization and none of these have been granted by the centralized procedure, and in the case of unanimous agreement among the Member States within the Coordination Group, INFARMED, I.P., takes the necessary measures to keep, amend, suspend or revoke the marketing authorizations according to the provisions of article 179, according to the schedule for the implementation established in the achieved agreement.

Article 173-E

Supervision and assessment

1 – In what concerns the authorized medicinal products under this decree-law, INFARMED, I.P., in cooperation with the Agency:

a) Supervises the results of the measures to minimize the risks included in the risk management plans and the conditions mentioned in nos. 2 and 5 of article 24 or in nos. 1 to 5 of article 26-A;

b) Assesses the risk management system updates;

c) Supervises the information in the *Eudravigilance* database, in order to check if there are new risks or if the risks have changed, and if those risks have an impact on the risk-benefit ratio.

2 - INFARMED, I.P., and the holder of the marketing authorization inform each other, as well as the Agency and the competent national authorities of the other Member States, and receive information from them, in the case of:

a) New risks or altered ones;

b) Changes in the risk-benefit ratio are detected.

Article 175-A

Procedure

1 – Along with the publication by the Agency of the notice announcing the initiation of the procedure on the European web-portal of medicinal products mentioned in no. 1 of article 170-A, INFARMED, I.P. may announce publicly the initiation of t the same the procedure on the national web-portal of medicinal products with regard to the same article.

2 - INFARMED, I.P., takes part on the urgent procedure of the European Union according to the terms and cases provided for in the Union law.

Article 175-B

Measures

1 – In case none of the marketing authorizations has been granted through the centralised procedure and a unanimous agreement exists among the Member States within the Coordination Group, INFARMED, I.P. takes the necessary measures to keep, amend, suspend, or revoke the marketing authorizations according to the provisions of article 179, according to the schedule for the implementation established in the achieved agreement.

2 – If the achieved agreement involves an amendment, the holder of the marketing authorization submits to INFARMED, I.P., an appropriate request for amendment, including the summary of the medicinal product characteristics and the package leaflet, within the established schedule for the implementation.

3 – In case there is no unanimous agreement or an authorization has been granted by the centralized procedure, the applicable procedure is complied with, according to what is established in the European Union law, and it is incumbent on INFARMED, I.P., to implement the decisions that have been made as to that matter and of which it is the recipient.

Article 175-C

General rules

1 – This section applies to the non-interventional post-authorization safety studies carried out in the Portuguese territory, initiated, managed of funded by the holder of the marketing authorization, on its own initiative or according to the obligations provided for in no. 5 of article 24 or nos. 1 to 5 of article 26-A, involving the collection of safety-related data conveyed by patients or healthcare professionals.

2 - This section is without prejudice to the requirements provided for in the legislation in force about clinical trials, or the European Union law, intended to guarantee the well-being and the rights of those taking part in the non-interventional post-authorization safety studies.

3 – The studies that promote the use of the concerned medicinal products are prohibited.

4 – Payments to healthcare professionals for their participation in non-interventional post-authorization safety studies should be restricted to compensation of time and expenses incurred.

5 – If the study is also being carried out in other Member State or Member States, INFARMED, I.P., may request the holder of the marketing authorization to submit the protocol and the interim reports to the respective competent national authorities.

6 – The holder of the marketing authorization sends the final report to INFARMED, I.P. and, if that is the case, to the competent national authorities mentioned in the previous number, within 12 months, counting from the end of the data collection.

7 – During a study, the holder of a market authorization:

a) Checks the data produced and analyses their implications on the risk-benefit ratio of the concerned medicinal product;

b) Provides the competent authorities of the Member States where the medicinal product is authorized, according to the provisions of subparagraphs b), f) and i) of no. 1 of article 29, with all and any information likely to have an influence on the assessment of the risk-benefit ratio of the medicinal product;
c) Provides, by means of the periodic safety reports, the information on the results of the studies, according to the provisions of article 173.

Article 175-D

Studies as a condition

1 – The provisions of articles 175-E to 175-G apply to the studies provided for in no. 1 of the previous article carried out in compliance with the obligations imposed according to no. 5 of article 24 or nos. 1 to 5 of article 26-A.
2 – The studies mentioned in the previous number that should be carried out in more than one Member State comply with the provisions of the European Union law.

Article 175-E

Requirements to carry out the study

1 – Before carrying out a study according to the provisions of no. 1 of the previous article, the holder of the marketing authorization submits to o INFARMED, I.P., a protocol project.
2 – Within 60 days, counting from the submission of the protocol project, INFARMED, I.P., adopts and notifies the holder of the marketing authorization of one of the following decisions:
a) It approves the protocol project;
b) It opposes fundamentally the study, in case it considers that:

i) The development of the study promotes the use of the medicinal product;

ii) The way the study was designed is not suitable to meet the purposes of the mentioned study;

iii) The study is a clinical trial and should comply with the respective legislation.

3 – The study mentioned in the previous numbers may only be initiated after it is approved by INFARMED, I.P., according to the provisions of subparagraph a) of the previous number.

Article 175-F

Amendments

1 – After a study has been initiated, all major amendments to the protocol should be submitted by the holder of the marketing authorization to INFARMED, I.P., prior to its development.

2 - INFARMED, I.P., analyses the amendments and notifies the holder of the marketing authorization of its approval or substantiated objection.

Article 175-G

Final Report

1 – After the completion of the study, the holder of the marketing authorization submits the final report according to the provisions of no. 6 of article 175-C, unless INFARMED, I.P., has exempted it, in writing, from that submission.

2 – The holder of the marketing authorization assesses the possible impact of the results of the study on the marketing authorization and, if necessary, submits to INFARMED, I.P., a request for amending the marketing authorization.

3 – Together with the final report, the holder of the marketing authorization submits, electronically, to INFARMED, I.P. a summary of the results of the study.

Article 175-H

Repercussions on the authorization

1 – According to the results of the non-interventional safety study carried out exclusively in Portuguese territory, INFARMED, I.P., takes the necessary measures for its execution, under the provisions of article 179.

2 – In the case of a study carried out in the Portuguese territory and in, at least, another Member State, if there is an unanimous agreement of the Member States within the Coordination Group in order to amend, suspend or revoke the marketing authorization, INFARMED, I.P., takes the necessary measures for its execution, under the provisions of article 179, in compliance with the schedule established in the achieved agreement.

3 – If the measure taken by INFARMED, I.P., according to the provisions of no. 1 or the agreement achieved according to the provisions of no. 2, involve an amendment, the holder of the marketing authorization submits to INFARMED, I.P., an appropriate request for amendment, including the update of the summary of the medicinal product characteristics and the package leaflet, within the established schedule for the implementation.

4 – If there is no unanimity according to the provisions of no. 2, the applicable procedure is complied with, according to the provisions of the European Union law, and it is incumbent on INFARMED, I.P. to enforce the decision taken for that matter and of which it is the recipient.

Article 181-A

Ancillary sanctions

Whenever the seriousness of the offence and the guilt of the agent so justifies, INFARMED, I.P., may, in addition to the fines that may be provided for, apply the following ancillary sanctions:

a) The confiscation of objects, equipment and illicit devices;

b) Disqualification in the exercise of the respective activity, up to a maximum of two years;

c) Deprivation of the right to participate in public tenders, up to a maximum of two years;

d) Suspension of authorizations, licences or other titles granting rights, up to a maximum of two years.»

Article 5

Change of the system of Decree-Law no. 176/2006, of 30th August

1 - Section IX, with the title «Advanced therapy medicinal products, which integrates article 149-A is added to chapter VIII of Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October, and by Laws nos. 25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March.

2 - Chapter X of Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October, e by Laws nos. 25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March, has the following system from now on:

a) A section I titled «General Provisions », which includes articles 166 to 170;

b) A section II titled «Transparency and communication», which includes articles 170-A and 170-B;

c) A section III titled «Record, communication and assessment of pharmacovigilance data», which is subdivided in the following four sub-sections:

i) Sub-section I, titled «Record and report of suspected adverse reactions», which includes articles 171 and 172;

ii) Sub-section II, titled «Periodic safety reports», which includes article 173;

iii) Sub-section III, titled «Detection of signs», which includes articles 173-A to 173-E;

iv) Sub-section IV, titled «Urgent procedure of the European Union », which includes articles 174 to 175-B.

d) Section IV, titled «Post-authorization safety studies supervision», which includes articles 175-C to 175-H.

3 - Chapter XII do Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October and by Laws nos. 25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March, is from now on titled «INFARMED – National Authority of Pharmacy and the Medicinal Product, I.P.».

Article 6

Revoking rules

Subparagraph ppp) of no. 1 of article 3, subparagraph r) do no. 2 of article 15, subparagraph c) of no. 1 of article 45, nos. 2 to 4 of article 46, subparagraph c) of no. 1 of article 52, nos. 2 to 4 of article 53, no. 2 of article 95, no. 2 of article 103, subparagraph l) of no. 4 of article 153, subparagraph a) of no. 4 of article 154, no. 4 of article 173, no. 4 of article 175, subparagraph l) of no. 1 of article 176, no. 6 of article 181 and nos. 7. and 8.1. of annex II of Decree-Law no. 176/2006, of 30th August, amended by Decree-Laws nos. 182/2009, of 7th August, 64/2010, of 9th June, and 106-A/2010, of 1st October, and Laws nos. 25/2011, of 16th June, 62/2011, of 12th December, and 11/2012, of 8th March are amended.

Article 7

Transitional provisions

1 – The first audit foreseen in no. 1 of article 167 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, should be take place until 21st September of 2013.

2 - Notwithstanding the provisions of nos. 3 to 5, the holders of marketing authorizations granted before 21st July of 2012 are not under the obligation to apply a risk management system for each medicinal product.

3 – In case the risks affecting the risk-benefit ratio of a medicinal product give rise to concern, INFARMED, I.P., may, on suitable grounds and by means of a notification, require the holder of the marketing authorization to:

a) Apply a risk management system, as mentioned in subparagraph c) of no. 4 of article 170 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument;

b) Submit, within the period of time established in the notification, a detailed description of the risk management system it intends to introduce for the concerned medicinal product.

4 – If within 30 days, counting from the notification provided for in the previous number, the holder of the marketing authorization so requests, INFARMED, I.P. should grant it the opportunity, within an established time-limit, to submit its written observations.

5 – Taking into account the written indictment of the holder of the marketing authorization, INFARMED, I.P., may revoke or confirm the obligation notified according to the provisions of no. 3; in this case the marketing authorization should be amended accordingly, in order to take into account the measures to include in the risk management system as conditions for the marketing authorization mentioned in subparagraph a) of no. 5 of article 24 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument.

6 – The holders of the marketing authorizations granted before 21st July 2012, which do not provide for conditions with regard to the frequency and the dates to submit the periodic safety reports, should submit these reports in compliance with the provisions of no. 2 of article 173-A of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, until one of the following situations occur:

a) Another frequency is established;

b) Other dates to submit the reports in the marketing authorization are established;

c) The decision provided for in nos. 3 and 4 of the same article 173-A. is adopted.

7 – The obligation on the holder of the marketing authorization to manage and provide, upon request, a master file for pharmacovigilance system with regard to one or more medicinal products according to the provisions of subparagraph b) of no. 4 of article 170 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, applies only to marketing authorizations granted before 21st July 2012, from one of the following dates, whichever occurs first:

a) Date of the renewal of the marketing authorization;

b) 21st July 2015.

8 – The procedure provided for in articles 175-C to 175-H of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, applies only to the studies starting after 21st July 2012.

9 - The obligation on the holder of the marketing authorization to convey electronically to the Eudravigilance database information on suspected adverse reactions, provided for in subparagraphs c) and d) of no. 1 and no. 3 of article 171 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, applies only six months after the database functionalities have been established and that fact has been announced by the Agency.

10 - While the Agency cannot guarantee the functionalities of the Eudravigilance database, as they are described in article 24 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004, the holders of the marketing authorizations should, within 15 days, counting from the date they are aware of it, notify:

a) INFARMED, I.P., of all suspected serious adverse reactions occurring within the Portuguese territory;

b) The Agency of all suspected serious adverse reactions occurring in the territory of third countries;

c) According to a request to that effect, the same suspicions mentioned in the previous paragraph reported to the competent national authorities of the Member States in which the medicinal product is authorized.

11 - While the Agency cannot guarantee the functionalities of the Eudravigilance database, as they are described in article 24 of the Regulation (EC) no. 726/2004, of the European Parliament and the Council, of 31st March 2004, the holders of the marketing authorizations should, within 90 days, counting from the date they are aware of it, notify INFARMED, I.P., of all suspected non-serious adverse reactions occurring within the Portuguese territory.

12 – In the case provided for in subparagraph a) of no. 10, the provisions of subparagraph a) of no. 6 of article 172 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, applies.

13 - The obligation on the holder of the marketing authorization to convey to the Agency periodic safety reports according to the provisions of no. 1 of article 173 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal

instrument, applies only 12 months after the functionalities of the repository have been established and that fact having been announced by the Agency.

14 - While the Agency cannot guarantee the functionalities of the repository of the periodic safety reports, the holders of the marketing authorizations should submit the periodic safety reports to INFARMED, I.P.

15 – The provisions of nos. 5 to 7 of article 159 of Decree-Law no. 176/2006, of 30th August, with the wording given by this legal instrument, only takes effect when it comes into force.

Article 8

Republication

1 - Decree-Law no. 176/2006, of 30th August, with its current wording and the necessary material corrections, is republished in annex II to the current legal instrument, of which it is an integral part.

2 – For the purposes of republication, where it reads «INFARMED», «Minister of Health», «joint ordinance of The Ministers of Employment and Social Solidarity, Education and Health» and «Institute» should read, respectively, «INFARMED, I.P.», «member of the Government responsible for health», «ordinance of the members of the Government responsible for employment, education and health» and «National Authority», in this case, when meaning INFARMED – National Authority for Medicinal and Health Products, I.P.

Article 9

Coming into force

This legal instrument comes into force the day following its publication.

Reviewed and approved in Council of Ministers of 6th December 2012. — Pedro Passos Coelho — Vítor Louçã Rabaça Gaspar — Paulo Sacadura Cabral Portas — Paula Maria von Hafe Teixeira da Cruz — Álvaro Santos Pereira — Paulo José de Ribeiro Moita de Macedo — Nuno Paulo de Sousa Arrobas Crato.

Promulgated on 30th January 2013.

To be published.

The President of the Republic, ANÍBAL CAVACO SILVA.

Endorsed on 1st of February 2013.

The Prime Minister, Pedro Passos Coelho.

ANNEX I

(mentioned in article 3)

«ANNEX I

[…]

PART I

1 - […].

2 - […].

2.1 - […].

2.2 - […].

2.3- […].

2.4 – Non-clinical overview.

An integrated and critical assessment of the non—clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines should all be included.

In the case of biological medicinal products, an assessment of the impurities and degradation products should be included along with their potential pharmacological and toxicological effects. The implications of any differences on chirality, chemical form and impurity profile between the compound used in the nonclinical studies and the medicinal product to be marketed shall be discussed.

In the case of biological medicinal products the comparison between the material used in non clinical and clinical studies and the medicinal product to be marketed shall be assessed.

Any novel excipient should be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for human use should be discussed.

2.5 - […].

2.6 - […].

2.7- […].

3 - […].

3.1 - […].

3.2 - […]:

3.2.1 - […].

3.2.1.1 – […].

3.2.1.2 – [...].

3.2.1.3 – [...].

3.2.1.4 – [...].

3.2.1.5 – [...].

3.2.1.6 – [...].

3.2.1.7 – [...].

3.2.2 - [...].

3.2.2.1 – Description and composition of the finished product.

A description and composition of the finished product should be submitted. Information should include a description of the pharmaceutical form and the composition with all constituents of the finished medicinal product, their amount on per-unit basis and the function of the constituents:

– Of the active substance(s);

– Of the excipients, whatever their nature or the used quantity, including colouring matter, preservatives, adjuvants, stabilizers, thickners, emulsifiers, taste correctives, flavourings, etc., intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, gelatine capsules, rectal capsules, coated tablets, film coated tablets, etc.).

– These particulars should be supplemented by any relevant data with regard to the immediate packaging and, where appropriate its manner of closure together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

– The «usual terminology», to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in subparagraph a) of no. 2 of article 15:

– In respect of substances which appear in the European Pharmacopoeia or, failing this, in the Portuguese pharmacopoeia, the main name on the title of the monograph in question with reference to the concerned Pharmacopoeia;

– In respect of other substances, the international non-proprietary name or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details;

– In respect of colouring matter, the designation by the "E" code assigned to them in Directive 2009/35/CE, of the European Parliament and the Council of 23rd April de

2009, regarding the approximation of the Member States legislation with regard to the colouring matter that can be added to medicinal products or Directive 94/36/CE, of the European Parliament and the Council, of 30th June 1994, on colours to use in foodstuffs, transposed to national legal system by Decree-Law 193/2000, of 18th August, with the latest wording given by Decree-Law no. 166/2002, de 18th July.

–In order to specify the «quantitative composition» of the active substance or substances of the finished product, it is necessary, depending on the pharmaceutical form concerned, to specify the mass or the number of units of biological activity per dosage unit or per unit of mass or volume of each active substance.

– The active substances present in the form of compounds or derivatives should be described quantitatively by their total mass, and if necessary or relevant, by the mass of the active fraction or fractions of the molecule.

– In the case of medicinal products which contain an active substance which is the subject of an application for a marketing authorization in any Member State for the first time, the quantitative statement of an active substance which is a salt or hydrate should be systematically expressed on the mass of the active fraction or fractions of the molecule. All subsequently authorized medicinal products in the Member States should have their quantitative composition stated in the same way for the same active substance.

– The units of biological activity should be specified with regard to the substances which cannot be defined molecularly. Where the World Health Organization has defined a given international unit of biological activity, that unit should be used. Where no international unit has been defined, the unit of biological activity should be expressed in such way as to provide unambiguous information on the activity of the substance, by using, where applicable, the European Pharmacopeia Units.

3.2.2.2 - [...].

3.2.2.3 - [...].

3.2.2.4 - [...].

3.2.2.5 - [...].

3.2.2.6 - [...].

3.2.2.7 - [...].

3.2.2.8 - [...].

4 - [...].

5 - [...].

ANEXO II

[…]

1 - […]:

a) […];

b) […];

c) […];

d) […];

e) […];

f) The patients.

2 - […].

3 – Within the framework of its responsibilities, the department responsible for pharmacovigilance of INFARMED, I.P. ensures, in particular, the suitable interaction with healthcare professionals, the patients and the holders of the marketing authorizations of medicinal products, in respect with the dissemination of the safety profile of the medicinal products and the actions to develop due to the new safety-related data regarding the respective medicinal products.

4 - […].

5 - […].

6 - […].

7 - [Revoked].

8 - […].

8.1- [Revoked].

8.2 - […].»