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DEVELOPING SPECIFIC REGULATIONS TO ENSURE THE PRESENCE ON THE MARKET OF "MEDICINAL PRODUCTS WITHOUT COMMERCIAL INTEREST": a retrospective review

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Abstract

Objective: To confirm that there is a defined group of products to be protected in the Spanish therapeutic arsenal known as "medicinal products without commercial interest" (hereon in MPWCI).

Design: a retrospective review of proposed MPWCI based on a survey.

Setting: a search on the Spanish Medicine Agency (AEMPS) website and a survey conducted among 44 companies belonging to Farmaindustria.

Results: products proposed as MPWCI are old (50% of them have an authorisation of more than 50 years) and are developed by active substances of chemical origin, parenterally administered much more frequently than the rest of the general market (44% vs 6.6 % respectively). Unlike oral forms, injectable forms require adequate manufacturing facilities to guarantee the quality and sterility of the product, which naturally increases the cost of the product and if the price is low or obsolete.

Conclusions: As shown in the results, an upward revision of prices is necessary to contribute to the permanence in the market of these presentations. On the other hand, the experts of the companies have not valued the current Spanish price revisions as a sufficiently satisfactory mechanism to change the consideration of these products with respect to the interest on the part of some MAHs to maintain the future commercialization of these presentations. A specific regulation seems necessary to ensure the continuity on the market of these proposed products.

Article summary

Strengths and limitations of this study

- This is the first article to propose that a group of products be considered as MPWCI, originating from a list of products identified by the Spanish Agency of Medicines and Medical Devices (AEMPS), taking into account the opinion of a group of experts from the Marketing Authorisation Holders (MAH)
- The analysis of the products to be considered as MPWCI has been strengthened by the results of a survey that allows conclusions to be drawn about the need to typify and regulate MPWCI in Spain
- The results of the survey are limited to those products belonging to companies associated to Farmaindustria
- The data from the survey reflects the situation at a given time. The pharmaceutical sector situation is constantly changing, in a way that the number of presentations affected could vary depending on regulatory decisions that may be adopted.

Introduction

Spanish legislation refers to "medicinal products without commercial interest" (hereon in MPWCI) as those where there is an absence, or shortfall, of supply within the Spanish market, yet are still required to treat certain diseases or pathologies.

There are several causes which can affect the initial marketing authorisation conditions during a medicine's lifecycle, and this can lead to an absence or a lack of supply. For instance, the existence of other competitors, new implementation of regulatory requirements, additional restrictions derived from pharmacovigilance, entries of generic medicinal products (hereon in only referred to as 'products'), or simply, a decrease in demand due to obsolescence.

All of these circumstances ultimately affect marketing viability for certain products, leading to their disappearance from a market which is constantly changing. However, when this situation affects products that are still crucial for treating certain diseases, the lack of availability proposes a conflict that has an effect on patients and healthcare professionals, reducing treatment options and damaging the pharmaceutical industry's image.

The fact that it is still necessary to guarantee the availability of certain products and, more precisely some presentations (defined hereon in as specific strength, pharmaceutical form and content in weight, volume or units of dosage), denotes that further development of Spanish regulation seems necessary in order to ensure the commercialisation of these products with high healthcare interest but low economical interest.

In accordance with current Spanish legislation, and in order to ensure the supply of products, the Government can adopt special measures in relation to its manufacture, import, distribution, and dispensing. In particular, and in the case of MPWCIs, in addition to the above-mentioned measures, Spanish legislation allows those relating to the economic and fiscal regime in favour of such products.

In this paper, an identification of these types of products is suggested, the description of their characteristics, the main causes that threaten their marketing viability and several considerations regarding the need to develop regulations for this matter in Spain.

Marketing conditions

The marketing authorisation (herein MA) establishes the main marketing conditions of the product's authorisation throughout its life cycle. The MA includes, amongst other elements, the Summary of product characteristics, which gathers all the therapeutic conditions of use, such as authorised indications or contraindications. The MA is granted, on one side, by the European Commission for those cases in which products are authorised by Centralized Procedure[1] and, by the Member States of the European Union for the remaining the cases[2].

Once the product is authorised, the competent authorities make a decision about its price and reimbursement. In Spain, the procedure includes the participation of the Inter-Ministerial Pharmaceutical Pricing Commission (CIPM)[3]. When this process has ended, the MAHs communicate to the AEMPS the intention to effectively market the drug, requesting its inclusion in the official Presentation Catalogue of the Pharmaceutical Provision of the National

Health System. From the moment of the product's publication in the Presentation Catalogue, retail products can then be marketed immediately, but in the case of products in hospitals, the MAH must frequently manage additional procedures for regional access in the different Regions[4, 5].

The initial conditions of authorisation change throughout the life cycle of the product and can be divided into two stages: (i) when the original product is in an exclusive situation; (ii) when the protection offered by both the patent and the data protection has expired. Figure 1 summarizes the main causes that modify the conditions of the initial authorisation of the original products.

Figure 1: Causes that modify the authorisation conditions: a) causes that affect all commercialized products (patented or not), b) causes that only affect those products without patent protection or data protection

Objectives

1. Confirm that there is a defined group of products to be protected in the Spanish therapeutic arsenal (MPWCI proposed).
2. Propose the adoption of measures aimed at avoiding, or reducing, the lack of supply of said products.

Methods

Data collection

In order to identify within the presentations formally marketed in Spain, those whose shortage could have an impact on the NHS and patients, AEMPS was asked to provide a list of them. The list provided by AEMPS took into consideration those products at risk, whose shortage could have an impact on healthcare at a given time (January 2017).

This list contained **462** products, ordered by authorisation number in the case of products registered in Spain and with other registration numbers in the remaining cases. The list had been developed by AEMPS in accordance with the following criteria (see Figure 2):

- A **comparison** of the **WHO's Essential Medicines List (EML)** and a list of products authorised in Spain, stored in **CIMA** (Online Medicine Information Centre), selecting the cases where, for each essential active substance, only 1 or 2 medicinal products were authorised. Those cases that have two or more therapeutic alternatives authorised and marketed in Spain are not considered to be at risk.
- Those cases that have two or more therapeutic alternatives authorised and marketed in Spain are not considered to be at risk and were, therefore, **removed** from the list. The resulting list had a total of 357 products which were divided as it follows:
  a. 293 products commercialised in Spain with essential active substances according to the EML
  b. 9 products commercialised in Spain with a unique pharmaceutical form and contain essential active substances according to the EML
  c. 55 authorised, but not commercialised, products with essential active substances according to the EML (imported through Foreign Medicinal Products Service)

Some products that were not considered essential by the WHO but are still essential in the Spanish market were **added** to the list.

d) 37 products commercialised in Spain
e) 68 authorised but not commercialised products in Spain (imported through Foreign Medicinal Products Service)

Figure 2: Distribution of essential products for the Spanish market. Source: AEMPS.

This initial relationship was subjected to the process outlined in Figure 3 and is described below.

Figure 3: Diagram of the review carried out for the different medicinal product presentation lists whose viability of commercialization has been reviewed in the present list.

REG Number: Registration Number

NPC: National Product Code

AEMPS provided a list of 462 **products** considered to be at risk, whose shortage could have an impact on healthcare, which were then divided into two groups in order to be able to consult the companies.

I. List of products belonging to companies associated to Farmaindustria (258 records)
II. List of products belonging to other companies (204 records)

The list of products was divided up accordingly and distributed to experts from the corresponding affected company (associated to Farmaindustria) together with an assessment questionnaire. It is important to point out that the questionnaire reflected the experts' opinions and that it did not involve an official or binding response from the MAH.

The questionnaire was created to obtain the following answers:

1. Confirm if the products in the reviewed list from the company could effectively identify the products to be protected in order to ensure their continuity in the market
2. Remove those products that, in the original list, despite being considered at risk of commercialization by AEMPS, did not present a threat either in the viability or in the supply, according to an expert's judgement
3. Add new products that, even though not having been considered at risk of commercialization by AEMPS, do still pose a threat to viability and supply, according to an expert's the judgement

From this, a list of products valued by experts from companies associated to Farmaindustria was obtained, which, with the confirmations (164), additions (168), no answers (7) and deletions (87) went from 258 to 339 records

The list of products reviewed by the experts of companies associated to Farmaindustria, together with the list without further validation (339 + 204 = 543 records) needed, for the purpose of better research, the conversion from products (REG Number) to presentations (as defined on page 1), since the commonly used databases (IMS, BOt Plus, Catalogue from Farmaindustria) use the presentation identified by its National Product Code (NN).

The list of 543 products increased to 589 presentations because, as expected, some product records are marketed in several presentations.

A new revision was carried out on the list of 589 presentations, and the following categories were removed:

1. Presentations that still have market exclusivity (due to patent or data protection), considering that these products, although they had a critical therapeutic role in case of shortages, were not part of the products to be protected due to the lack of interest in their commercialization by pharmaceutical companies.
2. The presentations of products that have two or more generic or competitors marketed, considering that the negative effects of non-commercialization of the original product could be remedied by the commercialization of generics or competitors, and vice versa.
3. The suspended or revoked presentations of products still authorised in other presentations, which are normally imported as foreign medication.

The resulting list, which is named "original list", contained 568 presentations.

Regarding this original list, its distribution by MA longevity, ATC group and route of administration, with respect to the general market has been considered. The active substances in this group of presentations have also been listed.

Out of the presentations from the initial list, 341 correspond to companies associated to Farmaindustria, which we have called "reviewed list".

Regarding the reviewed list, there is additional information obtained by the responses to a questionnaire to assess the reasons for a possible lack of viability due to production, economic causes, or both.

Although the ideal would have been to consult experts from all the MAHs of the products included in the initial list, the difficulties in submitting the questionnaire, as well as obtaining and analyzing the corresponding answers, has resulted in circumscribing this list to the evaluation of the experts from the field of pharmaceutical regulation in the form of a technical working group of Farmaindustria (RTM Group).

In relation to the causes of a possible non-permanence in the market of a certain presentation derived from production, the questionnaire (see figure 4) offered the following possibilities:

1. The lack, or shortage, of raw material supply, mainly due to the fact that the MAHs of this type of product with limited consumption and outdated prices may have problems in finding a guaranteed manufacturer/supplier of the active substance.
2. Problems in manufacturing derived from the industrial repositioning in the manufacturing priorities of these products and contract manufacturing in some cases.
3. The obligation to include safety features (unique identifier and an anti-tampering device) on the packaging of certain products for human use for the purposes of allowing their identification and authentication, as a consequence of the application of Commission Delegated Regulation (EU) 2016/161 that may be a subsequent cause and make a certain presentation unfeasible.
4. The delays in the variations procedure in some cases (manufacture or control changes in active substance or finished product).
5. Other causes different from the previous ones.

In relation to the causes of a possible non-permanence in the market of a certain presentation derived from economic regulation, the questionnaire (see figure 5) offered the following possibilities:

1. The application of the Reference Price System (RPS), since it may affect certain presentations with a small content of active substance and consequently very low price (for example, low dosages, oral solutions, amongst others) that do not have a marketed competitor but that are affected by the lower cost per treatment, per day of the group. In particular, it asked whether the options to remove the threat of lack of viability in commercialization would mean the exclusion of the presentation of the RPS or the application of the so-called weighted reference price (applied to those presentations with special dosages, or which are indicated for serious pathologies, or

whose prices have been revised by the CIMP in the last 2 years due to their low profitability), or if there was any other suggested option.

2. The price of the presentation. The intervened price of products financed by the NHS may become obsolete, especially in the case of old marketing authorisations. The questions in the questionnaire asked whether the threat to stay in the market was due to a lack of viability of the price or to a lack of viability of the price even after having been revised upwards. It also contemplated whether the continuity in commercialization was influenced both by the price and by the lack of interest to continue by the marketing authorisation holder.
3. Other causes different from the previous ones.

Patient and Public Involvement

Patients or public were not involved in this study.

Results

I. ORIGINAL LIST

The original 568 presentations were studied in various areas.

1. **By active substance.** The active substances of the proposed initial MPWCI relationship are shown in Annex 1. For the purposes of this classification, if two or more presentations contain the same active substance, the active substance only appears once in the table. Likewise, the different salts and derivatives of an active substance are considered as the same active substance. The active substances that are formulated as a single ingredient appear with their name. If they are part of an association of two or more active substances, the figure shows the number of active substances and the names of the medicinal products combination at a fixed dose.
2. **Date of the marketing authorisation.** Products whose lack of commercialization could have an impact on welfare are old. More than 75% of the products in the list were authorised in the last century and almost 50% of the products considered essential have an authorisation of more than 50 years.

   The comparison of the age of the proposed MPWCI with the rest of the products in the reimbursable market[19] is shown in Figure 4. Predictably, most of the old products marketed in Spain before the year 2000 belong to this category of products to be protected.

Figure 4: Distribution of product presentations studied due to the age of the marketing authorisation in Spain compared to the rest of the reimbursable presentations in Spain.

3. **Therapeutic group.** The distribution by therapeutic groups, according to the ATC classification (Anatomical, Therapeutic & Chemical) has been another aspect taken into consideration in the initial list of the proposed MPWCI. The comparison between the presentations of products in the reimbursable market (IMS data) in relation to the initial relation of MPWCI proposed is shown in figure 5.

Figure 5: Distribution of product presentations studied by therapeutic group.

4. **Route of administration.** In the case of the proposed MPWCIs, the results show a more than remarkable concentration of these products of interest in certain routes of administration, with a very different distribution compared to the reimbursable market (IMS data). Although expected, it is striking, with a high proportion of injectable forms in the case of MPWCIs proposed with 44.12% of the total presentations of the category, compared to only 6.63% of presentations in the reimbursable market (IMS data). Similarly, this occurs in the ophthalmic forms in which the proposed MPWCIs represent 7% of the total sample compared to 1.42% of the presentations in the reimbursable market (IMS data). See figure 6.

Figure 6: Distribution of product presentations studied by administration route.

II. REVIEWED LIST

As mentioned above, the questionnaire was sent to experts from 44 companies belonging to Farmaindustria, where 37 **responses** were received from the experts of these companies, representing **84%** of those consulted. The data collection was carried out from February to July 2017.

The experts from these companies indicated that they are not concerned by reasons only resulting from production. For only 4% of the cases, the continuity of the strategic presentations could be at risk of permanence in the market for reasons exclusively relating to production. The isolated economic aspects have a greater relevance, since they represent 20% of the assumptions considered. This percentage rises to 76% if we consider both causes, that is, those derived from regulation and production.

For some experts, the alignment of the increasing difficulties to obtain a regular supply of active substances or of intermediate products under suitable conditions of price and service, the requirements of the regulation for the processing of the registry variations relative to the places of manufacture and the modifications that the serialisation of products will entail, can jeopardize the viability in the marketing of certain presentations (figure 7).

Figure 7: Main causes that may lead to a possible non-permanence of MPWCI presentations in the Spanish market.

Causes derived from production

The lack, or shortage, of supply of raw materials does not constitute a problem for the viability in the supply of the proposed MPWCI. The main concern is focused on the pending approval of procedures that can delay, or even stop, the supply of a particular product and the serialisation rules that involve modifying the conditioning lines of many companies to incorporate both anti-tamper devices and the unique identifier of each of the containers affected by Delegated Regulation (EU) 2016/161. (Figure 8)

In the segment 'others' (see below), the main threats to the permanence of these presentations in the market are: a difficulty in updating the registration dossier (which could be critical the BREXIT scenario), the absence of a raw material in a product on a global scale, the cost of the device of administration regarding the price of the medicine, the complexity of the manufacture or the lack of a manufacturer, especially in the case of products that are marketed in only a few countries (sometimes only in one single country).

Figure 8: Main causes related to production that may lead to possible non-permanence of MPWCI presentations in the Spanish market.

Causes derived from economic regulation

The low prices of the products studied would be the first factor in causing a threat to the continuity in commercialization. In this case, the products are not affected by the Reference Price System since they are products that have no marketed competitor and, therefore, the reference group has not been established.

In the case of products with a competitor Reference Price System affects all the presentations included in said group, which are subject to a price review every year. According to the

answers obtained (Figure 9), the feasibility for minority consumption presentations in these groups, which contains active substances within the proposed MPWCI, are at risk.

Experts have responded to other causes also, including the absence of regulatory development for the transfer of MAH, as envisaged by RD 1345/2007 which regulates in Spain the Registration of Products or the risk of an avoidable national shortage if the presentations were to be subject to an exceptional prior notification, regulated in order to be sent to another Member State [20].

Figure 9: Main causes related to economic regulation that may lead to a possible non-permanence of MPWCI presentations in the Spanish market.

In relation to the presentations included in the Reference Price System, the solution considered most appropriate to guarantee the permanence in the market of these presentations would be their exclusion from the System (84%). The option of reducing the fall in prices through the application of weighted prices is a minority one (7%).

As mentioned, many of the proposed MPWCI presentations are unique (77%) if we consider their pharmaceutical form and dosage. (Figure 10)

Figure 10: Main causes related to economic regulation that may lead to a possible non-permanence of the MPWCI submissions proposed in the Spanish market related to the Reference Price System.

With regards to the price of products, 85% of the total of responses indicates that the price would not be viable in order to advance the continuity in commercialization at a high percentage.

Regarding the upward revision of prices, the experts' stance indicates that in some cases, the increases experienced by certain affected presentations have not eliminated the threat in the continuity of these products (7%) and in other cases (8%) the price band of the presentations would not be of the interest to the companies. (Figure 11)

Figure 11: Main causes related to the economic regulation that may lead to a possible non-permanence of the MPWCI presentations in the Spanish market related to the price revision.

Finally, the experts' contribution towards possible solutions has seen some proposals of interest to reduce the risk of lack of supply of these presentations.

The consideration of an upward revision of the price of products, whose age exceeds a certain threshold, for example 20 years, has been proposed. It also advises the modification of regulations on reference prices and allowing for certain unique presentations to remain outside the System or that there be a different consideration for products whose formulation and dosage have a different therapeutic focus.

Another aspect needing to be rectified is that, currently some products are sold at a loss, due to the legal obligation to keep their marketing within Spain and the impossibility of withdrawing market presentations, precisely due to the refusal of AEMPS to revoke the marketing authorisation. Lastly, some responses mention the formal need to regulate the so

called “therapeutic gap” to ensure that the criteria determine the obligation to keep the product on the market (Figure 12).

Figure 12: Main solution proposals related to economic regulation to contribute to the greater permanence of MPWCI presentations.

Discussion

At the time of conducting this study, the authors considered whether the category of products without commercial interest (MPWCI) that complies with Spanish legislation was, in effect, a real group of presentations of authorised and effectively marketed products, or merely just a theoretical approximation by the legislator, since the matter is still pending development.

The authors opted for the first option. In Spain there is a series of products that would respond to the need for special measures in relation to their manufacture, import, distribution, dispensation, economic and fiscal regime to ensure their supply be considered necessary for the treatment of certain diseases or pathologies, in terms consistent with those included in article 3.3 of Royal Legislative Decree 1/2015, of July 24, which approves the revised text of the Law on guarantees and rational use of products and healthcare products.

Although this relationship is changing because treatments evolve over time and the commercialization of new products turns obsolete therapies into well established ones, there are some products that maintain their place within the therapeutic sphere despite the passage of time. This has been recognized by AEMPS who have drawn up a list of products whose disappearance would have a impact on healthcare and on patients.

Furthermore, the legislation in force in Spain regulates a figure, which authorises the competent authority to not grant the temporary suspension, or the revocation of the marketing authorisation of a product "*when there are health reasons or healthcare interest, as in the case if a therapeutic gap is created, whether in the market in general or in the pharmaceutical provision of the National Health System, the Spanish Agency of Products and Medical Devices will maintain the validity of the authorisation and demand the effective commercialization of the medication.* " [21]

The figure of the *therapeutic gap* envisaged in the Spanish regulations in which it is considered a very serious infringement for "*the marketing authorisation holder to cease the supply of a medicinal product in the event that there are health reasons or healthcare interest, for example if there were a therapeutic gap, either in the market in general or in the pharmaceutical provision of the National Health System*"[22], has not prevented the discontinuation of the marketing of certain products when the holder has perceived them no longer viable for the Spanish market. The therapeutic gap figure does not have an explicit 'fit' within the EU legislation, which for the discontinuation of commercialization (temporary or permanent) requires that the MAH inform the competent authorities within a two month period. The aim of the MAH is to try to maintain the supply, in order to avoid the discontinuation of commercialization in Spain, in some cases however this is not so and AEMPS has had to justify the acquisition of certain products through foreign medication [23].

In short, both the positive list from AEMPS and the possibility of stating that the exclusion or revocation of the marketing authorisation of a certain product would create a therapeutic gap, point to the need to consolidate a group of products with special characteristics, which should carry MPWCI conditions.

Membership under proposed MPWCI status has also been endorsed by a group of experts from the companies associated to Farmaindustria who have found themselves obligated to

maintain the effective commercialization of these products, given the absence of others with the same composition and taking into consideration the role in which the product has in therapeutics.

However, the price erosion that occurs with the proposed MPWCIs and the absence of measures that protect them from technical and economic regulations, may lead to a gradual lack of supply for any of these products. Not only does this lack of regulation diminish the authorised treatment options, but it also discourages the presentation of new pharmaceutical form innovations intended for the unmet medical needs that are of interest to patients, healthcare professionals, administrations and industry.

It seems clear that the regulations that regulate certain matters such as reference prices or future serialisation, may contribute to the lack of viability in continuing marketing certain presentations without competition (despite their protection rights having expired). Also, the lack of protection for these strategic presentations makes it difficult to not carry out initiatives to commercialize innovations of these known products, since they would also be negatively affected by said regulation [24].

The Directorate General of Basic Healthcare Services Portfolio and Pharmacy (DGCBSF) mentions that it is working on the modification of the legislation to avoid that "*the purely mathematical mechanisms of the Reference Price System may exert perverse effects and provoke the departure of the pharmaceutical supply of medicinal products of proven therapeutic efficacy.*"

For its part, AEMPS has considered within the Plan for Guarantees of Medicinal Product Supply, that one of the measures aimed at preventing supply problems is the identification of products at risk, whose shortage could have a welfare impact, for the purpose of adopting specific preventative measures [25].

Conclusions

In short, the following conclusions can be drawn from the study carried out:

1. This work can be considered as the first study that establishes a perimeter of products presented as MPWCI. From the original AEMPS list, a further list of affected active substances has been identified with the contributions of a significant number of experts from pharmaceutical companies associated to Farmaindustria.
2. As the results show, the products proposed as MPWCI are old and are developed by active substances of chemical origin, parenterally administered much more frequently than the rest of the general market. Unlike oral forms, injectable forms require adequate manufacturing facilities to guarantee the quality and sterility of the product, which naturally increases the cost of the product and if the price is low or obsolete, the pharmaceutical form can also be used to decrease the viability in order to maintain the marketing of these presentations.
3. Since many products proposed as MPWCI are old, prices may have become obsolete. As shown in the results, an upward revision of prices is necessary to contribute to the permanence in the market of these presentations. On the other hand, the experts of the companies have not valued the current price revisions as a sufficiently satisfactory mechanism to change the consideration of these products with respect to the interest on the part of some MAHs to maintain the future commercialization of these presentations.
4. The Reference Price System is currently regulated and does not benefit the permanence in the market of products proposed as MPWCI, since some presentations without competition in the market suffer from regular price erosion with the successive annual updates of the system, generating a situation of unfeasibility for commercialization, which implies an insufficiency in the supply or the effective disappearance of the market.
5. It seems necessary to develop a regulation that protects the products proposed as MPWCI whilst maintaining the conditions of the absence of alternatives and therapeutic relevance for patients. This regulation should establish that, the formal consideration of MPWCI allows the review of the price of the product until its viability is guaranteed in the commercialization and the exclusion of the Reference Price System, in the event that the absence of a competitor could jeopardize the continued supply of the medicine.

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Annex 1. Active ingredients included in the original list of proposed MPWCI

ABACAVIR SULFATO	BACLOFENO	CLOFAZIMINA	DISOPIRAMIDA	FLUDARABINA FOSFATO	ISOFLURANO	METOPROLOL TARTRATO	PENICILAMINA	SOTALOL HIDROCLORURO	TRANEXAMICO ACIDO	2 - ESTRADIOL HEMIHIDRATO,NORE TISTERONA ACETATO
ACENOCUMAROL	BCG CULTIVO VIVO DESECADO	CLOMETIAZOL	DOBUTAMINA	FLUDROCORTISONA	ISOPRENALINA SULFATO	METOTREXATO	PENTAMIDINA ISETIONATO	SULBACTAM SODICO	TRETINOINA	2 - FENILEFRINA HIDROCLORURO,TET RACAINA
ACETATO CALCIO	BENZBROMARONA	CLOMIFENO CITRATO	DORNASA ALFA	FLUORESCEINA	TRACONAZOL	METOXALENO	PENTOSTATINA	SULFADIAZINA ARGENTICA	TRIFLUOPERAZINA DIHIDROCLORURO	2 - FENILEFRINA HIDROCLORURO,TRO PICAMIDA
ACETAZOLAMIDA	BEXAROT	CLOMIPRAMINA HIDROCLORURO	DOXEPINA HIDROCLORURO	FLUOROMETOLONA	KETAMINA HIDROCLORURO	METRONIDAZOL	PERFENAZINA	SULPIRIDA	TRIMETOPRIMA	2 - FLUORESCEINA SODICA,OXIBUPROCA INA HIDROCLORURO
ACETILCOLINA CLORURO	BIPERIDENO HIDROCLORURO	CLONAZEPAM	DOXICICLINA HICLATO	FLUOROURACILO	LAUROMACROGOL 400	MICOFENOLATO DE MOFETILO	PERMETRINA	SUXAMETONIO CLORURO	TROPICAMIDA	2 - FLUPENTIXOL DIHIDROCLORURO,M ELITRACENO
ACETILSALICILATO LISINA	BLEOMICINA SULFATO	CLORAMBUCILO	DOXORUBICINA HIDROCLORURO	FOLINATO CALCIO	LEVOMEPROMAZINA HIDROCLORURO	MICOFENOLATO SODIO	PILOCARPINA HIDROCLORURO	TASONERMINA	TUBERCULINA	2 - ISONIAZIDA,PIRIDOX INA HIDROCLORURO
ACICLOVIR	BUDESONIDA	CLORANFENICOL	EDROFONIO BROMURO	FOSAMPRENAVIR CALCICO	LEVOTIROXINA SODICA	MIDAZOLAM HIDROCLORURO	PIRANTEL EMBONATO	TENOFOVIR DISOPROXILO FUMARATO	VALGANCICLOVIR	2 - ISONIAZIDA,RIFAMPI CINA
ALBENDAZOL	BUPIVACAINA HIDROCLORURO	CLORAZEPATO DIPOTASIO	EFEDRINA HIDROCLORURO	GENTAMICINA SULFATO	MAGNESIO SULFATO HEPTAHIDRATO	MIFEPRISTONA	PIRIDOSTIGMINA BROMURO	TENSIOACTIVO PULMONAR BOVINO	VALPROATO SODIO	2 - NAFAZOLINA HIDROCLORURO,TET RACAINA
ALDESLEUKINA	BUSULFANO	CLOROQUINA FOSFATO	EPINEFRINA BITARTRATO	GLICEROFOSFATO SODIO	MANITOL	MITOMICINA	PIRIMETAMINA	TENSIOACTIVO PULMONAR PORCINO	VALPROATO SODIO	2 - OXIBUPROCAINA HIDROCLORURO,TET RACAINA
AMIODARONA HIDROCLORURO	BUSULFANO	CLORPROMAZINA HIDROCLORURO	ERITROMICINA	HALOPERIDOL	MAPROTILINA HIDROCLORURO	MORFINA HIDROCLORURO	POLIESTIRENOSULFO NATO SODIO	TERBUTALINA SULFATO	VERAPAMILO HIDROCLORURO	2 - SULFAMETOXAZOL,T RIMETOPRIMA
AMITRIPTILINA	CAFEINA CITRATO	CLORTETRACICLINA HIDROCLORURO	ESCOPOLAMINA BUTILBROMURO	HIDRALAZINA HIDROCLORURO	MEBENDAZOL	NALOXONA HIDROCLORURO	PREDNISOLONA ESTEAGLATO	TESTOSTERONA CIPIONATO	VINBLASTINA SULFATO	2 - VALPROATO SODIO,VALPROICO ACIDO
AMITRIPTILINA HIDROCLORURO	CALCITRIOL	CLOXACILINA SODICA	ESCOPOLAMINA HIDROBROMURO	HIDROCORTISONA ACETATO	MEDROXIPROGESTE RONA ACETATO	NEOSTIGMINA METILSULFATO	PROCAINA HIDROCLORURO	TESTOSTERONA UNDECANOATO	VINCRISTINA SULFATO	3- TENOFOVIR DISOPROXIL FUMARATO,
AMOXICILINA SODICA	CAPREOMICINA SULFATO	DACARBAZINA	ESMOLOL HIDROCLORURO	HIDROCORTISONA FOSFATO SODIO	MEDROXIPROGESTE RONA ACETATO	NIFEDIPINO	PROCAINAMIDA HIDROCLORURO	TETRACAINA HIDROCLORURO	VINDESINA SULFATO	3 - BENCILPENICILINA POTASICA,BENCILPENICILINA
AMPICILINA SODICA	CARBAMAZEPINA	DAPSONA	ESPIRONOLACTONA	HIDROXICARBAMIDA	MEGLUMINA ANTIMONIATO	NITROFURANTOINA	PROCARBAZINA HIDROCLORURO	TETRACICLINA HIDROCLORURO	virus fiebre amarilla cepa 17 D	3 - DEXAMETASONA FOSFATO DISODIO,GENTAMICI
APOMORFINA HIDROCLORURO	CEFADROXILO MONOHIDRATO	DAUNORUBICINA HIDROCLORURO	ESTREPTOMICINA SULFATO	HIDROXICLOROQUIN A	MELFALAN	NITROGLICERINA	PROPRANOLOL HIDROCLORURO	TETRACOSACTIDA	virus rabia inactivado	3 - DEXAMETASONA,NE OMICINA
ASCORBICO ACIDO	CEFUROXIMA AXETILO	DEFEROXAMINA MESILATO	ETAMBUTOL	HIDROXIZINA DIHIDROCLORURO	MERCAPTOPURINA	NITROPRUSIATO SODIO	PROTAMINA SULFATO	TIAMINA HIDROCLORURO	VORICONAZOL	3 - ESTRADIOL HEMIHIDRATO,NORE TISTERONA
ATAZANAVIR	CICLOFOSFAMIDA	DEXAMETASONA	ETOPOSIDO	IBUPROFENO	MESNA	OCTREOTIDA ACETATO	RALTITREXED	TIGECICLINA	WARFARINA SODICA	4 - ERGOCALCIFEROL,FI TOMENADIONA,RETI
ATENOLOL	CICLOPENTOLATO HIDROCLORURO	DEXAMETASONA FOSFATO DISODIO	FENILEFRINA HIDROCLORURO	IDARUBICINA HIDROCLORURO	METADONA HIDROCLORURO	OXICODONA HIDROCLORURO	RIBAVIRINA	TINIDAZOL	ZIDOVUDINA	4 - ETAMBUTOL HIDROCLORURO,ISO NIAZIDA,PIRAZINAMI
ATROPINA SULFATO	CICLOSPORINA PARA MICROEMULSION	DIAZEPAM	FENOBARBITAL	IFOSFAMIDA	METILDOPA	OXITOCINA	RIFABUTINA	TIOGUANINA	2 - AMILORIDA HIDROCLORURO,HID ROCLOROTIAZIDA	5+ Cloruros Cr,Cu,Fe,Mn,Zn; Ioduro K, Fluoruro
ATROPINA SULFATO	CIPROFLOXACINO HIDROCLORURO	DIDANOSINA	FENOXIMETILPENICIL INA-BENZATINA	IMIPRAMINA HIDROCLORURO	METILERGOMETRINA MALEATO	PAMIDRONICO ACIDO	RITONAVIR	TIZANIDINA HIDROCLORURO	2 - AMOXICILINA SODICA,CLAVULANA TO POTASIO	5+ Glutation, Manitol, Acs Lactobionico,
AZATIOPRINA	CITARABINA	DIGOXINA	FITOMENADIONA	INMUNOGLOBULINA ANTIRRABICA	METILPREDNISOLONA	PAROMOMICINA	SILDENAFILO	TOBRAMICINA	2 - BENSERAZIDA HIDROCLORURO,LEVODOPA	5+ ICODEXTRINA,Clorur o Na,S-Lactato Na,
AZTREONAM	CLADRIBINA	DINOPROSTONA	FLECAINIDA ACETATO	INTERFERON BETA-1B	METOCLOPRAMIDA HIDROCLORURO	PEGVISOMANT	SILIBININA SUCCINATO SODIO	TOLCAPONA	2 - DEXAMETASONA,TO BRAMICINA	

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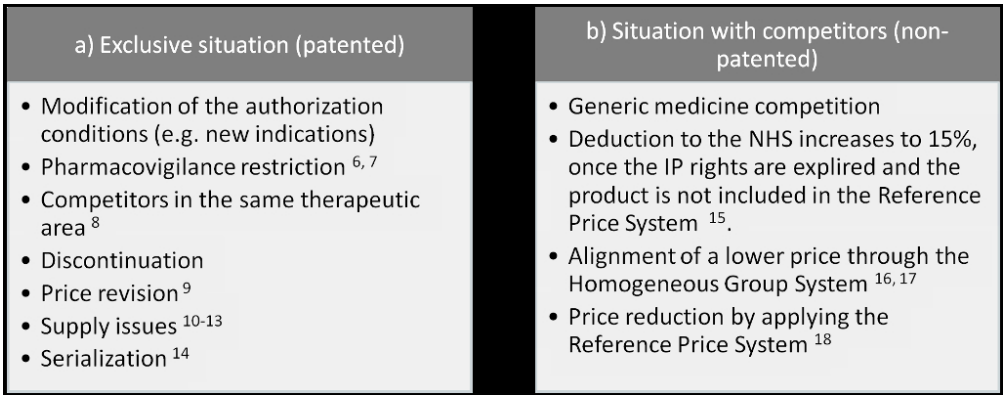

Figure 1: Causes that modify the authorisation conditions: a) causes that affect all commercialized products (patented or not), b) causes that only affect those products without patent protection or data protection

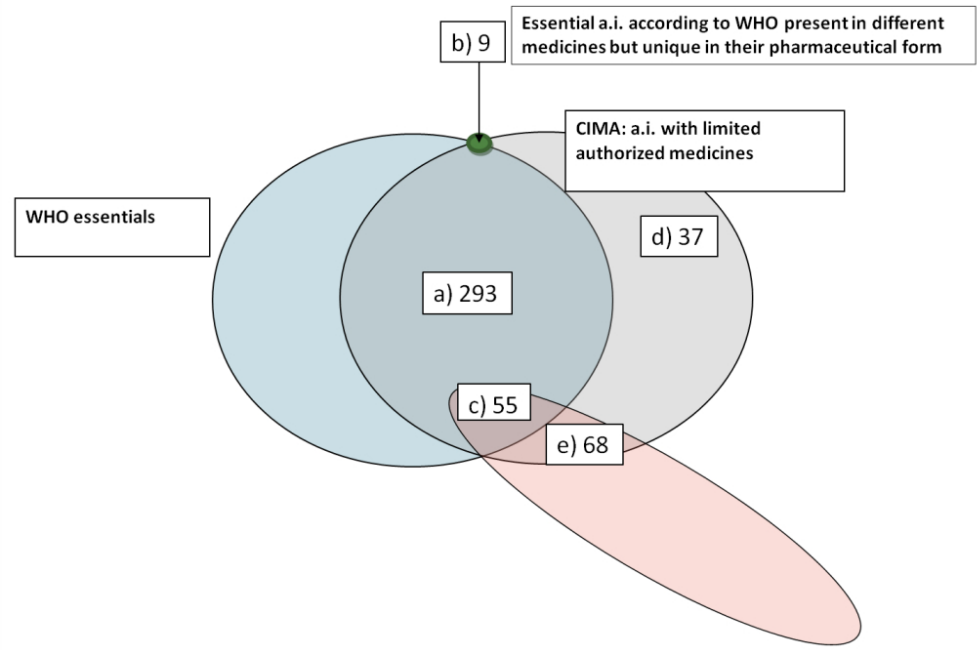

Figure 2: Distribution of essential products for the Spanish market. Source: AEMPS.

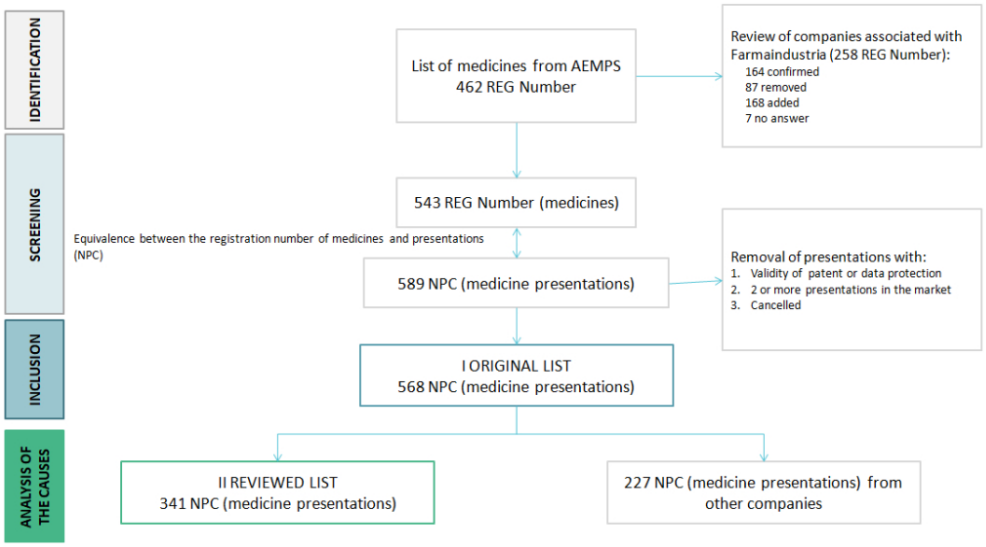

Figure 3: Diagram of the review carried out for the different medicinal product presentation lists whose viability of commercialization has been reviewed in the present list.
REG Number: Registration Number
NPC: National Product Code

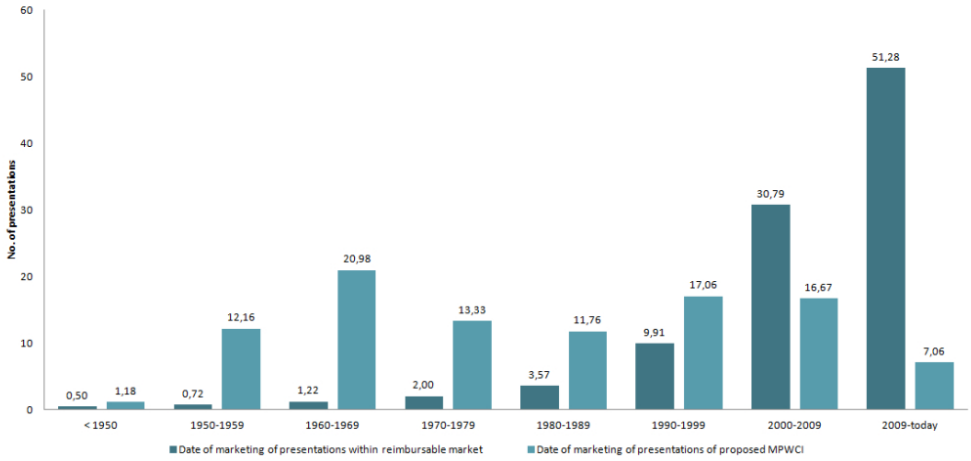

Figure 4: Distribution of product presentations studied due to the age of the marketing authorisation in Spain compared to the rest of the reimbursable presentations in Spain.

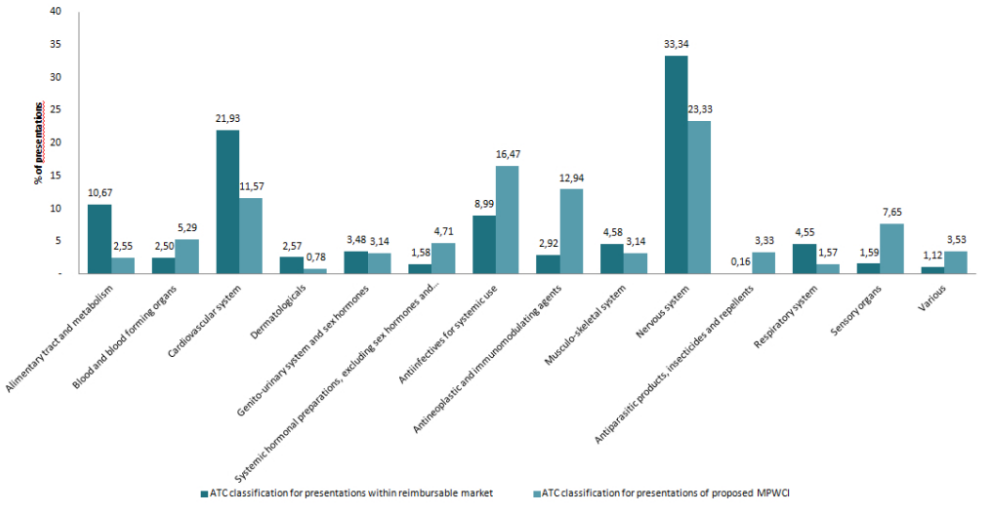

Figure 5: Distribution of product presentations studied by therapeutic group.

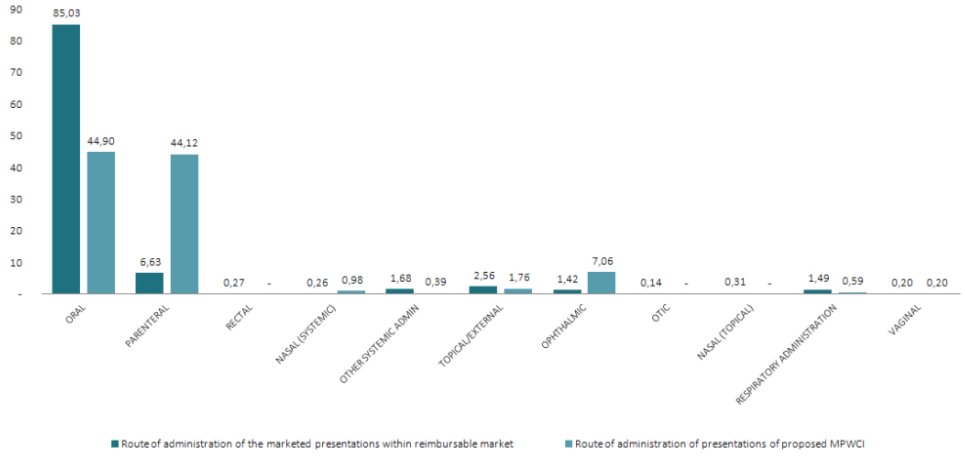

Figure 6: Distribution of product presentations studied by administration route.

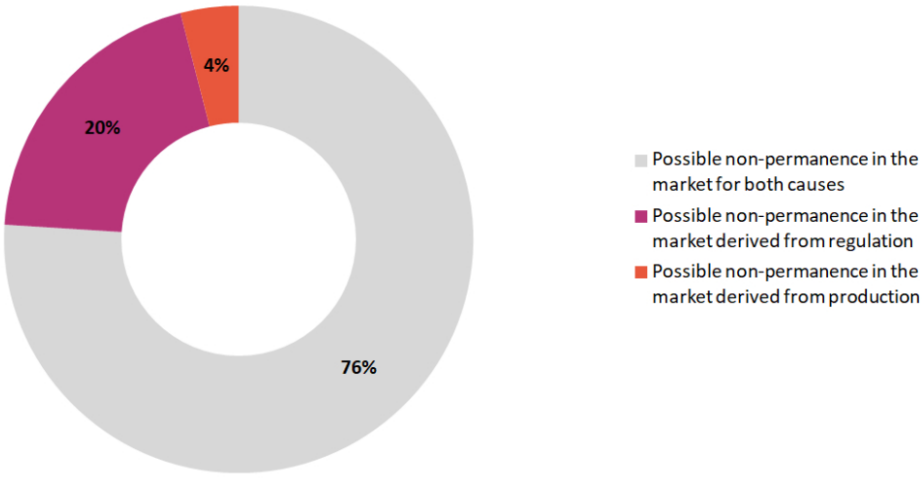

Figure 7: Main causes that may lead to a possible non-permanence of MPWCI presentations in the Spanish market.

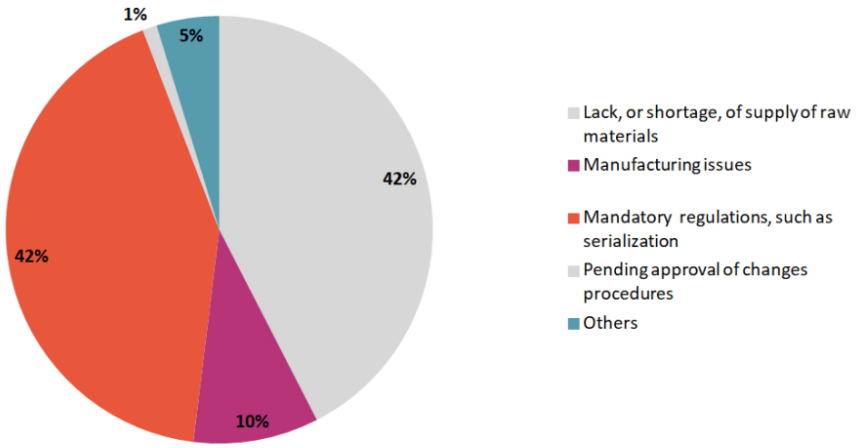

Figure 8: Main causes related to production that may lead to possible non-permanence of MPWCI presentations in the Spanish market.

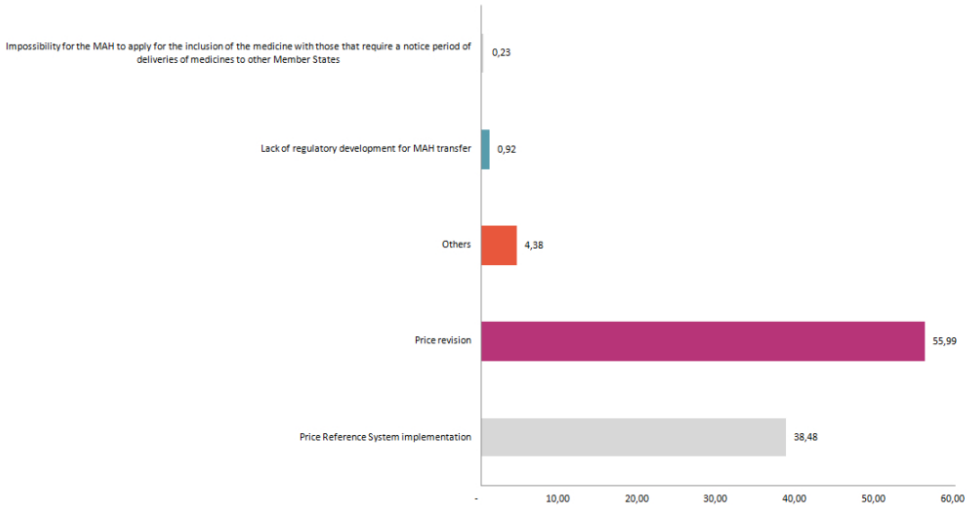

Figure 9: Main causes related to economic regulation that may lead to a possible non-permanence of MPWCI presentations in the Spanish market.

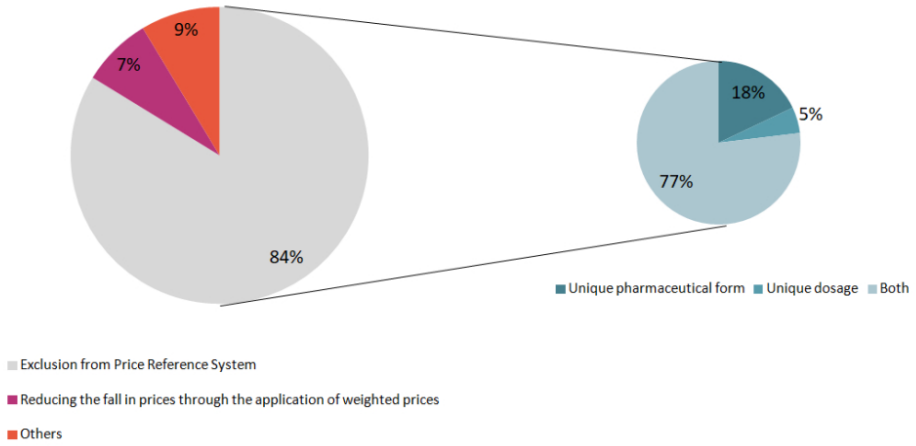

Figure 10: Main causes related to economic regulation that may lead to a possible non-permanence of the MPWCI submissions proposed in the Spanish market related to the Reference Price System.

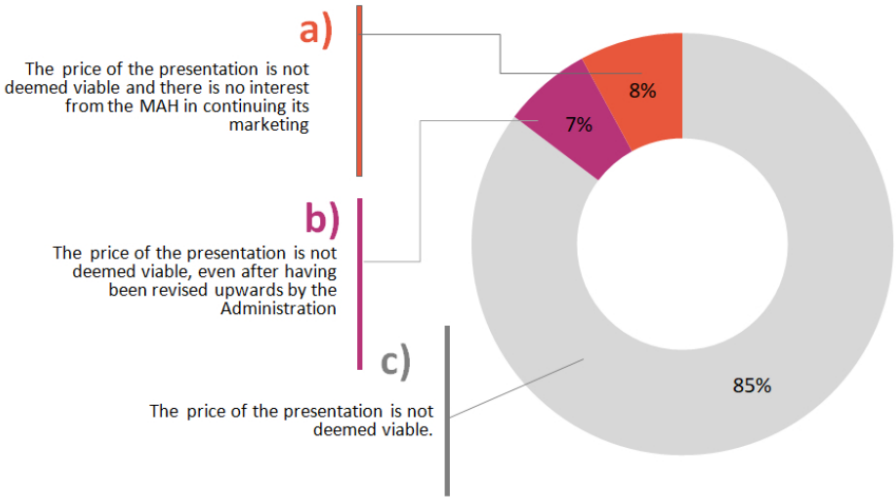

Figure 11: Main causes related to the economic regulation that may lead to a possible non-permanence of the MPWCI presentations in the Spanish market related to the price revision.

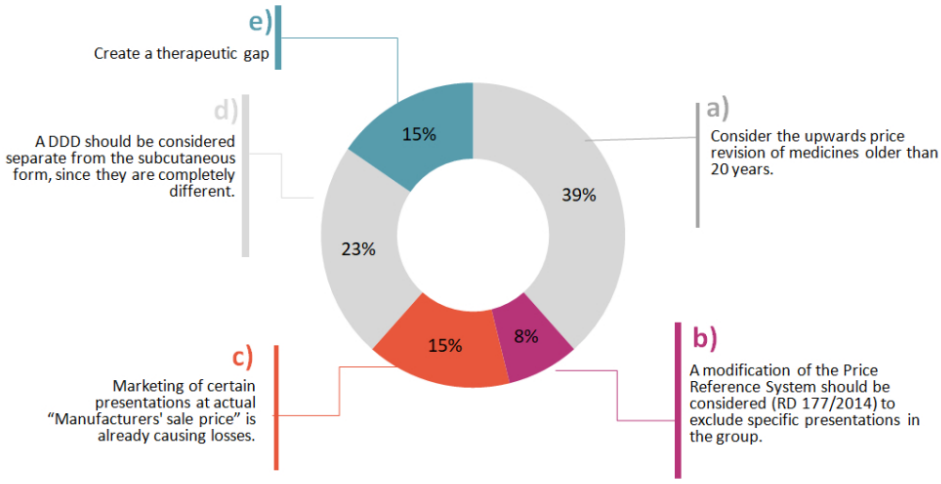

Figure 12: Main solution proposals related to economic regulation to contribute to the greater permanence of MPWCI presentations.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	-
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	-
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

A cross-sectional study on medicinal products without commercial interest (MPWCI) in the Spanish market

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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Health policy
Keywords:	Essential medicinal products, shortages, supply, price, discontinuation

"A cross-sectional study on medicinal products without commercial interest (MPWCI) in the Spanish market"

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Keywords:
Essential medicinal products; shortages; supply; price; discontinuation.

Word count: 5.757

Abstract

Objective: To confirm that there is a defined group of products to be protected in the Spanish therapeutic arsenal known as "medicinal products without commercial interest" (MPWCI) and propose the adoption of legal measures aimed at avoiding, or reducing, the lack of supply of said products.

Design: a cross-sectional study of proposed MPWCI based on a survey. The Spanish Agency of Medicines and Medical Devices (AEMPS) was asked for a list of presentations of medicines in order to identify those whose lack could have an impact on welfare.

Setting: a search on the AEMPS website and a survey conducted among 44 companies belonging to Farmaindustria has allowed for the development of a proposal list of presentations that should continue to be marketed in Spain.

Results: products proposed as MPWCI are old (50% of them have an authorisation of more than 50 years) and are developed by active substances of chemical origin, parenterally administered much more frequently than the rest of the general market (44% vs 6.6 % respectively). Unlike oral forms, injectable forms require adequate manufacturing facilities to guarantee the quality and sterility of the product, which naturally increases the cost of the product and if the price is low or obsolete. The company experts have not valued the current price revisions as a sufficient enough mechanism to change the consideration of these medicines with respect to the interest on the part of some MAH to maintain their commercialisation.

Conclusions: As shown in the results, an upward revision of prices is necessary to contribute to the permanence of these presentations in the market, although some experts do not consider the

current price revisions satisfactory enough to maintain these presentations in the Market. Therefore, a specific regulation seems necessary to ensure the continuity on the market of these proposed products.

Article summary

Strengths and limitations of this study

- This is the first article to propose that a group of products be considered as MPWCI, originating from a list of products identified by the Spanish Agency of Medicines and Medical Devices (AEMPS), taking into account the opinion of a group of experts from the Marketing Authorisation Holders (MAH)
- The analysis of the products to be considered as MPWCI has been strengthened by the results of a survey that allows conclusions to be drawn about the need to typify and regulate MPWCI in Spain.
- The results of the survey are limited to those products belonging to companies associated to Farmaindustria. Future studies could be expanded and include the opinions of healthcare professionals or experts from other fields, such as University.
- The data from the survey reflects the situation at a given time. The pharmaceutical sector situation is constantly changing, in a way that the number of presentations affected could vary depending on regulatory decisions that may be adopted.

Introduction

Spanish legislation refers to “medicinal products without commercial interest” (hereon in MPWCI) as those where there is an absence, or shortfall, of supply within the Spanish market, yet are still required to treat certain diseases or pathologies.

There are several causes which can affect the initial marketing authorisation conditions during a medicine’s lifecycle, and this can lead to an absence or a lack of supply. For instance, the existence of other competitors, new implementation of regulatory requirements[1], additional restrictions derived from pharmacovigilance[2], entries of generic medicinal products[3] (hereon in only referred to as ‘products’), or simply, a decrease in demand due to obsolescence.

All of these circumstances ultimately affect marketing viability for certain products, leading to their disappearance from a market which is constantly changing. However, when this situation affects products that are still crucial for treating certain diseases, the lack of availability poses a conflict that has an effect on patients and healthcare professionals, reducing treatment options and damaging the pharmaceutical industry’s image because the MAH is blamed for the fact that the medicine can no longer be used by patients and health professionals.

The fact that it is still necessary to guarantee the availability of certain products and, more precisely some presentations (defined hereon in as specific strength, pharmaceutical form and content in weight, volume or units of dosage), denotes that further development of Spanish regulation seems necessary in order to ensure the commercialisation of these products with high healthcare interest but low economical interest.

In accordance with current Spanish legislation, and in order to ensure the supply of products, the Government can adopt special measures in relation to its manufacture, import, distribution, and dispensing. In particular, and in the case of MPWCIs, in addition to the above-mentioned measures, Spanish legislation allows those relating to the economic and fiscal regime in favour of such products[4].

In this paper, we aim to answer whether there is a group of marketed products that could be considered MPWCI; a legal category of medicines described but not developed in Spanish legislation. An identification of these types of products is suggested, the description of their characteristics, the main causes that threaten their marketing viability and several considerations regarding the need to develop regulations for this matter in Spain.

Once we had confirmed and studied the presence of a group of MPWCI in Spain, we considered the need of adopting a legislative development to protect these products’ marketing viability. As a matter of fact, the absence or lack of supply of essential medicines in Spanish market could represent a great issue for the Health System, healthcare professionals and patients.

Marketing conditions

The marketing authorisation (herein MA) establishes the main marketing conditions of the product's authorisation throughout its life cycle. The MA includes, amongst other elements, the Summary of product characteristics, which gathers all the therapeutic conditions of use, such as authorised indications or contraindications. The MA is granted, on one side, by the European Commission for those cases in which products are authorised by Centralized Procedure[5] and, by the Member States of the European Union for the remaining the cases[6] . In Spain, the competent authority for issuing marketing authorisations is the Spanish Agency of Medicines and Medical Devices (AEMPS) [7].

Once the product is authorised, the Spanish competent authorities make a decision about its price and reimbursement regardless of the procedure for which the medication was authorised. In Spain, the procedure includes the participation of the Inter-Ministerial Pharmaceutical Pricing Commission (CIPM) [8]. When this process has ended, the MAHs communicate to AEMPS the intention to effectively market the drug, requesting its inclusion in the official Presentation Catalogue of the Pharmaceutical Provision of the National Health System. From the moment of the product's publication in the Presentation Catalogue, retail products can then be marketed immediately, but in the case of products in hospitals, the MAH must frequently manage additional procedures for local access in the different Regions[9, 10].

The initial conditions of authorisation change throughout the life cycle of the product and can be divided into two stages: (i) when the original product is in an exclusive situation; (ii) when the protection offered by both the patent and the data protection has expired. Figure 1 summarizes the main causes that modify the conditions of the initial authorisation of the original products [3; 11-22].

Figure 1: Causes that modify the authorisation conditions: a) causes that affect all commercialized products (patented or not), b) causes that only affect those products without patent protection or data protection

Objectives

1. Confirm that there is a defined group of products to be protected in the Spanish therapeutic arsenal (MPWCI proposed).
2. Propose the adoption of legal measures aimed at avoiding, or reducing, the lack of supply of said products.

Methods

Data collection

The Spanish Agency of Medicines and Medical Devices (AEMPS) was asked for a list of medicine presentations in order to identify, within the presentations of medicines marketed in Spain, those whose lack could have an impact on the NHS and patients. The list provided considered those medicines at risk and whose lack could have an impact on healthcare at a specific time (January 2017 in this instance). It also noted the necessary safeguards that have a list of medicines whose clinical use is contingent to multiple factors that may change over time.

This list contained **462** products, ordered by authorisation number in the case of products registered in Spain and with other registration numbers in the remaining cases.

The list had been developed by AEMPS in accordance with the following criteria (see Figure 2):

- A **comparison** of the **WHO's Essential Medicines List (EML)** and a list of products authorised in Spain, stored in **CIMA** (Online Medicine Information Centre), selecting the cases where, for each essential active substance, only 1 or 2 medicinal products were authorised. Those cases that have two or more therapeutic alternatives authorised and marketed in Spain are not considered to be at risk.
- Those cases that have two or more therapeutic alternatives authorised and marketed in Spain are not considered to be at risk and were, therefore, **removed** from the list. The resulting list had a total of 357 products which were divided as follows:
  a. 293 products commercialised in Spain with essential active substances according to the EML
  b. 9 products commercialised in Spain with a unique pharmaceutical form and contain essential active substances according to the EML
  c. 55 authorised, but not commercialised, products with essential active substances according to the EML (imported through Foreign Medicinal Products Service)

Some products that were not considered essential by the WHO but are still essential in the Spanish market were **added** to the list (a total of 105 products, containing 84 active ingredients). The AEMPS considers that in addition to the WHO's list of essential medicines, in Spain it is necessary to maintain the commercialisation of other medicines (or of certain dosages or pharmaceutical forms of administration) since they constitute the only authorised presentation in Spain for a certain indication. The MAHs have applied this same criterion.

d) 37 products commercialised in Spain
e) 68 authorised but not commercialised products in Spain (imported through Foreign Medicinal Products Service)

Figure 2: Distribution of essential products for the Spanish market. Source: AEMPS.

This initial relationship was subjected to the process outlined in Figure 3 and is described below.

Figure 3: Diagram of the review carried out for the different medicinal product presentation lists whose viability of commercialization has been reviewed in the present list.

REG Number: Registration Number

NPC: National Product Code

AEMPS provided a list of 462 **products** considered to be at risk, whose shortage could have an impact on healthcare, which were then divided into two groups in order to be able to consult the companies.

I. List of products belonging to companies associated to Farmaindustria (258 records)
II. List of products belonging to other companies (204 records)

The list of products was divided up accordingly and distributed to experts from the corresponding affected company (associated to Farmaindustria) together with an assessment questionnaire. It is important to point out that the questionnaire reflected the experts' opinions and that it did not involve an official or binding response from the MAH.

The questionnaire was created to obtain the following answers:

1. Confirm if the products in the reviewed list from the company could effectively identify the products to be protected in order to ensure their continuity in the market
2. Remove those products that, in the original list, despite being considered at risk of commercialization by AEMPS, did not present a threat either in the viability or in the supply, according to an expert's judgement
3. Add new products that, even though not having been considered at risk of commercialization by AEMPS, do still pose a threat to viability and supply, according to an expert's judgement

This consultation was restricted to the MAH experts because they are the ones who can best assess the two reasons addressed in the survey and are characteristic of the companies' internal knowledge: i) derived from production (raw material supply, manufacturing problems, obligation to serialize, delays in the processing of variations) or ii) derivatives of economic regulation that affect the MAH (reference prices, price revisions).

From this, a list of products valued by experts from companies associated to Farmaindustria was obtained, which, with the confirmations (164), additions (168), no answers (7) and deletions (87), went from 258 to 339 records

The list of products reviewed by company experts associated to Farmaindustria, together with the list without further validation (339 + 204 = 543 records) needed, for the purpose of better research, a conversion from products (REG Number) to presentations (as defined on page 1), since the commonly used databases (IMS, BOt Plus, Catalogue from Farmaindustria) use the presentation identified by its National Product Code.

The list of 543 products increased to 589 presentations because, as expected, some product records are marketed in several presentations.

A new revision was carried out on the list of 589 presentations, and the following categories were removed:

1. Presentations that still have market exclusivity (due to patent or data protection), considering that these products, although they had a critical therapeutic role in case of shortages, were not part of the products to be protected due to the lack of interest in their commercialization by pharmaceutical companies.
2. The presentations of products that have two or more generic or competitors marketed, considering that the negative effects of non-commercialization of the original product could be remedied by the commercialization of generics or competitors, and vice versa.
3. The suspended or revoked presentations of products still authorised in other presentations, which are normally imported as foreign medication.

The resulting list, which is named “original list”, contained 568 presentations. The 568 presentations were listed as authorised and marketed in the database (CIMA) of AEMPS.

Regarding this original list, its distribution by MA longevity, ATC group and route of administration, with respect to the general market has been considered. The active substances in this group of presentations have also been listed.

Out of the presentations from the initial list, 341 correspond to companies associated to Farmaindustria, which we have called "reviewed list".

Regarding the reviewed list, there is additional information obtained by the responses to a questionnaire to assess the reasons for a possible lack of viability due to production, economic causes, or both.

Although the ideal would have been to consult experts from all the MAHs of the products included in the initial list, the difficulties in submitting the questionnaire, as well as obtaining and analyzing the corresponding answers, has resulted in circumscribing this list to the evaluation of the experts from the field of pharmaceutical regulation in the form of a technical working group of Farmaindustria (RTM Group).

In relation to the causes of a possible non-permanence in the market of a certain presentation derived from production, the questionnaire (see figure 4) offered the following possibilities:

1. The lack, or shortage, of raw material supply, mainly due to the fact that the MAHs of this type of product with limited consumption and outdated prices may have problems in finding a guaranteed manufacturer/supplier of the active substance.
2. Problems in manufacturing derived from the industrial repositioning in the manufacturing priorities of these products and contract manufacturing in some cases.

3. The obligation to include safety features (unique identifier and an anti-tampering device) on the packaging of certain products for human use for the purposes of allowing their identification and authentication, as a consequence of the application of Commission Delegated Regulation (EU) 2016/161 that may be a subsequent cause and make a certain presentation unfeasible.
4. The delays in the variations procedure in some cases (manufacture or control changes in active substance or finished product).
5. Other causes different from the previous ones.

In relation to the causes of a possible non-permanence in the market of a certain presentation derived from economic regulation, the questionnaire (see figure 5) offered the following possibilities:

1. The application of the Reference Price System (RPS), since it may affect certain presentations with a small content of active substance and consequently very low price (for example, low dosages, oral solutions, amongst others) that do not have a marketed competitor but that are affected by the lower cost per treatment, per day of the group. In particular, it asked whether the options to remove the threat of lack of viability in commercialization would mean the exclusion of the presentation of the RPS or the application of the so-called weighted reference price (applied to those presentations with special dosages, or which are indicated for serious pathologies, or whose prices have been revised by the CIMP in the last 2 years due to their low profitability), or if there was any other suggested option.
2. The price of the presentation. The intervened price of products financed by the NHS may become obsolete, especially in the case of old marketing authorisations. The questionnaire asked whether the threat to stay in the market was due to a lack of price viability or due to a lack of price viability even after having been revised upwards. It also contemplated whether the continuity in commercialization was influenced both by the price and by the lack of interest to continue by the marketing authorisation holder.
3. Other causes different from the previous ones.

Patient and Public Involvement

Neither patients nor the public were involved in this study.

Results

I. ORIGINAL LIST

The original 568 presentations were studied in various areas.

1. **By active substance.** The active substances of the proposed initial MPWCI relationship are shown in Annex 1. For the purposes of this classification, if two or more presentations contain the same active substance, the active substance only appears once in the table. Likewise, the different salts and derivatives of an active substance are considered as the same active substance. The active substances that are formulated as a single ingredient appear with their name. If they are part of an association of two or more active substances, the figure shows the number of active substances and the names of the medicinal products combination at a fixed dose.
2. **Date of the marketing authorisation.** Products whose lack of commercialization could have an impact on welfare are old. More than 75% of the products in the list were authorised in the last century and almost 50% of the products considered essential have an authorisation of more than 50 years.

   The comparison of the age of the initial MPWCI with the rest of the products in the reimbursable market[23] shows that more than three-quarters of the total medicines proposed as MPWCI (76.27 %) are authorised before the year 2000. In the case of the remaining presentations within the reimbursable market, most of the commercialised presentations (82.07 %) have a marketing authorisation after the year 2000.
   Predictably, most of the old products marketed in Spain before the year 2000 belong to this category of products to be protected. See Figure 4.

Figure 4: Distribution of product MPWCI presentations (original list) studied due to the age of the marketing authorisation in Spain compared to the rest of the reimbursable presentations in Spain.

3. **Therapeutic group.** The distribution by therapeutic groups, according to the ATC classification (Anatomical, Therapeutic & Chemical) has been another aspect taken into consideration in the initial list of the proposed MPWCI. The comparison between the presentations of products in the reimbursable market (IQVIA data) in relation to the initial list of MPWCI shows differences in the distribution of medicines by therapeutic groups. For example, in the rest of presentations within the reimbursable market, the antineoplastic and immunomodulating agents reach 3% (2.92%) while in the MPWCI group this proportion reaches 13% (12.94), which could indicate that in certain areas (Antiparasitic, Antiinfectives, Ofthalmic, Blood derived products or certain hormones) those products continue to play a therapeutic role. See figure 5.

Figure 5: Distribution of authorised product presentations in Spain by therapeutic group comparing MPWCI (original list) to the rest of the reimbursable presentations.

4. **Route of administration.** In the case of the proposed MPWCIs, the results show a more than remarkable concentration of these products of interest in certain routes of administration, with a very different distribution compared to the reimbursable market (IMS data). Although expected, it is striking, with a high proportion of injectable forms in the case of MPWCIs proposed with 44.12% of the total presentations of the category, compared to only 6.63% of presentations in the reimbursable market (IMS data). Similarly, this occurs in the ophthalmic forms in which the proposed MPWCIs represent 7% of the total sample compared to 1.42% of the presentations in the reimbursable market (IMS data). See figure 6.

Figure 6: Distribution of authorised product presentations in Spain by administration route comparing MPWCI (original list) to the rest of the reimbursable presentations.

II. REVIEWED LIST

As mentioned above, the questionnaire was sent to experts from 44 companies belonging to Farmaindustria. Thirty-seven **responses** were received from the experts of these companies, representing **84%** of those consulted. The data collection was carried out from February to July 2017.

These company experts from these companies indicated that they are not concerned by reasons only resulting from production. For only 4% of the cases, the continuity of the strategic presentations could be at risk of permanence in the market for reasons exclusively relating to production. The isolated economic aspects have a greater relevance, since they represent 20% of the assumptions considered. This percentage rises to 76% if we consider both causes, that is, those derived from regulation and production.

For some experts, the alignment of the increasing difficulties to obtain a regular supply of active substances or of intermediate products under suitable conditions of price and service, the requirements of the regulation for the processing of the registry variations relative to the places of manufacture and the modifications that the serialisation of products will entail, can jeopardize the viability in the marketing of certain presentations (figure 7).

Figure 7: Main causes that may lead to a possible non-permanence of MPWCI (reviewed list) presentations in the Spanish market.

Causes derived from production

In the experts' opinion, the lack, or shortage, of supply of raw materials constitutes a problem for the viability in the supply of the proposed MPWCI (42% responses). The other main concern is about procedures (42% responses) that can delay, or even stop, the supply of a particular product due to the serialisation rules that involve modifying the conditioning lines of many companies to incorporate both anti-tamper devices and the unique identifier of each of the containers affected by Delegated Regulation (EU) 2016/161. (Figure 8)

Another cause refers to the manufacturing issues (10% responses), especially in case of modification of the production strategy of some products in a certain manufacturing plant. In the segment 'others' (5% responses), the main threats to the permanence of these presentations in the market are: a difficulty in updating the registration dossier (which could be critical BREXIT scenario), the absence of a raw material in a product on a global scale, the cost of the administration device regarding the price of the medicine, the complexity of the manufacture or the lack of a manufacturer, especially in the case of products that are marketed in only a few countries (sometimes only in one single country). See figure 8.

Figure 8: Main causes related to production that may lead to possible non-permanence of MPWCI (reviewed list) presentations in the Spanish market.

Causes derived from economic regulation

In the experts' opinion, the low prices of the products studied would be the first factor (55.99% responses) in causing a threat to the continuity in commercialization. In this case, the products are not affected by the Reference Price System since they are products that have no marketed competitor and, therefore, the reference group has not been established.

In the case of products with a competitor Reference Price System, they affect all the presentations included in said group, which are subject to a price review every year. According to the answers obtained (38.48 % responses), the feasibility for minority consumption presentations in these groups, which contains active substances within the proposed MPWCI, are at risk.

Experts have responded to other causes (4.38% responses) also, including the absence of regulatory development for the transfer of MAH, as envisaged by RD 1345/2007 which, in Spain, regulates the Registration of Products or the risk of an avoidable national shortage if the presentations were to be subject to an exceptional prior notification, regulated in order to be sent to another Member State [24]. See figure 9.

Figure 9: Main causes related to economic regulation that may lead to a possible non-permanence of MPWCI (reviewed list) presentations in the Spanish market.

In relation to the presentations included in the Reference Price System, the solution considered most appropriate to guarantee the permanence in the market of these presentations would be their exclusion from the System (84%). The option of reducing the drop in prices through the application of weighted prices is a minority one (7%).

As mentioned, many of the proposed MPWCI presentations are unique (77%) if we consider their pharmaceutical form and dosage. See Figure 10.

Figure 10: Main causes related to economic regulation that may lead to a possible non-permanence of the MPWCI submissions proposed in the Spanish market related to the Reference Price System.

With regards to the price of products, 85% of the total of responses indicates that the price would not be viable in order to advance the continuity in commercialization at a high percentage.

Regarding the upward revision of prices, the experts' stance indicates that in some cases, the increases experienced by certain affected presentations have not eliminated the threat in the continuity of these products (7%) and in other cases (8%) the price band of the presentations would not be of the interest to the companies. See Figure 11.

Figure 11: Main causes related to the economic regulation that may lead to a possible non-permanence of the MPWCI (reviewed list) presentations in the Spanish market related to the price revision.

Finally, the experts' contribution towards possible solutions has seen some proposals of interest to reduce the risk of lack of supply of these presentations.

The consideration of an upward revision of the price of products, for those that were approved more than twenty years ago, has been proposed (39% responses). It also advises the modification of regulations on reference prices and allowing for certain unique presentations to remain outside the System (8% responses) or that there be a different consideration for products whose formulation and dosage have a different therapeutic focus (23% responses).

Another aspect needing to be rectified is that, currently some products are sold at a loss, due to the legal obligation to keep their marketing within Spain and the impossibility of withdrawing market presentations, precisely due to the refusal of AEMPS to revoke the marketing authorisation (15% responses). Lastly, some responses mention the formal need to regulate the so called "therapeutic gap" to ensure that the criteria determine the obligation to keep the product on the market (15% responses). See Figure 12.

Figure 12: Main solution proposals related to economic regulation to contribute to the greater permanence of MPWCI presentations.

Discussion

At the time of conducting this study, the authors considered whether the category of products without commercial interest (MPWCI) that complies with Spanish legislation was, in effect, a real group of presentations of authorised and effectively marketed products, or merely just a theoretical approximation by the legislator, since the matter is still pending development.

The authors opted for the first option because, in Spain, AEMPS requires a justification from the MAH in order to suspend or stop the commercialisation of a medicine which, "will accredit the specific cause (technological, scientific, economic or other reasons), as well as the estimated date of the exhaustion of stock"[25]. If there are situations of sanitary interest, AEMPS can not only maintain the validity of the authorisation, but also demand the effective commercialisation of the medication[3].

Therefore, in Spain there is a series of products that would respond to the need for special measures in relation to their manufacture, import, distribution, dispensation, economic and fiscal regime to ensure their supply be considered necessary for the treatment of certain diseases or pathologies, in terms consistent with those included in article 3.3 of Royal Legislative Decree 1/2015, of July 24, which approves the revised text of the Law on guarantees and rational use of products and healthcare products.

In certain cases, lack of availability may result in a financial loss for the MAH, since the medicine is not marketed; but in other cases, the commercialisation is not viable for a longer time due to the impossibility of passing on cost increases in production (particularly in the acquisition of the active ingredients), since the price of the medicine is fixed for reimbursement reasons and price revisions are unsatisfactory, in the opinion of the experts (see figure 9).

Although this relationship is changing because treatments evolve over time and the commercialization of new products turns obsolete therapies into well established ones, there are some products that maintain their place within the therapeutic sphere despite the passage of time. This has been recognized by AEMPS who have drawn up a list of products whose disappearance would have an impact on healthcare and on patients.

Despite the fact that European legislation has established the centralised procedure as a single procedure to achieve the commercialisation of a medicine throughout the EU and that there are incentives for micro, small or medium-sized companies or other kind of aids that contribute to obtaining the Authorisation to market certain types of medicines, such as orphan medicines[26], the medicines analysed have a marketing authorisation granted previously to those provisions (see figure 7). In fact, of the 568 presentations studied, only 30 (5.28 %) have been authorised by centralised procedure.

As noted, the legislation in force in Spain regulates a figure, which authorises the competent authority to not grant the temporary suspension, or the revocation of the marketing authorisation of a product "*when there are health reasons or healthcare interest, as in the case if a therapeutic gap is created, whether in the market in general or in the pharmaceutical provision of the National*

Health System, the Spanish Agency of Products and Medical Devices will maintain the validity of the authorisation and demand the effective commercialization of the medication. " [7]

The figure of the *therapeutic gap* envisaged in the Spanish regulations in which it is considered a very serious infringement for "*the marketing authorisation holder to cease the supply of a medicinal product in the event that there are health reasons or healthcare interest, for example if there were a therapeutic gap, either in the market in general or in the pharmaceutical provision of the National Health System*"[4], has not prevented the discontinuation of the marketing of certain products when the holder has perceived them no longer viable for the Spanish market. The therapeutic gap figure does not have an explicit 'fit' within the EU legislation, which for the discontinuation of commercialization (temporary or permanent) requires that the MAH inform the competent authorities within a two month period. The aim of the MAH is to try to maintain the supply, in order to avoid the discontinuation of commercialization in Spain, in some cases however this is not so and AEMPS has had to justify the acquisition of certain products through foreign medication [27].

In short, both the positive list from AEMPS and the possibility of stating that the exclusion or revocation of the marketing authorisation of a certain product would create a therapeutic gap, point to the need to consolidate a group of products with special characteristics, which should carry MPWCI conditions.

Membership under proposed MPWCI status has also been endorsed by a group of experts from the companies associated to Farmaindustria who have found themselves obligated to maintain the effective commercialization of these products, given the absence of others with the same composition and taking into consideration the role in which the product has in therapeutics.

However, the price erosion that occurs with the proposed MPWCIs and the absence of measures that protect them from technical and economic regulations, may lead to a gradual lack of supply for any of these products. Not only does this lack of regulation diminish the authorised treatment options, but it also discourages the presentation of new pharmaceutical form innovations intended for the unmet medical needs that are of interest to patients, healthcare professionals, administrations and industry.

It seems clear that the regulations that regulate certain matters such as reference prices or future serialisation, may contribute to the lack of viability in continuing marketing certain presentations without competition (despite their protection rights having expired). Also, the lack of protection for these strategic presentations makes it difficult to not carry out initiatives to commercialize innovations of these known products, since they would also be negatively affected by said regulation [28].

The Directorate General of Basic Healthcare Services Portfolio and Pharmacy (DGCBSF) mentions that it is working on the modification of the legislation to avoid that "*the purely mathematical mechanisms of the Reference Price System may exert perverse effects and provoke the departure of the pharmaceutical supply of medicinal products of proven therapeutic efficacy."*

For its part, AEMPS has considered within the Plan for Guarantees of Medicinal Product Supply, that one of the measures aimed at preventing supply problems is the identification of products at risk, whose shortage could have a welfare impact, for the purpose of adopting specific preventative measures [29].

One school of thought is that because these products are not new chemical entities, they should not be very expensive, because drug companies would have made profits from their initial marketing phases. In fact, generally speaking, it is true that the medicine cycle determines that the main return of the investment made in R&D is made in the initial phases since, once the protection of the original medicine is completed, a necessary and progressive price erosion occurs of the original medicines for the entry of generic and biosimilar medicines.

The authors consider that the case of MPWCI medicines would be different. MPWCI medicines have been licensed for many years and, despite lack of protection, they do not always have generic competitors or other brands. In these circumstances, the attraction to market these medicines is low, due to the sum of several factors: i) MPWCI prices are not attractive enough (since they have not increased or have been reduced because they are affected by reference prices), ii) the small volume of units that are commercialised and iii) the difficulties in maintaining the medicinal product on the market due to a regulatory or manufacturing reasons, including the problems for obtaining certain active ingredients, iv) the poor prioritisation of these products in the overall strategy of a certain company.

For this reason, as has been done with the regulation of another category of medicines, such as orphan medicines[30] and paediatric medicines[31], the competent authorities could establish MPWCI qualification procedures to avoid stock-outs in certain Member States, encourage the permanence of these medicines in the EU and contribute to the adoption of measures that, without destabilizing public health systems, avoid the shift of prescription to more expensive alternatives.

Conclusions

In short, the following conclusions can be drawn from the study carried out:

1. This work can be considered as the first study that establishes a perimeter of products presented as MPWCI. From the original AEMPS list, a further list of affected active substances has been identified with the contributions of a significant number of experts from pharmaceutical companies associated to Farmaindustria.
2. As the results show, the products proposed as MPWCI are old and are developed by active substances of chemical origin, parenterally administered much more frequently than the rest of the general market. Unlike oral forms, injectable forms require adequate manufacturing facilities to guarantee the quality and sterility of the product, which naturally increases the cost of the product and if the price is low or obsolete, the pharmaceutical form can also be used to decrease the viability in order to maintain the marketing of these presentations.
3. As shown in the results, an upward revision of prices is necessary to contribute to the permanence in the market of these presentations. On the other hand, the experts of the companies have not valued the current price revisions as a sufficiently satisfactory mechanism to change the consideration of these products with respect to the interest on the part of some MAHs to maintain the future commercialization of these presentations.
4. The Reference Price System is currently regulated and does not benefit the permanence in the market of products proposed as MPWCI, since some presentations without competition in the market suffer from regular price erosion with the successive annual updates of the system, generating a situation of unfeasibility for commercialization, which implies an insufficiency in the supply or the effective disappearance of the market.
5. It seems necessary to develop a regulation that protects the products proposed as MPWCI whilst maintaining the conditions of the absence of alternatives and therapeutic relevance for patients. This regulation should establish that, the formal consideration of MPWCI allows the review of the price of the product until its viability is guaranteed in the commercialization and the exclusion of the Reference Price System, in the event that the absence of a competitor could jeopardize the continued supply of the medicine.

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Figures legend

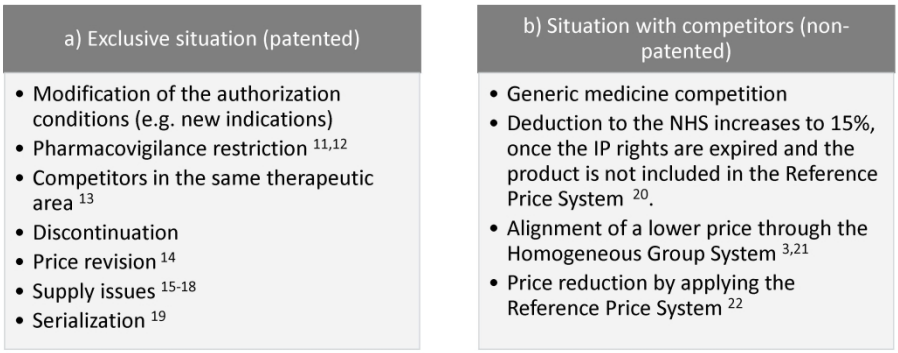

Figure 1: Causes that modify the authorisation conditions: a) causes that affect all commercialized products (patented or not), b) causes that only affect those products without patent protection or data protection

338x190mm (300 x 300 DPI)

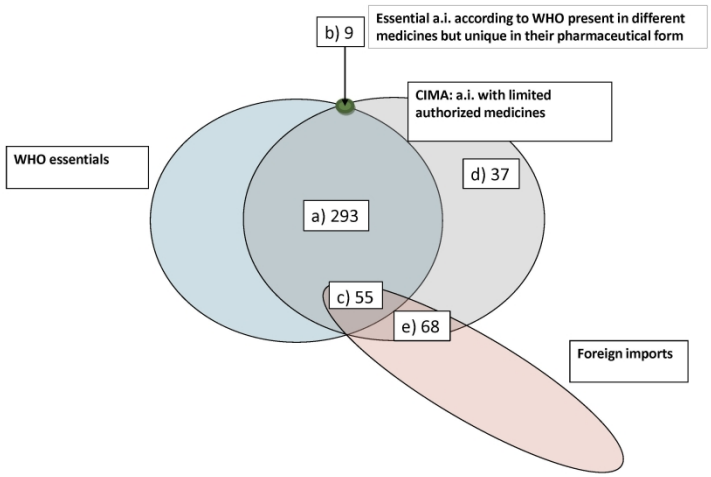

Figure 2: Distribution of essential products for the Spanish market. Source: AEMPS.

338x190mm (300 x 300 DPI)

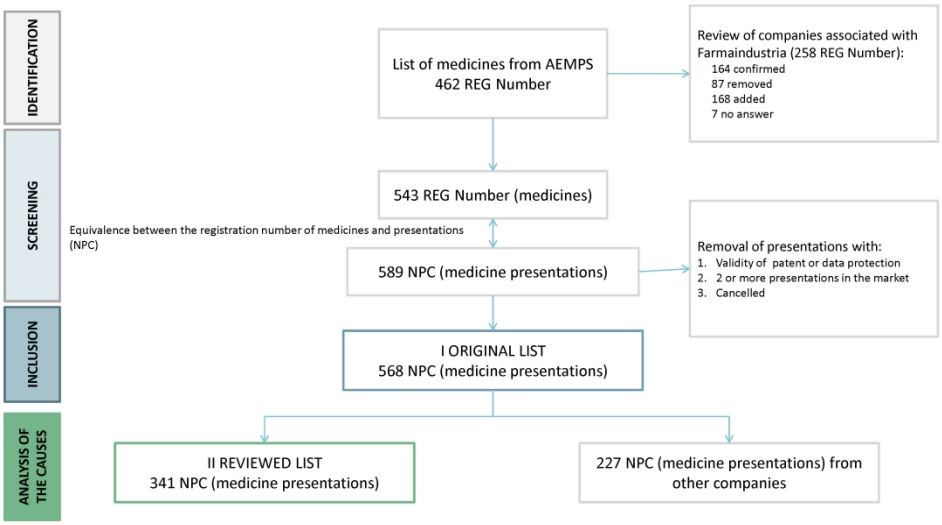

Figure 3: Diagram of the review carried out for the different medicinal product presentation lists whose viability of commercialization has been reviewed in the present list.

338x190mm (300 x 300 DPI)

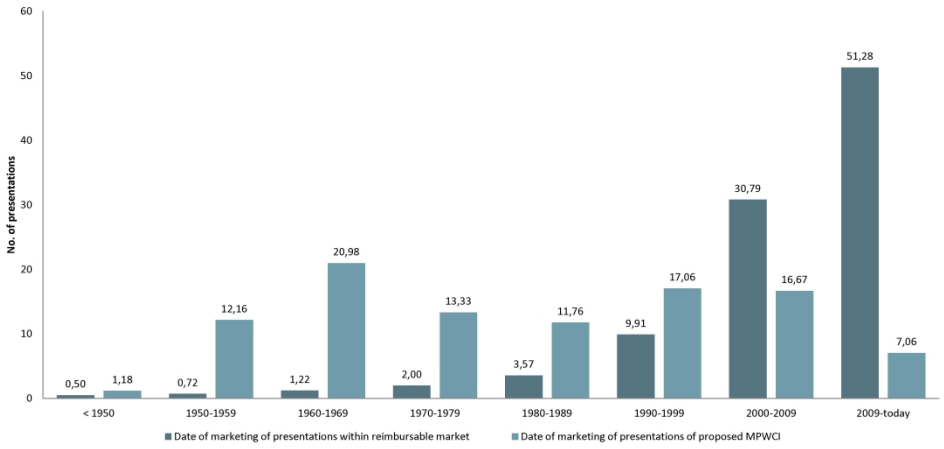

Figure 4: Distribution of product MPWCI presentations (original list) studied due to the age of the marketing authorisation in Spain compared to the rest of the reimbursable presentations in Spain.

338x190mm (300 x 300 DPI)

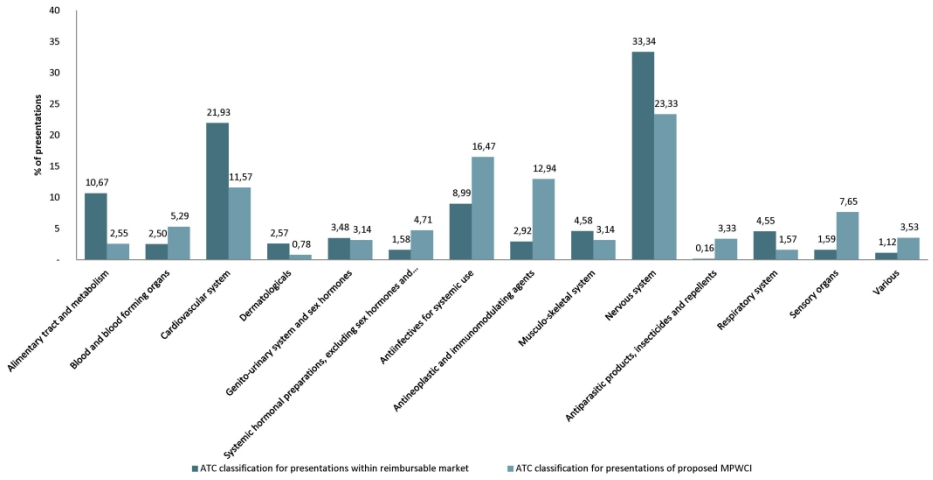

Figure 5: Distribution of authorised product presentations in Spain by therapeutic group comparing MPWCI (original list) to the rest of the reimbursable presentations.

338x190mm (300 x 300 DPI)

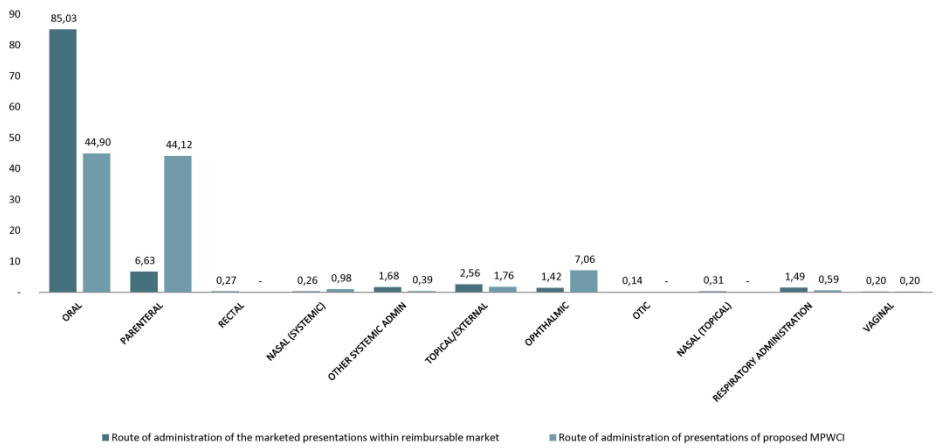

Figure 6: Distribution of authorised product presentations in Spain by administration route comparing MPWCI (original list) to the rest of the reimbursable presentations.

338x190mm (300 x 300 DPI)

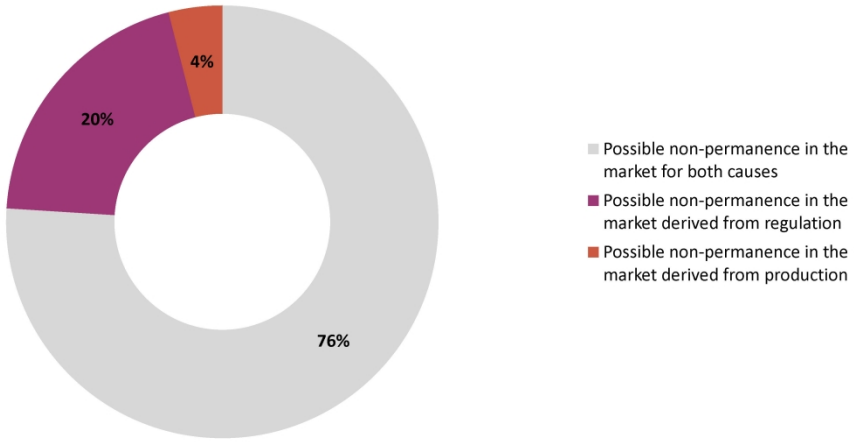

Figure 7: Main causes that may lead to a possible non-permanence of MPWCI (reviewed list) presentations in the Spanish market.

338x190mm (300 x 300 DPI)

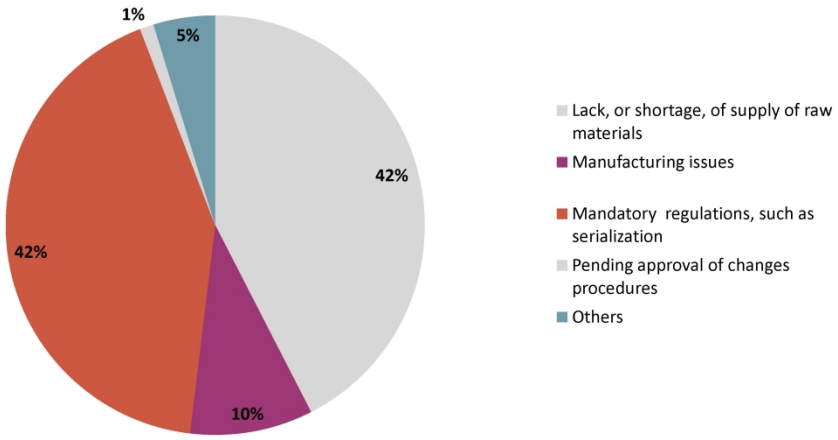

Figure 8: Main causes related to production that may lead to possible non-permanence of MPWCI (reviewed list) presentations in the Spanish market.

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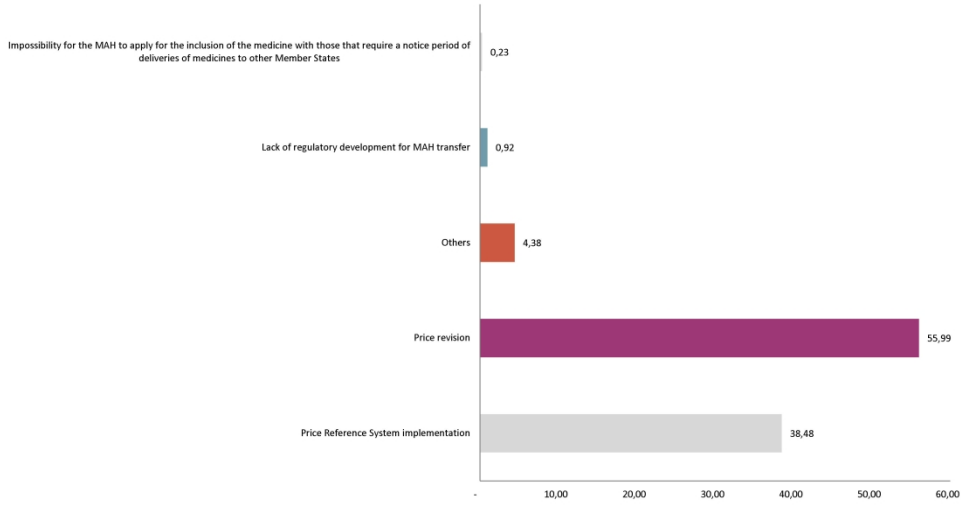

Figure 9: Main causes related to economic regulation that may lead to a possible non-permanence of MPWCI (reviewed list) presentations in the Spanish market.

338x190mm (300 x 300 DPI)

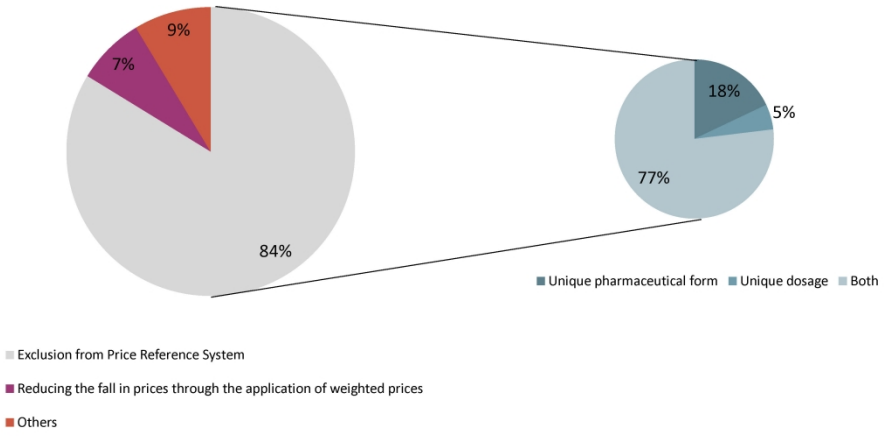

Figure 10: Main causes related to economic regulation that may lead to a possible non-permanence of the MPWCI submissions proposed in the Spanish market related to the Reference Price System.

338x190mm (300 x 300 DPI)

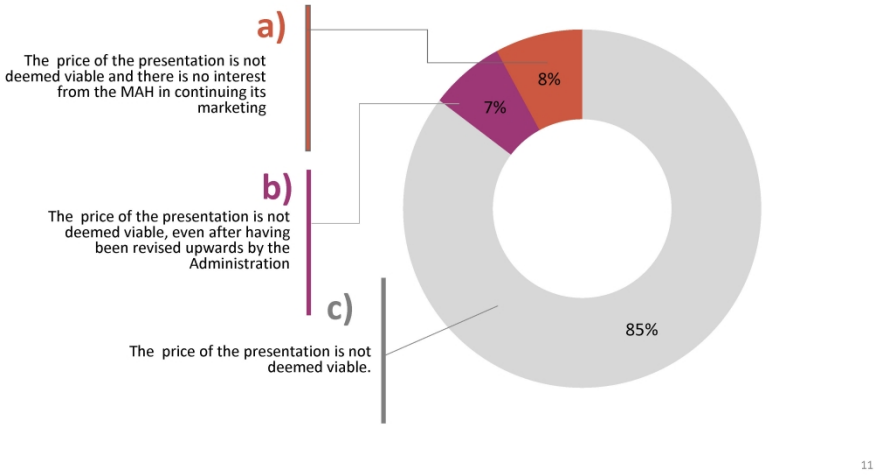

Figure 11: Main causes related to the economic regulation that may lead to a possible non-permanence of the MPWCI (reviewed list) presentations in the Spanish market related to the price revision.

338x190mm (300 x 300 DPI)

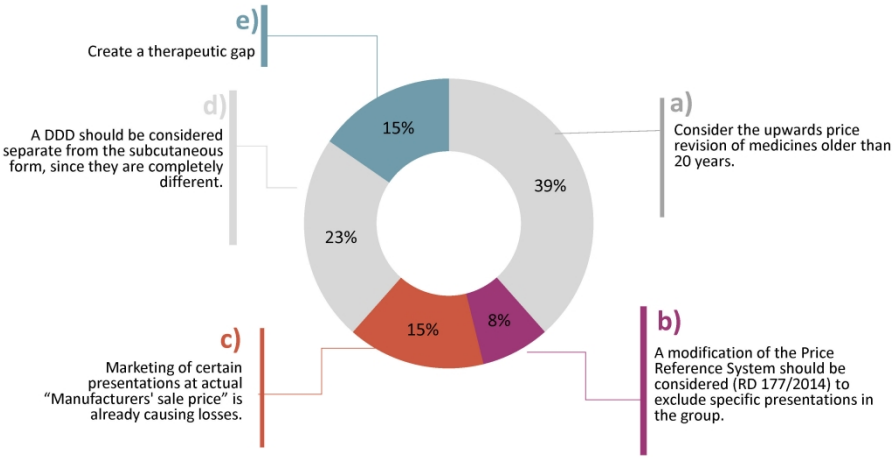

Figure 12: Main solution proposals related to economic regulation to contribute to the greater permanence of MPWCI presentations.

338x190mm (300 x 300 DPI)

Annex 1. Active ingredients included in the original list of proposed MPWCI

ABACAVIR SULFATO	BACLOFENO	CLOFAZIMINA	DISOPIRAMIDA	FLUDARABINA FOSFATO	ISOFLURANO	METOPROLOL TARTRATO	PENICILAMINA	SOTALOL HIDROCLORURO	TRANEXAMIC O ACIDO	2 - ESTRADIOL HEMIHIDRATO,NORE TISTERONA ACETATO
ACENOCUMAROL	BCG CULTIVO VIVO DESECADO	CLOMETIAZOL	DOBUTAMINA	FLUDROCORTISONA	ISOPRENALINA SULFATO	METOTREXATO	PENTAMIDINA ISETIONATO	SULBACTAM SODICO	TRETINOINA	2 - FENILEFRINA HIDROCLORURO,TET RACAINA
ACETATO CALCIO	BENZBROMARONA	CLOMIFENO CITRATO	DORNASA ALFA	FLUORESCEINA	TRACONAZOL	METOXALENO	PENTOSTATINA	SULFADIAZINA ARGENTICA	TRIFLUOPERAZI NA DIHIDROCLORU RO	2 - FENILEFRINA HIDROCLORURO,TRO PICAMIDA
ACETAZOLAMIDA	BEXAROT	CLOMIPRAMINA HIDROCLORURO	DOXEPINA HIDROCLORURO	FLUOROMETOLONA	KETAMINA HIDROCLORURO	METRONIDAZOL	PERFENAZINA	SULPIRIDA	TRIMETOPRIMA	2 - FLUORESCEINA SODICA,OXIBUPROCA INA HIDROCLORURO
ACETILCOLINA CLORURO	BIPERIDENO HIDROCLORURO	CLONAZEPAM	DOXICICLINA HICLATO	FLUOROURACILO	LAUROMACROGOL 400	MICOFENOLATO DE MOFETILO	PERMETRINA	SUXAMETONIO CLORURO	TROPICAMIDA	2 - FLUPENTIXOL DIHIDROCLORURO,M ELITRACENO
ACETILSALICILATO LISINA	BLEOMICINA SULFATO	CLORAMBUCILO	DOXORUBICINA HIDROCLORURO	FOLINATO CALCIO	LEVOMEPROMAZIN A HIDROCLORURO	MICOFENOLATO SODIO	PILOCARPINA HIDROCLORURO	TASONERMINA	TUBERCULINA	2 - ISONIAZIDA,PIRIDOX INA HIDROCLORURO
ACICLOVIR	BUDESONIDA	CLORANFENICOL	EDROFONIO BROMURO	FOSAMPRENAVIR CALCICO	LEVOTIROXINA SODICA	MIDAZOLAM HIDROCLORURO	PIRANTEL EMBONATO	TENOFOVIR DISOPROXILO FUMARATO	VALGANCICLOVIR	2 - ISONIAZIDA,RIFAMPI CINA
ALBENDAZOL	BUPIVACAINA HIDROCLORURO	CLORAZEPATO DIPOTASIO	EFEDRINA HIDROCLORURO	GENTAMICINA SULFATO	MAGNESIO SULFATO HEPTAHIDRATO	MIFEPRISTONA	PIRIDOSTIGMINA BROMURO	TENSIOACTIVO PULMONAR BOVINO	VALPROATO SODIO	2 - NAFAZOLINA HIDROCLORURO,TET RACAINA
ALDESLEUKINA	BUSULFANO	CLOROQUINA FOSFATO	EPINEFRINA BITARTRATO	GLICEROFOSFATO SODIO	MANITOL	MITOMICINA	PIRIMETAMINA	TENSIOACTIVO PULMONAR PORCINO	VALPROATO SODIO	2 - OXIBUPROCAINA HIDROCLORURO,TET RACAINA
AMIODARONA HIDROCLORURO	BUSULFANO	CLORPROMAZINA HIDROCLORURO	ERITROMICINA	HALOPERIDOL	MAPROTILINA HIDROCLORURO	MORFINA HIDROCLORURO	POLIESTIRENOSULF O NATO SODIO	TERBUTALINA SULFATO	VERAPAMILO HIDROCLORUR O	2 - SULFAMETOXAZOL,T RIMETOPRIMA
AMITRIPTILINA	CAFEINA CITRATO	CLORTETRACICLIN A HIDROCLORURO	ESCOPOLAMINA BUTILBROMURO	HIDRALAZINA HIDROCLORURO	MEBENDAZOL	NALOXONA HIDROCLORURO	PREDNISOLONA ESTEAGLATO	TESTOSTERONA CIPIONATO	VINBLASTIN A SULFATO	2 - VALPROATO SODIO,VALPROICO ACIDO
AMITRIPTILINA HIDROCLORURO	CALCITRIOL	CLOXACILINA SODICA	ESCOPOLAMINA HIDROBROMURO	HIDROCORTISONA ACETATO	MEDROXIPROGEST E RONA ACETATO	NEOSTIGMINA METILSULFATO	PROCAINA HIDROCLORURO	TESTOSTERONA UNDECANOATO	VINCRISTIN A SULFATO	3- TENOFOVIR DISOPROXIL FUMARATO,
AMOXICILINA SODICA	CAPREOMICINA SULFATO	DACARBAZINA	ESMOLOL HIDROCLORURO	HIDROCORTISONA FOSFATO SODIO	MEDROXIPROGEST E RONA ACETATO	NIFEDIPINO	PROCAINAMIDA HIDROCLORURO	TETRACAINA HIDROCLORURO	VINDESINA SULFATO	3 - BENCILPENICILINA POTASICA,BENCILPE NICILINA
AMPICILINA SODICA	CARBAMAZEPINA	DAPSONA	ESPIRONOLACTONA	HIDROXICARBAMIDA	MEGLUMINA ANTIMONIATO	NITROFURANTOINA	PROCARBAZINA HIDROCLORURO	TETRACICLINA HIDROCLORURO	virus fiebre amarilla cepa 17 D	3 - DEXAMETASONA FOSFATO DISODIO,GENTAMICI
APOMORFINA HIDROCLORURO	CEFADROXILO MONOHIDRATO	DAUNORUBICINA HIDROCLORURO	ESTREPTOMICINA SULFATO	HIDROXICLOROQUI N A	MELFALAN	NITROGLICERINA	PROPRANOLOL HIDROCLORURO	TETRACOSACTIDA	virus rabia inactivado	3 - DEXAMETASONA,NE OMICINA
ASCORBICO ACIDO	CEFUROXIMA AXETILO	DEFEROXAMINA MESILATO	ETAMBUTOL	HIDROXIZINA DIHIDROCLORURO	MERCAPTOPURINA	NITROPRUSIATO SODIO	PROTAMINA SULFATO	TIAMINA HIDROCLORURO	VORICONAZOL	3 - ESTRADIOL HEMIHIDRATO,NORE TISTERONA
ATAZANAVIR	CICLOFOSFAMIDA	DEXAMETASONA	ETOPOSIDO	IBUPROFENO	MESNA	OCTREOTIDA ACETATO	RALTITREXED	TIGECICLINA	WARFARINA SODICA	4 - ERGOCALCIFEROL,FI TOMENADIONA,RETI
ATENOLOL	CICLOPENTOLATO HIDROCLORURO	DEXAMETASONA FOSFATO DISODIO	FENILEFRINA HIDROCLORURO	IDARUBICINA HIDROCLORURO	METADONA HIDROCLORURO	OXICODONA HIDROCLORURO	RIBAVIRINA	TINIDAZOL	ZIDOVUDINA	4 - ETAMBUTOL HIDROCLORURO,ISO NIAZIDA,PIRAZINAM
ATROPINA SULFATO	CICLOSPORINA PARA MICROEMULSION	DIAZEPAM	FENOBARBITAL	IFOSFAMIDA	METILDOPA	OXITOCINA	RIFABUTINA	TIOGUANINA	2 - AMILORIDA HIDROCLORURO, HID ROCLOROTIAZIDA	5+ Cloruros Cr,Cu,Fe,Mn,Zn; Ioduro K, Fluoruro
ATROPINA SULFATO	CIPROFLOXACINO HIDROCLORURO	DIDANOSINA	FENOXIMETILPENICI L INA-BENZATINA	IMIPRAMINA HIDROCLORURO	METILERGOMETRIN A MALEATO	PAMIDRONICO ACIDO	RITONAVIR	TIZANIDINA HIDROCLORURO	2 - AMOXICILINA SODICA,CLAVULA NA TO POTASIO	5+ Glutation, Manitol, Acs Lactobionico,
AZATIOPRINA	CITARABINA	DIGOXINA	FITOMENADIONA	INMUNOGLOBULIN A ANTIRRABICA	METILPREDNISOLO N A	PAROMOMICINA	SILDENAFILO	TOBRAMICINA	2 - BENSERAZIDA HIDROCLORURO,LE V ODOPA	5+ ICODEXTRINA,Clorur o Na,S-Lactato Na,
AZTREONAM	CLADRIBINA	DINOPROSTONA	FLECAINIDA ACETATO	INTERFERON BETA-1B	METOCLOPRAMID A HIDROCLORURO	PEGVISOMANT	SILIBININA SUCCINATO SODIO	TOLCAPONA	2 - DEXAMETASONA, TO BRAMICINA	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	-
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	-
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	10-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.