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COMISIÓN NACIONAL DE LOS MERCADOS Y LA COMPETENCIA

STUDY OF THE WHOLESALE DISTRIBUTION MARKET FOR MEDICINES

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The Spanish National Markets and Competition Commission
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STUDY OF THE WHOLESALE DISTRIBUTION MARKET FOR MEDICINES

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SUMMARY:

The study analyses the market for the sale and distribution of prescription medicines for human use that are dispensed through pharmacies in Spain, from the perspective of competition and the principles of efficient economic regulation. The study identifies areas where public health objectives can be achieved more effectively by incentivising competition and economic efficiency and makes some recommendations for regulatory improvement in this regard.

KEYWORDS: medicines for human use; Spanish National Health System; wholesale distribution of medicines; competition promotion.

JEL CODES: H4; I11; I18; K2; K32.

Contents

INDEX OF ACRONYMS

AEMPS	Spanish Agency for Medicines and Healthcare Products (Agencia Española de Medicamentos y Productos Sanitarios)
CNA	Competent National Authority
CIPM	Spanish Interministerial Medicines Pricing Committee (Comisión Interministerial de Precios de los Medicamentos)
DGCYF	Directorate General for the Common Portfolio of Services of the National Health and Pharmacy System (Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia; until 2020, Directorate General for the Basic Portfolio of Services of the National Health System and Pharmacy, DGCBSF).
GPE	Generic Pharmaceutical Equivalent
MS	European Union member states
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GMP	Good Manufacturing Practices
GDPr	Good Distribution Practice
INGESA	Spanish National Institute of Health Management (Instituto Nacional de Gestión Sanitaria)
CPI	Consumer price index
TPR	Therapeutic positioning report
ISFAS	Spanish Armed Forces Social Institute (Instituto Social de las Fuerzas Armadas)
DM	Distribution margin
MUFACE	Mutuality of State Civil Servants (Mutualidad de Funcionarios Civiles del Estado)
MUGEJU	Judicial General Mutuality (Mutualidad General Judicial)
OTC	Over-the-counter (not subject to medical prescription)
GDP	Gross Domestic Product
LSP	Laboratory Sale Price (also, industrial price or manufacturing price)

DSP	Distributor Sales Price
RP	Retail Price (VAT not included)
RP VAT	Retail Price including VAT
SNHS	Spanish national health system
RPS	Reference Pricing System
EU	European Union

GLOSSARY

- **Homogeneous grouping:** each homogeneous grouping comprises the dosage form of funded medicines containing the same active substance, strength, content, pharmaceutical configuration and administration route, which may be the subject of interchangeable dispensing. Homogeneous groupings are tighter than reference sets.
- **Contract warehouse:** entity that acts as a third party, with which a laboratory or a wholesale warehouse signs a contract to carry out certain drug distribution activities.
- **Reference set:** in the reference pricing system, reference sets are groups of medicines made up of all the dosage forms of medicines included in the pharmaceutical provision of the SNHS that have the same level, 5, in the World Health Organisation anatomical therapeutic chemical classification of medicines (ATC5) and administration route.
- **Wholesale drug distribution:** any activity that consists of obtaining, storing, preserving, supplying or exporting medicines, excluding their dispensing to the public.
- **Drug dose:** the active ingredient content, expressed in quantity per intake unit, per unit volume or weight depending on the dosage form.
- **Dosage form or pharmaceutical configuration**: the way in which the active ingredients and excipients are adapted to form a medicinal product. This is defined by the combination of the form in which the pharmaceutical product is presented by the manufacturer and the format in which it is administered, e.g., capsules, tablets, ointments, syrups, aerosols, etc.
- **Drug configuration:** number of units contained in the container and/or its content.
- **Drug brokerage**: all activities related to the sale or purchase of medicines, except for those included in the definition of wholesale distribution, which do not include physical contact with them and which consist of negotiating independently and on behalf of another legal or natural person. Drug brokerage entities are known as brokers.
- **Biological medicines**: these contain one or more active ingredients produced or derived from a biological source, whether human, animal or micro-organism.
- **Biosimilar medicines**: these are biological medicines that contain a version of the active substance of an original biological product or reference product, whose patent has expired, and for which it can be

demonstrated that the physical, chemical and biological differences do not affect the quality, efficacy and safety.

- **Biotechnology medicines**: these are medicines of biological origin obtained from genetically modified cell lines using genetic engineering techniques[1].
- **Medicinal products for human use**: any substance or combination of substances presented as having properties for treating or preventing disease in human beings or which may be used in human beings or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or for making a medical diagnosis.
- **Generic medicine:** any medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form, and whose bioequivalence with the reference medicinal product has been demonstrated through appropriate bioavailability studies.
- **Reference price:** maximum amount at which the dosage form of medicinal products included in each of the reference sets are funded, provided that they are prescribed and dispensed at public expense. Calculated as the lowest cost/treatment/day of the different dosage forms that form part of the set.
- **Lowest price:** on a monthly basis, within the system of homogeneous groupings, the "lowest price" is updated with the voluntary price reductions for the medicines included in the grouping.
- **Lower Price:** the "lower price" within each homogeneous grouping corresponds to the lowest price of the group of dosage forms that comprise it at the time of its formation and which may be revised downwards at each quarterly update.
- **Pharmaceutical service of the Spanish National Health System**: this comprises medicines and medical devices and the set of actions aimed at ensuring that patients receive them in a form appropriate to their clinical needs, in the doses required by their individual circumstances, for the appropriate period of time, and at the lowest possible cost to them and to the community.
- **Dosage form of a medicine:** each of the combinations in which the medicine is prepared for use, including its composition, pharmaceutical formulation, dose, and configuration.

[1] *Guía de Medicamentos Biosimilares para Médicos [Biosimilar Medicine Guide for Doctors]*, Asociación Española de Medicamentos Biosimilares (Biosim), 2020.

- **Active ingredient or active substance:** any substance or mixture of substances intended for the manufacture of a medicinal product and which, when used in the production of a medicinal product, becomes an active constituent intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to making a diagnosis.

EXECUTIVE SUMMARY

The distribution and marketing of medicines, due to its special characteristics, is a heavily regulated activity. This intervention is based on the necessary safeguarding of public health, the existence of market failures and the impact on public finances that pharmaceutical provision entails. All these factors, and in particular the major benefits that the proper functioning of this activity can generate for society as a whole, are the main social and economic reasons for the public financing of medicines.

The necessary protection of the public interest is inherent in the regulation of this market in terms of safety, quality, efficacy and access to medicines. Similarly, it is also essential, in the defence of the general interest, that regulation complies with the principles of necessity and proportionality, avoiding the introduction or maintenance of competition restrictions that unjustifiably prevent more efficient market performance or an improvement in the general welfare of the population.

This study mainly focuses on an analysis of the market for the commercialisation and distribution of prescription drugs for human use that are distributed through pharmacies. The aim of the study is to assess to what extent the measures implemented in recent years, as well as the regulation or the structure and functioning of the sector itself, inhibit or encourage effective competition in the market for the commercialisation and distribution of medicines through pharmacies. To this end, national and international comparative experience has been taken into consideration, as well as the respect for the overriding reasons of general interest, in order to draw conclusions and recommendations on the most favourable configuration for competition and an efficient economic regulation in this market.

The analysis carried out has identified a series of restrictions derived from health regulations and policies that significantly affect the level of effective competition in the market.

Thus, in the case of innovative medicines (protected under patent) subject to medical prescription, a lack of transparency has been detected related to the economic evaluation of these, as well as in the internal organisation of REvalMed[2]. In addition, the analysis of therapeutic positioning is sometimes ambiguous or incomplete[3]. In relation to the long-term therapeutic and economic

[2] Network for the Evaluation of Innovative Medicines comprising the Ministry of Health, the Spanish Agency of Medicines and Medical Products (AEMPS) and representatives of the Autonomous Communities.

[3] The place that a medicine should occupy within the therapeutic scheme for a clinical indication or a specific health problem.

evaluation of medicines, the study points out the importance of continuous and repeated assessment over time. In this sense, the evidence generated by using big data in the evaluation and oversight of medicines has enormous potential, allowing for a more expeditious, complete and real-time therapeutic and economic assessment of medicines.

In the case of competing medicines (originator, generic, biological[4] and biosimilar[5]) that require a prescription, the study highlights the lack of flexibility of the current reference pricing system, which should be reformed in order to foster more effective competition between market players. Thus, the current lack of price differentials between competing medicines is problematic, and it is also necessary to develop new dispensing programmes and incentives for clinicians and pharmacists. The lack of development in terms of information and health education programmes is also highlighted. These initiatives should clarify doubts about the use of medicines among the general public, in terms of quality, safety, efficacy and value, as well as their importance in ensuring the sustainability of the health system.

In the specific case of biosimilars, the absence of a formal position on the interchangeability of biological and biosimilar medicines, and the heterogeneity of the different actions in the Spanish National Health System (SNHS) regarding this issue, are brought to the attention of the competent authorities.

Finally, at the level of the wholesale and retail distribution channels, the study has identified a number of restrictions that are inefficient and detrimental to both competition and the general interest, including: (i) the wholesale mark-up system, whose remuneration system should be linked to distribution services; (ii) the current retail mark-up system, which should move from a purely product-oriented system to a mixed, more patient-oriented system; (iii) the current regulations regarding vertical integration in wholesale distribution; and (iv) the lack of implementation of a clawback system, which would help to improve the efficiency of the remuneration system, reduce the public cost of pharmaceutical provision,

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4 Biological medicines are those that contain one or more active ingredients produced or derived from a biological source, whether human, animal or micro-organism. They differ from generic or chemically synthesised medicines in that they have a biological rather than a chemical source or origin.

5 Biosimilar medicines are biological medicines that contain a version of the active substance of an original biological product or reference product, whose patent has expired, and for which it can be demonstrated that the physical, chemical and biological differences do not affect the quality, efficacy and safety of the treatment.

and free up resources to facilitate the sustainability of the system or the financing of other treatments.

To alleviate these restrictions, the study proposes the following recommendations:

FIRST. Strengthen Therapeutic Positioning Reports (TPRs) as a comprehensive and transparent reference document to support financing and pricing decisions for innovative medicines

It is proposed that TPRs should be improved and strengthened as a reference document for funding and pricing decisions. To this end, it would be advisable to: (i) include a comprehensive pharmaco-economic analysis of medicines, in addition to an analysis of therapeutic positioning that is neither ambiguous nor incomplete. It is also necessary to further develop the different aspects included in the Plan for the consolidation of Therapeutic Positioning Reports in relation to the economic evaluation, in order to clarify the methodology to be used and to add transparency to the economic evaluation process, as well as to explain how the economic evaluation will be carried out when there is insufficient evidence available, or when there are no valid comparators. (ii) Streamline the preparation of TPRs and send the draft reports to the various market stakeholders. In this regard, it would be advisable for the stakeholders to be able to make comments not only on the first draft, but also on the final draft. (iii) Make a greater effort to improve the transparency of REvalMed's internal organisation, its decision-making, its organisation, its independence and the members that comprise it.

SECOND. Implement continuous and repeated therapeutic and economic evaluation of innovative medicines over time through the use of new technologies and big data.

It is necessary to improve the assessment of the medium- and long-term therapeutic effectiveness of funded medicines, where effectiveness is understood as the efficacy of a medicine in patients under real clinical practice conditions. To this end, it is recommended that therapeutic and economic evaluation be carried out continuously and repeatedly over time, especially for medicines with a significant budgetary impact. In this sense, new technologies and big data provide a unique opportunity for generating economic data and assess real therapeutic effectiveness in clinical practice in a more expeditious, comprehensive and real-time manner. This information could be used for funding decisions, optimisation of drug use recommendations and price adjustments, as well as for more efficient

implementation of risk-sharing agreements.[6] It is also important to take advantage of the framework provided by the new Digital Health Strategy to facilitate the sharing of data between the different SNHS information systems and thus provide easier access to relevant information and enable it to be processed to draw conclusions. The Valtermed medicines register should also be developed, with a large number of medicines being included in the platform, in order to generate data on the efficiency and efficacy of medicines in real clinical practice over time. The information included in Valtermed should be accessible to healthcare professionals, granting access to the therapeutic assessment of a large number of different patients and profiles, enabling problems in clinical practice to be pinpointed, identifying clinical subgroups with lower or higher effectiveness, and characterising the uncertainty or long-term outcome of treatments by patient type, among other potential benefits. If access to the information could generate problems in terms of data confidentiality, anonymised or aggregated access to the information could be achieved.

THIRD. Reform the Reference Price System (RPS) to encourage real price competition

We propose implementing a more flexible RPS, allowing laboratories to freely set the wholesale price of the medicine, with the maximum reimbursement price being fixed through the reference price. In the event that the price set by the laboratory is below the reference price, the SNHS would reimburse this lower price. In this case, this lower price would be taken into account when calculating the patient's co-payment. In the opposite case, for medicines priced above the reference price, the reference price would be reimbursed, with the patient-consumer paying the difference between the reference price and the price set by

[6] Risk-sharing agreements are signed between the laboratory that owns the innovative medicine and the public sector (there are agreements signed by both the State Administration and the Autonomous Communities). They are aimed at reducing or alleviating the conditions of uncertainty to facilitate public access to the medicine through public financing. Two types of risk-sharing agreements can be distinguished:

- Payment-by-results schemes: these can be undertaken when there are uncertainties about the clinical effectiveness of the medicine. For example, such an agreement may involve the laboratory repaying the public health system for treatment for patients who do not respond to the medicine.
- Financial agreements: these are appropriate when there are budgetary uncertainties, for example because the number of patients to be treated with the new medicine is unknown. They can take many forms, such as price-volume agreements (where the price is set according to the volume of drugs consumed) or expenditure ceilings (the public sector bears a maximum cost, so that if the drug is consumed to a greater extent, the rest of the cost is borne by the incumbent laboratory).

the laboratory (avoidable co-payment). This system of flexible pricing would encourage competition in terms of price and quality, helping the sustainability of the system, favouring variety through innovation and the entry of new operators, and would thus be key to facilitating an adequate level of effective competition in the market.

This does not preclude the possibility, in areas and circumstances where market shortcomings are detected or where there are other overriding reasons of general interest, of adopting more intensive intervention measures, including the establishment of maximum prices when this is necessary and proportionate, such as to protect public health, equal access to medicines, or certain disadvantaged groups.

In addition, it is recommended that the terminology used in the reference price and homogeneous grouping systems be reviewed and clarified as it is confusing, misleading and there is an overlap between the terms used. It is therefore recommended to clarify both the concepts and the way these systems work.

For this reform of the RPS to promote real competition, it must be accompanied by changes to prescription and dispensing policies, as discussed in the following recommendation.

FOURTH. Modify prescribing and dispensing policies to encourage competition between originator and generic medicines, promoting patient choice

It is recommended that medicines should be prescribed according to their active ingredient, except for those medicines that cannot be substituted by the dispensing pharmacy. This would favour the introduction of generic medicines into the market, promote innovation and transparency, mitigate conflicts of interest between the prescriber and the industry, and improve patient information.

We also propose changing the pharmacist's obligation to replace the prescribed medicine with the lowest-priced one for an indicated substitution. Under this system, the pharmacist would inform the consumer about the price alternatives and medicines available on the market. In the case of medicines priced below the reimbursement price, the pharmacist should dispense one of the medicines below that price. This would correct the single, compulsory dispensing of only one medicine (the one with the lowest price, or those with the lowest price if several coincide), thus eliminating the strong incentive to align and maintain prices that the current system generates. This would increase the variety of medicines on offer, consumer choice and the level of competition, promoting price

reductions and innovation. This does not preclude the possibility that, in the event the selected medicine has a higher price than the maximum reimbursement price (reference price), because there is no alternative with a lower price, consumers would have to pay the difference out of their own pocket (avoidable co-payment)[7].

Finally, it is necessary to reflect on the possibility of facilitating the personalisation of drug dispensing in pharmacies. This personalised dosage could be implemented either manually or automatically by using drug dispensing robots that allow medication to be repackaged into single-dose or multi-dose systems. This type of personalised and automated dispensing would not only limit the over-sale of medicines in the retail pharmacy channel, reducing costs for the SNHS, but would also improve patient-consumer service, especially for particularly vulnerable groups, such as the elderly or polymedicated persons, for whom a grouped dosage of medication would limit human error and facilitate treatment adherence. Similarly, introducing this kind of dispensing robots would improve dispensing efficiency and increase competition in the retail pharmacy channel.

Finally, the prescription aid systems that the health services in the Autonomous Communities make available to healthcare professionals to assist them in their clinical activity could incorporate criteria that encourage efficient prescribing and thus facilitate the economic sustainability of the system. For example, and among other alternatives, they could indicate to healthcare professionals which drugs have the best cost-effectiveness ratio for the treatment in question.

FIFTH. Define the reference sets of the Reference Pricing System as pro-competitively as possible

It is recommended that the reference sets be defined as broadly as possible in order to encourage competition between the different drugs comprising the set.

The proposal included in the Ministry of Health's Action Plan to promote the use of generic and biosimilar medicines is along these lines. The CNMC welcomes this measure, and recommends, whenever possible, considering extending the reference sets to a broader scope (ATC4 or beyond) than the current level (ATC5), at least for certain therapeutic indications in which it is feasible or indicated under clinical and cost-effectiveness criteria.

[7] In these cases, the authorities may intervene in the price of medicines when it is excessive. This intervention must be justified, time-limited, and based on reasons of public health protection, equal access to medicines, or actual or potential harm to the interests of certain disadvantaged groups.

This does not preclude the creation of more limited sets where this is therapeutically appropriate for medicinal products that cannot be considered equivalent in clinical practice. In these cases, exceptional sets should be applied in accordance with the appropriate clinical criteria, whether this is the ATC5 level, the active ingredient, or another appropriate designation.

SIXTH. Establish a formal stance on the interchangeability of biological and biosimilar medicines when there is favourable clinical evidence

The *switching* or interchangeability policy is an essential element and facilitates competition between biological and biosimilar medicines. For this reason, the competent authorities are urged to conduct an analysis of the clinical evidence on the interchangeability of biosimilars with biological medicines, in order to determine the safety of the drug interchangeability when prescribing.

In the event that the existing evidence supports prescription interchangeability, it is recommended that a formal stance be taken in favour of the interchangeability of biological and biosimilar medicines. The aim is to standardise the different actions in the Spanish National Health System, increase competition in the market, promote the sustainability of the healthcare system and guarantee access to affordable and effective biological medicines for patients who require them.

SEVENTH. Develop informative and health education campaigns on generic and biosimilar medicines

It is necessary to continue developing informative and health education campaigns on the use of medicinal products, both chemically synthesised (originator and generic) and biological and biosimilar medicines, both for clinicians and patient-consumers. Otherwise, there could be an unjustified bias favouring the use of one or other medicine, hindering the prescription of these medicines and generating doubts among patients. These initiatives should be conducted in a transparent manner using objective and verified information.

EIGHTH. Reform the current system of distribution margins proportional to price, to one linked to the services provided

In the case of wholesale distribution margins, the current system of remuneration, proportional to the price of medicines, should be based, at least partially, on the medicine distribution services provided by wholesale operators (in terms of

safety, efficacy, speed and control of medication, or distribution to rural and depopulated areas) and on the logistical specifics of the products distributed (boxes, injectables, solutions, fragile items, cold storage, etc.), ensuring fair remuneration for all medicines and an adequate supply to the most remote and depopulated rural areas.

In relation to retail distribution margins, where the remuneration system is also based on the price of the medicine, it is recommended to consider a more patient-oriented remuneration system, combining a fixed fee for dispensing in pharmacies, with added remuneration for certain services defined by the SNHS that contribute to the population's health.

We also recommend the introduction of a system of incentives for pharmacists to encourage the dispensing of lower-priced medicines within the reference price system. In this way, the possibility is raised of introducing partial reimbursement (as a percentage) of the difference between the wholesale price and the reimbursement price set by the administration for those medicines sold at a lower price than the reimbursement price for their set or group.

Also, to help ensure adequate care in small population centres, a selective fixed payment based on certain agreed community services or a minimum guaranteed income could be added.

NINTH. Introduce a return, or *clawback system*

We recommend that a clawback mechanism be established whereby part of the discounts offered to wholesale distributors and pharmacies in the distribution channel for funded medicines would be passed on as lower costs to the SNHS. This would help to reduce the public cost of pharmaceutical provision, free up resources to fund other treatments and benefit end-consumers. For such a refund mechanism to be successful, it must be designed with caution in areas such as access to commercially sensitive information by operators.

TENTH. Review the notified price system

The notified price system generates a regulatory asymmetry between defunded medicines and their competitors that were never funded by the SNHS, by subjecting the former to a price control for a series of reasons that could well be applied to the latter (protection of public health, equal access to medicines or real or potential harm to the interests of disadvantaged groups). The CNMC recommends reviewing this system to assess its necessity and proportionality, both in relation to the medicines that are subject to it and in terms of the time

during which it is considered necessary to subject them to administrative control. Furthermore, the CNMC considers that the systematic rejection of price changes in line with the evolution of the CPI is not appropriate and urges the Ministry of Health and the Interministerial Medicines Pricing Committee to analyse each price change proposal individually, in accordance with the particular circumstances of the medicinal product, and to provide sufficient reasons for its decision.

Finally, the CNMC considers that other public interventions that could help to solve the root of possible problems of excessive prices for defunded medicines should be assessed.

ELEVENTH. Review the regulations on vertical integration between the wholesale and retail distribution channels

It is recommended that the regulations on the vertical integration between the wholesale and retail distribution of medicines be reviewed (Article 4.2. and second transitional provision of Royal Legislative Decree 1/2015, of 24 July, approving the Consolidated Text of the Law on guarantees and the rational use of medicines and healthcare products) insofar as it introduces a restriction or prohibition on vertical integration that only applies to certain operators (cooperatives or pre-existing commercial companies), while others benefit from the possibility of being able to do this. This asymmetry distorts the market and means, in practice, a closure of the market in favour of the incumbent operators.

1. INTRODUCTION

The commercialisation and distribution of medicines, due to their nature and characteristics, are unique and heavily regulated activities. This public intervention is based on the necessary safeguarding of public health, the existence of market failures and the impact on public finances that pharmaceutical provision entails. For this reason, they have also traditionally been subjected to constant scrutiny by the CNMC, both from the point of view of advocacy and competition enforcement[8].

In this regard, in 2015 the CNMC published the Study on the retail distribution market for medicines in Spain, which proposed, among other measures, to adopt a less restrictive pharmaceutical planning model with a view to reducing the barriers to the entry and operation of pharmacies in Spain and fostering greater competition between them. The benefits of further opening up the retail segment of medicine distribution to competition were to be reinforced by a parallel increase in the level of effective competition in upstream markets. This study therefore continues the work started at that time and includes a detailed analysis of the upstream market for the distribution and marketing of medicines.

The aim of the study is to analyse the market for the commercialisation and distribution of medicines for human use subject to medical prescription and funded by the Spanish National Health System (SNHS) that are dispensed through pharmacies in Spain. The hospital channel is thus beyond the main focus of this work.

The market is atypical, and the SNHS plays a pivotal role as a purchaser. Likewise, the essential nature of medicines, due to their importance in preserving health and the positive benefits that their proper functioning generates for society as a whole, are the main social and economic reasons for the public financing of

[8] From a competition advocacy point of view, see, inter alia, the following: E/CNMC/003/15 Study on the retail distribution market for medicinal products; INF/CNMC/059/19 Report on the Action Plan to promote the use of market-regulated medicinal products in the Spanish National Health System: biosimilar medicines and generic medicines; IPN/CNMC/025/18 on the Draft Royal Decree on the financing and margins of medical devices; IPN/CNMC/023/15 Draft Royal Decree regulating the financing and pricing of medicines and medical devices and their inclusion in the pharmaceutical provision of the National Health System; or IPN/CNMC/05/15 on the Consolidated Text of the Law on Medicines.
From a competition advocacy perspective, the following cases, among others, stand out: C/1054/19 COFARES-COFARTA; S/0644/18 RADIOFARMACOS; C/1053/19 BOSTON SCIENTIFIC CORPORATION/BTG; C/0958/18 BIDAFARMA-ZACOFARVA; C-0959/18 BIDAFARMA/SOCOFASA; C/0925/18 Recordati/Mylan; C/0832/17 Janssen/Esteve-Activos; C-0745/16 CECOFAR/GRUPO FARMANOVA; o C-0725/16 HEFAME/COOFAMEL-ACTIVOS.

medicines. Hence, achieving optimal price regulation and appropriate health policies is a fundamental requirement for the efficiency of the healthcare system as a whole.

It also highlights the significance of this market in social and economic terms and the high proportion of public pharmaceutical spending in terms of healthcare spending and public finances. Since the onset of the last economic crisis in 2008, numerous measures have been implemented to reduce pharmaceutical spending and increase the efficiency of the system. Among others, cost-effectiveness and budget impact criteria were introduced in the financing of medicines, as were discounts in the price of medicines funded by the SNHS and reductions in wholesale and retail margins.

Furthermore, the use of new technologies and, in particular, the internet and big data, as instruments for boosting competition and potential tools for efficient management and fundamental technological innovation in this market, have not yet been developed to their full potential.

In this context, it is imperative to assess, using competition and efficient economic regulation criteria, to what extent the measures implemented in recent years, as well as the regulation or the very structure and functioning of the sector, inhibit or encourage effective competition in the market for the commercialisation and distribution of medicines. To this end, the study takes into consideration national and international comparative experience in order to draw conclusions and recommendations on the most pro-competitive and economically efficient configuration of this market, while fully respecting the overriding reasons of general interest invoked.

The study consists of four sections, in addition to this introduction. The second section presents a legal-economic characterization of the marketing and distribution of medicines in Spain. The third section assesses the regulation from a competition perspective. The fourth section contains the main conclusions drawn from the analysis; and, in the fifth section, recommendations for boosting competition and improving the functioning of the market in the general interest are proposed for the competent authorities.

2. LEGAL-ECONOMIC CHARACTERIZATION

Medicinal products for human use are substances or combinations of substances with properties that enable the treatment or prevention of disease in humans or which may be used or administered to humans to restore, correct or modify physiological functions, by exerting a pharmacological, immunological or metabolic action, or to establish a medical diagnosis[9].

The medicinal product for human use commercialisation and distribution sector is subject to intense regulation in Spain, which is justified for multiple reasons of public interest. Firstly, medicines have a direct impact on people's health, which calls for special safeguards by the public sector. Secondly, the pharmaceutical sector is characterised by the existence of market failures, which also hinder fair access to health protection: asymmetric information, problems of agency and moral hazard, uncertainty, externalities and the knowledge as a public good. It is also of strategic importance in the economy and is one of the most innovation-intensive sectors. Finally, since most of the medicines authorised in Spain are funded with public money, the pharmaceutical service of the Spanish National Health System has a major impact on the public purse[10].

Regulated activities cover the entire medicine chain: drug research and development, industrial production, marketing, public funding and pricing decisions, wholesale distribution of medicines to hospitals and pharmacies, as well as the dispensing of medicines by pharmacies, hospitals and primary care centres to patients and the prescription of medicines by doctors.

These activities are regulated at the European and national levels.

2.1. European regulatory framework

The legal framework of the pharmaceutical sector in the European Union is mainly constituted by[11]:

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9 Article 2 of Royal Legislative Decree 1/2015, of July 24, which approves the consolidated text of the Law on guarantees and rational use of medicines and healthcare products.

10 At the end of 2018, of the 31,200 dosage forms of medicines authorised in Spain, 20,873 were funded by the Spanish National Health System (2019 AEMPS Activity Report and the 2019 SNHS Annual Report from the Ministry of Health).

11 The following provisions also affect the European pharmaceutical sector:

- Directive 89/105/EEC on the transparency of the measures that regulate the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

- Regulation (EC) 726/2004 of March 31, 2004, establishing community procedures for the authorisation and control of medicines for human and veterinary use and creating the European Medicines Agency.
- Directive (EU) 2017/1572 OF THE COMMISSION of September 15, 2017, supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to the principles and guidelines of good manufacturing practices for medicines for human use.
- Directive 2010/84/EU of the European Parliament and of the Council, of December 15, 2010, on pharmacovigilance.
- Directive 2001/83/EC establishing a community code on medicinal products for human use.
- The Guidelines of November 5, 2013, on the correct distribution practices for medicines for human use (2013/C 343/01).
- The Guidelines of March 19, 2015, on the correct practices for the distribution of active ingredients for medicinal products for human use (2015/C 95/01).

All the Member States (MS) of the European Union (EU) are governed by the aforementioned legislation, which standardises the requirements for the authorisation and surveillance of medicinal products.

The **European Medicines Agency (EMA)** is responsible for "*coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products*" in the EU. To this end, it is responsible for facilitating the development of and access to medicinal products, evaluating part of the applications for marketing authorisation, monitoring safety throughout the product life cycle and providing information to healthcare professionals and the public, among other functions (Art. 57.1 Regulation (EC) 726/2004)[12].

For their part, **the national competent authorities (NCAs)** of the MS are responsible for assessing marketing authorisation applications for certain medicinal products (as explained below), authorising clinical trials, making decisions on the pricing and public financing of medicinal products by their

- Directive 2011/62/EU of the European Parliament and of the Council, of June 8, 2011, amending Directive 2001/83/EC establishing a community code on medicinal products for human use, with regard to preventing the entry of counterfeit medicines into the legal supply chain.
- EU Regulation 2016/793 of the European Parliament and of the Council, of May 11, 2016, to avoid trade diversion into the European Union of certain key medicines.

[12] Article 55 of Regulation (EC) 726/2004.

respective national health systems, and controlling the advertising of non-prescription medicines, among other things.

Box 1

SOME ROLES OF THE EUROPEAN MEDICINES AGENCY AND NATIONAL AUTHORITIES

EMA	NCA
- To coordinate MS resources in terms of scientifically evaluating the quality, safety and efficacy of medicinal products subject to authorisation procedures in the EU. - To facilitate the development of and access to medicinal products. - To evaluate part of the marketing authorisation applications. - To monitor the safety of medicinal products throughout their life cycle. - To provide information to healthcare personnel and the public.	- To assess all other marketing authorisation applications for medicinal products and to supervise and monitor the quality, safety and efficacy of medicinal products authorised and marketed within the national scope. - To authorise clinical trials. - To make pricing and public financing decisions on medicinal products for their national health systems. - To control the advertising of non-prescription medicines. - To grant manufacturing, import and distribution licences. - To inspect manufacturers.

The EMA and NCAs work together in a network of regulators: the European medicines regulatory system is based on a network of some 50 regulatory authorities in the European Economic Area countries, the European Commission and the EMA. This network facilitates collaboration and dissemination of scientific knowledge between agencies; enables the formation of multinational teams for the evaluation of drug applications; facilitates the exchange of information on suspected adverse reactions; works on the supervision of clinical trials and inspections to monitor compliance with good clinical, manufacturing and distribution practices for all medicinal products available on the European market; and monitors the safety of all medicinal products available on the European market. In addition to risk assessment, the EMA works within the European medicines regulatory network on risk management plans and the post-commercialisation benefit-risk assessment of medicines.

For their part, **manufacturers, importers and distributors of medicines in the EU must be authorised before they can begin operations**. Each MS is responsible for granting licences for activities taking place within its territory, although all manufacturing, import and distribution licences are entered into

"EudraGMDP", a publicly accessible European database operated by the EMA[13]. Manufacturers listed in the dossier of an application to commercialise a medicinal product in the EU are inspected by a competent authority in the EU, including those located outside the EU, unless there is a mutual recognition agreement between the EU and the country of manufacture. Common legislation and cooperation measures between authorities ensure common inspection procedures and equivalence of inspections between MS. In order to be released on the EU market, each batch of medicinal products must have been manufactured in accordance with good manufacturing practice and in conformity with the marketing authorisation of the operators[14].

In addition to the operators, **all medicinal products must be authorised before they can be launched on the EU market**[15]. The title holder of the medicinal product to be marketed must apply to the relevant medicines agency and submit preliminary studies demonstrating that the requirements, especially safety and efficacy, are met. The agency then assesses the application for marketing authorisation for that medicinal product. There are different routes for obtaining marketing authorisation for a medicinal product, although the regulations and requirements are identical for all of them.

First, the centralised European procedure allows a medicinal product to be marketed on the basis of a single European assessment. Pharmaceutical laboratories submit a single marketing authorisation application to the EMA, which analyses it and issues a recommendation to the European Commission on whether or not it should be granted. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU MS. The use of this centralised procedure is mandatory for certain types of[16] innovative medicines, including those indicated for rare diseases and biological and biosimilar

13 Article 111 of Directive 2001/83/EC.
14 European Medicines Agency (EMA).
15 Article 6 of Directive 2001/83/EC.
16 The centralised procedure is mandatory for medicinal products for human use containing a new active ingredient to treat: human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS); cancer; diabetes; neurodegenerative diseases; autoimmune and other immune dysfunctions; viral diseases; medicines derived from biotechnological processes, such as genetic engineering; advanced therapy medicines, such as gene therapy, somatic cell therapy or tissue engineered medicines; and orphan drugs (medicines for rare diseases). It is optional for other medicinal products containing new active substances for indications other than those listed above; which are a significant therapeutic, scientific or technical innovation; the authorisation of which would be in the interest of public or animal health at EU level.

medicines of biotechnological origin[17]. To ensure transparency in decision-making, the EMA publishes a "European Public Assessment Report", or EPAR, for each medicinal product that is either granted or refused a marketing authorisation.

However, most medicinal products that are authorised in the EU are not authorised within the scope of the centralised procedure. Instead, they are authorised by the NCAs. In Spain, the competent authority for granting marketing authorisation for medicinal products is the Spanish **Agency for Medicines and Healthcare Products (AEMPS)**, which also issues a public assessment report when authorising a medicinal product.

In the event that marketing authorisation is sought in several countries and the centralised procedure is not used, laboratories can opt for the following approaches:

- The decentralised procedure: a laboratory can apply for simultaneous authorisation of a medicinal product in more than one EU MS, provided that it has not been previously authorised in any EU country and is not subject to the centralised procedure. The various agencies assess the medicinal product in a coordinated manner and, at the end of the process, all agencies issue an identical authorisation valid for their respective territories of competence.
- The mutual recognition procedure: when a medicinal product is authorised in one of the EU Member States, it is possible to apply for recognition of this authorisation in other EU countries, since the regulations and requirements for pharmaceuticals in the EU are identical. This process allows each Member State to rely on the scientific assessments of the others.

Of the 1,299 new authorisations for medicinal products for human use in Spain in 2020, 51% followed the decentralised or mutual recognition procedures, 27.5% followed the national procedure, explained below, and around 15.6%

[17] Biological medicines are those that contain one or more active ingredients produced or derived from a biological source, whether human, animal or micro-organism.
Biotechnological medicines are medicines of biological origin obtained from genetically modified cell lines using genetic engineering techniques.
A biosimilar is a biological medicine that contains a version of the active ingredient of an originator medicine or reference product, whose patent has expired, and for which it can be demonstrated that any physical, chemical and biological differences do not affect the quality, efficacy and safety (Asociación Española de Biosimilares, Biosim).

corresponded to medicinal products registered in Spain from a centralised procedure[18].

Once marketing authorisation has been granted and the medicinal product has been included in the AEMPS Register of Medicinal Products, decisions regarding the price applicable to the medicinal product and its inclusion or not in public funding are taken by the competent authorities of each Member State, taking into account the potential function of the product and its use in the context of the health system of the country in question[19]. With regard to the applicable European pricing rules, the European Commission gives the MS a wide margin of freedom in terms of their public funding and pricing decisions. However, it does set out several requirements, including maximum time limits for funding and pricing decisions (180 days when both decisions are made in a single administrative procedure) and any administrative decisions must be reasoned and based on objective and verifiable[20] criteria.

2.2. Regulatory framework in Spain and economic characterisation of the medicines for human use sector

In Spain, industrially manufactured medicinal products for human use, once they have been authorised for marketing, must be offered to the public health system (Spanish National Health System, SNHS) so that the Ministry of Health can decide whether or not they are to be publicly funded (if they are included in the SNHS common services portfolio), and if necessary, their price is set by the Interministerial Medicines Pricing Committee (hereinafter CIPM), in which the Autonomous Communities are represented. Healthcare is a competence of the Autonomous Communities and, therefore, they are the ones responsible for managing medicines and financing the cost of the portfolio of pharmaceutical products from their budgets.

Medicine distribution and dispensing activities are regulated in many respects, including their margins, which are set according to the prices of the medicines distributed (regardless of whether or not they are funded). Furthermore, the dispensing of medicines is the exclusive responsibility (in addition to hospital pharmacy services, health centres and primary care) of pharmacies.

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[18] 2020 AEMPS Activity Report.

[19] Article 21 of Royal Decree 1345/2007, of October 11, which regulates the authorisation procedure, registration and dispensing conditions of industrially manufactured medical products for human use.

[20] Directive 89/105/EEC on the transparency of the measures that regulate the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

Distribution of competences in the field of medicines between the State and the Autonomous Communities

In Spain, the National Health System comprises all the Health Services under State and the Autonomous Community administration, and integrates all the health functions and services that are the responsibility of the public authorities to fulfil the right to health protection[21].

The portfolio of common SNHS services is the set of techniques, technologies and procedures by means of which health services are implemented and intended to guarantee the basic and common conditions for healthcare. Preventive, diagnostic, therapeutic, rehabilitative, rehabilitative and health promotion and maintenance services for citizens are considered to be SNHS services[22]. The catalogue of services includes, among others, pharmaceutical services[23].

According to the Spanish Constitution, the fundamentals and general coordination of health and foreign health are the **exclusive competence of the**

[21] Articles 44 and 45 of Law 14/1986, of April 25, on General Health.

[22] Article 7 of Law 16/2003 of May 28, on the cohesion and quality of the National Health System.

[23] The provision of pharmaceuticals through official medical prescriptions invoiced in pharmacies consists of medicines (97.8% in terms of volume and 94.7% of the value of the total), medical devices (2.1% in volume and 4.4% in value) and other magistral formulae (compounded preparations), medicinal preparations, individualised anti-allergic and bacterial vaccines (0.1% in volume and 0.9% in value) (Prestación Farmacéutica en el Sistema Nacional de Salud - Monographic Report, Ministry of Health, 2019).

State, although the Autonomous Communities may take on competences in health matters[24]. In the area of medicines, the State is responsible for:

- Legislating on pharmaceutical products[25].
- Establishing standards for processing, manufacturing, transport and storage[26].
- Assessing the healthcare suitability of medicines, both to authorise their circulation and use and to control their quality[27].
- Regulating, authorising and registering medicines. In the case of medicinal products intended for foreign trade or which may affect public safety, the State exercises the powers of inspection and quality control[28].
- Regulating and authorising the activities for preparing, developing and manufacturing medicinal products, as well as determining the minimum requirements to be met by wholesale distributors and the authorisation of those who carry out their activities in more than one Autonomous Community. When the activities relate to medicinal products intended for foreign trade or which may affect public safety, the State exercises the powers of inspection and quality control[29].
- Requiring prior licensing of natural or legal persons engaged in the import, processing, manufacture, distribution or export of medicinal products and their laboratories and establishments (without prejudice to the competences of the Autonomous Communities in relation to the establishments and activities of natural or legal persons engaged in the manufacture of customised medical devices. In any case, the criteria for granting the prior licence are the responsibility of the Ministry of Health)[30].
- Including medicines in the pharmaceutical provision for public funding, establishing the financing and price conditions within the SNHS (although, as explained below, the Autonomous Communities participate in the price

[24] Article 149.1.16 of the Spanish Constitution.
[25] Article 149.1.16 of the Spanish Constitution.
[26] Article 100.2 of Law 14/1986.
[27] Article 95.1 of Law 14/1986.
[28] Article 40.5 of Law 14/1986.
[29] Article 40.6 of Law 14/1986.
[30] Article 100.1 of Law 14/1986.

decision as part of the committee responsible for setting the price, the CIPM)[31].

- Setting the remuneration margins for the distribution and dispensing of medicines and the deductions applicable when invoicing medicines to the SNHS[32].

Within the remit of the State, the **Ministry of Health** is responsible for managing, developing and implementing pharmaceutical policy, exercising the functions that fall to the State in terms of public financing and setting the price of medicines, as well as the special conditions for prescribing and dispensing medicines in the SNHS. The **AEMPS** assumes the evaluation, registration, authorisation, inspection, surveillance and control of medicinal products for human use, without prejudice to the executive powers of the Autonomous Communities[33].

For this reason, the Ministry of Health establishes, among other things, the content and scope of the pharmaceutical provision included in the SNHS common portfolio of services; however, SNHS healthcare has been completely decentralised to the Autonomous Communities since 2002, including the management of pharmaceutical provision and its financing[34].

The **Autonomous Communities** hold the powers they have assumed in their Statutes of Autonomy, as well as those transferred or delegated to them by the State and public decisions and actions not expressly reserved to the State[35]. In the autonomous cities of Ceuta and Melilla, the National Institute of Health Management (INGESA) is in charge of health services[36].

In this respect, the Autonomous Communities have broad management powers. In addition to guaranteeing access for all users to the SNHS common portfolio of services and allocating the necessary economic resources for funding this, they

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31 Article 92 of Royal Legislative Decree 1/2015, of July 24, approving the consolidated text of the Law on guarantees and the rational use of medicines and medical devices.

32 Article 94 of Royal Legislative Decree 1/2015.

33 Article 31 of Law 16/2003.

34 With the exception of INGESA, which is in charge of health benefits in Ceuta and Melilla, and the administrative mutual funds –the Mutualidad de Funcionarios Civiles del Estado (MUFACE), the Mutualidad General Judicial (MUGEJU) and the Instituto Social de las Fuerzas Armadas (ISFAS)– which are responsible for the benefits for civil servants assigned to the three mutual funds of the General State Administration. INGESA, MUFACE, MUGEJU and ISFAS are all part of the SNHS. Mutual societies for civil servants can approve their respective portfolio of services, which must include, at least, the portfolio of common SNHS services. In 2017, the Autonomous Communities managed around 95% of the total pharmacy expenditure of the SNHS (Independent Authority for Fiscal Responsibility -AIReF-, 2019).

35 Article 41 of Law 14/1986.

36 Article 15 of Royal Decree 1087/2003, of August 29, which establishes the organisational structure of the Ministry of Health and Consumer Affairs.

can extend publicly funded services through their complementary portfolio (including services not included in the SNHS common portfolio, subject to justification based on the funding criteria included in Law 1/2015, for which they must establish the necessary additional resources[37]). Likewise, through their management powers, the Autonomous Communities can also establish policies to prioritise certain treatments, promote the most efficient diagnostic and therapeutic alternatives (to this end, they can carry out drug evaluation reports, positioning reports, and adopt protocols and pharmacotherapeutic guidelines establishing the list of drugs recommended for prescription in a given area), establish strategies aimed at intensifying the rational use of drugs, as well as income policies that affect the remuneration systems and economic incentives for healthcare professionals and centres[38].

The regulation of the medicinal products for human use sector in Spain and its economic characterisation is explained in more detail below, starting with its classification.

2.2.1. Classification of medicines and their regulation in Spain

The basic legislation on medicines is contained in *Royal Legislative Decree 1/2015, of 24 July, which approves the revised text of the Law on Guarantees and the Rational Use of Medicines and Medical Devices* (hereinafter, **Consolidated Text**)[39]. This text regulates, within the scope of the State's

[37] Article 8 quinquies of Law 16/2003.

[38] Statement of reasons in Royal Legislative Decree 1/2015.

[39] There are, similarly, various regulations applicable to the Spanish pharmaceutical sector. Among these, we can highlight the following:
Law 14/1986, of April 25, on General Health.
Law 16/2003 of May 28, on the cohesion and quality of the Spanish National Health System.
Royal Decree 1345/2007, of October 11, which regulates the authorisation procedure, registration and dispensing conditions of industrially manufactured medical products for human use.
Royal Decree 824/2010, of June 25, which regulates pharmaceutical laboratories, manufacturers of active ingredients for pharmaceutical use, and the foreign trade in medicines and medicines being researched.
Royal Decree 577/2013, of June 26, which regulates the pharmacovigilance of medicines for human use.
Royal Decree 1718/2010, of December 17, on medical prescriptions and dispensing orders.
Royal Decree 782/2013, of October 11, on the distribution of medicinal products for human use.
Royal Decree 823/2008, of May 16, which establishes the margins, deductions and discounts corresponding to the distribution and dispensing of medicinal products for human use.
Royal Decree 870/2013, of November 8, which regulates remote sales to the public, through websites, of over-the-counter medicinal products for human use.

competences, medicines, the set of activities that make up the medicine chain, as well as the actions of the health and economic agents involved in these activities[40].

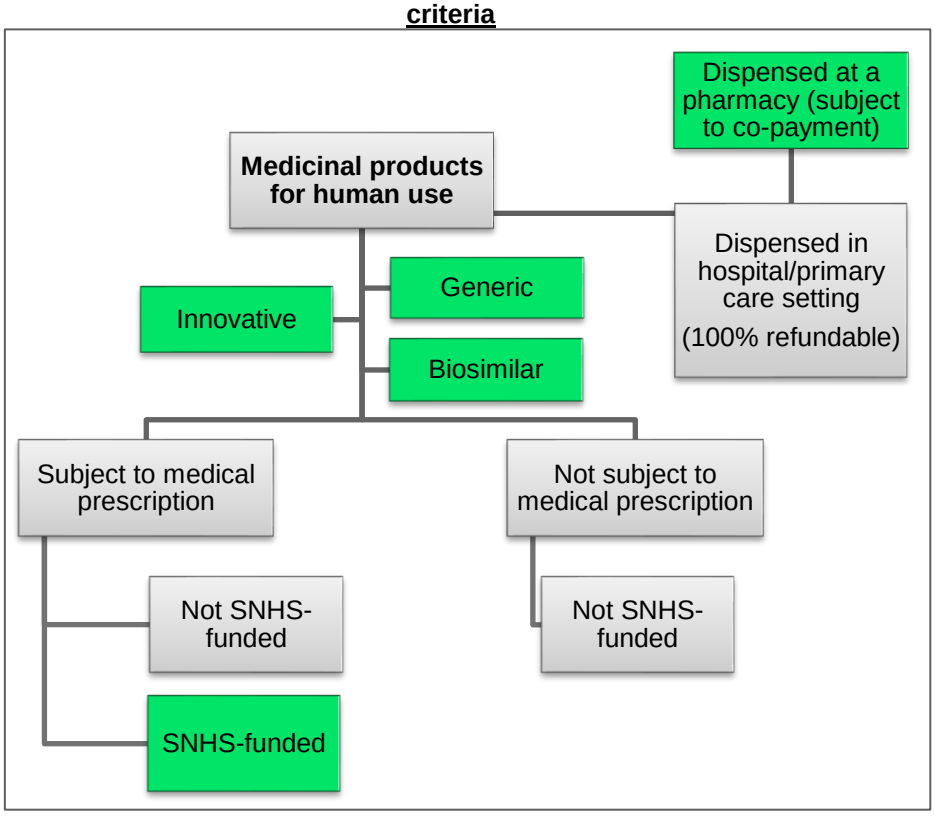
In order to better understand the existing types of medicinal products and their characteristics, below are presented the various classifications of medicinal products for human use, according to prescription type, financing and dispensing:

Royal Decree 1416/1994, of June 25, which regulates the advertising of medicinal products for human use.
Royal Decree 1369/2000, of July 19, which modifies Royal Decree 822/1993, of May 28, which establishes the principles of good laboratory practices and their application when conducting non-clinical studies on chemical substances and products.
Royal Decree 1015/2009, of June 19, which regulates the availability of special medicines.
Royal Decree 1348/2003, of October 31, which adapts the anatomical classification of medicines to the ATC classification system.

40 As a consequence of the economic crisis of 2008 and the austerity measures implemented to contain health and pharmaceutical spending, the regulation of medicines was modified on several occasions. Although some modifications were of a healthcare-related nature, such as those relating to guarantees of efficacy, safety and quality of medicines and healthcare products, the most significant changes involved economic aspects, with the ultimate aim of containing public pharmaceutical spending. To this end, the following regulations, among others, were enacted in 2010, 2011 and 2012:

- Royal Decree-Law 4/2010, of March 26, rationalising the spending on pharmaceuticals charged to the Spanish National Health System.
- Royal Decree-Law 8/2010, of May 20, which adopts extraordinary measures to reduce the public deficit.
- Royal Decree-Law 9/2011, of August 19, on measures to improve the quality and cohesion of the Spanish National Health System, to improve fiscal consolidation, and to increase the maximum amount of State guarantees for 2011.
- Royal Decree-Law 16/2012, of April 20, on urgent measures to guarantee the sustainability of the Spanish National Health System and improve the quality and safety of its services.

Diagram 1. Classification of medicinal products for human use according to different criteria



Source: prepared in-house.
Note: the categories with green boxes refer to those medicines that fall within the scope of this study.

Innovative, generic or biosimilar medicine

Medicines can be classified as **innovative** (which we will refer to as **originators**[41] once they are off-patent and may face competition)**, generic, and biosimilar**.

An **innovative** medicinal product contains a new active substance and has undergone comprehensive research and development, from its chemical or biological synthesis to its clinical use[42]. It is, therefore, the first drug to demonstrate safety and therapeutic efficacy data, i.e., no equivalent drug has

41 Note that this distinction is made to facilitate a better understanding and to be able to distinguish the period of patent protection or exclusivity of a medicinal product from the period once that patent has expired. It is not, therefore, a formal definition.

42 Active ingredients are substances designed for the manufacture of medicinal products, capable of exerting a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or making a diagnosis (Article 2 of the Consolidated Text).

previously established its safety and efficacy[43]. Innovative medicines are protected by patents and/or by data exclusivity rights.

Box 2

INNOVATION IN THE PHARMACEUTICAL SECTOR AND COMMERCIAL PATENT PROTECTION

Pharmaceutical companies and laboratories are able to produce and sell medicines after an intensive and costly research and development process that entails considerable commercial risks. The pharmaceutical industry is ranked second in the world in terms of R&D&I[44].

From the start of pre-clinical research through to marketing, a medicine goes through multiple production stages, all of which are protected by a patent, which is applied for at the start of the research. On average, it takes 12 to 13 years from the first pre-clinical research phase to the *de facto* marketing of the medicine[45]. After this period, the medicine is marketed on an exclusive basis until the expiry of the patent (20 years in total from the start of R&D&I).[46] In specific cases and for justified circumstances, the patent can be extended by means of a supplementary protection certificate (SPC), which extends the exclusivity of the medicinal product for a maximum of 5 additional years after the expiry of the patent[47]. In addition, exclusivity can be extended by one year in the case of a new therapeutic indication. Effective exclusivity rarely extends beyond 10-12 years, given the long research and development period of a drug[48].

Furthermore, in addition to the patent protection afforded to the original medicine, generic medicines cannot be marketed until ten years after the date on which the reference medicine was first authorised (data exclusivity)[49]. This exclusivity usually does not extend beyond the period covered by the patent and SPC, although it may be exceeded in some cases.

These market exclusivity rights are intended to incentivise R&D&I by allowing pharmaceutical companies to recoup the costs of their investments by giving them a temporary monopoly on the drug. However, competition concerns can arise when the originator companies use their intellectual property rights to restrict or delay the market entry of generic medicines.

When innovative medicines become off-patent or lose their exclusivity rights, they can be marketed and compete in the market with generic medicines (if they are chemically synthesised medicines), or biosimilars (if they are biological, i.e., if

[43] Diez & Errecalde (1998).
[44] Hernandez et al. (2018).
[45] See EFPIA (European Federation of Pharmaceutical Industries and Associations), 2019. Likewise, it should be noted that only 11.8% of molecules that reach the clinical phase are finally marketed (DiMasi, Grabowski and Hansen, 2016).
[46] Article 58 of Law 24/2015, of July 24, on Patents.
[47] Regulation (EC) No. 469/2009 of the European Parliament and of the Council, of May 6, 2009, regarding the supplementary protection certificate for medicinal products.
[48] Source: Farmaindustria.
[49] Article 18 of the Consolidated Text.

they contain active ingredients produced or derived from a biological source, whether human, animal or microorganism[50]).

A **generic medicine (Generic Pharmaceutical Equivalent, GPE)** is considered to be any medicine that has the same composition (qualitative and quantitative) in active ingredients and the same pharmaceutical form[51], and whose bioequivalence with the reference medicine has been demonstrated[52]. In other words, generics are medicines with the same characteristics that are interchangeable with the corresponding originator medicines ("reference medicines"). Generic medicines were introduced in Spain in 1997 and since then have coexisted with originators. Generic medicines are homogenous and bioequivalent, and compete with the originator reference products (the former innovative medicines) once their patents have expired[53]. This competition takes the form of improved production efficiency, lower production costs and lower prices (since they do not reflect the investment in research and development of the medicine, as the originator medicines do).[54]

Biosimilar medicines can enter the market when the original reference biological loses its exclusivity rights (analogous to generics for chemically synthesised medicines). A biosimilar is a version of an original or reference biological medicine against which biosimilarity has been demonstrated through a comparability exercise, demonstrating that any slight physicochemical and biological differences do not affect quality, efficacy and safety[55]. The development of biosimilar medicines is a relatively recent phenomenon: the first biosimilar was approved in the EU in 2006.

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50 For example, biological drugs are immunological drugs and those derived from human blood and plasma. Biotechnological drugs are drugs of biological origin obtained from genetically modified cell lines using genetic engineering techniques (Asociación Española de Biosimilares, BioSim, 2017).

51 The pharmaceutical form is defined by the combination of the format in which the pharmaceutical product is presented by the manufacturer and the form in which it is administered, e.g., capsules, tablets, ointments, syrups, aerosols, etc. The various immediate-release oral pharmaceutical forms are considered to be the same pharmaceutical form (Article 2 of the Consolidated Text).

52 Article 2 of the Consolidated Text.

53 In 2006, through the second final provision of Law 29/2006, the “Bolar clause” was introduced in the Patent Law, which allowed generics to enter the market as soon as a patent expires. This regulatory amendment introduced an exception to the patent right in that the experimental and research use of generic medicines is not considered a patent infringement. This allows Spanish laboratories to apply for and obtain marketing authorisations in Spain and abroad before the expiry of the patents protecting them in Spain, so that the generic can enter the market as soon as the patent expires. Up to that point, generic market entry times had been longer, with time elapsing from the end of the patent to the marketing of the generic.

54 2018 SNHS Annual Report (Ministry of Health).

55 Biosim (2017).

These medicines contribute to reducing public expenditure on medicines, without compromising their quality and efficacy, foster competition and promote price reductions in branded competitors[56].

Generic and biosimilar medicines have distinguishing characteristics, as chemically synthesised medicines are more easily imitated than biological ones: the molecular structure of biological medicines is more complex than that of generics; as they are chemically synthesised, generics are exact copies of the reference originals, while biosimilars are not identical, but similar, to the reference biological (as they are synthesised using living organisms and are therefore subject to the variability inherent in any production process in which they are involved). Once authorised, after demonstrating similarity and an equivalent benefit/risk profile to the original, they can be used for the same indications[57]. In addition, biosimilars require more complex clinical studies with a larger number of patients than generics, and the development of biosimilars involves a significantly higher investment in terms of time and money[58].

Prescription and non-prescription medicines

Medicines can be classified according to whether they are **prescription-only or non-prescription medicines (OTC)**; this is determined by the authority competent to authorise the medicine[59].

Medicinal products are **prescription only** if they fall into one of the following categories[60]:

1) They may present a danger, directly or indirectly, even under normal conditions of use, if used without medical supervision.
2) They are used frequently, and to a very considerable extent, under abnormal conditions of use, and this may, directly or indirectly, present a danger to health.

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56 2018 SNHS Annual Report (Ministry of Health).
57 Del Llano-Señarís (2014).
58 The development of biological medicines requires between 6 and 7 years, on average, compared to 2-3 years for generics. In terms of cost, some sources suggest that the investment in the development of biosimilars can be between 30 and 100 million euros and that of generics between 0.6 and 4 million euros (Larráyoz, 2015), while other sources suggest a figure of between 100-300 million euros for biosimilars and 1-3 million for generics (Dorrego, 2017).
59 Article 70 of Directive 2001/83/EC and Article 19 of the Consolidated Text.
60 Article 19.2 of the Consolidated Text.

3) They contain substances or preparations based on such substances, the activity and/or adverse reactions of which need to be studied in more detail.

4) They are administered parenterally, except in exceptional cases, via medical prescription.

Medicines subject to medical prescription are the only ones that can be publicly funded by the SNHS, through an official SNHS prescription[61]. Due to their characteristics, they are heavily regulated in aspects such as their marketing (for example, they cannot be sold via mail order or remotely, and may not be advertised).[62]

Non-prescription, or over-the-counter medicines can be defined as medicines for processes or conditions that do not require a precise diagnosis and whose toxicological, clinical evaluation data, or their use and administration route do not require a medical prescription, so that they can be used for self-care[63]. They are also known as *over-the-counter* (OTC) medicines. The price of these medicines is unregulated (with exceptions presented below) and not publicly funded –except for use in hospitals– and they are subject to fewer regulatory restrictions (e.g., they can be advertised and retailed through the websites of authorised pharmacies[64]).

Publicly funded or unfunded medicine

Another possible classification of medicines is according to whether they are **funded or not by the SNHS**.

Medicines subject to medical prescription, once authorised for marketing, can be included in the pharmaceutical services provided by the SNHS (in its common portfolio of services)[65]. In this way, they are funded with public funds from the Autonomous Communities, INGESA and the Administrative Mutual Societies, or they are not included in the SNHS pharmaceutical service[66]. To market a medicine in Spain, it is essential to have previously offered it to the SNHS[67]. For

61 Article 92.2 of the Consolidated Text.
62 Article 80 of the Consolidated Text and Royal Decree 870/2013, of November 8, which regulates remote sales to the public, through websites, of over-the-counter medicinal products for human use.
63 Article 19.4 of the Consolidated Text.
64 Royal Decree 870/2013, of November 8, which regulates remote sales to the public, through websites, of over-the-counter medicinal products for human use.
65 Article 92.2 of the Consolidated Text.
66 In some cases, access is only partially restricted and it may be prescribed for certain types of patients or situations.
67 Article 94.2 of the Consolidated Text.

a medicine to be funded by the SNHS, it must be included in the pharmaceutical service by express resolution of the Directorate General for the Common Portfolio of Services of the National Health and Pharmacy System (DGCYF) of the Ministry of Health. The general criteria for such inclusion are as follows[68]:

a) Severity, duration and sequelae of the different pathologies for which they are indicated.

b) Specific needs of certain groups.

c) Therapeutic and social value of the medicine and its incremental clinical benefit, taking into account its cost-effectiveness[69].

d) Rationalisation of public spending on pharmaceutical provision and budgetary impact on the SNHS.

e) Existence of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost.

f) Degree of innovation of the medicine.

For a medicine to be included in the SNHS pharmaceutical service, its funding must be considered necessary to cover the basic health needs of the Spanish population; medication indicated for the treatment of less severe syndromes and/or symptoms are not funded[70]. Similarly, new medicines that are more effective or less costly than those already available can be funded with public funds[71]. In addition, in order to decide whether to finance medicines with the same health outcome (i.e., that are equally effective), their contribution to the sustainability of the SNHS is assessed through their contribution to the Gross Domestic Product (GDP)[72].

In practice, AEMPS informs the Ministry of Health of the procedures for initiating the authorisation of medicinal products, so that the Ministry can open *ex officio* funding and pricing procedures for that product[73]. However, funding and pricing procedures are not always processed for all dosage forms of the same

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68 Article 92 of the Consolidated Text.

69 Cost-effectiveness analysis is a way of economically evaluating medicines by quantifying treatment costs (in monetary terms) and patient health outcomes (in units used in clinical practice) to determine which interventions are a priority in order to maximise the clinical benefit of the available economic resources (Prieto et al., 2004).

70 Article 92.2 of the Consolidated Text. This selective financing of medicines, according to the criterion of "basic need", is one of the measures to reduce public pharmaceutical spending that was incorporated by Royal Decree-Law 16/2012, of 20 April, on urgent measures to guarantee the sustainability of the Spanish National Health System and improve the quality and safety of its services.

71 Additional Provision 5 of Law 14/1986.

72 Article 92.8 of the Consolidated Text.

73 And the presentation of the request for a national drug code by the laboratory.

medicine[74]. In its analysis, the DGCYF takes into account: 1) the incremental therapeutic value of the medicine compared to equivalents, according to cost-effectiveness studies; 2) the conclusions of the Therapeutic Positioning Reports (TPRs, see box 3); 3) the price requested and the price in other EU countries; and 4) R&D information and budgetary impact estimated by the pharmaceutical company[75]. The value dossier provided by the company, or the EPAR (European Public Assessment Report), is also taken into consideration, as well as other aspects. With all this data, the DGCYF evaluates the product according to the above criteria, assesses the input of the new molecule/medicine and decides whether or not to include it in the SNHS common services portfolio[76].

Box 3

THERAPEUTIC POSITIONING REPORTS

Spain has a Drug Evaluation Network **(REvalMed SNHS**) made up of professionals from the DGCYF, the AEMPS, and the Autonomous Communities, which is responsible for preparing and approving TPRs[77].

TPRs provide an objective view of the existing knowledge about the medicine, in terms of its comparative effectiveness and safety (with other medicines that have the same clinical indications), and may include a financial and budgetary impact assessment.

TPRs are prepared for all medicines authorised through the centralised procedure, for new indications for already authorised medicines, and for those authorised through the national procedure involving new molecules and others, as deemed appropriate. Medicines can be re-evaluated and TPRs revised in cases where new scientific evidence emerges.

TPRs serve as one of the bases on which to make selective funding and pricing decisions for medicines and as a reference for any action related to the procurement and promotion of their rational use.

In 2019, the total number of drug presentations included in SNHS public funding, regardless of their marketing, was 21,383[78], representing 66% of the total of 32,348 authorised.[79] Among them, 13,190 (61% of those funded) were dispensed through SNHS medical prescriptions in pharmacies, while the rest were for hospital use. 60% of the funded dosage forms were generic medicines compared

74 AIRef (2019).
75 AIReF (2019) and Ministry of Health.
76 Ministry of Health.
77 Action plan for the consolidation of Therapeutic Positioning Reports on medicines in the SNHS.
78 Data provided by the Ministry of Health.
79 AEMPS Annual Activity Report (2020).

to 40% non-generic.[80] Medicines publicly funded by the SNHS and those not funded could both be marketed and prescribed outside the SNHS, and purchased privately[81].

Medicines dispensed in retail pharmacies or in the hospital setting

Depending on the channel through which medicines are dispensed to patients, they can be classified into those dispensed through **retail pharmacies and those dispensed in the hospital setting**[82]**.** High-cost innovative medicines indicated for treating serious illnesses are mainly dispensed in hospitals.

Medicines funded by the SNHS that are dispensed to patients through SNHS hospitals and primary care centres are 100% publicly funded. However, in the case of medicines dispensed through pharmacies by prescription, part of the price is funded by patients through the "pharmaceutical co-payment" scheme[83]. The co-payment consists of a contribution from users and beneficiaries, whereby they pay a percentage of the price of the medicine according to their income level. There are maximum monthly contribution ceilings for pensioners and their beneficiaries, and certain groups are exempt from contributing[84]. In the case of patients with chronic diseases, there are medicines that require a reduced contribution from the user. The rest is covered by the SNHS, paid from the public funds of the Autonomous Communities, INGESA and the administrative mutual insurance system: on a monthly basis, pharmacies (with an intermediary from the Official Associations of Pharmacists) send the Health Services of the

80 Data provided by the Ministry of Health.
81 Article 94.6 of the Consolidated Text.
82 Medicines subject to medical prescription and dispensed in the hospital setting include medicines for hospital use which, due to their pharmacological characteristics, their novelty or for public health reasons, are reserved for treatment in hospitals or authorised care centres (Article 24 of Royal Decree 1345/2007).
83 Article 102 of the Consolidated Text.
84 Thirty-fifth final provision of Law 11/2020, of December 30, on General State Budgets for the year 2021. The following are exempt from contributions: users and their beneficiaries who are affected by toxidrome and people with disabilities in the cases contemplated in their specific regulations; people receiving social integration income; people receiving non-contributory pensions; unemployed people who have lost the right to receive unemployment benefit for as long as their situation persists; persons undergoing treatment derived from an accident at work or occupational illness; persons receiving the minimum living wage; minors with a recognised degree of disability equal to or greater than 33%; persons receiving Social Security benefits for a dependent child or minor in permanent foster care or guardianship for the purpose of adoption; Social Security pensioners, whose annual income is less than 5,635 euros who tick the general and savings taxable base box on their Personal Income Tax return, and those who, if they are not obliged to file such a return, receive an annual income of less than 11,200 euros.

Autonomous Communities the pharmaceutical invoices for the medicines included in the pharmaceutical service that they have dispensed through official medical prescriptions that month, so that the SNHS can pay them[85].

This study focuses on medicinal products for human use subject to medical prescription and funded by the SNHS that are dispensed through pharmacies, as they are subject to strict regulatory intervention. The hospital dispensing channel is beyond the main focus of this study, as it has particular characteristics that would require a different analysis to the one presented here. Even so, this dispensing channel is mentioned in order to contextualise and compare aspects of hospital medicines with those dispensed in retail pharmacies.

2.2.2. Current medicine pricing systems

As a complementary measure to the public funding decision, the price of funded medicines is strictly regulated. In contrast, medicines that are not funded by the SNHS are, in general, unregulated in terms of price (with exceptions, as discussed below).

- General system

The Government is responsible for establishing the criteria and procedures for the pricing of medicines that can be funded by the SNHS[86]. The Interministerial Medicines Pricing Committee (CIPM, see Box 4) is responsible for setting the maximum industrial price (laboratory selling price, LSP) for financing the dosage forms of medicines that are to be included or are already included in the SNHS pharmaceutical service and that are dispensed in Spain[87].

Box 4

INTERMINISTERIAL MEDICINAL PRODUCT PRICING COMMITTEE

The Interministerial Medicines Pricing Committee (CIPM) is a collegiate body attached to the Secretary of State for Health, made up of representatives of the Ministry of Health, the Ministry of Economic Affairs and Digital Transformation, the Ministry of Industry, Trade and Tourism,

[85] The Official Associations of Pharmacists are intermediaries between pharmacies and the SNHS with regard to the billing and collection of prescriptions for medicines included in the SNHS pharmaceutical service, through the signing of agreements with the Health Departments of the respective Autonomous Communities (CNMC, 2015).

[86] Article 94.1 of the Consolidated Text.

[87] Article 94.5 of the Consolidated Text. It should also be noted that each of the combinations in which the medicinal product is available for use, including its composition, pharmaceutical form, dose and configuration, is referred to as the dosage form (Article 2 of Royal Decree 1345/2007).

the Ministry of Finance and the Autonomous Communities. All Autonomous Communities (on a rotating basis) are members of the CIPM as members (and the others attend as observers).

The CIPM is made up as follows[88]:

- President: the Secretary of State for Health,

- Vice president: the head of the Directorate General for the Common Portfolio of Services of the National Health and Pharmacy System.

- Members:

- One person from the Ministry of Economic Affairs and Digital Transformation with the rank of Director-General;
- One person from the Ministry of Industry, Commerce and Tourism with the rank of Director-General;
- Two people from the Ministry of Finance, with the rank of Director-General;
- Three representatives from the Autonomous Communities, at the proposal of the Interterritorial Council of the National Health System, chosen from among its members.
- The head of the Sub-directorate General for Pharmacy of the Directorate General for the Common Portfolio of SNHS and Pharmacy Services, who will act as Secretary.
- An official from the Directorate General for the Common Portfolio of SNHS and Pharmacy Services.

- Each Autonomous Community that does not have a member has a representative who attends as an observer.

Although the decisions to finance medicines and to set their industrial price are taken by two different bodies (as explained above, the DGCYF makes the financing decision, while the CIPM makes the pricing decision), a single the resolution establishing the financing and pricing conditions is issued by the DGCYF[89]. In the framework of the pricing procedures, the CIPM can propose to the DGCYF, among others, guidelines and general criteria to be applied in the procedures for financing and including (or excluding) medicines from the SNHS pharmaceutical service, although the final financing decision rests with the DGCYF[90].

The CIPM must make a reasoned price decision, based on objective criteria[91]. It should also take into account cost-effectiveness and budgetary impact analyses[92]. To this end, the pharmaceutical companies that own the medicines

[88] First additional provision of Royal Decree 485/2017, of May 12, which develops the basic organic structure of the MSCBS, and current composition of the Interministerial Medicinal Product Pricing Committee (July-December 2021).
[89] Article 94.5 of the Consolidated Text.
[90] Internal regulations of the Interministerial Commission on Drug Prices (CIMP).
[91] Article 94.5 of the Consolidated Text.
[92] Article 94.1 of the Consolidated Text.

must provide technical, economic and financial information on these medicines[93]. The CIPM also takes into account pharmacoeconomic reports from the Advisory Committee for the Funding of the Pharmaceutical Service of the National Health System (CAPF)[94]. This body also considers that therapeutic positioning reports (TPR) are an important tool when selecting medicines from among the existing alternatives, for prescribing and to support pricing and funding decisions[95]. In this regard, and since 2013, TPRs have been one of the criteria for selective financing and, where appropriate, pricing of medicinal products for human use, as well as a reference for any action related to the acquisition and promotion of the rational use of medicines[96].

Moreover, medicines funded by the SNHS can also be marketed for prescription outside the SNHS [97]but, as a general rule, the SNHS financing price will be lower than or equal to the price applied when dispensed outside the SNHS[98].

Negotiations are then initiated with the company to establish a laboratory selling price (LSP) in line with the CIPM funding criteria. This procedure is particularly important and applies when setting the maximum LSP for innovative medicines, since in the case of competing medicines (generics, biosimilars and originator

93 Article 97.1 of the Consolidated Text.

94 The Advisory Committee for the Financing of the Pharmaceutical service of the Spanish National Health System is scientific-technical in nature and in charge of advising, evaluating and consulting on the relevance, improvement and monitoring of the economic evaluation necessary to support the decisions of the CIPM. This Committee is made up of a maximum of seven experts in pharmaco-economic evaluation appointed by the Ministry of Health. This body was introduced by Royal Decree-Law 16/2012 and was created by Agreement of the Council of Ministers on March 22, 2019.

95 Consensus Document from the Advisory Committee for the Financing of the Pharmaceutical Service of the National Health System (CAPF) on the therapeutic positioning reports (TPRs) of SNHS medicines.

96 Document Proposed collaboration of the Spanish Agency for Medicines and Healthcare Products (AEMPS), the Directorate General for the Basic Portfolio of the National Health Service and Pharmacy (DGCBSF), and the Autonomous Communities in the preparation of therapeutic positioning reports on medicines - Document approved by the Standing Committee on Pharmacy of the SNHS, 21 May 2013.

97 Article 94.6 of the Consolidated Text.

98 Given that the price of the medicine when dispensed within the SNHS is, in general, lower than when it is dispensed outside it, the same medicine operates with different prices (regulated price for dispensing within the SNHS and price when it is dispensed outside it); however, prior to it being dispensed, the operators cannot know at which price it will finally be dispensed. For this reason, pharmaceutical laboratories, distribution entities and pharmacies, through the Professional Pharmaceutical Organisation (Organización Farmacéutica Colegial), must provide the necessary information to subsequently reimburse pharmacies for medicines dispensed outside the SNHS (Article 94.7 of the Consolidated Text).

medicines that have lost their exclusivity rights) there is a specific pricing system, the reference price system, which is explained below[99].

The price set by the CIPM can be revised *ex officio* or at the request of one party, among other cases, when required by changes in financial, technical or health circumstances or in the assessment of the therapeutic usefulness of the medicine. The Council of Ministers may also revise or set conditions for periodic price reviews for all or some of the medicines included in the SNHS pharmaceutical service[100].

The retail price (RP) is established indirectly, by adding the LSP and the wholesale distribution and retail margins (which are regulated as a percentage of the price, both for funded and non-funded medicines, see Sections 2.2.4. and 2.2.5.)[101]. VAT is added to this RP (at a super-reduced rate of 4%) to calculate the retail price of the medicine (RP VAT). The calculation of the RP and the RP VAT of medicines can be expressed with the following formula:

$$LSP + wholesale\ DM + retail\ DM = RP$$
$$LSP + wholesale\ DM + retail\ DM + VAT = RP\ VAT$$

Note: DM stands for distribution margin.

Each dosage form of a medicine that is funded by the SNHS has a single maximum industrial price (LSP) and, therefore, also a single RP. However, throughout the distribution chain, commercial conditions (discounts for prompt payment, management costs, etc.) may be applied by pharmaceutical companies to wholesale distributors, or by wholesale distributors to pharmacies, due to the competitive dynamics that exist within the distribution chains[102]. This means that the price actually applied in the supply chain may vary and not be in line with the regulated price; however the RP does not alter, and remains the sum of the

[99] This is also applicable in the case of other medicines, such as orphan drugs, which, in general, are excluded from the reference price system, as explained below (Resolution of 2 June, 2020, of the Directorate General for the Common Portfolio of National Health System and Pharmacy Services, publishing the Agreement of the Council of Ministers of 3 March, 2020, establishing the economic regime for orphan drugs, under the provisions of Article 3.3 of the rewritten text of the Law on guarantees and rational use of medicines and healthcare products, approved by Royal Legislative Decree 1/2015, of 24 July).

[100] Article 96 of the Consolidated Text.

[101] Article 94.10 of the Consolidated Text.

[102] There may be other discounts within the chain, given that pharmaceutical laboratories can also market medicines directly to pharmacies and apply favourable commercial conditions.

maximum LSP and the regulated margins. In this regard, any discounts that are applied within the supply chain for funded medicines dispensed through pharmacies are not passed on to the consumer through the final price of the drug, but rather alter the margins of each operator in the chain (increasing or decreasing it depending on whether they receive or grant the discount). As a result, they do not translate into lower prices for the final purchasers (the State and patients), who must pay the regulated RP. In other countries, such as the United Kingdom, there is a clawback mechanism meaning that these discounts are partially passed on as a lower cost to the national health system.[103]

Public procurement procedures also end up reducing the effective purchase price below the maximum financing price set by the CIPM, but in these cases the discounts obtained do positively impact the SNHS's purse. For example, in the case of medicines dispensed through the hospital channel, hospitals usually negotiate their own prices directly with pharmaceutical companies. There are also centralised purchasing procedures at different levels (central, regional, hospital groupings) where the commercial conditions may vary from the maximum regulated price. Finally, for certain cases of innovative medicines that generate clinical or financial uncertainty, risk-sharing agreements have been put in place; these affect the commercial conditions of said medicines[104].

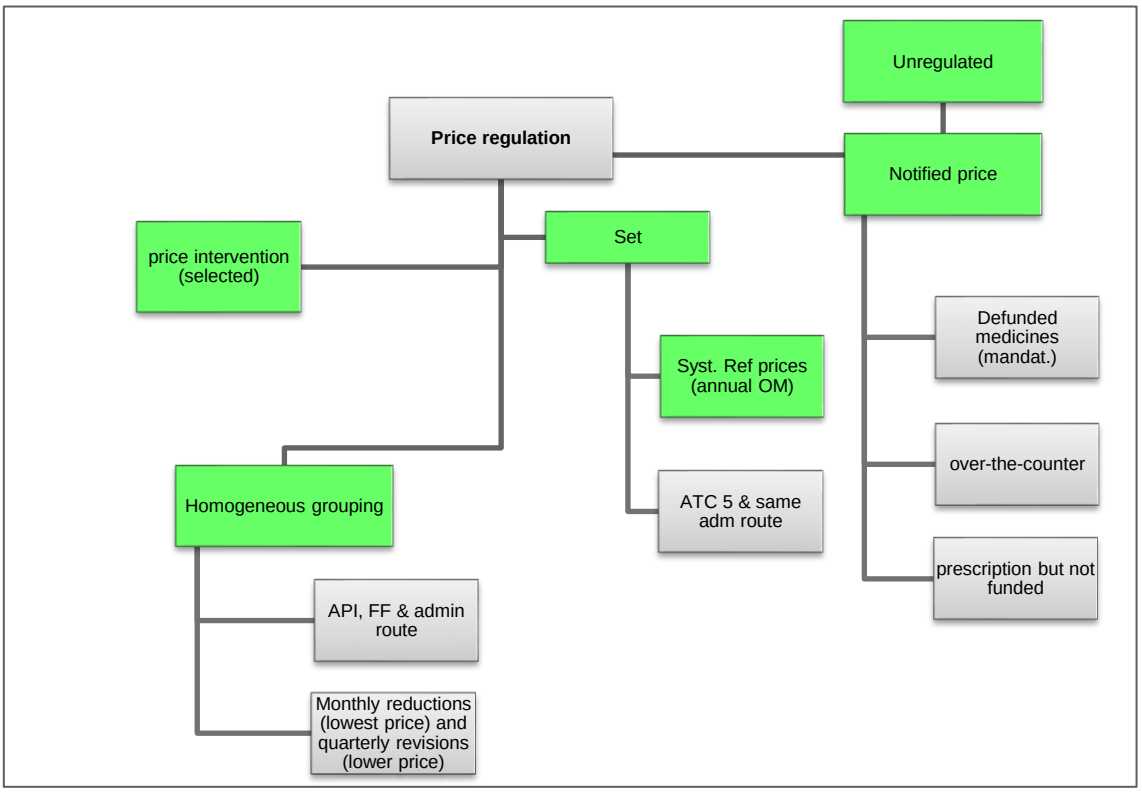
There are also drug pricing systems applicable to specific groups of medicines, such as: reference pricing systems (joint and homogeneous grouping); notified pricing systems; selection systems; and unregulated pricing.

[103] CNMC (2015). More information available at https://psnc.org.uk/dispensing-supply/endorsement/discount-deduction/

[104] Risk-sharing agreements are signed between the laboratory that owns the innovative medicine and the public sector (there are agreements signed by both the State Administration and the Autonomous Communities). They are aimed at reducing or alleviating the conditions of uncertainty to facilitate public access to the medicine through public financing. Two types of risk-sharing agreements can be distinguished:

- Payment-by-results schemes: these can be undertaken when there are uncertainties about the clinical effectiveness of the medicine. For example, such an agreement may involve the laboratory repaying the public health system for treatment for patients who do not respond to the medicine.
- Financial agreements: these are appropriate when there are budgetary uncertainties, for example because the number of patients to be treated with the new medicine is unknown. They can take many forms, such as price-volume agreements (where the price is set according to the volume of drugs consumed) or expenditure ceilings (the public sector bears a maximum cost, so that if the drug is consumed to a greater extent, the rest of the cost is borne by the incumbent laboratory).

Diagram 2. Classification of funding types



Source: prepared in-house.
Note: the categories with green boxes refer to those medicines that fall within the scope of this study.

- Reference pricing systems: sets and homogeneous groupings

In the case of originator medicines that are subject to competition, all of them (whether originator, generic or biosimilar) enter the **reference price system**[105]. In Spain, despite not being contemplated in the current regulation, in practice, the first generic medicine enters the market at a price 40% lower than the original reference medicine, and around 20%-30% lower in the case of biosimilars[106]; it is then incorporated into the reference groups[107].

[105] Article 98 of the Consolidated Text.
[106] Spanish Association of Biosimilar Medicines (Asociación Española de Medicamentos Biosimilares; BioSim).
[107] Ministry of Health and Rovira et al. (2012).

Reference sets[108] are groups of medicines[109] made up of all the dosage forms of medicines included in the SNHS pharmaceutical service (both originator medicines and generic or biosimilar medicines) that have the same level, 5, in the World Health Organisation's anatomical therapeutic chemical classification of medicines (ATC5)[110] and administration route[111]. Normally, the creation of reference sets takes place after the first generic or biosimilar enters the market[112]. However, a reference set can also be created when the reference medicinal product or its main active substance has been authorised for at least 10 years in an EU Member State and there is another medicinal product other than the originator medicine (without the need for it to be generic or biosimilar)[113], so that a set can exist only for "branded" medicines[114].

The **reference price** is the maximum amount at which the dosage forms of medicinal products included in each of the sets are funded, provided that they are prescribed and dispensed at public expense[115]. The reference price of each set

[108] Until the entry into force of Law 11/2020, of December 30, on General State Budgets for the year 2021, the Consolidated Text contemplated that the reference sets included all dosage forms of medicines funded with the same active ingredient and an identical administration route.

[109] Orphan drugs (drugs for rare diseases) included in the SNHS service portfolio are excluded from the reference price system, provided that there is no therapeutic alternative in the SNHS pharmaceutical service or that, if there is, the new drug provides significant clinical benefit. This differentiation of orphan drugs when setting their price is intended to provide an incentive to title holders of those medicines, to encourage research with drugs already on the market and to guarantee their availability (Resolution of 2 June 2020, of the Directorate General for the Common Portfolio of Services of the National Health System and Pharmacy, which publishes the Agreement of the Council of Ministers of 3 March, 2020, establishing the economic regime for orphan drugs, under the provisions of Article 3. 3 of the rewritten text of the Law on guarantees and rational use of medicines and healthcare products, approved by Royal Legislative Decree 1/2015, of 24 July).

[110] The ATC classification is a European five-level coding system for pharmaceutical substances and medicinal products according to the effector system or organ as well as pharmacological effect, therapeutic indications, and the drug's chemical structure. The five levels are as follows: first level (anatomical): organ or system on which the drug acts (there are 14 groups in total); second level: therapeutic subgroup; third level: therapeutic or pharmacological subgroup; fourth level: therapeutic, pharmacological or chemical subgroup; fifth level: name of the active substance or medicinal association. Each drug has an ATC code, which is specified on its data sheet. Saladrigas, M.V. (2004). *The ATC classification system for pharmaceutical substances for human use*. Panace, *5*(15), 59.

[111] Article 98.2 of the Revised Text and Articles 3.1 and 3.2 of Royal Decree 177/2014.

[112] For the purposes of set formation, the drug dosage forms integrated into the reference sets must be effectively commercialised (Article 3.4 of Royal Decree 177/2014). This helps guarantee the supply of lower-priced medicines, facilitates the proper management of pharmaceutical services, and avoids healthcare disruption.

[113] Article 3.2 of Royal Decree 177/2014.

[114] Lobo (2013).

[115] Article 98.1 of the Consolidated Text and Article 2 of Royal Decree 177/2014.

is calculated as the lowest cost/treatment/day of the different dosage forms that are part of the set. The calculation takes into account the defined daily doses contained in each dosage form, so that, within each set, the reference price of each dosage form is proportional to the dose it contains[116].

There are exceptions to the general calculation system, aimed at avoiding a disproportionate effect, to ensure the quality of pharmaceutical service and to avoid negative consequences for the SNHS: (1) if the industrial reference price corresponding to a dosage form is less than 1.60 euros, this amount is set as the industrial reference price; and (2) a weighted reference price is established (taking into account the packages invoiced) for medicinal product dosage forms for which the corresponding reference price does not guarantee their economic viability, provided that they have special dosages, are useful in serious diseases or where the prices have been revised due to lack of profitability over the preceding two years.

Each year, the Ministry of Health, following a report from the Government's Delegated Commission for Economic Affairs, updates the reference price system by establishing new sets and the reference prices of the dosage forms included in them, as well as revising the prices of the dosage forms included in existing sets and removing sets if they no longer meet the necessary requirements[117]. The reference price system is applied to new dosage forms of medicines included in the SNHS pharmaceutical service, as of the annual update, provided that their characteristics allow them to be included in one of the existing sets (due to there being a set containing medicines with the same ATC5 and administration route)[118].

Thus, once the reference set is created (with the entry of generics and biosimilars onto the market), the original reference medicines begin to compete with the generics/biosimilars within the sets, with their maximum SNHS funding prices being equalised via the reference price. The annual update of the reference prices may involve a mandatory price reduction, although the reference price may also be revised upwards[119].

In addition, there is a **system of homogeneous groupings**, which is complementary to the reference price system. **Homogeneous groupings** are narrower than the reference groups, as each homogeneous group comprises the dosage forms of funded medicinal products with the same active substance,

[116] Articles 4.1 and 4.2 of Royal Decree 177/2014.
[117] Article 5.1 of Royal Decree 177/2014.
[118] Article 5.2 of Royal Decree 177/2014.
[119] Article 4.4 of Royal Decree 177/2014.

strength, content, pharmaceutical form and administration route, which can be dispensed interchangeably[120].

Within each homogeneous group, a **"lower price"** is set, which corresponds to the lowest price for the group of dosage forms at the time of its formation. This may be revised downwards at the time of each update, which is every three months[121]. The quarterly update of the "lower price" does not automatically drop the RP of all the dosage forms included in the grouping, but those dosage forms that have not lowered their RP to match the "lower price" are disadvantaged by the dispensing rules presented in Box 5.

Over the course of these three months, medicine title holders can apply to the DGCYF to voluntarily lower their industrial price below the **"lower price"** to become the "lowest price" until the next quarterly update of "lower prices"[122]. The "lowest prices" are updated on a monthly basis. At the beginning of each month, the DGCYF publishes the list of price reduction requests it has accepted and gives the title holders of the remaining dosage forms in the homogeneous grouping three days to apply for a voluntary price reduction to match the "lowest price". All such voluntary price reductions that are accepted take effect the following month, so that the information on the "lower" and "lowest" pricing of the homogeneous groupings are actually updated on a monthly basis[123].

Voluntary price drops, to become the "lowest prices", are translated into "lower prices" through the quarterly update of these and, similarly, the reduction of the "lower" and "lowest" prices is eventually passed on to the reference sets through the annual revision of those sets and their respective reference prices.

This system of homogeneous groupings introduces some short-term competitive pressure by allowing for frequent "lower" and "lowest" price updates and due to the implications for the regulations on the prescribing and dispensing of medicines, which are set out in Box 5.

[120] Article 8.1 of Royal Decree 177/2014.

[121] Articles 8.4 and 8.6 of Royal Decree 177/2014.

[122] In terms of lower prices, the request for a price reduction is only taken into account if it represents a reduction of at least 10% of the LSP. The wording of Article 9 of Royal Decree 177/2014 leaves open the possibility that requests for voluntary price reductions may be communicated with a reduction of less than 10% in order to determine the lowest price (Faus, 2014).

[123] Article 9 of Royal Decree 177/2014.

Box 5

THE PRESCRIBING AND DISPENSING OF MEDICATION

The prescription of medicines in the SNHS should be carried out in the most appropriate way for patients, while protecting the sustainability of the SNHS itself. In general, medicines are prescribed according to active ingredient, although for chronic processes where the prescription corresponds to ongoing treatment, this can be done by trade name. Similarly, prescription by trade name is possible if the greatest efficiency for the system is respected and where the medicine under consideration cannot be substituted[124].

The pharmacist must dispense the medicine prescribed by the doctor, but in case of shortages or urgent dispensing needs, the pharmacist may substitute a lower-priced medicine[125]. When the prescription refers to the active ingredient, the pharmacist must dispense the "lowest priced" medicine from the homogeneous grouping[126]. When prescribing by trade name, if the price of the prescribed medicine is above that of the "lower price" in its homogeneous grouping, the pharmacist must substitute the prescribed medicine for the "lowest price" medicine in the grouping[127].

Between 2012 and 2015, the regulation stipulated that the pharmacist should dispense the "lowest price" medicine if the prescription was made by active substance, or by trade name if the price of the prescribed medicine was above the "lower price" (in the same way as nowadays), but added that, when the prices were the same, the pharmacist should dispense the generic medicine[128].

Thus, the homogeneous grouping system creates a certain incentive for voluntary price reductions to make the medicine the lowest-priced, in order to temporarily

[124] Article 87 of the Consolidated Text. Biological medicines are among the medicines that cannot be substituted (Order SCO/2874/2007, of 28 September, which establishes the medicines that constitute an exception to the possible substitution by the pharmacist in accordance with Article 86.4 of Law 29/2006, of 26 July, on guarantees and the rational use of medicines and healthcare products).

[125] The exception is in the case of medicinal products determined by the Ministry of Health, due to their bioavailability characteristics and narrow therapeutic range (Articles 89.1, 89.2 and 89.4 of the Consolidated Text).

[126] Article 87.4 of the Consolidated Text.

[127] Except in the case of biosimilars, which are governed by specific regulations on substitution and interchangeability (Article 89.5 of the Consolidated Text). In Spain, pharmacists in pharmacies are not authorised to substitute a medicine of biological origin for another medicine, irrespective of whether the biosimilar or the originator medicine has been prescribed (Order SCO/2874/2007).

[128] This positive discrimination against generic medicines was introduced by Article 4 of Royal Decree-Law 16/2012 and was eliminated by the twentieth final provision of Law 48/2015, of October 29, of the General State Budgets for the year 2016.

gain market share. Due to the prescribing and dispensing rules, this will remain the case until another medicine included in the homogeneous grouping aligns with the price reduction or reduces it even further.

- Unregulated prices

Industrial prices are unregulated for medicines that are not funded by public funds as long as the mechanisms for setting the retail prices are not regulated, unless otherwise decided by the Government's Delegated Commission for Economic Affairs, for reasons of general interest[129]. The Government may regulate the price-setting mechanism for over-the-counter medicines, as well as for other products necessary to protect the health of the population that are dispensed in Spain, following an objective and transparent system. In addition, when there is an exceptional health situation, in order to protect public health, the CIPM may fix the maximum retail price of these medicinal products for the duration of the exceptional situation[130].

At present, medicines that are not funded by the SNHS and do not benefit, either voluntarily or compulsorily, from the notified price system, are governed by a system of unregulated industrial prices, which can be set by the pharmaceutical companies that own them.

- Notified prices

This approach covers a number of different medicines.

On the one hand, manufacturers of medicines that have been excluded from the SNHS pharmaceutical service (defunded) are obliged to notify the DGCYF of the prices at which they are going to be marketed, as well as their price variations[131]. This body then decides whether or not it agrees with the proposed prices, and in the event of disagreement, the proposed prices are referred to the CIPM, while the maximum industrial price (the price in force before the intention to change the price was communicated) is maintained. Pricing decisions must be based on reasons of public health protection, equal access to medicines or actual or potential harm to the interests of disadvantaged groups[132]. Since 2019, the DGCYF has issued decisions denying price increases for medicines defunded in 2012 and 2013, on grounds that the requested increases exceed the annual

[129] Third transitory provision of Royal Decree-Law 16/2012.
[130] Article 94.3 of the Consolidated Text, modified by Royal Decree-Law 7/2020, of March 12, which adopts urgent measures to respond to the economic impact of COVID-19.
[131] Article 93.3 of the Consolidated Text.
[132] Articles 93.4 and 93.5 of the Consolidated Text.

Consumer Price Index[133]. These decisions have been motivated by the need to guarantee equal access to medicines for patients and to avoid actual or potential harm to the interests of disadvantaged groups that could result from the proposed increases[134].

On the other hand, in the case of medicines dispensed in Spain that are not subject to prescription, or subject to prescription and not funded by the SNHS, the holders of the marketing authorisations may voluntarily market the medicines at notified prices; this is understood as the communication of the price to the Ministry of Health, which may object to it on public interest grounds[135].

Finally, medicines funded by the SNHS, when dispensed outside the SNHS, may have a dual price: one price when funded by the SNHS and another price, the notified price, when dispensed privately (which will generally be more expensive than the former)[136].

- Selected prices

The selected price system is based on a Ministry of Health proposal to the suppliers of certain medicines of the maximum price for their funding[137]. Drug suppliers may or may not express their intention to participate, without proposing an alternative lower price[138]. Based on the submissions from the suppliers, the Ministry will prepare a formal proposal containing the maximum price selected, which must be approved by the CIPM[139]. Medicines that exceed the established maximum price, and are therefore not selected, are excluded from SNHS funding for the two-year period for which the selected price is valid[140].

This system can be applied to funded medicines subject to reference prices (taking into account the consumption of the reference set, the budgetary impact, the existence of at least three medicines in the set, and a zero risk of stockouts)

[133] Through the Resolutions of August 2, 2012, and February 18, 2013, of the General Directorate of the Basic Portfolio of SNHS and Pharmacy Services, more than 400 drug dosage forms were excluded from public funding, predominantly because they were indicated for the treatment of minor symptoms.
[134] According to the Resolutions of the Directorate General for the Basic Portfolio of SNHS and Pharmacy Services on price variations of article 93.4 TR, on procedures for price variations of medicines in which the non-acceptance of the variation communicated has been agreed.
[135] Articles 94.4 and 94.5 of the Consolidated Text.
[136] Article 94.4 of the Consolidated Text.
[137] Article 99 of the Consolidated Text.
[138] Article 99.6 of the Consolidated Text.
[139] Articles 99.2 and 99.3 of the Consolidated Text.
[140] Articles 99.8, 99.9 and 99.11 of the Consolidated Text.

and to medicines not funded by the SNHS but which may be considered to be of public health interest[141].

As far as the CNMC is aware, this system has not yet been effectively applied in any case. For this reason, the specific details of how this system would be implemented are not known, although it is understood that it would be a kind of public tender for medicines that are subject to competition (not applying to medicines protected by patent or exclusivity rights), which could be both previously funded and unfunded, where the Ministry would propose a funding price for a group of medicines (for example, they could be those belonging to each reference set or homogeneous grouping) and only those medicines whose title holders are willing to provide them at that price would be selected and publicly funded, with the remaining dosage forms belonging to that group being excluded from funding for two years[142].

2.2.3. Quantitative characterisation of the medicines included in the SNHS pharmaceutical service

Evolution of public spending on the SNHS pharmaceutical service in terms of medicines dispensed in pharmacies

In Spain, public expenditure on medicines reached 11,788 million euros in 2019, representing 0.95% of GDP, of which almost all (11,242 million) corresponds to expenditure on prescriptions dispensed in pharmacies[143].

Since 2010, in order to balance public finances during the economic crisis, the Spanish authorities have been containing public pharmaceutical spending through regulatory changes and promoting the rational use of medicines[144]. As a

[141] Articles 99.1, 99.4 and 99.14 of the Consolidated Text.

[142] The selected price system could, in some respects, resemble the successive calls for tender launched by the Andalusian Health Service between 2012 and 2019, popularly known as "auctions" and formally known as "selection of medicines to be dispensed by Andalusian pharmacies, when in the official prescriptions and dispensing orders of the National Health System, medicines are prescribed or indicated by active ingredient", in accordance with Article 60 bis of the Andalusian Pharmacy Act 22/2007, of 18 December 2007.

[143] Data provided by the Ministry of Health. It should also be noted that pharmaceutical spending in pharmacies accounts for 15% of total public spending on healthcare. In the EU, this figure ranges from 7% (in Denmark and Norway) to 41% in Bulgaria (OECD, 2019).

[144] Among the regulatory reforms to contain pharmaceutical spending, the following stand out:

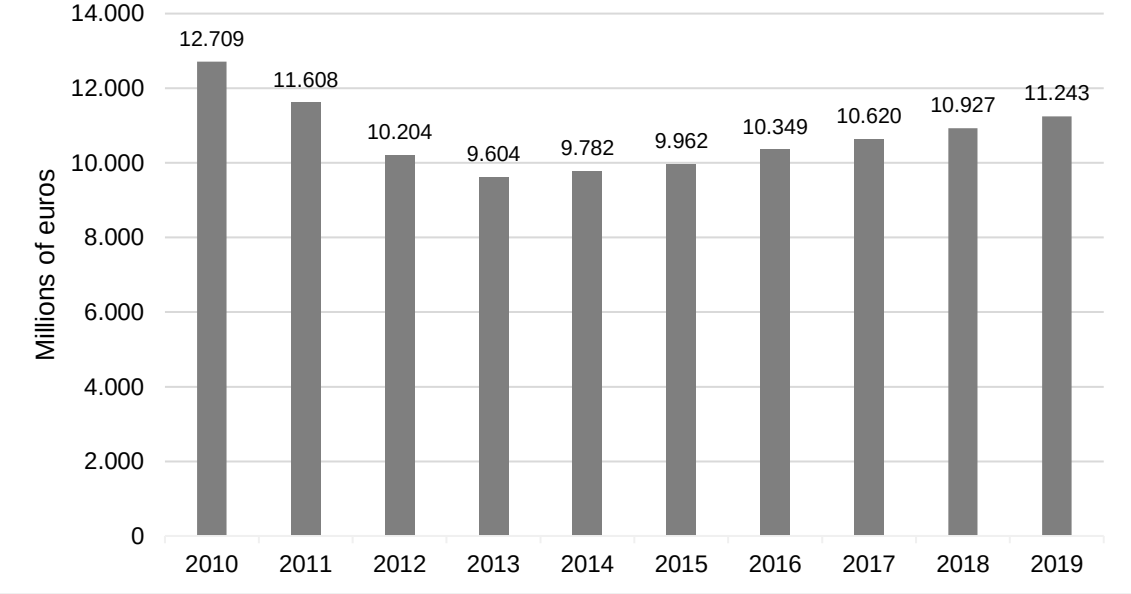
- Royal Decree-Law 4/2010, which lowered the price of generic drugs and modified the reference price system (the reference price was no longer calculated using the weighted average of the three lowest-priced drugs and was established at the lower price level).
- Royal Decree-Law 8/2010, which introduced a procedure for the centralised purchase of medicines (voluntary adherence by the Autonomous Communities) and established

result, between 2010 and 2013, public pharmaceutical spending on medicines dispensed in pharmacies (prescription medicines) fell by almost 25%. Since then, it has grown by an average of 2.6% per year, although in 2019 it was still below the 2011 level (Figure 1).

deductions from the retail price of medicines dispensed to be invoiced by pharmacies at the expense of the SNHS: 7.5% for non-generic drugs or reference prices and 4% for orphan drugs.

- Royal Decree-Law 9/2011, which established a 15% deduction for non-generic or biosimilar originator medicines that have been funded for more than 10 years, imposed the obligation to prescribe by active ingredient (this was made more flexible in Royal Decree-Law 16/2012), created the homogeneous groupings regime, obliged brands to match the price of generics in reference groups from the outset, eliminated the priority to dispense generic medicines at the same price provided for in the 2006 Medicines Act (this was reinstated in 2012 until 2015), and made the reference price system applicable to biological and biosimilar medicines.
- The exclusion of more than 400 drug dosage forms from the SNHS pharmaceutical service by the Resolutions of 2 August, 2012, and 18 February, 2013, of the DGCYF.
- Royal Decree-Law 16/2012, which established a co-payment system based on income level and socio-occupational status, reorganised the different price regimes and created new ones (notified and selected prices), introduced the possibility that funded medicines could be sold on the market in private transactions at a higher price than that established for the public system, and restored the priority to dispense generic medicines, at equal prices (this positive discrimination was eliminated in Law 48/2015).
- Royal Decree 177/2014, which regulated the system for reference prices and homogeneous groupings. This was the first time that the system of homogeneous groupings was developed and allowed the creation of reference groups without the need for a generic medicine to exist as an integral part of the group, as long as it was ten years after the initial authorisation and it contained a funded medicine other than the originator medicine and its licences
- The autonomous communities also implemented strategies for more efficiently managing medicines and programs to promote the rational use of medicines.

Figure 1. Pharmaceutical expenditure through SNHS prescriptions dispensed in pharmacies, in millions of euros (Autonomous Communities, INGESA and mutual societies), 2010-2019.

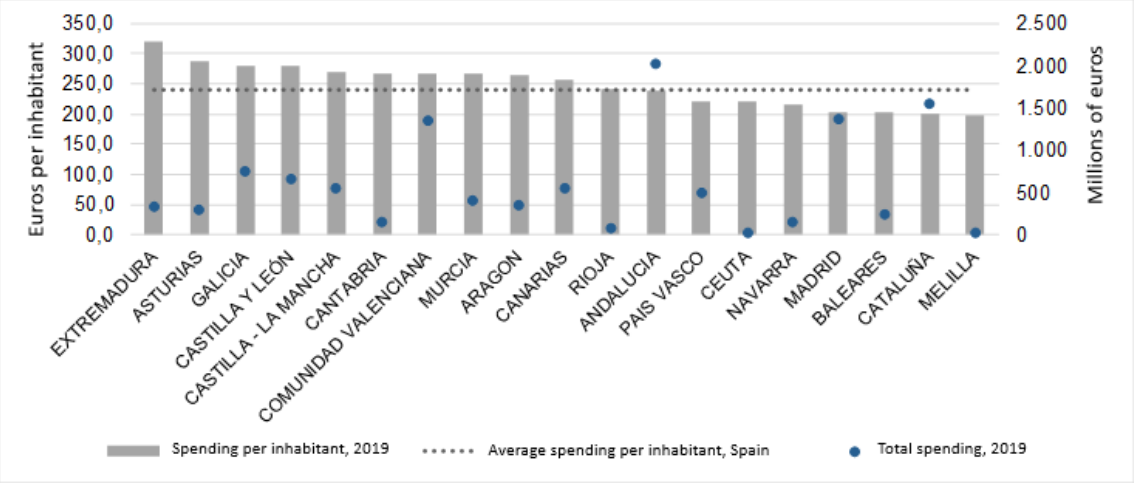


Note: pharmaceutical expenditure is the pharmaceutical amount invoiced at RP VAT minus the inputs from users, pharmacies and the deductions of Royal Decree-Law 8/2010.
Source: 2018 SNHS Annual Report (Ministry of Health) and data provided by the Ministry of Health.

According to 2019 data, by Autonomous Community, public pharmaceutical spending on prescriptions dispensed in pharmacies is very uneven, due to differences in the resident population between Autonomous Communities, but there are also differences in spending per inhabitant (Figure 2)[145]. The leading region in terms of total expenditure is Andalusia, followed by Catalonia, Valencia and Madrid. These four regions account for 59% of the Spanish population and around 55% of national pharmaceutical spending[146].

[145] 2018 SNHS Annual Report and data provided by the Ministry of Health.
[146] INE (registered population as of January 1, 2020).

Figure 2. Pharmaceutical spending on SNHS prescriptions dispensed in pharmacies, per inhabitant and total spending, by Autonomous Community (2019).



Source: developed in-house from data provided by the Ministry of Health and Spanish National Statistics Institute, INE (for the data used relating to the population registered as of January 1, 2020).

The public pharmaceutical expenditure generated by SNHS prescriptions *per capita* in 2019 ranges from 319 euros per year in Extremadura to 198 in Melilla, with the Spanish average standing at 239 euros. Except in the case of the Valencian Community, the larger communities are below average in *per capita* spending (Figure 2[147]). The variation in spending per inhabitant is partly explained by interrelated issues, such as the age structure of the population, the different spending profile per prescription between the regions, and the number of prescriptions per inhabitant (Figure 3).

Of note is the high average expenditure per prescription in Melilla (12.82 euros) and, in contrast, the lower costs in Andalusia, the Community of Madrid and Catalonia (10.55, 10.64 and 10.78 euros, respectively). In Andalusia and Catalonia, distinct pharmaceutical management policies have been implemented, particularly in terms of the search for efficiency; these are reflected in the lower cost per prescription: selection of cost-efficient drugs in Andalusia[148] and

[147] With more than 3 million inhabitants.

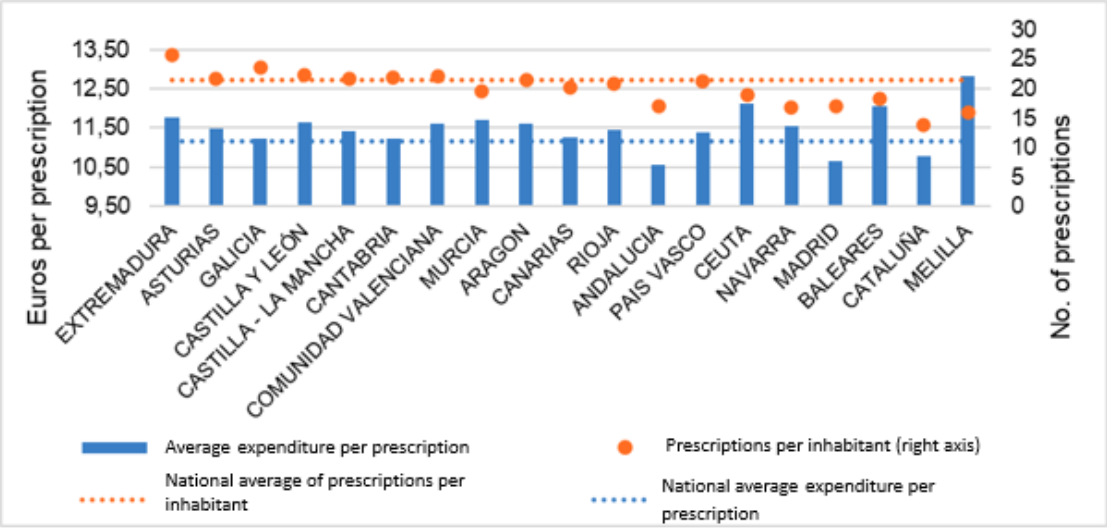
[148] Since 2012, the Andalusian Health Service (AHS) has launched successive calls for the selection of medicines (popularly known as "auctions", although they do not constitute a public procurement procedure) and formally called "selection of medicines to be dispensed by Andalusian pharmacies, when in the official prescriptions and dispensing orders of the National Health System, medicines are prescribed or indicated by active ingredient", in accordance with Article 60 bis of the Andalusian Pharmacy Act 22/2007, of 18 December 2007. These ceased to be renewed by the Andalusian government from September 2019, with

pharmaco-therapeutic harmonisation programmes in Catalonia[149], rational drug use programmes, and the promotion of generics (prescription by active ingredient in 100% of prescriptions in Andalusia and indirect promotion based on policies prioritising certain drugs and rational use in Catalonia, both of which have the highest share of generic consumption in Spain), among other measures.

the model being phased out at the end of 2020. Through these procedures, the interested pharmaceutical laboratories owning the groups of medicines included in the call were invited to present "economic improvements" (price reductions compared to the maximum authorised by the SNHS). The drug (or, exceptionally, drugs) that entailed the lowest final cost for the AHS was selected from among those proposed, for a two-year period. When the prescription was based on active ingredient, pharmacies were obliged to dispense the selected medicine, except in the event of shortages or urgent dispensing needs, in which case it could be substituted by a medicine with a price equal to or lower than the corresponding "lower price". It should be noted that under this system the price of the medicine did not vary, and each month the selected pharmaceutical companies were responsible for paying the amount of the improvement offered (Report 2/2014 in the framework of the information on barriers or obstacles to market unity under Article 28 LGUM of the Andalusian Agency for Competition Advocacy).

[149]The Pharmacotherapeutic Harmonisation Program of the Catalan Health Service (CatSalut) comprises two areas: in the first, the advisory councils technically assess the medicinal products; and, in the second, the Pharmacotherapeutic Commission evaluates them and issues an agreement on the criteria for the use, access and supply of harmonised medicinal products. This programme is intended to ensure equity in terms of access to hospital and prescription medicines, and to improve efficiency, efficacy and therapeutic usefulness, in accordance with the principles of rational use, taking into account resource availability and optimisation. CatSalut (2020), taken from https://catsalut.gencat.cat/ca/proveidors-professionals/farmacia-medicaments/programa-harmonitzacio-farmacoterapeutica/#

Figure 3. Average expenditure per SNHS prescription and number of prescriptions per inhabitant, dispensed in pharmacies by Autonomous Community (2019).



Source: developed in-house from data provided by the Ministry of Health.

Pharmaceutical spending can be broken down into the volume of funded medicines dispensed and the price of each of these. Next, the prices of medicines funded in Spain and the volume of medicines dispensed at the expense of the SNHS are analysed.

Evolution of the LSP of medicines funded by the SNHS

The **average laboratory selling price (LSP)** of the dosage forms of medicines funded by the SNHS on 31 December, 2019, was 137.50 euros (see Figure 4, Panel 4.1.[150]): 20.10 euros on average for prescription medicines dispensed in pharmacies (corresponding to an RP of 29.20 euros) and 450.30 euros for hospital medicines[151].

If we distinguish between non-generic and generic medicines included in the SNHS service as of December 2019, the price of non-generics (LSP) was, on average, almost six times higher than generics (272.50 euros versus 47.10 euros, respectively[152]). Moreover, the price of non-generics had increased by 47%

[150] Data provided by the Ministry of Health.

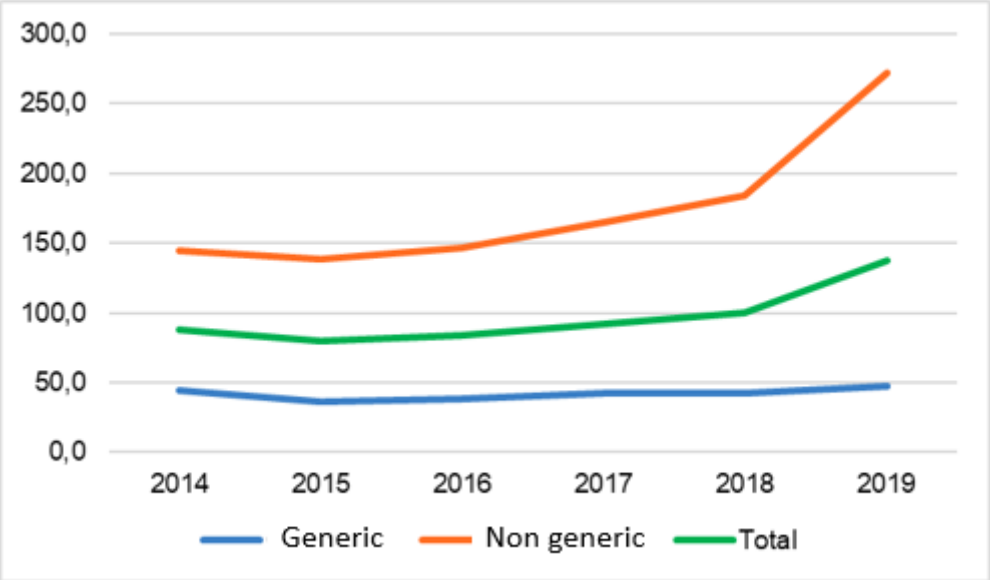
[151] Clinical packages and medicinal products for hospital use and dispensing. Although this study does not focus on hospital medicines, it is interesting to compare price data for medicines dispensed through pharmacies and through the hospital channel in order to contextualise the characteristics of medicines dispensed through each.

[152] This includes both originators within the reference price system (originators with competition within the sets and whose price will be, at most, the reference price) and originators outside

compared to 2018, while overall generics increased their price by 1%[153]. The gap between the two categories is even wider if we focus only on the new medicines included in the funding each year (see Figure 4, panel 4.2.), and especially on those that were introduced in 2019, where non-generic medicines entered with an average price of 1,995 euros, while the average price of generics was 138.20 euros. The increased prices of new non-generic dosage forms are due to the entry of next-generation medicines, which are more expensive. It should also be noted that the generics entering the public funding system since 2014 have been doing so at increasingly higher prices (those entering in 2017 were 54% more expensive than those entering in 2014, while in a single year, from 2018 to 2019, they went up by 47%).

Figure 4. Average LSP of all medicine dosage forms funded by the SNHS at the end of each year (solid lines) and those newly included in the SNHS provision each year (dashed lines), distinguishing between generics and non-generics.

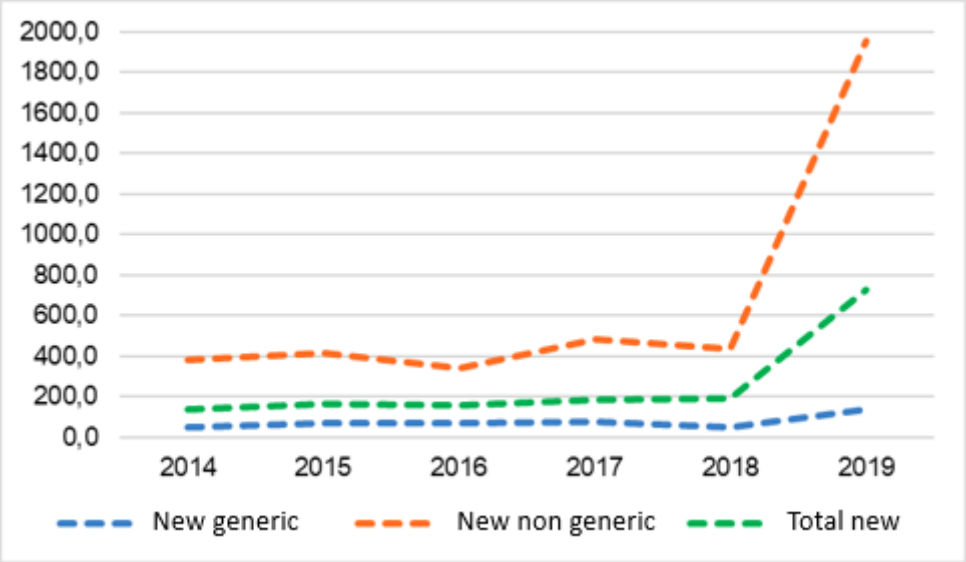
Panel 4.1 Average LSP of all funded medicines at the end of the year (total, generic and non-generic)



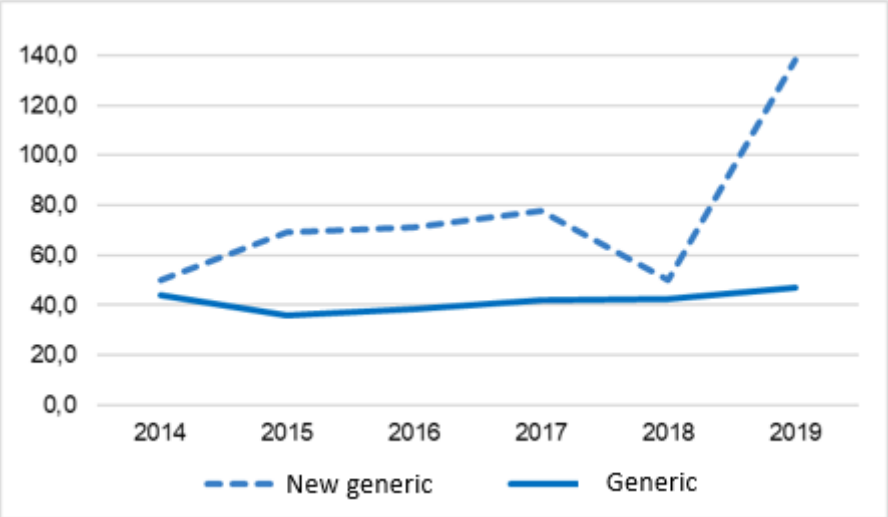
the reference price system (originators and innovators not included in reference sets). Medications dispensed through any channel are included, without distinguishing between those from pharmacies and hospitals.

[153]The time period covered by the charts in this section differs, since data availability is not the same for all variables. In this case, reference is made to 2014 as it is the first year for which information is available.

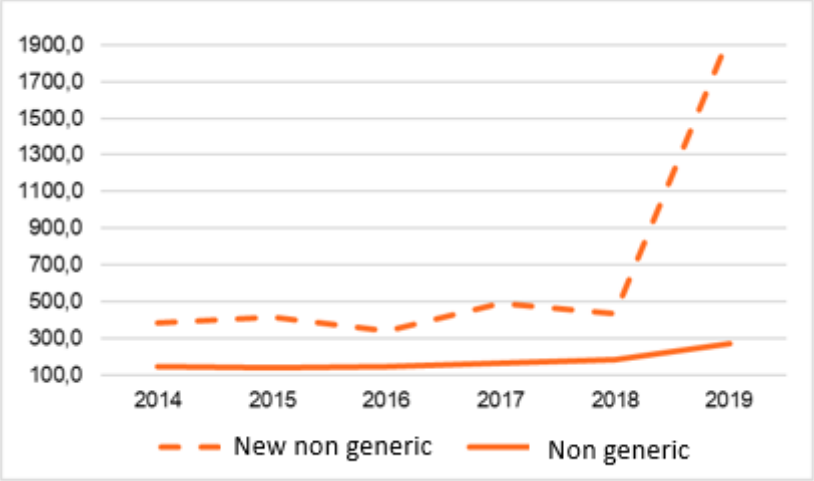
Panel 4.2 Average LSP of new medicines funded each year (total, generic and non-generic)



Panel 4.3 LSP of funded generic drugs (total and new)



Panel 4.4 LSP of funded non-generic drugs (total and new)



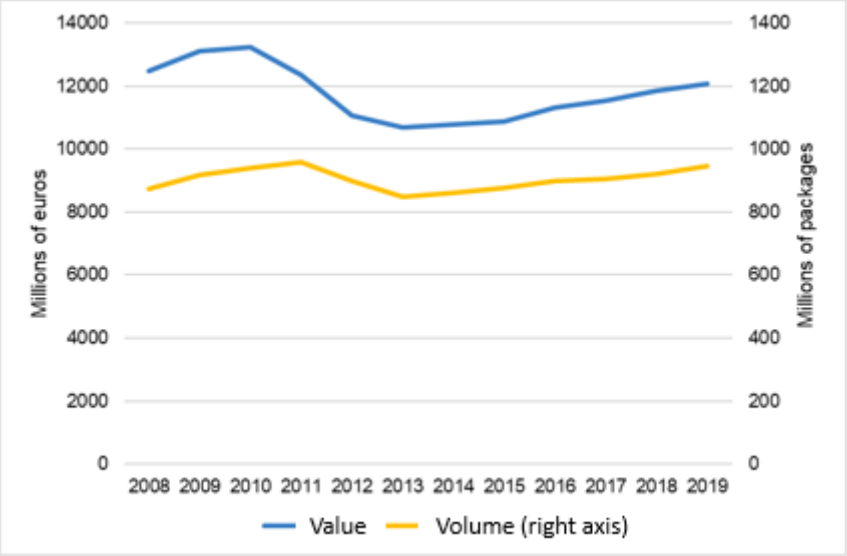
Source: developed in-house from the Annual Reports of the SNHS 2015-2018 (Ministry of Health) and data provided by the Ministry of Health.
Note: Includes medicines dispensed through any channel, without distinguishing between those dispensed in pharmacies and those dispensed in hospitals.

Sales trends of medicines funded by the SNHS and dispensed in pharmacies. Market shares of originator and generic medicines.

With regard to **sales of medicines funded by the SNHS and dispensed in pharmacies**, Figure 5 shows their trends in terms of volume (millions of packages dispensed) and value (at RP VAT, in millions of euros[154]). Between 2008 and 2010, sales of these medicines grew steadily, but thereafter the sales dropped off, both in value (they fell by 19% in value between 2010 and 2013) and volume (this fall began in 2011 and was more moderate, limited to 11% in volume). From 2013 onwards they began to climb again, but in no case did they return to their peak values.

[154] This figure for the sales of medicines funded by the SNHS and dispensed by pharmacies (Figure 5) does not coincide with public expenditure on this type of medicine, represented in the Figure 1, because pharmaceutical expenditure refers to the pharmaceutical amount invoiced at RP VAT minus the inputs from users, pharmacies and the deductions of Royal Decree-Law 8/2010, while sales correspond to the amount invoiced at RP VAT.

Figure 5. Sales of funded medicines dispensed in pharmacies, in volume (millions of packages dispensed) and value (RP VAT, in millions of euros).



Source: developed in-house based on information provided by the Ministry of Health in response to a request for information made by the CNMC.

The **market shares of originator and generic medicines funded by the SNHS** and dispensed in pharmacies underwent significant changes over the period 2008-2019[155]. Information on the trends of biosimilar medicines is not included due to their low share of total sales of funded prescription medicines (in 2019, they accounted for just 0.08% in volume and 0.4% in value)[156]. This is because, with some exceptions, they are usually dispensed through hospitals. In any case, a text at the end of this section details their specific situation.

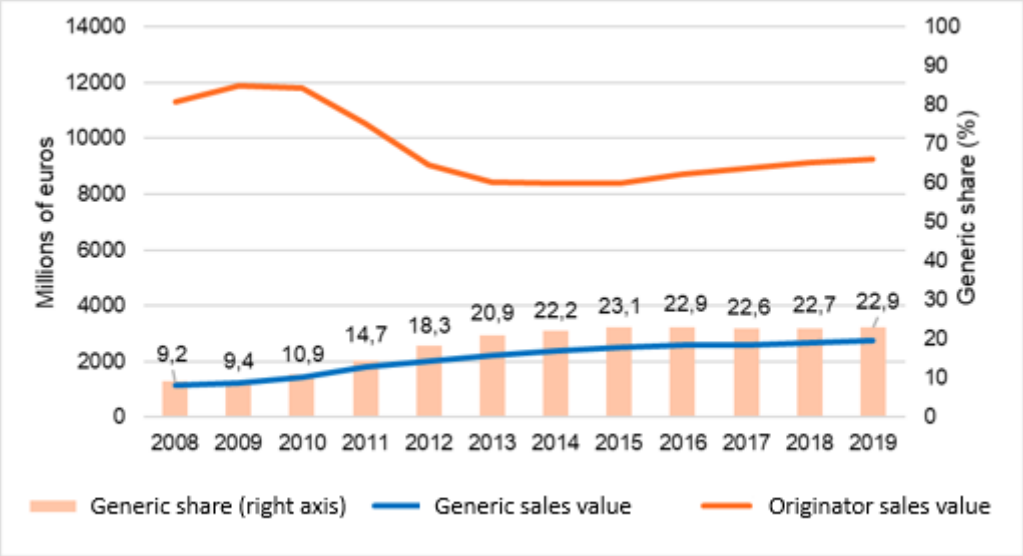
As Figure 6 shows, in 2008, in terms of value, originator medicines accounted for 91% of all medicines funded by the SNHS and distributed through pharmacies (at RP VAT, in millions of euros), a share that declined thereafter. The drop was very noticeable up to 2013 (due to the intense losses in sales of originator products and the growth of generics), but then stabilised and grew slightly, to around 77% of the market share. On the other hand, generics had a 9% share in 2008, but grew rapidly during the economic crisis, gaining market share to the detriment of originator drugs and doubling their turnover in the period analysed. However, from 2013 onwards, their growth slowed down, reaching a peak share

[155] From chemical or biological synthesis.

[156] Information provided by the Ministry of Health in response to a request for information made by the CNMC.

of 23% in 2015, before decreasing slightly until 2017. They have never fully regained the levels reached in 2015.

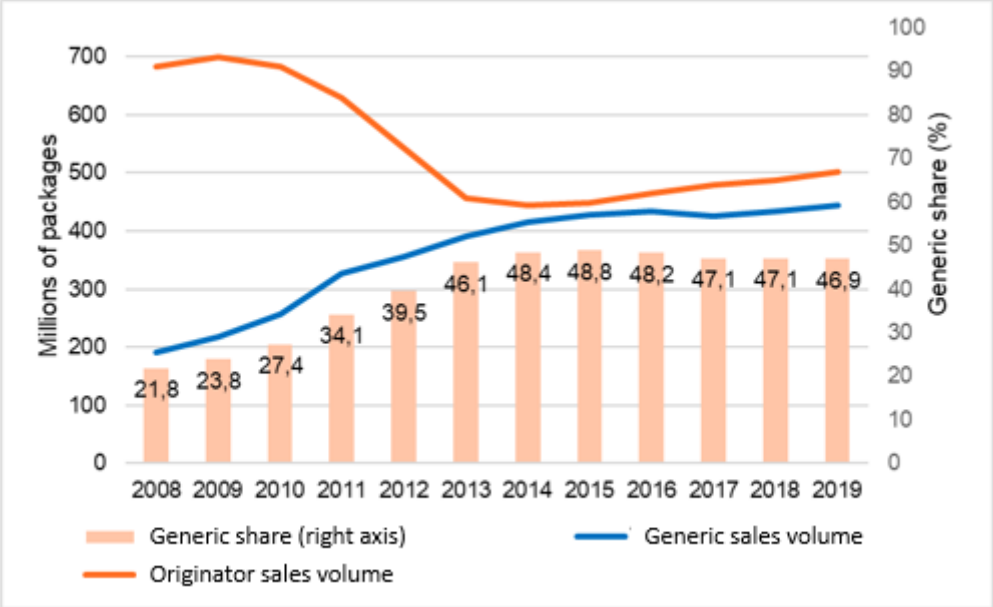
Figure 6. Sales value (RP VAT, in millions of euros) of originator and generic medicines and market share of generics out of the total of funded medicines dispensed in pharmacies.



Source: developed in-house based on information provided by the Ministry of Health in response to a request for information made by the CNMC.

In terms of **volume** in 2008 (millions of packs dispensed, see Figure 7), originator medicines accounted for 78% of all medicines funded by the SNHS and distributed through pharmacies. This figure declined particularly sharply between 2010 and 2013 in favour of generic medicines (due to the fall in sales of originator medicines and the growth of generics). In 2015, originator medicines reached a low of 51%, but since then, and up to 2019, their share grew slightly to 53%. On the other hand, generics, which in 2008 accounted for 22% of the funded prescription medicines in terms of volume, showed a very positive evolution up to 2014, after which their share stagnated at around 48%, decreasing slightly to 46.9% in 2019.

Figure 7 Sales volume of originator and generic medicines out of the total of funded medicines dispensed in pharmacies (millions of packages dispensed) and the market share of generics.



Source: developed in-house based on information provided by the Ministry of Health in response to a request for information made by the CNMC.

The magnitude of the **difference between the volume of sales and value of generics and originators is quite remarkable**: in 2019, originator drugs, with a 53% share of sales in terms of volume, had a 77% share of the value; while generics, with almost 47% of the volume, had just a 23% share of the value. These discrepancies are due to the price differential between them; generally originator drugs are much more expensive (as shown in Figure 4).

The evolution of the pharmaceutical market is related to cyclical factors, such as those caused by economic crises, as well as to regulatory reforms. During the period when generics were at their peak, the patent on high-consumption medicines expired and, in addition, regulations were implemented that encouraged their market penetration, such as the generalisation of prescriptions according to active ingredient rather than brand (from 2011, although between 2011 and 2012 there were even obligatory sales), and the positive discrimination of generics in dispensing terms, at the same price as the original (between 2012 and the end of 2015)[157]. The subsequent stagnation and even reduction in generic penetration since 2015 is due, in part, to the elimination of this positive

[157] Spanish Association of Generic Medicines (AESEG).

discrimination[158]. In this regard, it is worth mentioning that, in 2019, the Pharmacy Standing Committee of the SNHS Interterritorial Council published an Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilars and generics[159]. The plan proposes measures to promote competition and encourage their use[160].

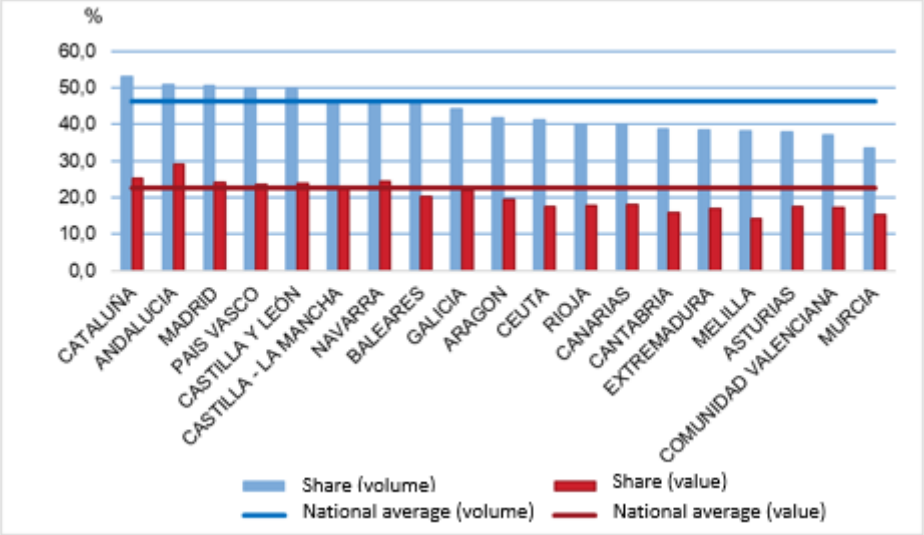
On the other hand, the share of generic sales from the total of prescription medicines dispensed in pharmacies differs greatly **according to Autonomous Community**, (Figure 8); this may be due to the different policies and strategies adopted. The Spanish average for generic consumption by volume (packs) in 2019 was around 46%, but three regions (including three of the largest) were above 50%: Catalonia, in the lead with more than 53%, followed by Andalusia (50.9%) and the Community of Madrid (50.7%). These regions, together with Navarre, also stand out in terms of value share (amount at RP VAT) above the Spanish average (which is around 22%). In last place, with a generic share of 33.5% in volume terms, is the Region of Murcia, followed by the Valencian Community (36.9%), and Asturias (37.8%); however, if value shares were considered, the Region of Murcia, Melilla and Cantabria would be in last place (below 16%).

[158] 2018 SNHS Annual Report (MSCBS). Moreover, according to Cinfa, the penetration share of generics launched between 2005 and 2010 was as high as 70% during the first year of marketing, compared to 9% between 2015 and 2016 (Diariofarma, 2017). In the same vein, IQVIA argues that, at present, new generics have less penetration than those launched a few years ago: after two years of being on the market they only reached 14%, compared to 37% in 2011, and IQVIA adds that there are no incentives for patients or authorities to use generics (Diariofarma, 2020).

[159] The Interterritorial Council of the SNHS is the permanent body for coordination, cooperation, communication and reporting information between the autonomous health services and with the State Administration (Article 69 of Law 16/2003, of 28 May, on the cohesion and quality of the Spanish National Health System).

[160] The Plan was published with the aim of opening a period of public consultation to gather input from stakeholders, through the organisations or associations that represent them. The final document is pending approval.
The CNMC published a report (INF/CNMC/059/19) on the draft of this plan. In it, the CNMC considers that the strategy proposed is positive because these medicines provide an opportunity to boost competition, and a series of recommendations to improve some aspects of the proposal were issued.

Figure 8. Share of generic medicines from the total number of funded medicines dispensed in pharmacies, by Autonomous Community and national average (2019).



Source: data provided by the Ministry of Health.

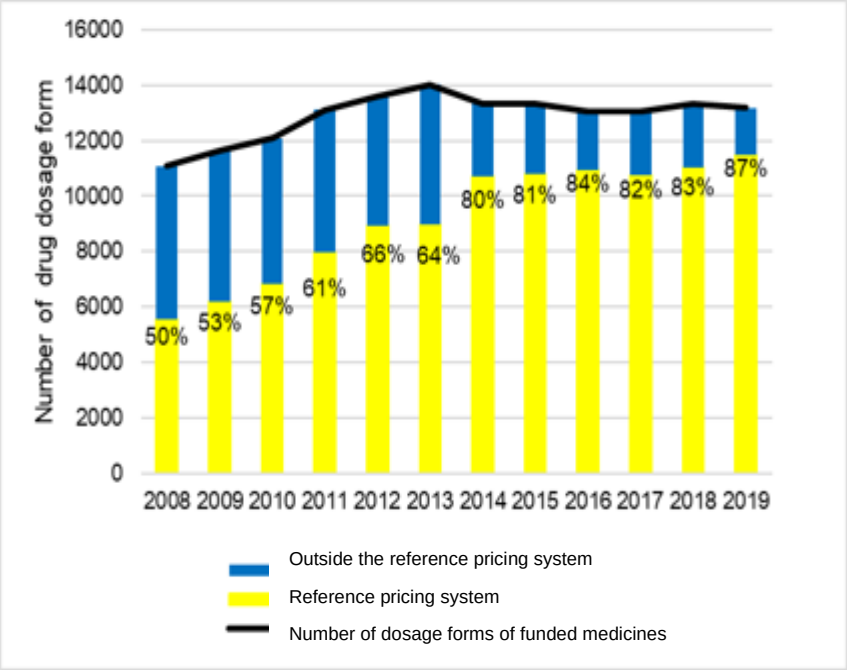
Evolution of the sales of funded medicines dispensed in pharmacies, distinguishing between those outside and inside the RPS

All medicines included in the reference pricing system (RPS) are subject to competition from other drug dosage forms (remember that each reference set is made up of originator medicines and generics or biosimilars with the same ATC5 and administration route). For this reason, it is interesting to know the share of medicines included in this price system in the total number of funded prescription medicines and, within this, what percentage are originator medicines and what share generics have.

In 2008, 50% of SNHS-funded dosage forms of medicines that could be dispensed in pharmacies were part of the RPS, while in 2019 the percentage rose to 87% (Figure 9). The creation of new reference sets due to the expiry of exclusivity rights for originator medicines and the appearance of new generic medicines have contributed to this evolution. Between 2008 and 2014, the number of medicines included in the RPS increased markedly (especially in 2014, probably due to regulatory changes), and this has remained stable since then at between 80% and 87% of the total[161].

[161] In 2014, with the approval of Royal Decree 177/2014, for the first time, the creation of sets was allowed without the need for them to contain a generic medicine, it being sufficient that ten years had passed since the authorisation of the medicine in either Spain or any other EU

Figure 9. Number of dosage forms of funded medicines available in pharmacies. Share (%) of those included in the reference pricing system.



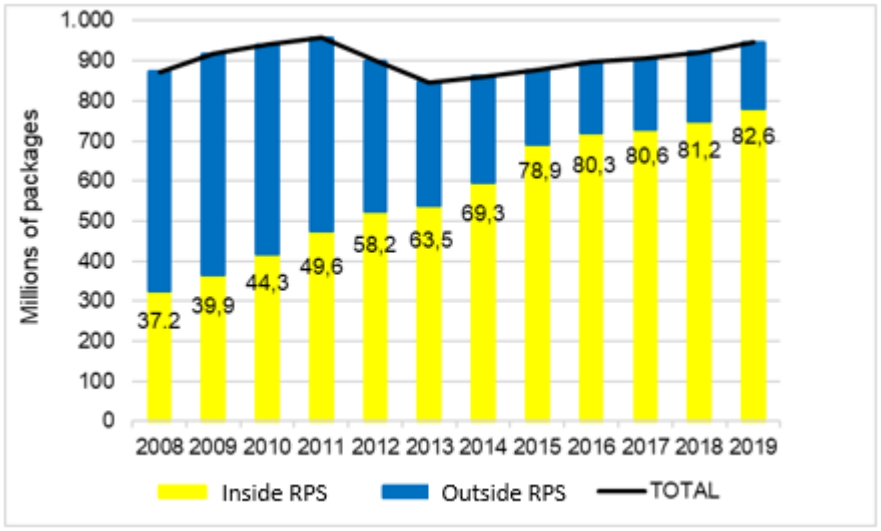
Source: developed in-house based on information provided by the Ministry of Health in response to a request for information made by the CNMC.
NOTE: the percentages shown above the yellow bars represent the dosage forms of medicines at reference prices out of the total number of funded medicines dispensed in pharmacies.

A distinction is made below between the proportion of sales of funded medicines in the RPS and those not in that system, dispensed in pharmacies, according to volume and value (Figure 10, panels 1 and 2).

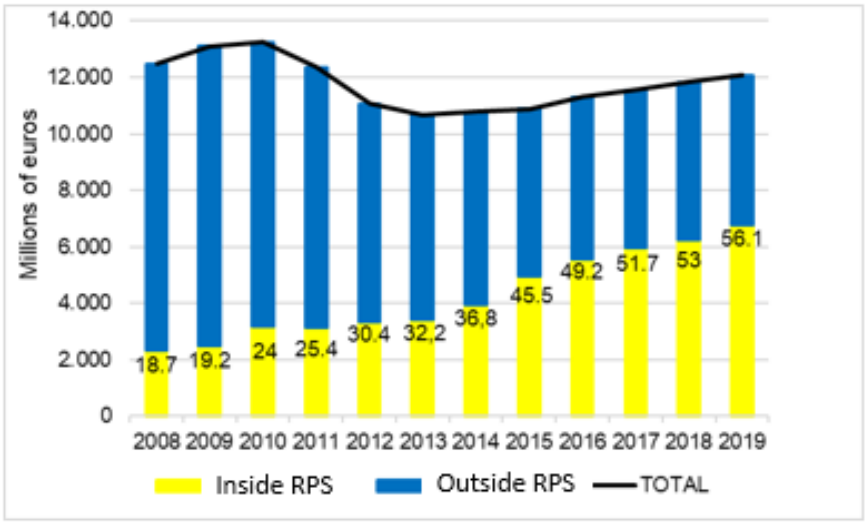
Member State, provided that there was at least one medicine funded by the SNHS other than the originator medicine and its licences (MSCBS press release of 21 March, 2014, available at https://www.mscbs.gob.es/gabinete/notasPrensa.do?id=3238).

Figure 10. Sales of funded medicines dispensed in pharmacies, distinguishing between those included in the RPS and those not included in that system (in volume and value).

Panel 10.1. Volume of sales



Panel 10.2. Value of sales (RP VAT)



Source: developed in-house based on information provided by the Ministry of Health in response to a request for information made by the CNMC.
NOTE: the percentages shown refer to the sales share of medicines within the RPS in terms of total sales of funded medicines dispensed in pharmacies

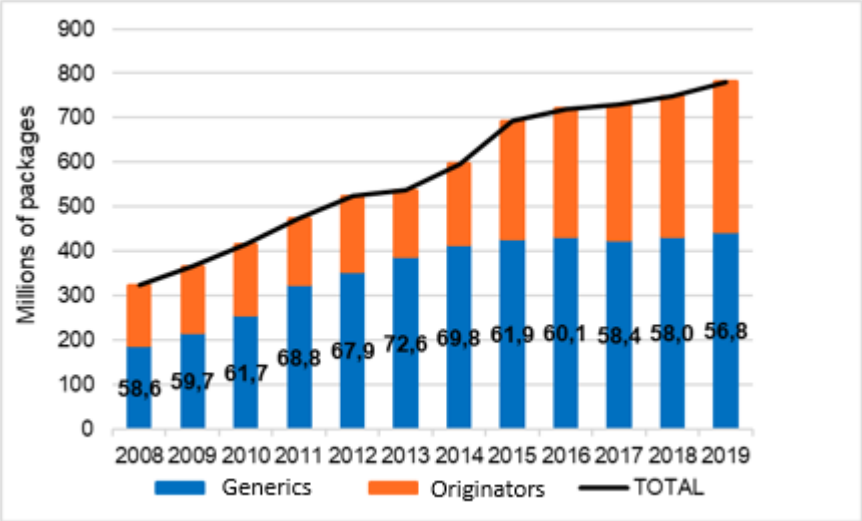
In 2008, among the funded medicines dispensed in pharmacies, those not in the RPS accounted for the vast majority of sales. However, the sales share of dosage forms included in the RPS grew significantly up to 2015, with growth stagnating thereafter. The share trend may have been influenced by a number of factors,

including public spending restraint measures, regulatory changes and the loss of patents, and subsequent entry of high-consumption medicines into the RPS. As a result of these developments, in 2019, medicines within the RPS accounted for 82% of total sales in terms of volume and 56% in value. Again, this disparity in terms of volume and value stems from the price differences of the dosage forms within the RPS (lower, as all dosage forms have to be priced at or below the reference price) and outside that system (where medicines are under patent and therefore have no competition from other similar medicines).

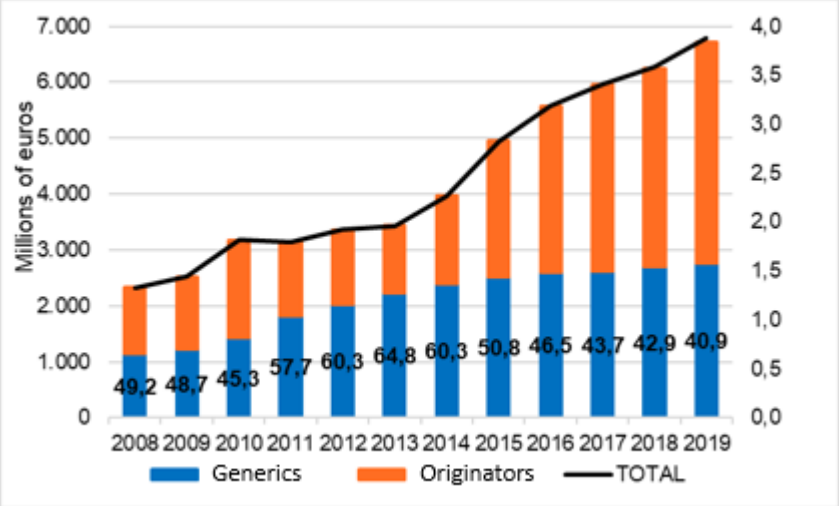
Below, within the RPS (where all dosage forms have competition from other medicines with the same ATC5 and administration route), the proportion of originator medicines and generics is differentiated (Figure 11, panels 1 and 2).

Figure 11. Sales of funded medicines, dispensed in pharmacies and included in the RPS, distinguishing between originator and generic medicines (in volume and value).

Panel 11.1. RPS sales volume



Panel 11.2. RPS sales value



Source: developed in-house based on information provided by the Ministry of Health in response to a request for information made by the CNMC.
NOTE: the percentages shown refer to the share of generics from the total of the RPS.

Sales of originator medicines within the RPS remained very stable between 2008 and 2013, both in volume and value (the size of the orange bar is similar for these years). This stagnation in sales, together with the average annual increase of 15% in generic sales during this period, led to a reduction of the share of originator drugs in the RPS (and a gain in generic share) of 14 percentage points.

However, between 2014 and 2019, sales of generics stagnated (coinciding with the elimination of positive discrimination in their dispensing), while sales of originator medicines within the RPS doubled in volume and multiplied in value[162]. Thus, their share began to rise at the expense of generics, in 2019 reaching 44% in volume and 60% in value of medicine sales in the RPS (with generics accounting for 56% and 40%, respectively[163]).

Biological and biosimilar medicines

Due to their characteristics, biological and biosimilar medicines are usually dispensed through the hospital channel. In 2019, in Spain there were 55 biosimilar dosage forms that were SNHS-funded, corresponding to 7 active ingredients, but only 3 of these were dispensed through pharmacies[164]. Of the more than 11.2 billion euros annual sales of funded medicines dispensed in pharmacies in 2019, biosimilars accounted for just 38.64 million euros (0.4% of the total in value and 0.088% in volume of packages dispensed)[165]. The low dispensing level of biosimilars in pharmacies may be influenced by several factors.

The development of biological and biotechnological medicines is relatively recent, so many of them are still patent-protected while others have recently lost their patents. This means that biosimilars have only been on the market for a short period of time (the first biosimilar dosage form to enter the SNHS service was in

[162] In the RPS, all the dosage forms of the same reference set have a price equal to or less than the reference price. The data available to the CNMC on the trends relating to volume and value of sales of originators and generics within the RPS is aggregate data and may have a composition effect. Thus, the differences in value observed between originators and generics within the RPS may be due to:
- The creation of new reference sets, priced higher than the average, in which more originators are sold than generics.
- It is possible that the originators whose sales increase more than the generics are those in higher priced reference sets.
- The reference price is a maximum price. Through the system of homogeneous groupings, medicines can lower their price to be, temporarily, the lower or lowest priced within their group. If the medicines that lower their price are, on average, generics rather than originators, the same result may be seen.

[163] By Autonomous Community, in terms of volume, Andalusia, Castile and Leon, the Basque Country, Madrid and Catalonia stand out, with more than 60% of the total number of medicines included in the RPS being sales of generics. In terms of value, only in Andalusia do generics account for more than a 50% share of the RPS (information provided by the Ministry of Health in response to a request for information from the CNMC).

[164] Information provided by the Ministry of Health in response to a request for information made by the CNMC.

[165] Information provided by the Ministry of Health in response to a request for information made by the CNMC.

2007, and the first dosage form of each of the 3 active ingredients that can be dispensed in pharmacies became SNHS-funded in 2014, 2016 and 2017, respectively[166]).

On the other hand, given the characteristics of biological medicines, the rules for substitution by the pharmacist (of the prescribed medicine for the "lowest-priced" one) differ from the general regulation[167]. In Spain, a pharmacist in a pharmacy cannot substitute a prescribed medicine of biological origin for another, regardless of whether the biosimilar or the originator medicine has been prescribed[168].

The prescription of the medicine depends on the doctor and, although biosimilars have demonstrated their biosimilarity to the original reference drug, as they are not identical (unlike chemically synthesised medicines), the practice of exchanging one biological for another once a patient has started treatment is not as widespread, and there has been a certain degree of reluctance on the part of prescribers[169]. However, some European regulatory agencies have taken a stance in favour of the interchangeability of biosimilars under the supervision of prescribers[170].

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166 2018 SNHS Annual Report, MSCBS.

167 Article 89.5 of the Consolidated Text.

168 Sole article of Order SCO/2874/2007, of 28 September, establishing the medicines that constitute an exception to the possible substitution by the pharmacist in accordance with Article 86.4 of Law 29/2006, of 26 July, on guarantees and the rational use of medicines and healthcare products. According to a note from the AEMPS, this prohibition of substitution in the case of biological medicines does not apply to hospital dispensing (the policy on the use of medicines in the hospital setting is set by interdisciplinary committees that promote the rational use of medicines in accordance with the law and good practice, including therapeutic exchange). Available at https://www.aemps.gob.es/medicamentos-de-uso-humano/medicamentos-no-substituibles/

169 Zozoya & Gonzalez (2018).

170 The Dutch, Finnish, Scottish, Irish and German authorities consider that, due to the high degree of similarity between the reference medicine and the biosimilar, there is no evidence showing that the immune system reacts differently if the reference medicine is exchanged for the biosimilar, so that any interchange between the reference medicine and the biosimilar can be considered safe. The Spanish Society of Hospital Pharmacy is aligned with this position and advocates that interchangeability should always be carried out under the supervision of the prescriber, with adequate clinical monitoring of the patient, and informing the patient. In the hospital setting this is possible, provided it is approved by the Pharmacy and Therapeutics Commissions of the hospital centres and deemed appropriate by the prescribing physician (Martínez-López de Castro et al., 2018). As of 2018, 9 of the 28 EU Member States expressly prohibited automatic substitution by pharmacists for biosimilars, including in Spain, Italy and the United Kingdom, while Estonia, Latvia and Poland allowed this practice. In countries such as France and Germany, substitution was allowed, but under certain restrictions (Zozoya & González, 2018).

Finally, the reference price system also applies to biological medicines and biosimilars, so that the maximum marketing price for both is set by the reference price and there is no positive discrimination for the biosimilar. Furthermore, the system of homogeneous groupings does not apply to biological medicines and biosimilars because they may not be exchanged at the time they are dispensed (a requirement to form part of these groupings), so that the dynamics of voluntary "lower prices" and "lowest prices" for dosage forms as a mechanism to gain market share through the dispensing rules do not apply to these medicines.

It should be noted that some Autonomous Communities have strategies to promote the use of biosimilars (such as quota targets, training for prescribers and patients, or *gain sharing contracts*, more common in the hospital setting, which allow part of the savings generated by the use of biosimilars to be reinvested into improving healthcare services[171]). In addition, as previously mentioned, in 2019 the SNHS Interterritorial Council published an Action Plan to promote the use of biosimilar and generic medicines.

The following is a description of the last links in the medicine chain: the operation and regulation of wholesale and retail medicine distribution.

2.2.4. Wholesale medicine distribution:

The main function of the medicines distribution activity is to supply medicines to pharmacies and pharmacy services, to which they must guarantee a quality service with an adequate and continuous supply of medicines, so that patient needs are covered[172].

In Spain, authorised medicines are distributed either by **distribution entities** (wholesale warehouses, contract warehouses[173] or bonded warehouses under customs control or surveillance[174]) or directly by the pharmaceutical company that holds the marketing authorisation for the medicines in question[175].

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[171] George Cohen, Carlos Crespo and Jaume Ribera (2020): *Variability in the adoption of biosimilars*.

[172] Article 67.2 of the Consolidated Text and Article 2.2 of Royal Decree 782/2013, of October 11, on the distribution of medicinal products for human use.

[173] A contract warehouse entity that acts as a third party, with which a laboratory or a wholesale warehouse signs a contract to carry out certain drug distribution activities (Article 2 of the Consolidated Text).

[174] Article 1.2 of Royal Decree 782/2013. It should be noted that warehouses for medicines under customs control or supervision are distribution warehouses located in customs zones, including duty free zones and bonded warehouses.

[175] Article 67.1 of the Consolidated Text.

Other types of entities **(brokers) are also involved in brokering medicines**[176]. Brokers solely act as negotiators for the purchase and sale of medicines, but do not buy or sell the medicines themselves and do not own the medicines or have physical contact with them. They are therefore subject to fewer regulatory requirements than distribution entities[177].

Wholesale warehouses, as well as **contract warehouses**, are subject to prior authorisation by the Autonomous Community where the warehouse is located and, in addition, they must notify the health authorities of those Autonomous Communities where they are not located but where they carry out distribution activities[178]. The maximum period for an authorisation decision for a distribution entity is ninety days from the receipt of the application by the competent health authority (positive administrative silence)[179]. In addition, distribution entities must have a valid certificate attesting compliance with good distribution practices, issued by the competent health authority[180]. In any case, distribution entities must directly notify the AEMPS of the commencement of their activities[181]. The AEMPS maintains a public catalogue of authorised entities[182]. It also sends distribution licences and certificates of good distribution practices to be entered into the European database "EudraGMDP", operated by the EMA[183].

Pharmaceutical manufacturing or importing laboratories that distribute the medicinal products included within the scope of their authorisation do not need to be authorised as distribution entities, although they must comply with the applicable sections of the European Union's good distribution practices[184].

Finally, **intermediary entities established in Spain (brokers)** require no authorisation, but these must be registered in a publicly accessible AEMPS

[176] Drug brokering refers to all activities related to the sale or purchase of medicines, except for those included in the definition of wholesale distribution, which do not include physical contact with them and which consist of negotiating independently and on behalf of another legal or natural person (Article 2 of the Consolidated Text).
[177] Article 1.2 of Royal Decree 782/2013.
[178] Except in the case of drug warehouses under customs control or surveillance, in which case the AEMPS must authorise these as drug distribution entities. Article 69 of the Consolidated Text and Article 13 of Royal Decree 782/2013.
[179] Article 15.4 of Royal Decree 782/2013.
[180] Article 20 of Royal Decree 782/2013. Good distribution practices are understood to be that part of quality assurance which ensures that the quality of medicines is maintained at all stages of the supply chain, from the manufacturer's site to the pharmacy or pharmacy service (Article 20.1 of Royal Decree 782/2013); these are contained in the Guidelines of 5 November, 2013, on good distribution practices for medicinal products for human use (contained in European Commission Communication 2013/C 343/01).
[181] Article 68 of the Consolidated Text.
[182] Article 19 of Royal Decree 782/2013.
[183] Articles 111 of Directive 2001/83/EC and Article 22.1 of Royal Decree 782/2013.
[184] Article 1.5 of Royal Decree 782/2013.

register before starting their activities. The regional health authorities have access to this register for inspection purposes, and to check compliance with the obligations imposed by the regulations and the applicable good distribution practices[185].

The **requirements** for distribution entities and pharmaceutical laboratories that directly distribute their products are the following[186]:

a) To have premises and equipment with the personnel, material and technical means to ensure the proper storage and distribution of medicinal products, with full guarantees for public health.
b) To ensure compliance with the general and specific conditions for the storage of medicinal products and, in particular, the maintenance of the cold chain throughout the distribution network by means of standardised procedures.
c) To maintain a minimum stock of medicines to ensure adequate continuity of supply.
d) To ensure delivery deadlines, minimum delivery frequency, permanent pharmaceutical technical advice and support resources for pharmacies and pharmacy services.
e) To perform on-call services and disaster prevention.
f) To have an emergency plan that guarantees the effective application of any withdrawal from the market ordered by the competent health authorities.
g) To have an alert system in place that covers all pharmacies in the region in which it operates.
h) To comply with the regulations of good distribution practices that have been promoted or authorised by the competent health authorities and collaborate with these to ensure quality pharmaceutical services.
i) To comply with other obligations imposed by law or regulations.

In addition, all authorised distribution entities must have a **pharmaceutical technical manager** for each facility (with a degree or diploma in pharmacy, and with adequate training and experience in good distribution practices) whose position is incompatible with other activities of a healthcare nature that involve direct interests in the manufacture or dispensing of medicinal products or that are detrimental to the proper performance of their duties. The technical manager is responsible for ensuring the application of and compliance with the good

[185] Article 71 of the Consolidated Text.
[186] Article 69 of the Consolidated Text.

distribution practices established in the European Union, as well as with the applicable regulations in force[187].

Furthermore, the distribution of medicines is subject to **strict regulation of remuneration margins** for the provision of the services (analogous to the retail sector, as will be seen below), which applies to all industrially manufactured medicines for human use, whether these are SNHS-funded or not, depending on their price[188].

The **wholesale distributor's regulated margin** is 7.6% of its distribution selling price or DSP (equivalent to 5.48% of the RP) for all medicines with an LSP of 91.63 euros or less (equivalent to a pre-tax RP of 137.54 euros)[189]. Above this price, wholesalers receive a fixed margin of 7.54 euros per package. In other words, the regulated distributor margin is a linear function of price, except for high-priced medicines where, above the threshold, the remuneration is fixed. The regulated distributor selling price is therefore the LSP plus this margin. As will be discussed below, in Section 3.5.1, this remuneration system based on distribution sales prices is inefficient.

[187] Articles 5, 6 and 7 of Royal Decree 782/2013.

[188] Article 1 of Royal Decree 823/2008, of May 16, which establishes the margins, deductions and discounts corresponding to the distribution and dispensing of medicines for human use.

[189] The regulation of Royal Decree 782/2013 establishes the distribution margins referenced to the sale price of the distributor without taxes in its proportional bracket (7.6% of the DSP) and in a fixed amount if the LSP of the medicine exceeds a threshold (7.54 € if the LSP exceeds 91.63 €). In order to clarify, simplify and be able to graphically represent them in this study, the wholesale (and retail, as will be seen in section 0) distribution thresholds and margins are also referenced to the RP, so that they have a common reference.2.2.5 The calculations for finding equivalence are explained in Annex I. There is one exception: the margin for the distribution of industrially manufactured medicinal products for human use packaged in clinical packages (medicinal products intended for the hospital setting) is 5% of the distributor's selling price excluding tax (Article 1 of Royal Decree 823/2008).

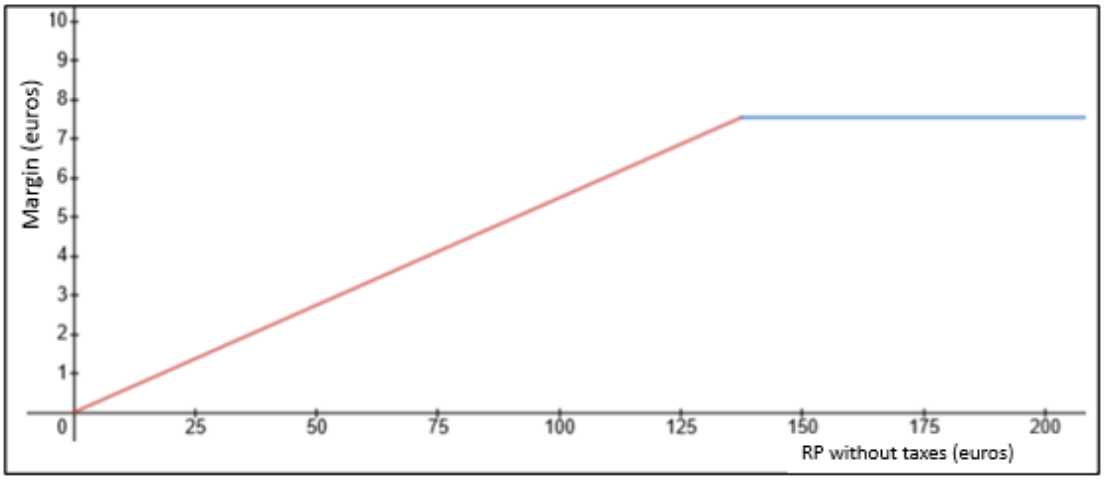
Table 1. Regulated wholesale distribution margins for medicines

Price of the medicine (in euros)	Distributor margin
LSP ≤ 91.63 (equivalent to RP ≤ 137.54)	7.6% of the DSP (equivalent to 5.48% of the RP)
LSP > 91.63 (equivalent to RP > 137.54)	7.54 euros per package

Notes: LSP is the laboratory selling price or industrial price; DSP is the dealer selling price; RP is the retail price without taxes. For more details on the calculations, see Annex I.
Source: developed in-house based on Royal Decree 823/2008.

Graphically, the remuneration of wholesale distribution in terms of RP excluding taxes for medicines can be represented as follows:

Figure 12. Regulated wholesale distribution margins for medicines



Source: developed in-house based on Royal Decree 823/2008.

According to FEDIFAR, around 50% of the operations carried out by "full range" pharmaceutical distribution companies (which work with the full range of medicines marketed in Spain) are loss-making, i.e., the margin they obtain is

lower than their distribution cost[190]. This situation aggravated due to the reduction of margins by the authorities during the last economic crisis[191]. The distribution model of these distributors consists of compensating those operations that are not profitable (distribution of very cheap products, with low turnover or in difficult-to-access locations) with the resources obtained from those that are profitable (distribution of expensive products, with high turnover, or supply to pharmacies in large cities)[192].

Although the regulation refers to fixed margins, in practice the actual wholesale distribution margins may differ, since distributors may apply **discounts** to pharmacies (offset against their own margin) and may benefit from discounts from pharmaceutical laboratories (improving margins), meaning that the wholesaler's actual margin may be higher or lower than the regulated margin. The regulation, however, does not contemplate the possibility of passing on, either totally or partially, the discounts made in the wholesale distribution segment to the final patient-consumers, although it does include certain requirements for this. Thus, the regulation only allows discounts from distributors to pharmacies for prompt payment and for volume of purchases, provided that they do not encourage the purchase of one product over its competitors and these must be reflected in the invoice. In the case of SNHS-funded medicines, the regulation establishes that these discounts may be applied provided that a monthly register of discounts is kept in the title-holder companies and distribution entities, electronically interconnected with the Ministry of Health, but the CNMC is not aware that such a register exists, and the Ministry does not appear to have this information at its disposal[193].

Given the fact that pharmacies are prohibited from offering discounts for prescription-only medicines, price reductions resulting from the competitive dynamics within the distribution chain never reach the final link[194]: they do not benefit patients as final consumers and partial funders (through co-payment), nor do they reduce the cost for the SNHS. Consequently, any discounts applied

[190] FEDIFAR is the Federation of Pharmaceutical Distributors, the employers' association that brings together the full-range of pharmaceutical distribution companies operating in Spain. It comprises nine associations, representing 19 distribution companies, which have 140 warehouses and a 97% market share in the national pharmaceutical distribution sector.

[191] Royal Decree 823/2008, of May 16, which establishes the margins, deductions and discounts corresponding to the distribution and dispensing of medicinal products for human use.

[192] FEDIFAR (2020): http://fedifar.net/what-we-do/solidarity-model-distribution/

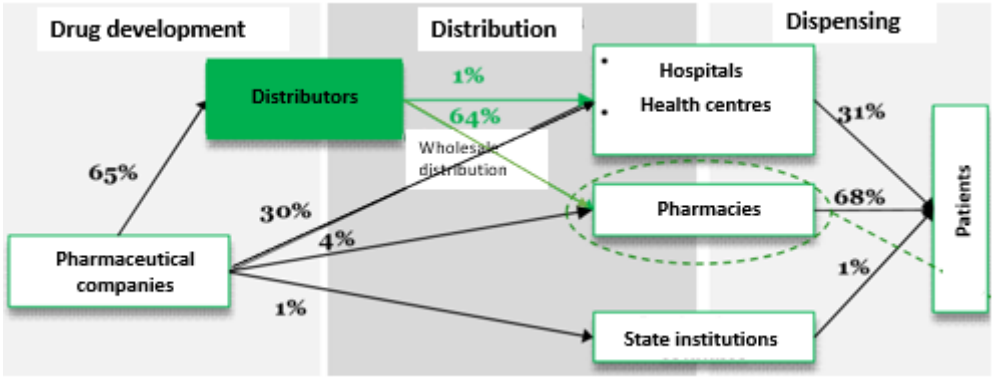
[193] Article 4.6 of the Consolidated Text.

[194] Article 91.3 of the Consolidated Text.

remain within the distribution chain in the form of higher margins for the operators who receive them[195].

As a guideline, the **structure of pharmaceutical distribution channels** in Spain in 2012 (latest available data) was the following: pharmaceutical companies sold 65% of their products to distributors, 30% directly to hospitals and health centres, 4% was sold to pharmacies, and 1% to state institutions[196]. Of the products distributed by wholesalers, 99% went to pharmacies, while 94% of the medicines and pharmaceuticals distributed by pharmacies were supplied by wholesale distributors (Figure 13).

Figure 13. Pharmaceutical distribution chain in Spain (2012)



Source: FEDIFAR (2013).

There are **several ways for pharmacies to obtain supplies**: through wholesale warehouses by means of "classic" or "proper" distribution, through "transfer" purchases (the pharmacy manages the purchase directly with the laboratory, but it is distributed through a wholesaler), or through direct purchases from pharmaceutical laboratories (which may use logistics or *picking* operators):

- The supply of medicines to pharmacies through **"classical" wholesale distribution** is the most widespread. This is where the wholesaler, acting in their own name and on their own account, receives the order from the pharmacy and supplies the requested medicines under their own commercial conditions. Wholesalers generally acquire ownership of the stocks of medicines which they then pass on to the individual pharmacies,

[195] In the case of advertised medicines, pharmacies can offer discounts of a maximum of 10% on the RP (taxes included), so patients and others who pay for these medicines cannot benefit from price reductions beyond that limit (Article 4 of Royal Decree 823/2008).
[196] FEDIFAR (2013).

receiving the corresponding margin according to the regulated distribution margin scheme[197].

- In the **"transfer" type of purchase**, the pharmacy manages the purchase directly with the laboratory, but the distribution and invoicing are done through a wholesaler, who is informed of the existence of the order and delivers it to the pharmacy (with the commercial conditions established by the laboratory and the pharmacies)[198]. The pharmacy can thus enjoy the advantageous commercial conditions offered by buying directly from the laboratory (without having to meet certain requirements usually demanded, such as a minimum order). It can also help the pharmacy to increase its volume of purchases from the wholesaler and thus achieve better commercial purchasing conditions[199]. The wholesaler applies a logistics charge (usually a low percentage of the retail price of the products in the order), in a departure from the usual scheme of regulated distribution margins[200].
- **Direct supply to pharmacies from pharmaceutical laboratories** bypasses the wholesale distributor in the chain and can be carried out through logistics operators. It usually involves certain products that are specially subsidised by the laboratory (such as generic or advertised medicines)[201]. Logistics operators act on behalf of an agent in the sector (usually a laboratory) providing logistics services by means of their facilities and human resources, which may be similar to those of a distribution company or constitute an outsourcing of some of the laboratory's obligations. It may therefore be obliged to comply with the applicable regulations (depending on the activities they carry out: authorisation as a distribution entity, compliance with good distribution practices, etc.). The relationship between laboratories and logistics operators is based on private agreements, in which their remuneration is agreed on the basis of the scope of their services, without necessarily being subject to regulated margins[202]. According to industry sources, in recent years, pharmaceutical companies have been intensifying their direct sales practices to pharmacies through logistics operators[203]. In

[197] Information provided by FEDIFAR in response to a request for information made by the CNMC.
[198] Information provided by FEDIFAR in response to a request for information made by the CNMC.
[199] Asefarma (pharmaceutical consultancy), available at https://www.asefarma.com/blog-farmacia/que-es-un-pedido-transfer-en-farmacia.
[200] Difarmed (2018).
[201] Asefarma (pharmaceutical consultancy), available at https://www.asefarma.com/blog-farmacia/que-es-un-pedido-transfer-en-farmacia.
[202] Information provided by FEDIFAR in response to a request for information made by the CNMC.
[203] Information provided by pharmaceutical laboratories in response to a request for information made by the CNMC.

2017, direct sales accounted for 4.7% of the medical products for human use distribution market in terms of value and 8.7% in terms of volume[204].

There are currently 314 wholesale pharmaceutical warehouses in Spain, 189 contract warehouses, and 7 bonded warehouses for medicines under customs control or surveillance (each has its own distribution authorisation, although the same company may employ multiple warehouses)[205]. Most of the offer in the wholesale distribution market is concentrated across a small number of "full range" distributors, which are vertically integrated with pharmacies and may have either a nationwide network or regional coverage (if they have only one or a small number of warehouses)[206]. There are also smaller operators, usually **independent "narrow-range" distributors** (focusing on the more profitable, high-priced or high-consumption products) that are not integrated downstream.

There are operators who provide their services nationwide, while others operate mainly within the Autonomous Community or province where their warehouses are located, sporadically carrying out activities in neighbouring provinces[207]. This is because, given the obligation to supply pharmacies and their limited storage capacity, the distribution of medicines requires frequency and speed (they usually supply between one and four times a day, sometimes in very small quantities and within at most 24 hours of the order). Accordingly, the potential area covered by the wholesale warehouses from which medicines are distributed is determined by an area of between 120 and 150 minutes radius (by road)[208]. Some provinces have a large population and high number of pharmacies, where there are several warehouses, while other less densely populated provinces are supplied from warehouses in neighbouring provinces[209].

The **national market shares** of the largest wholesale distributors of pharmaceuticals in Spain (in terms of value at the retail price of the products distributed) in recent years are shown in Table 2. It can be seen that most of the offer is concentrated across a small number of wholesale distributors: the first two operators each distribute more than 20% of the pharmaceutical products

[204] Information provided by Farmaindustria in response to a request for information made by the CNMC.
[205] Catalogue of Distribution Entities, AEMPS (accessed July 9, 2021).
[206] According to FEDIFAR, in most European countries the distribution market is dominated by three or four large operators.
[207] Information provided by FEDIFAR in response to a request for information made by the CNMC.
[208] According to precedents from CNMC files, the former CNC and the former TDC, such as the report and proposed resolution of file C-0745/16 CECOFAR/GRUPO FARMANOVA of the CNMC Competition Directorate.
[209] Report and proposed resolution of file C-0725-16 HEFAME/COOFAMEL-ACTIVOS- of the CNMC Competition Directorate.

distributed in Spain, the next two account for more than 10%, and the fifth largest has more than a 6% share. All the others have less than 3% of the market share.

Table 2. Market share of the largest pharmaceutical wholesale distribution companies of medicines and medical devices in Spain (% by LSP value)

BUSINESSES	MARKET SHARE (%)		
	2017	2018	2019
Grupo Cofares	27	27	27
Bidapharma	19	21	22
Hermandad Fca. Mediterráneo (Hefame)	11	11	11
Grupo Alliance-Healthcare	11	11	10
Federació Farmacéutica	6	6	6
Novaltia	<5	<5	<5
Coop. Fca. Noroeste (Cofano)	<5	<5	<5
Coop. Fca. Canaria (Cofarca)	<5	<5	<5
Coop. Fca. Asturiana (Cofas)	<5	<5	<5
Grupo Ctro. Fco., S.L.	<5	<5	<5
Top 2	46	48	49
Top 5	74	76	76

Source: developed in-house based on Diariofarma (2018, 2020) and CNMC data.

As a result, in 2019, the top two operators in the market ("top 2") had a share of almost 50%, the top five operators accounted for 75% of the market, and the top ten held 88%. The remaining pharmaceutical products were distributed by more than twenty operators with more modest activity.

Nevertheless, the structure of the pharmaceutical distribution market, although concentrated, is more dispersed in Spain than in other countries, with none of the wholesale distributors having a market share of more than 30% of the national market.

This structure of the Spanish distribution sector, concentrated across a limited number of operators, also existed in the past, although this concentration has been increasing. The change in the market structure can mainly be explained by the successive mergers that have taken place in the sector between operators already present in the market[210] (according to agents in the sector this has been in response to the risk of non-viability resulting from the previous economic crisis[211]). However, no significant new players have emerged, and despite the

[210] Proceedings C-0958-18 BIDAFARMA/ZACOFARVA, File C/0745/16 CECOFAR/GRUPO FARMANOVA, File C/0866/17 BIDAFARMA/COFAGA, File C/0867/17 BIDAFARMA/COFABU. File C-0725/16 HEFAME/COOFAMEL-ACTIVOS-, File. C-0745/16 CECOFAR/GRUPO FARMANOVA, and File C/0867/17 BIDAFARMA/COFABU, among others.

[211] Diariofarma (2020).

fact that the investments required for the installation of wholesale distribution warehouses are substantial, pharmaceutical laboratories have sufficient resources to implement them[212].

To ensure the independence of pharmacists, the regulations establish that the professional practice of pharmacists in pharmacies is incompatible with any kind of economic interest in distribution entities, brokers or pharmaceutical laboratories[213]. Thus, vertical integration between pharmacies and distribution entities is prohibited[214]. However, the regulations establish one **exception**: pharmacists who are members or who become members of cooperatives with a minimum of 20 cooperative members, or trading companies with a minimum of 100 shareholders or partners, in both cases made up exclusively of pharmacists and already in existence when Law 29/2006 of 26 July 2006 came into force, may participate in such enterprises. This participation will continue until the dissolution or termination of the cooperative and as long as it does not entail a potential conflict of interest[215].This exception allows the ownership of wholesale warehouses in Spain to be, for the most part, in the hands of pharmacists that own pharmacies, either vertically integrated into cooperatives (mainly) or in partnerships: of the ten companies shown in Table 2, nine are made up of pharmacist members (eight cooperatives and one limited company), while the remaining one (Alliance-Healthcare) is a limited company that is part of a multinational business group. However, pharmacists that own a pharmacy cannot join new cooperatives or distribution companies founded after 28 July, 2006, and which do not meet the other requirements mentioned above.

In addition to the wholesale distribution of medicines, cooperatives offer a number of other services to their members, such as support for their professional and business activities, consultancy and advisory services. By belonging to a cooperative, a pharmacy can access these services and, in return, must commit to certain obligations such as, for example, making a minimum number of annual purchases from the cooperative.

93% of pharmacies are supplied by two or more distributors[216]. This is the case even if the owner is a member of a distribution cooperative, in order to ensure

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[212] Report and proposed resolution of file C-0958-18 BIDAFARMA/ZACOFARVA of the CNMC Competition Directorate.

[213] Also in a retail commercial establishment, in livestock entities or groups or in a hospital pharmacy service and other care structures.

[214] Article 4.2 of the Consolidated Text.

[215] Second transitory provision of the Consolidated Text. Also pharmacists who at the entry into force of Law 29/2006, of July 26, had direct economic interests in pharmaceutical companies, may maintain those interests until the termination of the authorisation or transfer of the laboratory.

[216] Aspime (2017).

supply in any situation[217]. Independent pharmacies cannot cover their supply needs with independent warehouses (because they are usually "small-range"), so they also often turn to cooperatives[218].

2.2.5. Retail Distribution: pharmacies

The final link in the medicine chain is retail distribution, whereby medicines are dispensed to patients: pharmacies are the main channel for dispensing medicines to patients, accounting for 68% of retail distribution, while 31% is dispensed through hospital pharmacies or primary care centres and 1% through state institutions (Figure from the section 2.2.4)[219].

In Spain, there were 22,100 pharmacies in 2019, each serving, on average, 2,115 people. In that year, 76.4% of the turnover of Spanish pharmacies came from dispensing medicines (70.4% from prescription medicines and 6% from over-the-counter medicines).[220] In addition, that year more than 1 billion medical prescriptions were dispensed by the SNHS and charged to the public purses of the Autonomous Communities, INGESA and the administrative mutual insurance system[221].

In the study *E/CNMC/003/15, on the retail distribution market for medicines in Spain*, the CNMC analysed the characteristics and various restrictions to competition in the retail distribution market for medicines in Spain, from the perspective of efficient economic regulation. This study, therefore, does not look in depth at the problems of pharmacies, nor does it describe and assess certain issues[222]. It does address other aspects that are closely related to the rest of the links in the medicine chain as these, if not mentioned, would render the analysis incomplete.

In Spain, pharmacies are **private healthcare establishments operating in the public interest**, subject to the healthcare planning established by the Autonomous Communities, which must provide the population with a series of

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[217] Report and proposal for resolution of file C-0745/16 CECOFAR/GRUPO FARMANOVA of the CNMC Competition Directorate.

[218] FEDIFAR.

[219] As specified above, the custody, conservation and dispensing of medicines for human use corresponds exclusively to the pharmacy offices and pharmacy services of hospitals, health centres and primary care structures of the SNHS (Article 3.6 of the Consolidated Text).

[220] Approximately 25% of pharmacy turnover comes from other types of products, such as parapharmacy and dietary products.

[221] IQVIA (2020).

[222] Among other issues, this study does not deal with the Autonomous Community planning model for pharmacy offices, which was analysed in depth, from the perspective of competition and efficient economic regulation, in study E/CNMC/003/15.

basic services, including the following: the acquisition, safeguarding, conservation and dispensing of pharmaceutical products; surveillance, control and custody of prescriptions dispensed; preparation of magistral formulae (compounding) and medicinal preparations; the provision of information and monitoring of pharmacological treatments for patients; collaboration in the detection of adverse reactions; cooperation with the health authorities in quality assurance programmes related to pharmaceutical care and healthcare in general, health promotion and protection, disease prevention and health education; and the provision of training and information on the rational use of medicines, among other things[223].

The regulations require that pharmacists own and operate the pharmacies, and that each pharmacist may not own more than one pharmacy (horizontal integration is not allowed)[224]. It is also prohibited (as mentioned above2.2.4) to hold financial interests related to pharmaceutical laboratories, brokers or distributors (with some exceptions), in order to guarantee pharmacist independence[225].

Prescription medicines are more strictly regulated in terms of dispensing than over-the-counter medicines. On the one hand, the regulations in Spain totally prohibit the selling of prescription-only medicines through mail order and remote sales channels[226]. On the other hand, the advertising of these drugs is also prohibited. These restrictions do not apply to over-the-counter medicines, which may be advertised and retailed through the websites of legally authorised physical pharmacies that have reported this activity, with the involvement of a pharmacist and after receiving personalised advice[227].

On the other hand, as in the case of wholesale distribution, the **retail distribution margin** received by pharmacies is regulated and is established according to the price of the medicines they dispense. The margins obtained by pharmacies for the dispensing and sale to the public of industrially manufactured medicinal

[223] Article 1 of Law 16/1997, of April 25, on the Regulation of Pharmacy Office Services and Article 86.6 of the Consolidated Text.

[224] The rule regarding property and ownership is found in Article 103.4 of Law 14/1986. The limit restricting a pharmacist's ownership to a single pharmacy is not explicitly established in Law 16/1997, although it does include an indirect reference to this in Article 1, in addition to the fact that this is established in various pharmaceutical management laws from the Autonomous Communities.

[225] Article 4.2 of the Consolidated Text.

[226] Article 3.5 of the Consolidated Text and Royal Decree 870/2013, of November 8, which regulates the remote sale to the public, through websites, of over-the-counter medicines for human use.

[227] Articles 80 and 3.5 of the Consolidated Text.

products for human use (whether or not they are SNHS-funded) are shown in the following table[228].

Table 3. Pharmacy retail margins for dispensing medicines

Price of the medicine (in euros)[229]	Pharmacy margin
LSP ≤ 91.63 (equivalent to RP ≤ 137.54)	27.9% of the RP
91.63 < LSP ≤ 200 (equivalent to 137.54 < RP ≤ 245.91)	38.37 euros per package
200 < LSP ≤ 500 (equivalent to 250.91 < RP ≤ 550.91)	43.37 euros per package
LSP > 500 (equivalent to RP > 555.91)	48.37 euros per package

Notes: LSP is the laboratory selling price or industrial price; RP is the retail price without taxes. For more details on the calculations, see Annex I.
Source: developed in-house based on Royal Decree 823/2008.

The retail margins are a linear function of the price for medicines with an RP before tax of less than 137.54 euros. Above this price, they receive a fixed margin, the amount of which depends on which of the three brackets the price of the medicine dispensed falls into. In 2019, 99.49% of the units dispensed by pharmacies in Spain had an RP of less than 137.54 euros and were therefore in the variable retail margin bracket[230].

Regardless of the pricing system into which the medicines fall, the RP is determined by the sum of the LSP and the wholesale and retail margins. This

[228] Article 2 of Royal Decree 823/2008. Except for the margin on the dispensing of medicines packaged in clinical packages (medicines destined for the hospital environment), which is 10% of the retail price without taxes (Article 2.9 of Royal Decree 823/2008).

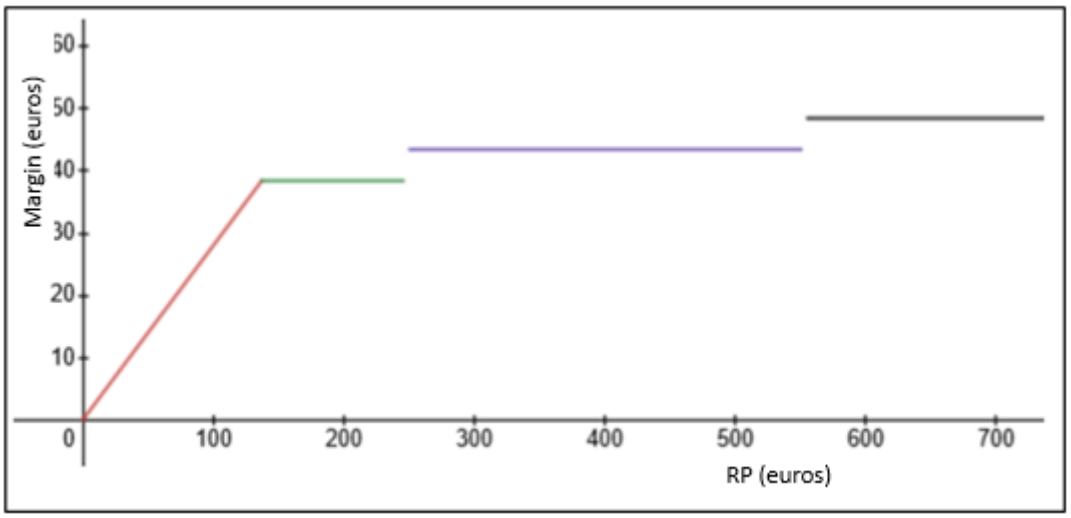
[229] The regulation of Royal Decree 782/2013 establishes the margins of dispensing and sale to the public based on the LSP price of medicines. In order to clarify, simplify and be able to graphically represent them in this study, the price thresholds are also referenced to the RP so that both these thresholds and the margins themselves have a common reference. The calculations to determine the equivalencies are explained in Annex I.

[230] Information provided by the General Council of Official Pharmaceutical Associations in response to a request for information made by the CNMC.

remuneration system, as will be discussed in detail in Section 3.5.2 below, is inefficient[231].

Graphically, the margins on medicines received by pharmacies in terms of RP excluding taxes can be illustrated as follows:

Figure 14. Pharmacy retail margins for dispensing medicines



Source: developed in-house based on Royal Decree 823/2008.

As explained above, the actual margins may differ from the regulated margins, as distributors can give **discounts** to pharmacies (offset against their own margin) and pharmacies may purchase medicines in other ways, such as directly from laboratories. As a result, the regulated margin for pharmacies acts as a lower threshold in the case of prescription-only medicines, for which patient discounts are prohibited[232]. In the case of over-the-counter medicines, the patient discount is limited to 10% of the RP (including taxes), meaning that the effective remuneration margin for pharmacies may also be different from the regulated margin[233].

Since the monthly register of discounts foreseen by the regulation (Article 4.6 of the Consolidated Text) does not seem to be in place at present, **the Ministry of Health is unable to trace the discounts made within the distribution**

[231] It should be noted that, although there is insufficient objective data to assess whether the specific margins set by the regulation is adequate, factors such as the existence of significant discounts in the distribution channel suggest that there is room for reductions.

[232] Article 91.3 of the Consolidated Text.

[233] Article 4 of Royal Decree 823/2008.

channel. However, some estimates of pharmacy margins for 2019 showed increasing figures depending on the level of turnover, ranging from 28.7% for those with a lower turnover (less than 300,000 euros per year) to 32% for those with a turnover of more than 2 million euros[234]. These estimates, in all cases higher than the regulated margin, point to the existence of discounts that are passed on as increased margins to pharmacies, and it seems that those with a greater turnover are able to obtain even greater discounts[235]. Other studies point in the same direction: a 2009 study commissioned by the Catalan Competition Authority showed the existence of average discounts of 40% on the LSP of generic medicines offered by pharmaceutical laboratories to pharmacies[236]; this increased as the number of generic competitors increased, illustrating the fact that there is considerable competition that is not being passed on in the prices paid by public authorities and private individuals, but which represents a higher margin for pharmacies[237].

The income received by pharmacies from the sale of industrially manufactured medical products for human use dispensed at the expense of SNHS public funds is reduced by a series of **deductions** established by the regulations[238]. These deductions are calculated on the basis of the volume of sales in terms of value (RP VAT) of these funded medicines, and are applied to each pharmacy's monthly invoice for these prescriptions.[239] In this way, pharmacies have greater deductions applied to their income the higher their sales of funded prescription drugs, according to the following scale[240].

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234 Aspime (2019).

235 However, it must be taken into account that, in addition to medicines, approximately 25% of pharmacy turnover comes from other types of products not subject to this regulation, such as parapharmacy and dietetic items, which are likely to alter the aggregate margin of pharmacies.

236 The study was carried out on the eight best-selling active ingredients for which there were generic drugs in Spain.

237 Puig-Junoy (2009).

238 In order to contain the growth of pharmaceutical spending charged to the public purse, necessary to guarantee the sustainability of the SNHS (Royal Decree 1193/2011, of August 19, which establishes the procedure for applying the joint scale of deductions to the monthly turnover of each pharmacy).

239 Article 2.5 of Royal Decree 823/2008.

240 To calculate monthly sales in order to apply deductions, in the case of medicines with a LSP above 91.63 euros, only the amount of 91.63 euros is taken into account, excluding the part that exceeds this price (Article 2.6 of Royal Decree 823/2008). In other words, when calculating monthly sales in order to apply deductions, a medicinal product with an LSP of 100 euros would be counted as if it had an LSP of 91.63 euros.

Table 4. Deductions on the monthly invoice for pharmacies

Total sales up to (RP VAT in euros)	Deductions (euros)	Excess up to (euros)	Applicable rate
0,00	0,00	37.500,00	0,00%
37.500,01	0,00	45.000,00	7,80%
45.000,01	585,00	58.345,61	9,10%
58.345,62	1.799,45	120.206,01	11,40%
120.206,02	8.851,53	208.075,90	13,60%
208.075,91	20.801,83	295.242,83	15,70%
295.242,83	34.487,04	382.409,76	17,20%
382.409,77	49.479,75	600.000,00	18,20%
600.000,01	89.081,17	Forward	20,00%

Note: RP VAT is the retail price plus VAT.
Source: developed in-house based on Royal Decree 823/2008.

In 2019, 52.4% of pharmacies in Spain invoiced less than 37,500 €, so no deduction was applied[241].

Given that pharmacy revenues are reduced by these deductions (they are higher the greater their turnover), their effective margins should be below the regulated 27.9%. However, the effective margins are actually higher, which again supports the theory that pharmacies receive discounts, further increasing their remuneration.

With the stated aim of guaranteeing the accessibility and quality of the service provided by pharmacies, as well as adequate pharmaceutical care for users of the SNHS, there is a system of **margin correction indexes** for pharmacies that are exempt from the previous deduction and which meet a series of requirements[242]. This system translates into a higher income for these pharmacies from the SNHS (as a ceiling, the amount payable to the pharmacy can reach 833.33 euros per month)[243].

[241] Information provided by the General Council of Official Pharmaceutical Associations in response to a request for information made by the CNMC.
[242] Article 2.8 of Royal Decree 823/2008.
[243] a) That they have not been subject to administrative sanction or professional disqualification, nor are they excluded from their agreement; b) that they participate in pharmaceutical care programmes and in activities aimed at the rational use of medicines established by the health authorities; and c) that their total annual sales did not exceed 200,000 euros in the preceding financial year.

Finally, in order to reduce pharmaceutical spending by the SNHS, the regulation[244] establishes a 7.5% **deduction** on the RP of medicines dispensed at the expense of the SNHS that pharmacies must apply to their invoicing[245]. The latter deductions do not apply to generic medicines or those covered by the reference price system[246]. In the case of orphan drugs, the deduction is 4%, while it rises to 15% for originator medicines for which there is no generic or biosimilar authorised in Spain if ten years have elapsed since the decision was taken to fund them from the public purse, unless they are protected by product patent in all EU Member States[247]. This deduction is divided proportionally among all the agents in the pharmaceutical chain[248]: the pharmacy deducts 7.5% of the RP, the distributor in turn deducts 7.5% of the DSP, and the pharmaceutical laboratory also applies a 7.5% deduction on the LSP, so that the margins of all the operators in the chain are reduced by this percentage.

[244] Article 8 of Royal Decree-Law 8/2010, of May 20, which adopts extraordinary measures to reduce the public deficit.
[245] A deduction of 7.5% is also applied on the purchase price of medicines charged to public funds of the SNHS formalised through the pharmacy services of hospitals, health centres and primary care structures (Article 9 of Royal Decree-Law 8/2010).
[246] As long as the set is not inactive.
[247] Article 10 of Royal Decree-Law 8/2010.
[248] Article 8 of Royal Decree-Law 8/2010.

3. ASSESSMENT FROM THE PERSPECTIVE OF COMPETITION

Having analysed the legal and economic framework for the marketing and distribution of medicines in Spain, the main restrictions to competition identified are discussed below. The aim is to correct existing distortions, increase the level of effective competition in the market and improve social welfare.

Firstly, we assess the obstacles identified in the regulations related to the marketing of medicines in Spain (financing decisions and price regulation), both for innovative medicines as well as generics and biosimilars. Secondly, we will analyse the restrictions in the regulations governing the distribution of medicines, at the wholesale and retail levels.

3.1. Innovative medicines

The CNMC considers that there is room for improved decision-making regarding the financing and pricing of innovative medicines. Specifically, two areas have been pinpointed where reforms could be introduced to contribute to more efficient, sustainable and pro-competitive regulations:

- On the one hand, while therapeutic efficacy aspects are the key element when pricing medicines, economic issues are also significant when determining cost-effectiveness. Currently, decision-making processes give insufficient importance to a thorough **pharmaco-economic assessment** of medicines; this could result in pricing that does not correspond to the therapeutic value provided by the medicines. Specifically, the CNMC considers that Therapeutic Positioning Reports (TPRs) should be given greater prominence as complete and transparent reference documents.
- On the other hand, the SNHS holds an enormous quantity of information that is not being shared appropriately among its members and used to its full potential. Any access to this information must, at all times, guarantee the protection of personal health data and its confidentiality. Advances in the digitalisation of the SNHS, the **use of big data** and artificial intelligence tools can improve the therapeutic and pharmaco-economic evaluation of medicines, as well as innovation, system sustainability and access to medicines over time.

Some of these issues were also raised by industry stakeholders in the Public Consultation on the medicines market launched by the CNMC in February 2021[249].

These issues are discussed in more detail below.

3.1.1. Insufficient prominence of economic evaluation in funding and pricing decisions and the role of Therapeutic Positioning Reports (TPRs)

As explained above (see Section 2.2.2), decisions concerning the funding of medicines and the setting of their industrial price are made by two different bodies: the funding decision is made by the DGCYF, while the pricing decision is the responsibility of the CIPM[250]. According to the regulations, the CIPM must adopt the pricing decision in a reasoned manner, in accordance with objective criteria[251]. To this end, it must take into account **cost-effectiveness** and budgetary impact analyses[252]. However, the mechanisms used and the internal discussion within the CIPM and DGCYF relating to the pricing of innovative medicines are not transparent. In particular, it would be advisable to shed light, in the interests of good governance and transparency, on the mechanisms and procedures used to economically assess and set the prices of patent-protected innovative medicines.

The CNMC considers that the **Therapeutic Positioning Reports (TPRs)**, which are currently used by the DGCYF to support its funding decisions (see Section 2.2.2), are a good tool for addressing these questions. At present, TPRs hardly touch upon economic issues. It would be advisable to include an economic analysis or assessment of medicines in these reports, to facilitate subsequent price setting by the CIPM, as well as to increase the transparency and predictability of pricing mechanisms for innovative medicines, in addition to providing a mechanism for monitoring public action. Similarly, the Ministry of

[249] In general, market players consider that economically evaluating innovative medicines is neither sufficient, transparent nor independent, and that too much emphasis is placed on the budgetary impact rather than on the efficacy of the medicine. They also point out that there is a lack of regulatory development and that the pricing process is very slow. In addition, and in relation to TPRs, they indicate that their drafting process is not regulated, as this is an internal procedure that does not guarantee transparency or the right of interested parties to be heard, and that it does not include a true economic evaluation, only a scientific-technical one.

[250] Article 94.5 of the Consolidated Text.

[251] Article 94.5 of the Consolidated Text.

[252] Article 94.1 of the Consolidated Text.

Health is urged to publish the pricing decisions taken by the CIPM, in order to increase medicine financing and pricing transparency.

TPRs represented a turning point in the medical evaluation process. They were created in 2013, as the result of an agreement of the Standing Committee on Pharmacy of the SNHS Interterritorial Council, and have been a benchmark since then. They aim to provide, in addition to medicine authorisation, relevant, realistic and unbiased information on the position of the new medicine in the market compared to other existing medicines or health measures[253]. They outline the pathology and describe the standard of care by means of a detailed description of the medicine, the clinical trial, and a comparison with other medicines. They therefore include a fairly comprehensive assessment of both comparative and relative efficacy. The analysis is also homogeneous.

However, after having been in place for 9 years, there is a consensus in the healthcare community that TPRs need to be re-evaluated and improved, both in terms of process and structure.

The main shortcomings of TPRs are a **lack of information related to the cost-effectiveness of the medicine** together with a lack of clarity and precision, on occasions, regarding the therapeutic positioning of a medicine[254]. This results in the end use of the medicine being uncertain or different depending on the medicine itself and the Autonomous Community. For example, on the basis of the same TPR, medicines may be funded in some Autonomous Communities and not in others, even though there are equivalent medicines available at a lower price[255]. It would therefore be advantageous for TPRs to include a **pharmaco-economic assessment and a clear therapeutic positioning evaluation**.

Another area for improvement concerns the **procedure for drafting TPRs**. For example, in theory, TPRs should be prepared within 3 months[256], but in practice this period is considerably longer[257]. In addition, market agents can present statements on the draft TPRs at the beginning of the process, but it is not possible to do so afterwards [258]. Finally, although Law 10/2013 mentions the binding

[253] The Interterritorial Council of the SNHS is the permanent body for coordinating, cooperating, communicating and informing the autonomous health services and State authorities (Article 69 of Law 16/2003, of 28 May, on the cohesion and quality of the Spanish National Health System).

[254] Action plan for consolidating Therapeutic Positioning Reports on medicines in the SNHS.

[255] In a survey of 80 hospitals conducted by Grupo Génesis, they conclude that a large number of the Autonomous Communities establish positions different from those included in the TPRs.

[256] Collaboration proposal for the preparation of Therapeutic Positioning Reports for medicinal products, 2013.

[257] Action plan for consolidating Therapeutic Positioning Reports on medicines in the SNHS.

[258] Collaboration proposal for the preparation of Therapeutic Positioning Reports for medicinal products, 2013.

nature of the TPRs for the positioning of a drug, they are not actually taken as binding[259]. TPRs are currently considered mandatory[260].

To improve TPRs, in 2020 the Ministry of Health launched an **Action Plan for the Consolidation of Therapeutic Positioning Reports for Medicines in the SNHS**. This was aimed at improving decision-making among the agents involved, achieving more cost-effective prescribing of medicines and enhancing the positioning of medicines in terms of pathologies. This Plan could correct some of the current problems or weaknesses of TPRs that have been identified *above*.

In relation to the **economic evaluation of medicines in TPRs**, to date this has been carried out within the Ministry of Health in a somewhat non-transparent manner. The TPR reform, however, raises the need to include detailed information in this respect in future reports. Specifically, the Plan envisages including pharmaco-economic information on the medicine in the TPRs, as well as improving the critical reading of clinical evidence and its limitations. This will involve an in-depth analysis of secondary sources of clinical evidence and a more complete examination of the efficacy of the medicine as well as its cost-benefit.

The inclusion of economic evaluation criteria in the TPRs is therefore a **major step towards greater transparency in the evaluation of medicinal products**. It is one of the most substantial changes in the reform proposed by the Ministry of Health and a possible tool for improving the positioning of medicines and their economic evaluation.

In addition, promoting this comprehensive analysis in TPRs may be key in the future, as the expected pharmaceutical innovation is going to represent a substantial change for the authorities. There are increasing numbers of indication expansions, exceptional approvals and conditional approvals. The first wave of advanced therapies with very high costs is also on its way[261]. **TPRs need to be a comprehensive and transparent reference document, which includes a full economic evaluation** of medicines. Currently, only 57% of TPRs set out restrictions on use (including pricing considerations), while 26% include (very)

[259] Third additional provision of Law 10/2013, of 24 July, transposing into Spanish law Directives 2010/84/EU of the European Parliament and of the Council, of 15 December, 2010, on pharmacovigilance, and 2011/62/EU of the European Parliament and of the Council, of 8 June, 2011, on the prevention of the entry of falsified medicinal products into the legal supply chain, and amending Law 29/2006, of 26 July, on guarantees and rational use of medicinal products and health products.

[260] Action plan for consolidating Therapeutic Positioning Reports on medicines in the SNHS.

[261] Annual Report of the European Medicines Agency, 2020, and Annual Reports on Medicinal Products for Human Use of the European Medicines Agency.

limited economic evaluation and do not provide sufficient detail on efficiency evaluation[262].

The Ministry of Health's proposed economic evaluation focuses on the 2016 Guide produced by the Grupo Génesis of the Spanish Society of Hospital Pharmacy (Sociedad Española de Farmacia Hospitalaria; SEFH), although it has also taken into account other national and international guides, as the Plan itself points out.[263] This guide incorporates recommendations for evaluating key aspects such as cost, a critical review of published economic evaluations, the selection of the most appropriate type of economic evaluation, the calculation of budgetary impact, and populational health outcomes. It also proposes a cost-effectiveness threshold to be applied in the reports, and defines the criteria for therapeutic positioning based on incremental cost-effectiveness and budgetary impact.

The Ministry of Health's Plan has incorporated most of these recommendations, including some essential features, such as the choice of comparators, target population, time horizon, sensitivity analysis, and the determination of incremental cost-effectiveness, where the guidelines from the different countries come to a general consensus. On the other hand, there are other aspects, such as costs, where, either due to regulatory issues or the peculiarities of each market, it is more difficult to unify criteria at the international level. In the case of the Ministry of Health's Plan, it has been decided to include cost-utility, cost-effectiveness, or cost-minimisation analyses depending on the evidence available.

In this sense, **the method proposed for the TPRs seems appropriate and clear.** The Plan's proposal for economic evaluation is, however, not without **problems.**

In general terms, the proposal included in the Plan is in line with other economic guidelines or recommendations, although **it does not go into sufficient detail on any of the aspects raised.** Furthermore, the Plan does not clarify whether the economic information in the TPRs will be provided in equivalent units based on the lowest cost comparator, or whether it will be provided in euros.[264] Nor does

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[262] *Therapeutic positioning reports- experience in Spain in the period 2013-2019*, Verónica García, Laura Corbalán, Sandra Baquero; Esther García-Esquinas; José Antonio Sacristán, Universidad Carlos III de Madrid - Universidad Autónoma de Madrid, 2020.

[263] A significant number of countries have guidelines or a set of recommendations for conducting economic evaluation studies of medicines or health interventions, including: Germany, Belgium, France, the Netherlands, the United Kingdom, Sweden, Canada and Australia.

[264] The prices of their alternatives are expressed as acquisition costs and can be converted into monetary format (in euros) or equivalent units. In this case, the unit will be taken as the one

it clarify whether a specific figure (in terms of price) will be chosen or whether the results of the economic evaluation will be included in the form of a range of prices. In fact, the Plan does not even specify what kind of economic valuation information will be published.

Moreover, the Plan does not explain how the **economic evaluation will be conducted when there is insufficient evidence available**, or when there are no valid comparators. This could be the case for disruptive medicines that, due to their inherent character, cannot be compared to any other medicine on the market. However, it is precisely in these cases that an economic evaluation is most necessary, as there is no comparator.

In summary, **the TPR reform contained in the Ministry's Plan seems to be well thought out, but needs to be developed in more detail**. Further development of the different aspects raised in the Plan in relation to economic evaluation is therefore necessary in order to clarify the method to be used and to add transparency to the economic evaluation process. In this sense, and taking into account the fact that the new TPRs will be used by the Ministry of Health to develop their medicine evaluation reports to study whether the CIPM should include them in the SNHS pharmaceutical service, as well as the pricing decision, it would be advisable to know how the information included in the TPRs will be used to prepare these reports, as well as the criteria that the Ministry of Health will actually utilise for these, as well as the analysis contained within them. This information would improve the clarity and transparency in the process of funding and fixing the price of medicines within the SNHS.

In terms of **procedure and decision-making**, the TPR reform proposed by the new Plan provides for the transformation of the Therapeutic Positioning Coordination Group (TPCG)[265] into a Drug Evaluation Network **(REvalMed SNHS**), which will include professionals from the DGCYF, the AEMPS and the Autonomous Communities, and which will be responsible for drafting and approving the TPRs. In this way, there is a shift away from the TPRs being developed by the AEMPS to them being a collaborative development between the AEMPS, the DGCYF and Autonomous Communities.

The new REvalMed will be divided into **two assessment teams:** (i) a **therapeutic assessment** team, which will draft the therapeutic sections of the

with the lowest cost and, depending on the different alternatives, the corresponding equivalence can be made according to that unit price.

[265] Group in charge of assessing TPRs. This involves the AEMPS, the Directorate General for the Common Portfolio of Services of the National Health and Pharmacy System of the Ministry of Health and the Autonomous Communities. The TPRs are prepared by an Evaluation Group, comprising only the AEMPS and two Autonomous Communities, which drafts the final report to be submitted to the GCPT.

TPRs; and (ii) a **pharmaco-economic assessment** team, which will prepare the pharmaco-economic sections (AEMPS staff will not form part of this team).

There will also be **evaluation nodes**, whose function will be to review the draft TPRs and make any inputs considered necessary. The nodes will be made up of expert management and clinical professionals appointed by the Autonomous Communities. Each node will be coordinated and led by one Autonomous Community and co-ordinated by another, with this coordination and co-coordination on a rotating basis. Finally, a **Coordination Group** will be created whose mission will be to identify the TPRs to be developed.

The Ministry of Health's Plan does not address the internal organisation of REvalMed, or its decision-making processes, so it is not clear whether decisions are to be made through consensus among all the members of the different teams or groups, or whether tasks and decision-making will be divided among the different members depending on their technical profile. Likewise, it does not seem that REvalMed will be led by any of its member institutions, but will rather be a collaborative effort of all its members.

The CNMC considers it positive that the TPRs will be the result of a collaborative effort between the institutions involved, which is a step forward compared to the previous situation where their development was the responsibility of an Assessment Group made up solely of the AEMPS and two Autonomous Communities, although greater **transparency is needed regarding the internal organisation of REvalMed, its decision-making processes, its independence and the members that comprise it.**

On the other hand, the reform also prioritises TPRs, involving a **reduction in the overall drafting time.** The CNMC supports the prioritisation of the TPRs, although it considers it desirable that the drafts be sent to the different stakeholders, including patient associations, clinical specialists, and so forth, for comments. In this regard, and in those cases in which the majority of the comments on the first draft of the TPR were negative and well-founded, it would be advisable that comments could be made not only on the first draft, but also on the final draft. Accordingly, in the same way that a draft TPR is currently sent for comments to the scientific societies involved, to the laboratories whose active ingredients are cited, and to patients' associations, a second round should be included, in which the agents involved could issue their comments on the final TPR document within a maximum period of 10 working days. This procedure, as noted above, should be exceptional in nature.

Likewise, and in the event that the reform proposed by the Ministry of Health intends to reinforce TPRs as a tool for **decreasing the discrepancy and heterogeneity in the use of medicines** between Autonomous Communities and

achieving more homogeneity and equity, it is necessary to ensure that the analysis in the TPRs is accurate, complete and rigorous, including not only a robust pharmaco-economic analysis, but also a therapeutic positioning study that is neither ambiguous nor incomplete.

3.1.2. Long-term therapeutic and economic evaluation and the use of big data

In addition to the improvements proposed in the area of TPRs, it is necessary to **strengthen the assessment of the medium- and long-term therapeutic effectiveness** of funded medicines, in order to optimise clinical practice and adjust or set medicine prices over time. In other words, there should be constant reassessment of the real therapeutic effectiveness of medicines over time, especially those with a high budgetary impact, where effectiveness is understood as the efficacy of a medicine under real conditions or clinical practice in patients. The goal is to determine their actual therapeutic value in clinical practice and whether this corresponds to the efficacy indicated in clinical trials.

There are several reasons why a continuous assessment of the therapeutic effectiveness of medicinal products is advisable. Firstly, there are interpretations or benefits included in clinical trials that, in certain subpopulations, are not achieved in practice. This is not because the conclusion of the trial is incorrect, but because the number of patients with these particular characteristics is limited during a trial, and the effect of the medication in this subgroup of patients cannot be determined with certainty[266]. On the other hand, without monitoring the effectiveness of medicines in actual clinical practice, it is not possible to determine whether the benefits reported in clinical trials are borne out in reality, or whether, on the contrary, the effectiveness of the medicine is greater, or less, than expected from the trial results. Similarly, continuous assessment of therapeutic effectiveness over time is necessary to determine whether the benefits of the medication are sustained in the long term, or whether new side effects come to light that were not detected during the clinical trial, among other aspects. Therapeutic monitoring is not only necessary for establishing criteria for initiating or suspending medication, but also for introducing mechanisms that allow for treatments and prices to be adjusted when the effectiveness in clinical practice changes, or criteria for substituting a drug for a more effective one when the effectiveness in certain patients or populational subgroups is not as expected.

[266] In general, for clinical trials, both the EMA and FDA require 20 to 100 people in Phase I, 100 to 300 in Phase 2 and 300 to 3,000 in Phase III clinical trials.

Continuous assessment of actual therapeutic effectiveness is therefore both necessary and essential for the proper functioning of the SNHS.

For this reason, many countries have introduced various health-related tools that assess the efficacy of new medicines not only according to their clinical trials, but also their therapeutic effectiveness over time.[267] This has led to the development of **methods for economically evaluating medicines**, through **pharmaco-economics**, a field that tries to determine which medicine is most efficient, or, in other words, assesses the health outcomes of medicines vs. the resources invested.

One source of information to help the authorities make decisions on the therapeutic and economic assessment of medicines are the Phase IV (or follow-up studies) clinical trials (see Box 6), which can be designed to prospectively collect clinical and economic information by including a section on the health resources used. Economic evaluations are increasingly implemented as part of clinical trial design; these can provide useful information under more realistic conditions and can be useful when making decisions about drug pricing or funding. In some countries, the **economic evaluation of medicines** is systematically used to establish **pricing, funding and/or recommendations for use**. This is the case in organisations including the British Medical Research Council and the US National Institute of Health. These organisations generally require the inclusion of economic evaluations in clinical trials prior to funding.

Box 6

CLINICAL TRIAL PHASES

According to the objectives pursued and the information available, the following phases of clinical trials in drug development can be distinguished:

1. Phase I clinical trials: these are the first step when investigating a new substance or medicinal product for human use. They provide preliminary information on the effect and safety of the product in healthy subjects or, in some cases, in patients, and provide guidance on the most appropriate administration regimen for subsequent trials.

2. Phase II clinical trials: these are the second stage in the evaluation of a new substance or medicinal product for use in humans. They involve patients suffering from the disease or clinical entity of interest. They are intended to provide preliminary information on the efficacy of the product, establish the dose-response relationship, determine the variables used to measure efficacy, and expand the safety data obtained in Phase I trials.

3. Phase III clinical trials: these are aimed at evaluating the efficacy and safety of the experimental treatment, trying to reproduce typical conditions of use, and considering the therapeutic alternatives available for the indication studied. They involve a larger sample of

[267] Australia, the United States and the United Kingdom, among others.

patients than the previous phase that is more representative of the general population for which the drug is intended.

4. Phase IV clinical trials or follow-up studies: these are performed using a medicine that has already been marketed. They focus on the long-term effects. These types of studies serve to monitor the effectiveness of the treatment, collect information on possible adverse effects associated with its widespread use, and determine whether it offers additional benefits, among other aspects.

In addition to the information included in the follow-up or Phase IV studies, it would be advisable for the SNHS to develop, either alone or in collaboration with academic institutions or independent experts, its **own tools for economically evaluating medicines over time**, using the information provided by the laboratories as complementary data. In this sense, **databases and the use of big data** provide a unique opportunity for generating economic and therapeutic effectiveness data on medicines. This information could be used to make decisions on funding, optimise drug use recommendations and adjust prices.

The EMA has also addressed the use of information technologies and, in particular, big data, setting up several working groups whose mission is to describe, from a regulatory standpoint, the current big data landscape and to identify how to integrate this into the regulatory process for medicines[268]. The evidence generated by using big data in the evaluation and oversight of medicines has enormous potential, allowing for a more expeditious, complete and real-time therapeutic and economic assessment of medicines.

In 2019 and 2020, the Ministry of Health launched **Valtermed** as a new tool to help tackle this improvement and implement a single, uniform evaluation system for the whole of Spain, with criteria for the initiation, monitoring and discontinuation of medicines. Valtermed is an information system for determining the therapeutic value, in real clinical practice, of medicines with a high healthcare and economic impact on the SNHS. It consists of a register where the Autonomous Communities and hospitals can enter data on certain medicines. Hospitals have access to their own data, the Autonomous Communities to the data of their entire community, but not to that of others, and the State to all the information. Currently, and for the time being, Valtermed records data on 11 high-impact drugs, most of which have an agreement signed with the SNHS for payment of results.[269] The intention is to add new medicines in the future.

[268] EMA Annual Report, 2019.

[269] Payment-by-results agreements are a type of risk-sharing agreement between laboratories and the SNHS. These are often implemented when there are uncertainties about the clinical effectiveness of the medicine. For example, such an agreement may involve the laboratory

The enormous scope of this tool for clinical management is clear. **If Valtermed were to become a benchmark in the healthcare field, it could provide crucial information for the optimisation of treatments, funding, price adjustment and risk sharing between the authorities and operators in almost real time**, with the end patient benefiting from this improvement in healthcare management, and the sustainability of the healthcare system being boosted.

On the one hand, in terms of better risk sharing between the authorities and operators in real time, risk-sharing agreements (see Box 7) would be easier to implement in the healthcare setting if there were sufficient information and data on the therapeutic effectiveness of medicines over time. The use of the information included in the Valtermed registers could be used to improve the implementation, monitoring and management of these agreements, which could considerably improve the sustainability of the SNHS and increase the efficiency and management of the health system as a whole. The use of this data should be encouraged, especially, but not only, for drugs with a high budgetary impact, and their management could be optimised through the use of big data tools, such as the Valtermed register. To this end, **the Ministry of Health ought to develop the Valtermed database further**, including a large number of new medicines on the platform, and implementing an appropriate information system that allows data on the therapeutic effectiveness of these medicines to be extracted easily and completely. To this end, it would be advisable to promote the interoperability of databases, such as Valtermed, with the information contained in the clinical records of SNHS patients, as well as an automatic feedback system, so that the common data would be displayed simultaneously in the databases and clinical records. This would facilitate the work of clinicians in terms of the collection and compilation of data, given that they would only have to be entered once, after which they would be automatically replicated in all the databases containing information on the patient. This same procedure could be applied to the results of diagnostic tests.

Only having to enter the data once would facilitate the completeness of clinical records and their associated databases, improving the evaluation and comparability of treatments by type of population (age, pathology, gender, etc.). For this to be possible, however, it would be necessary to further standardise and integrate the health systems of the different Autonomous Communities.

In this regard, it is important to take advantage of the framework provided by the Digital Health Strategy approved by the Ministry of Health in November 2021, which includes as one of its strategic lines the strengthening of data analytics and

repaying the public health system for treatment for patients who do not respond to the medicine.

the exploitation of information for the 'business intelligence' of the SNHS, linked to the creation of a Health Data Space. This Health Data Space could also facilitate data sharing between the different information systems and, in this way, provide access to relevant information and its processing to obtain conclusions.

Box 7

RISK-SHARING ARRANGEMENTS

Risk-sharing agreements are generally agreements signed between the drug company and the hospitals, or the authorities. There are two types:

- Health outcome agreements (payment-by-results schemes): these are implemented when there is uncertainty about the clinical effectiveness of the medicine, whether or not there is financial uncertainty. For example, such an agreement may involve the laboratory repaying the public health system for treatment for patients who do not respond to the medicine. They require a complete therapeutic register (of clinical data, patient data, treatments, treatment response, etc.) and are therefore complex to manage.
- Financial agreements: these should be adopted when there is uncertainty in terms of the budget or the number of patients to be treated. They can take many forms: price-volume agreements, cost ceilings, or a combination of these. Cost ceilings, in particular, are useful when there is uncertainty about the number of patients to be treated, or the duration of treatment.

In both schemes, patient perceived value can be considered as a variable to be taken into account. Within the framework of these agreements, follow-up meetings are held with those responsible for marketing the medicine in which, in the light of the information that is generated, the terms of the agreements, the patient entry criteria and other variables contained in the agreement can be modified.

For example, in payment-by-results agreements, the criteria for patient responders are set on the basis of expected results from clinical trials (or from clinical practice if they have previously existed in other countries and there is access to this data). However, the criteria are binary, in the sense that they are used to decide whether or not a patient stays on the medication. There are no gradations or any mention of a lower payment in view of poorer results than expected. In other words, if the criteria for the continuation of treatment are not fully met, the patient is excluded from the treatment.

This binary approach to the use of medicines may not be the most appropriate. It would be more efficient to use therapeutic effectiveness data not only to determine whether or not a patient receives treatment, but to **modulate the prices of medicines by taking into account actual therapeutic effectiveness.** In other words, when therapeutic outcomes are below those expected and included in the payment agreements, the price for that patient's treatment should

be decreased proportionally to the lack of outcomes, or payment for the treatment should even be suspended (this would not mean that the patient would stop receiving the medication, and they could continue to benefit from it if it is partially effective). In particular, Valtermed's information on the actual therapeutic effectiveness of medicines could be used to transfer part of the risk of lower effectiveness to pharmaceutical companies, without the entire risk having to be borne by the SNHS. This **dynamic results-based pricing adjustment approach** would be possible thanks to the use of the data generated in Valtermed.

In terms of the **information included in Valtermed**, neither access to the data nor the configuration of the Valtermed data registry is public. However, the pharmaco-clinical protocols for the use of the drugs included in Valtermed, which have been developed by a group of independent experts and approved by the Standing Committee on Pharmacy, are public. Each protocol includes a description of the treatment objective, patient selection criteria, general treatment considerations, the outcome variables according to the objectives set out in the outcome payment agreements (if such agreements exist), and the data necessary to evaluate and monitor the medicine. It is, therefore, information on the treatment, use and effectiveness of the medication.

The **information included in Valtermed should be accessible to healthcare professionals**, who should have access to the therapeutic assessment of a large number of different patients and profiles, enabling problems in clinical practice to be pinpointed *ex ante*, identifying clinical subgroups with lower or higher effectiveness, and characterising the uncertainty or long-term outcome of treatments by patient type, among other potential benefits. If access to the information could generate problems in terms of data confidentiality, anonymised or aggregated access to the information could be achieved.

3.2. Generic medicines

Most current pharmaceutical policies include the promotion of the use of generic medicines in healthcare systems. This is because these generate significant savings, without harming patients, while also encouraging competition with originator medicines and promoting prices closer to the marginal costs of production.

In this regard, the US Food and Drug Administration (FDA), in a 2019 report, quantified the savings generated by the entry of generic drugs into the market.[270]

[270] '*Generic Competition and Drug Prices: New Evidence Linking Greater Generic Competition and Lower Generic Drug Prices'*, Food and Drugs Administration (FDA), 2019.

According to the FDA, the entry of a generic medicine into competition with an originator reduces the price (LSP) of the medicine by 39%. With two generic competitors, the price (LSP) is reduced by 54%, with four generic competitors by 79%, and with six or more competitors, LSP reductions of more than 95% are seen compared to the prices of the originator.

As discussed in Section 2.2.3, the market share of generic medicines has undergone substantial changes in recent years. When the previous economic crisis started in 2008, generics had a small market share (9% in value terms) but this grew rapidly up to 2013, with them gaining market share to the detriment of originator medicines and doubling their turnover. However, from 2013 onwards their growth slowed, reaching a peak share of 23% in 2015 and stagnating, or decreasing slightly, thereafter.

The evolution of the pharmaceutical market is related to cyclical factors, such as those caused by economic crises, as well as to regulatory reforms and patent expiry. While the strongest growth period for generics saw the expiry of the patent on high-consumption medicines, a series of regulations were also successfully implemented that encouraged their penetration and undoubtedly contributed to their breakthrough[271]. These regulations included the generalisation of prescription by active ingredient and not brand name, and positive discrimination in the dispensing of generic medicines, at the same price as the originator. The subsequent stagnation in generic penetration since 2015 has probably been at least partially due to the elimination of this positive discrimination and more lax prescribing by active substance.

It should be borne in mind that generic medicines introduce competitive tension into the market by competing with originator medicines at lower prices (due to lower production costs). It is therefore appropriate to assess the functioning of the generic medicines market and the measures currently in place, in particular the pricing system, to determine what factors are influencing the development of generics and effective competition in the market for funded medicines distributed through pharmacies.

In this regard, it should be noted that almost all respondents to the CNMC's Public Consultation on medicines advocate a reform of the Reference Pricing System (RPS).[272]

[271] Spanish Association of Generic Medicines (Asociación Española de Medicamentos Genéricos; AESEG).

[272] According to these, the RPS lacks flexibility and poses a number of problems, such as proportional pricing based on the defined daily dose (DDD), lack of price competition, reduced incentives for innovation, little flexibility to raise prices when losses are incurred, or bundling

This is followed by an assessment of the current **reference pricing system** and **incentives for using generic medicines**. The purpose is to detect those factors that limit competition between generic and originator medicines and to identify measures to promote the correct competitive functioning of this market. Likewise, and as a complement to the RPS, later sections delve into the importance of developing **healthcare information and education programmes** for consumers and patients. Finally, there is an assessment of **public procurement systems**.

3.2.1. Reference Pricing System (RPS)

Although the RPS aims, among other things, to encourage price reduction and competition between medicines, **in practice the system has reduced, to the point of almost eliminating, competition in terms of reimbursement prices to the SNHS and prices at the final consumer level (RP)**, by taking into account voluntary price reductions submitted by laboratories in the annual review of the reference prices and by allowing other operators to match voluntary price reductions submitted by a laboratory. **Competition is thus limited to the existence of competitive discounts in the distribution channel in favour of distributors and pharmacies**, the average of which is estimated to be as high as 40%. These savings, however, have been absorbed by the wholesale and retail channel and have not been passed on to the SNHS or to patient-consumers and, therefore, have not led to reductions in public spending.[273]

The CNMC considers it advisable to **reform the Spanish RPS** in order to promote the proper functioning of the market, to the benefit of consumers and social welfare. To this end, the following will be analysed: (i) the initial pricing criteria in the RPS; (ii) incentives for lowering prices; (iii) the prescription policy; and (iv) the definition of reference pricing sets.

3.2.1.1. Initial pricing criteria

In Spain, despite not being contemplated in the current regulation, in practice, the first generic medicines enter the market with an initial **price that is 40% lower** than that of the originator medicines; this is then integrated into the reference pricing sets. This way of automatically setting the initial price of generic drugs is

based on the ATC5 , including drugs with different active ingredients. On the other hand, they also consider the system of homogeneous groupings to be very confusing as it is currently set up.

[273] There are alternatives to the Spanish reference pricing system, such as the (more flexible) Portuguese model, where the authorities set a maximum reimbursement price, allowing laboratories to compete with prices both above and below the reimbursement price. This scheme encourages competition between the different laboratories.

not appropriate, and introduces distortions to competition[274]. Although the initial price reduction represents clear budgetary savings, this price intervention may be limited to the short term[275]. There is evidence that countries that initially apply higher discounts obtain lower savings overall (in the medium and long term) due to **not having introduced the right incentives for the market to function competitively** over time[276].

In particular, under the current reference pricing system, operators are guaranteed a reimbursement price that is initially 40% lower than the price of the originator medicine at the time of going off-patent. This **removes incentives to offer discounts or lower upfront prices** because the authorities reimburse the full reference price to the laboratories. At the wholesale and retail channel levels, however, laboratories do have incentives to offer discounts, or other incentives, in order to increase their market presence, with wholesale and retail operators benefiting from these discounts, rather than public authorities or patients.

To alleviate these problems, and to encourage competition between upstream operators beyond the distribution channel level, a **more flexible reference pricing system is necessary.** This overall reform of the reference pricing system, which would also affect the initial price criteria, is discussed in more detail in the following section.

If this reform is not carried out and the current system is maintained, it would be advisable to introduce **differentiated pricing** mechanisms between originator medicines and generics for an initial period of time, **delaying the creation of the reference pricing set**, in order to encourage competition between them. This would facilitate the entry of generics once patents expire and would compensate for the market power that the originator medicine carries over from its previously exclusive period, allowing the generic medicine to gain market share over the originator medicine more quickly.

For this measure to be effective, it is also necessary to encourage the **rapid penetration of generics**. In Spain, 32.1% of generic molecules are launched within 24 months of patent expiry, compared to 46.4% in Portugal and 46.7% in the UK.[277] To expedite the penetration of generics, it is desirable to develop actions at the stage when the medicines are included in the SNHS

[274] Ministry of Health and Rovira et al. (2012).
[275] OECD (2018).
[276] Kanavos (2014) shows how the United Kingdom, Sweden and Denmark record generic prices with discounts of around 70% within 24 months of entry. In Spain, this figure did not reach 40% in those two years and, above all, it showed very little downward movement after its introduction
[277] AIReF –"Spending Review: Medicamentos dispensados a través de Receta Médica", 2019.

pharmaceutical service, for example, by speeding up the evaluation of generic medicine dossiers and reducing their processing time.

The Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilars and generics[278], approved by the Standing Committee on Pharmacy of the SNHS Interterritorial Council [279] in September 2019, points in this direction[280].

3.2.1.2. Incentives to lower prices

The interaction between the RPS, the Homogeneous Grouping System and the rules for dispensing medicines means that the **incentives for laboratories to voluntarily lower prices are very low or even non-existent.[281]** The current Homogeneous Grouping System, complementary to the RPS, allows laboratories to request a price drop within their homogeneous grouping. In practice, such voluntary price reductions do not occur frequently, as other manufacturers are

[278] The CNMC published a report (INF/CNMC/059/19) on the draft of this plan. In it, the Commission considered that the proposed strategy is positive because these drugs are an opportunity to boost competition, and it issued a series of recommendations to improve some aspects of the proposal.

[279] The Interterritorial Council of the SNHS is the permanent body for coordinating, cooperating, communicating and informing the autonomous health services and State authorities (Article 69 of Law 16/2003, of 28 May, on the cohesion and quality of the Spanish National Health System).

[280] The Standing Committee on Pharmacy of the National Health System (SNHS) Interterritorial Council agreed, on 24 September, 2019, to approve the update of the "Action Plan to promote the use of market-regulated medicines in the National Health System: biosimilar and generic medicines". It was also agreed to open a public consultation period to gather input from stakeholders, through the organisations or associations that represent them.
According to information provided by the Ministry of Health following a request for access to public information through the Transparency Information Unit of the Ministry of Health (File 001-055318, available at https://www.actasanitaria.com/wp-content/uploads/2021/06/Fcia-Expediente. pdf), in September 2020 the Standing Committee on Pharmacy of the SNHS Interterritorial Council approved a new version of the "Plan for the promotion of generic and biosimilar medicines in the SNHS", which includes some new features with respect to the previous one, although it will not be published until it has been ratified by the SNHS Interterritorial Council.

[281] See Section 2.2.2. The system of homogeneous groupings is complementary to that of reference prices. Homogeneous groupings are narrower than reference sets, as each homogeneous grouping integrates the dosage forms of funded medicines with the same active substance, dosage, content, pharmaceutical form and administration route, whereas the RPS reference sets are groups of medicines comprising all drug dosage forms included in the SNHS pharmaceutical service that have the same level, 5, of the World Health Organisation's anatomical-therapeutic-chemical classification of medicines (i.e., ATC5) and administration route.

encouraged to lower their prices to match.[282] This is due to the established dispensing regulations, whereby only medicines with the "lowest price" in their homogeneous grouping can be dispensed by the pharmacy, when funded by the public purse. In other words, in order to be dispensed by pharmacies, laboratories must match the initial voluntary price reduction, aligning themselves with the "lowest price" in their homogeneous grouping. The result of this dispensing policy is that all medicines in the same homogeneous grouping (the originator medicine and its generics) have strong incentives to set the same price. On the other hand, these price decreases are passed through to the annual calculation of the reference pricing of the reference set. There are therefore limited incentives for voluntary price decreases below the reference pricing.

The **system thereby functions as a price-cap system** with limited incentives for lowering prices, leaving no scope for competition and no greater margin in terms of consumer choice. The **dynamics of the system are also unclear**: the homogeneous grouping system interacts with the reference pricing system, which complements the former. In each there are different price thresholds with a somewhat misleading name ("reference pricing", "lower price", "lowest price", etc.), affecting larger (reference sets) or smaller (homogeneous groupings) sets. These terms are confusing, misleading and overlapping. In addition, prices in both systems are updated at different times (annually, reference pricing; quarterly, lower prices; and monthly, lowest prices), increasing the complexity and confusion within the system. It is therefore necessary to review both systems in order to eliminate confusing dynamics, clarify concepts and streamline the functioning of the reference pricing and homogeneous grouping systems.

All of the above results in **reduced effective competition**, not only at the **price level**, but also by **limiting the decision-making capacity of the patient-consumer**, who does not decide on the medicine to be dispensed, as the pharmacist must dispense the "lowest price" medicine[283].

Competitive pressure only exists at the industrial and wholesale (LSP) levels, through the discounts that laboratories offer in the channel to distributors and pharmacies. These discounts are not passed on to the consumer, as they are not reflected in the selling price (RP), which cannot be changed[284]. They do, however, benefit distributors and pharmacies, as they translate into an additional margin for them.

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[282] Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilar and generic medicines.

[283] See box 5 in Section 2.2.2.

[284] See Section 2.2.2. Article 91.3 of the Consolidated Text prohibits discounts on medications subject to medical prescription dispensed in pharmacies.

To alleviate this situation and improve the reference pricing system, in September 2019, the Standing Committee on Pharmacy of the SNHS Interterritorial Council approved the Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilar and generic medicines[285]. The plan includes a series of proposals to modify the RPS.

The main measure involves allowing a lower price than the reference price without affecting the calculation of the reference price in its annual review. The incentive for these voluntary price reductions is that the drug from the manufacturer that has offered the greatest "discount" ("**lowest discounted price**") must be dispensed, and that these voluntary price reductions will not impact the Ministry's annual review of the reference price. In the event of a voluntary price drop, other laboratories will have to match the reduction or offer even lower prices in order to sell their products.

Although this proposal improves the situation compared to the previous system, it **raises serious doubts about its effectiveness:**

- It is unclear to what extent it would reduce the incentive for operators to align around the reference price, with minimal markdowns.
- It does not correct the scant or non-existent margin for the patient-consumer to make a decision as to which medicine will be dispensed.
- Temporary monopolies can still be generated if the other laboratories do not match the discount offered. This implies a risk of market foreclosure if one laboratory offers a discount that the other laboratories cannot match because they incur losses, with the aim of driving them out of the market and reducing the number of suppliers (and thus competitors).

The Action Plan proposal does not appear to fully address the **problematic aspects of the RPS.**

The Spanish reference pricing system bears no resemblance to the theoretical model most widespread in other European countries. The existing pricing systems in other countries are usually based on a reference pricing system, which sets the maximum level of funding/reimbursement for the medicine, but higher prices are allowed, and lower prices are encouraged through voluntary reductions. This is the case, for example, in Denmark, the Netherlands and Germany, as well as others.

[285]The CNMC published a report (INF/CNMC/059/19) on the draft of this plan. In it, the Commission considered that the proposed strategy is positive because these drugs are an opportunity to boost competition, and it issued a series of recommendations to improve some aspects of the proposal.

- Denmark[286]: Denmark does not regulate the prices for pharmaceutical medicines, both originator and generic, exposed to competition. The prices are reported to the Danish Medicines Agency, which in turn publishes the selling price and the subsidised (or reference) price. The prices are set every two weeks. This means that laboratories can announce changes in their prices and product range every fortnight. The product with the lowest price in the respective group automatically becomes the most subsidised reimbursement price.

  The pharmacist is obliged to offer the lower-priced medicine, but the patient may choose another medicine if they wish. In this case, the patient must pay the difference in price ("avoidable co-payment").

- The Netherlands[287]: most health insurers only reimburse the cost of the cheapest version of a medicine containing the same active ingredient. This is known as preferential policy. By supplying cheaper versions of the same medicine: (i) health insurers spend less money on medicines; (ii) this allows them to keep premiums low; and (iii) patients pay the lowest price for the medicine. If a patient uses a medicine that costs more than this amount, they must pay the difference ("avoidable co-payment").

- Germany[288]: pharmaceuticals included in the same reference pricing group are assigned a maximum reimbursement price. If the price of the medicine exceeds the maximum reimbursement price, patients pay the difference. To contain pharmaceutical expenditure, pharmacists must suggest replacing the medicine with its cheaper generic, if available. Also, if the patient's health insurance has negotiated with a pharmaceutical company and agreed a lower price (or discount) on a prescribed medicine with the same active ingredient, the pharmacist is obliged to dispense the medicine to which the discount applies.

There is evidence that *price-cap* regulations, such as in the Spanish system, lead to a higher equilibrium price level than would result in the absence of this kind of regulation[289]. Meanwhile, in the case of reference pricing systems with a

[286] Danish Medicine Agency.
[287] Government of the Netherlands.
[288] Pharmaceutical Reimbursement and Pricing in Germany, OECD (2018).
[289] Puig-Junoy (2010) includes a review of articles published in English or Spanish between January 2000 and July 2009. The inclusion criteria included studies with quantitative empirical results for EU countries on the impact of '*price capping'* and/or reimbursement price regulation (reference pricing or similar systems) on price dynamics in relation to pharmacy sales of generic medicines. Among other things, the study concludes that the available evidence

maximum reimbursement price but no *price-cap*, the evidence suggests a clear reduction in the end-user price of medicines. In this respect, in some countries it has been observed that generic medicines priced below the reference price do not make further price reductions until the reference price decreases, even when there are other cheaper generic medicines on the market. In other words, there is an absence of price competition below the reference price[290]. For this reason, incentives should be provided for pharmacies to dispense the lowest-priced competing medicine (either generic or originator medicine) in order to enhance price competition within reference sets. It should also be possible to update the reference price more frequently.

Furthermore, studies on pricing policies indicate that allowing generic operators to set their own prices, together with incentives for clinicians and pharmacists to prescribe and dispense the lowest-priced medicines, is more effective in reducing prices over time than controlling prices through regulations.[291]

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indicates that ' *price-cap'* systems, similar to the one in Spain, result in higher medicine price levels. Conversely, systems with no ' *price-cap*' have lower price levels.

[290]See Puig-Junoy J. Impact of European pharmaceutical price regulation on generic price competition: a review. *Pharmacoeconomics*. 2010;28(8):649-663.

[291] See Wouters and Kanavos (2017) where generic drug prices and market shares in 13 European countries were compared, using 2013 data, to assess differences between countries. The article also reviewed evidence from recent studies on the pricing and use of generic medicines in Europe and the United States; it also examined peer-reviewed studies and books published since 2000, among other things. Wouters, O. J., Kanavos, P. G., *and* McKee, M. *(*2017*).* Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. London School of Economics and Political Science; London School of Hygiene and Tropical Medicine

Articles reviewed include:

- Danzon PM, Chao LW. Cross-national price differences for pharmaceuticals: how large, and why? *J Health Econ*. 2000;19(2):159-195.
- European Commission. *Pharmaceutical Sector Inquiry—Final Report*. Brussels, Belgium: European Commission; 2009.
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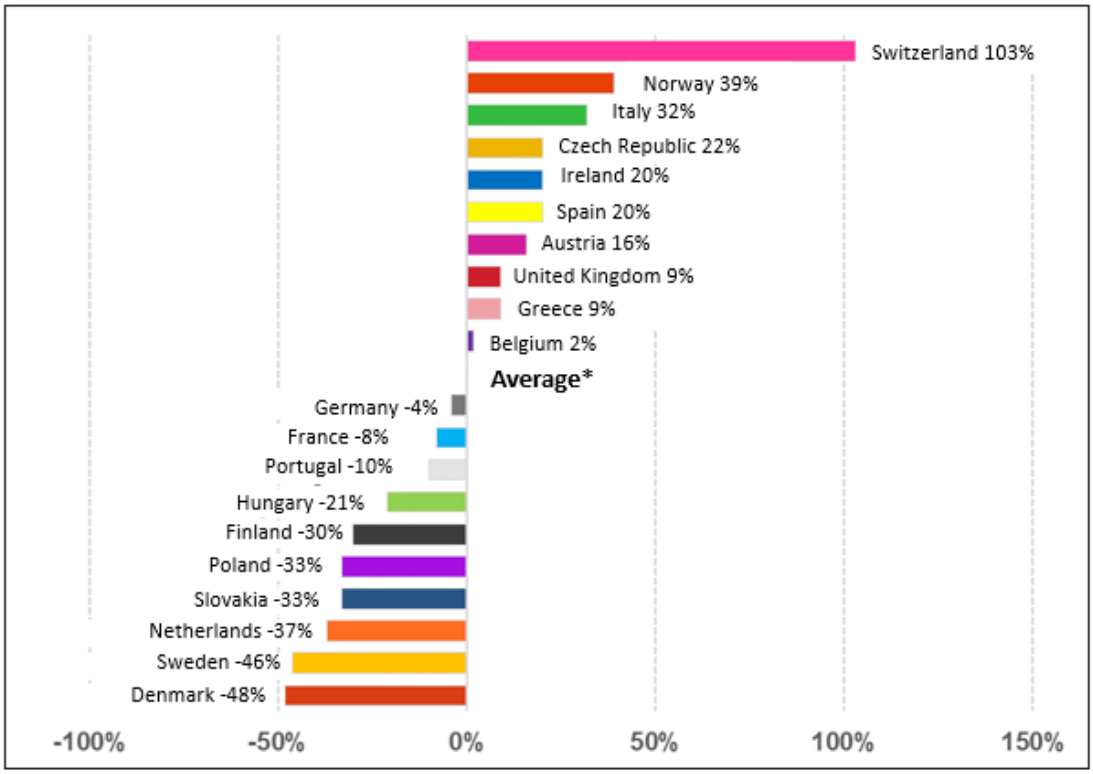
It is worth noting that this is the approach adopted in Denmark and Sweden, although in the Swedish case the authorities reserve the right to block significant price increases for generics. Under this type of pricing system, increases exceeding a certain percentage threshold could be blocked by the national authorities on economic or public health grounds (except for those increases that are for verifiable reasons beyond the control of the manufacturers, e.g. changes in the prices of active ingredients).

Figure 15: Competing Drug Price Comparison, 2021



Source: Swedish TLV (*Dental and Pharmaceutical Benefits Agency*) annual international drug price comparison report, 2021. The data includes an analysis of 623 competing medicines, is sourced from IQVIA and covers 89% of sales in Sweden in 2021. The figures reflect the percentage deviation in each country of the price level of the analysed medicines from the average of all the countries included in this analysis.

*: 'Average' is the average price level of the medicines analysed. The comparison includes average prices from the following European countries: Switzerland, Norway, Italy, Ireland, the Czech Republic, Spain, Austria, the United Kingdom, Greece, Belgium, Germany, France, Portugal, Hungary, Finland, Poland, Slovakia, the Netherlands, Sweden and Denmark.

As the figure above illustrates, the Netherlands[292], Sweden and Denmark are the three countries with the lowest average prices for competing medicines (originator and generic) of all the European countries analysed in the Swedish authority's report.[293] In contrast, Spain, together with Ireland and the Czech Republic, is the country with the fourth highest average prices for medicines in competition, the average price being 20% above the mean of the EU countries

[292] The Netherlands limits the avoidable co-payment to 250 euros per year per patient. If this threshold is exceeded, insurers must cover the remaining amount.

[293] Data from the Swedish agency report was provided by IQVIA.

analysed.[294] As noted above, Denmark, Sweden and the Netherlands have all implemented pricing policies for competing medicines (originator and generic) that allow laboratories to set their prices above the reimbursement price, together with the introduction of incentives to prescribe and/or dispense lower-priced products.

Similarly, **RPS systems with flexible pricing and avoidable co-payment** see increased market penetration of generics.[295] These systems foster competition (i) through differentiation, and (ii) price competition.

Medicines, both originator and generic, can compete on the basis of **differentiation** (or a higher positioning of the medicine through a higher price). In this case, the consumer can either choose to buy these higher-priced medicines (above the reference price), by paying an additional input, or choose a lower-priced medicine. This is known as **"avoidable co-payment"**.

While differentiation is possible for all medicines if they invest a sufficient marketing effort, originator medicines would be the natural candidates to differentiate themselves from generics through higher positioning (higher prices), as they have significant market power[296].

Allowing higher prices ensures that former incumbent operators of innovative medicines do not distort, or hinder, the penetration of operators in the generic market. Experience shows that this system, unlike the current one, promotes competition in the market and permits efficient solutions to be found.

On the other hand, a competitive reference pricing system encourages competition among generics through **voluntary price reductions** in order to gain market share. These voluntary price reductions should not lead to potential temporary monopolies, and **it is necessary to change the current dispensing policy to one that does not force pharmacists to dispense the lowest priced medicine.** The decision on which medicine to dispense should be indicated, not imposed.

In relation to the above, the available empirical evidence suggests that the market share by volume of generic medicines depends on the price reduction adopted

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[294] The analysis includes the average price in 20 European countries: Switzerland, Norway, Italy, Ireland, the Czech Republic, Spain, Austria, the United Kingdom, Greece, Belgium, Germany, France, Portugal, Hungary, Finland, Poland, Slovakia, the Netherlands, Sweden and Denmark.

[295] Health at a Glance, OCDE, 2018.

[296] Article 80 of the Consolidated Text prohibits the advertising of medicines subject to medical prescription in Spain. For this reason, marketing would focus on sales and promotion efforts aimed at the distribution channel or prescribers through pharmaceutical sales representatives, among other strategies.

by the originator medicine's laboratory; [297]in other words, the volume share of the generic would not be expected to increase if the originator medicine's laboratory lowers its price to the same level as the generic. This evidence therefore indicates that reference pricing schemes do not increase the overall use of generics if the price of the originator decreases to the level of the reference price of the generic, as is the case in Spain, where, due to dispensing regulations, there are few incentives for voluntary price decreases and strong incentives to align the prices of competing medicines (both originator and generic) around the reference price.

The above information leads **the CNMC to suggest the implementation of a more flexible RPS than the one proposed, allowing laboratories to set the LSP in an unregulated manner.** The maximum reimbursement price would be set according to the reference price of each medicine, and laboratories could choose to set the LSP below or above the medicine's reference price. In the event that the LSP is below the reference price, the SNHS would reimburse the lower price. The patient's co-payment would be calculated on the basis of the LSP, so they could also benefit from lower co-payments than in the current (and proposed) system. In the opposite case (medicines priced above the reference price), the reference price would be reimbursed, with the consumer paying the difference between the reference price and the LSP.

This alternative of flexible pricing, supported by measures to encourage the market penetration of generics in order to multiply the number of competitors, **is one of the measures proposed by the European Commission and the OECD.**[298] In such a system, developing the right measures and incentives to encourage the entry of new generic operators into the market is the key to achieving an adequate level of effective competition.

Finally, such a system would eliminate other problems with the current RPS:

- The reference set comprises those medicines with the same ATC level, 5, and administration route, without distinguishing the pharmaceutical configuration (capsules, sachets, tablets, etc.). The **price** is calculated proportionally to the defined daily dose for the whole set and **does not**

[297] See Kanavos (2014). The article develops a methodological framework to assess the performance of generic pharmaceutical policies after patent expiration in non-tender settings, comprising five indicators: availability of generics, lag time and speed of generic entry, number of generic competitors, the evolution of prices and the evolution of generic market share in terms of generic volume. To this end, a number of techniques for assessing performance are proposed. The paper then tests this framework in twelve EU member states using IMS data on 101 off-patent molecules over the period 1998-2010. Kanavos P., 2014, Measuring performance in off-patent drug markets: A methodological framework and empirical evidence from twelve EU Member States, Health Policy Volume 118, pp. 229-241.

[298] Carone, G., Schwierz, C., & Xavier, A. (2012).

take into account the different pharmaceutical configurations. However, it does not usually cost the same to produce the different pharmaceutical configurations (capsules, tablets, sachets, injectables, etc.), so this could lead to the higher-cost forms ceasing production.

In other words, different dosage forms within a set are funded at a price proportional to the defined daily dose. For example, a medicine with a 400 mg dose is funded at half the price of an 800 mg dose, when the cost of production is often not a perfect arithmetic mean.

An **RPS with flexible pricing would eliminate this problem by allowing different prices for distinct pharmaceutical configurations.** This would eliminate the risk of certain pharmaceutical configurations being driven out of the market due to lack of profitability and provide incentives for investment in new formats or administration routes.

- At times, the **reference prices of some medicines do not cover the cost of production**, which can lead to problems of shortages and cessation of production, for example, when the cost of raw materials rises.

  Although the reference pricing system makes it possible to increase prices, it does not do so systematically, nor does it adjust them over time; therefore it does not provide a rapid and effective solution to these circumstances. **A flexible pricing system would allow prices to be adjusted automatically**, eliminating the risk of market foreclosure or the exit of operators from the market due to a lack of economic viability.

This change in the general mode of intervention would not preclude the possibility, in areas and circumstances where market shortcomings are detected or where there are other overriding reasons of general interest, of adopting, either temporarily or structurally, more intensive intervention measures, including the establishment of maximum prices when this is necessary and proportionate in accordance with overriding reasons of general interest, such as the protection of public health, equal access to medicines, or the protection of certain disadvantaged groups.

3.2.1.3. Prescription and dispensing policies

Article 87 of the Consolidated Text establishes that the **prescription** of medicines included in the RPS or homogeneous groupings must be made **according to active ingredient**, although it includes a series of **exceptions** for chronic diseases, in the case of non-substitutable medicines and when the principle of greater efficiency for the system is respected.

When a prescription is written according to active ingredient, the pharmacist **will dispense** the medicine with the **lowest price** in its homogeneous grouping. If the prescription includes a name or brand name, the pharmacist must dispense the medicine prescribed by the doctor. In this case, the prescription aid systems that the health services in the Autonomous Communities make available to healthcare professionals to assist them in their clinical activity could incorporate criteria that encourage efficient prescribing. For example, these systems could introduce indicators or a drug ordering system that would help healthcare staff to identify those medicines that were the most suitable for the patient's treatment and that were the most cost-effective, thereby reinforcing both treatment quality and the economic sustainability of the SNHS, as envisaged in the regulation.[299]

The Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilars and generics proposes modifying the Consolidated Text so that, in general, medicines are prescribed on the basis of their active ingredient, except for those medicines that cannot be substituted by the pharmacy, as well as introducing the obligation for pharmacists to dispense the medicine with the lowest discounted price. These measures were previously in effect between 2011 and 2015, coinciding with the strongest period of market penetration by generics in Spain (see Section 2.2.3).

The CNMC considers the prescription, more generally than in the present Law, by active ingredient to be positive, as it **favours the introduction of generic medicines into the market** by promoting price competition.[300] It also promotes innovation and transparency, mitigates conflicts of interest between doctors and the pharma industry and improves patient information[301].

Additionally, although compulsory substitution has existed in the past, with respect to the lowest priced medicine, it still raises competition concerns. Any **obligation to dispense the lowest-priced medicine increases the risk of creating a temporary monopoly** for the period of time that the medicine in question has the lowest price; **it also generates price alignment around the lowest price offered.** This, as noted above, entails two risks: (i) the general loss of incentives to lower prices, for fear of a price war between competing laboratories, encouraging price alignment around a price above that which would be derived in a competitive market; and (ii) in the case of larger laboratories, it could generate incentives to offer the drug at very tight margins in order to drive their smaller competitors out of the market, as these would incur losses if they tried to compete at that price, thus enabling larger firms to take over the entire

[299] Article 87 of the Consolidated Text.
[300] Provided that such a prescription is therapeutically correct and in accordance with the special circumstances of chronic patients.
[301] CNMC (2019).

market. In the short term this would benefit the SNHS in terms of savings, but in the medium and long term the monopolising laboratory could raise drug prices above the initial level, to the detriment of the SNHS and general welfare.

To correct this situation, it is **advisable to alter the pharmacist's obligation to substitute** the lowest priced discounted medicine with an indicated substitution. Under this system, the pharmacist would be obliged to inform the consumer of the alternatives in terms of the prices and medicines available on the market for each prescription, and the consumer would ultimately be able to decide which medicine to buy. If there are medicines priced below the reimbursement price fixed for its grouping, the pharmacist should dispense one of the medicines below that price. This would correct the practice of dispensing only one medicine (the "lowest discounted price"), increasing the variety of medicines dispensed, the patient-consumer's choice and the level of competition. This does not preclude the fact that in the event that there were no alternatives below the reimbursement price, and the chosen medicine was priced above the maximum reimbursement price (reference pricing), the consumer would have to pay the difference out of pocket ("avoidable co-payment").

A similar system has been successfully introduced in many countries, including Portugal and Italy, where generic medicines have historically had very low penetration levels. Both countries have opted for measures to encourage the use of generics, including permitted (non-mandatory) indicated substitution by the pharmacist, and payment of the difference between the branded medicine and the generic ("avoidable co-payment") by the consumer[302].

It should be noted that, as indicated above, this does not preclude, in areas and circumstances where there are market failures or other overriding reasons of general interest, the introduction of more intensive market intervention measures, either temporary or structural, and, in particular, the option of price caps where necessary and proportionate.

Finally, it would also be necessary, as discussed below, to change the current system of retail remuneration to a system where payments are not linked to the price of medicines in order to limit pharmacists' incentives to dispense medicines on which there is a higher retail margin.

In addition to the above, it would be necessary to reflect on the possibility of tailoring the dispensing of medicines to the treatment needs of each patient-consumer. In other words, pharmacies could provide a personalised drug dosage service to patient-consumers, who would be dispensed the number of units necessary to

[302] AESEG – Spanish Association of Generic Medicines (Asociación Española de Medicamentos Genéricos).

complete or fulfil the prescribed treatment. This personalised dosage could be implemented either manually or automatically by using drug dispensing robots that allow medication to be repackaged into single-dose or multi-dose systems. In this sense, it should be noted that this type of automated dosage in pharmacies is already used in other countries, as well as in other establishments such as hospitals and prisons.[303].

This type of personalised and automated dispensing would not only limit the over-sale of medicines in the retail pharmacy channel, but would also improve patient-consumer service, particularly for more vulnerable groups, such as the elderly or polymedicated persons, for whom a grouped dosage of medication would limit human error and facilitate treatment adherence. Introducing this kind of dispensing robots would improve dispensing efficiency and increase competition in the retail pharmacy channel.

Box 8

REFERENCE PRICING SYSTEM

Current Reference Pricing System:

Example of a reference set with 1 originator drug and 4 competing generic drugs.
- Price (LSP) of an innovative medicine (during the patent period): 100 euros.
- Price of the reference set (and LSP) is 40% lower than the price of the reference drug: 100 x 0.6 = 60 euros.

The price can be revised quarterly or annually by the Ministry of Health, but it continues to be the same for all the drugs included in the reference set.

Proposed Reference Pricing System:

A system is proposed where the reference price is a maximum SNHS reimbursement price, and the selling price (LSP) of the medicine is unregulated and not linked to the reference price. Also, to encourage competition, the pharmacist is obliged to dispense those medicines whose price (LSP) is below the reference or reimbursement price.
Example of a reference set with 1 originator drug and 4 competing generic drugs.

- Price (LSP) of an innovative medicine (during the patent period): 100 euros.
- Reimbursement price of the initial set is 40% lower than the reference drug price: 100 x 0.6 = 60 euros maximum.
- Unrestricted sale price (LSP):

i. Originator LSP = 65 euros.
ii. Generic_1 LSP = 62 euros
iii. Generic_2 LSP = 60 euros
IV. Generic_3 LSP = 57 euros
v. Generic_4 LSP = 53 euros

With the new proposed system, the pharmacist will only be able to dispense those medications that fall below the set reimbursement price, in other words: generic_3 and generic_4.

[303] Catalan Competition Authority (ACCO).

The reimbursement price that the SNHS must pay to the laboratory generates a saving with respect to the current reference price system:

- Reimbursement price: 57 euros for generic_3, instead of 60 euros.
- Reimbursement price: 53 euros for generic_4, instead of 60 euros.

The co-payment incurred by the patient-consumer will also be lower when calculated according to the sale price (LSP), either 53 or 57 euros rather than 60 euros.

Finally, medicines that have been excluded from the market have incentives to lower their prices below the reference/reimbursement price in order to become competitive and be dispensed once more.

3.2.1.4. Definition of reference sets

It is common for medicine regulations to define reference sets based on the ATC classification of the World Health Organisation[304]. The classification ranges from broader groups of medicines (starting with ATC1, anatomical level) to narrower groups (ATC5, name of the active substance or drug combination). At least 20 EU Member States use reference pricing systems, generally based on sets established at the ATC5 level. Other countries such as the Netherlands and Germany establish broader sets that include alternative substances with the same therapeutic indication (ATC4)[305].

In Spain, from 2014 to 2019, the Ministry of Health established, in practice, sets based on the ATC5 level.[306] The Supreme Court has annulled various sets based on the ATC5 level in several rulings since 2017, on the grounds that the Ministry lacked a legal basis.[307] Among others, are rulings on the following laboratories:

[304] The ATC classification is a European five-level coding system for pharmaceutical substances and medicinal products according to the effect or system or organ and pharmacological effect, therapeutic indications and chemical structure of a drug. The five levels are as follows: first level (anatomical): organ or system on which the drug acts (there are 14 groups in total); second level: therapeutic subgroup; third level: therapeutic or pharmacological subgroup; fourth level: therapeutic, pharmacological or chemical subgroup; fifth level: name of the active substance or association of medicinal products. Each drug has its own ATC code, which is specified in its data sheet. Saladrigas, M.V. (2004). *El sistema de clasificación ATC de sustancias farmacéuticas para uso humano*. Panace, *5*(15), 59.

[305] Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilar and generic medicines.

[306] Although between 2014 and 2020, Art. 98.2. of the Consolidated Text established that "The sets will include all the funded drug dosage forms that have the same active ingredient and the same administration route".

[307] According to the Supreme Court, there was no regulation that expressly empowered the authorities to form reference groups according to the ATC classification, and therefore, in adopting this system to determine the reference groups, the Ministry of Health had no legal

Zambon, Pfizer, Bayer, Novartis, Baxalta and Chiesi. For this reason, in 2019, the Ministry designed the reference sets based on the same active ingredient and administration route. However, Law 11/2020, of 30 December, on the General State Budget for the year 2021 once again redesigned the sets, returning to groupings based on ATC5 (which includes the same active ingredient or pharmacological association) and identical administration route.[308]

The change involves moving to broader reference sets than those based solely on the same active ingredient. Hence, from a competition point of view, the design of reference sets based on the ATC5 level could increase potential competition. In fact, the CNMC has previously expressed its views in this respect, even suggesting the formation of reference sets at the ATC4 level, which would imply even broader groups than ATC5; in this case, the potential competition between the medicines included in the grouping would be even greater.[309]

Specifically, the CNMC has previously indicated that there are other systems that have obtained positive results (such as in Germany and the Netherlands) where medicines with different active ingredients but the same therapeutic indication (ATC4), are included within the same group. This scope seems reasonable, clinically and economically efficient and pro-competitive for therapeutically substitutable goods with identical efficacy. It would result in larger sets, where there would be more competition between medicines. Even so, each case must be assessed on a case-by-case basis taking into account all the circumstances according to scientific criteria. It seems, therefore, that grouping by active ingredient may be appropriate in certain cases[310].

basis. Likewise, and referring to the specific active ingredients examined, the judgments rule that these must be considered different when it is accredited that they have significantly different properties in terms of safety and efficacy.

308 Thirty-second final provision of the 2021 State Budget Law, which amends the revised text of the Law on guarantees and the rational use of medicines and health products, approved by Royal Legislative Decree 1/2015, of 24 July, modifying the reference pricing system (Art. 98.2 RDL 1/2015).

309 INF/CNMC/059/19.

310 According to the specialised press, in certain cases the ATC5 and active ingredient may not coincide, as in the case of coagulation factors, which share an ATC5 but which are very different drugs both in their production technology and their safety or efficacy profiles: https://www.diariofarma.com/2020/09/22/sanidad-inicia-la-tramitacion-de-la-opr-y-renuncia-a-los-conjuntos-atc-5?&utm_source=nwlt&utm_medium=regular&utm_campaign=09/22/2020&utm_source=diariofarma&utm_campaign=548de18cd9-20160129MasLeidas_COPY_01&utm_medium=email&utm_term=0_31971fe691-548de18cd9-244618669

In short, **as long as it is clinically appropriate, the definition of reference sets should be as broad as possible in order to favour competition between the different drugs that make up the set**. This does not preclude the creation of more limited sets where this is therapeutically appropriate for medicinal products that cannot be considered equivalent in clinical practice. In these cases, exceptional sets should be applied in accordance with the appropriate clinical criteria, whether this is the ATC5 level, the active ingredient, or another appropriate designation.

The proposal included in the Ministry of Health's Action Plan to promote the use of generic and biosimilar medicines seems to be along these lines; according to this, reference sets may be formed based on dosage forms of funded medicines that share the same ATC4, defined daily dose (DDD), same pharmaceutical configuration or grouping of configurations, and identical administration route, subject to the agreement of the Standing Committee on Pharmacy for those indications that are considered cost-effective. It thus appears that, as far as possible, and always based on clinical and cost-effectiveness criteria, the Ministry is considering the option of defining broader groupings at the ATC4 level.

The CNMC welcomes this measure, and recommends, whenever possible, considering extending the reference sets to a broader scope (ATC4 or beyond) than the current level (ATC5), at least for certain therapeutic indications in which it is feasible or indicated clinically or financially. The broader the sets, the more medicines will be included in them, and the more competition there will be between the different medicines in the set. Thus, the ATC5 level should be considered as a general approach to the creation of sets, but with the aim of extending them beyond this level whenever therapeutically possible to foster effective competition in the market[311].

3.2.2. Development of health information and education programmes

Beyond the reform of the reference pricing system and prescription and dispensing rules, in order for generic medicines to exert real competitive pressure, other complementary measures need to be adopted. Specifically, the CNMC has identified the advisability of implementing **informative and**

[311] This proposal would, moreover, be in line with the recommendations included in the judgment on Servier v. Commission (Case T 691/14), 12 December, 2018, of the CJEU. This ruling raises a question about the definition of relevant markets for medicines. Specifically, the case addressed the fundamental issue of defining medicine markets from a competition perspective. Although the judgment is clearly in the field of competition law and does not seek to establish groupings of medicines for either price calculation or based on their therapeutic value, the competition analysis carried out is, to a certain extent, in line with the proposals included in the Ministry of Health's Plan, as well as those put forward by the CNMC *ut supra*.

healthcare education programmes so that patient-consumers are aware of the existing alternatives to chemically synthesised medicines (originator and generic) and can make informed decisions. There is still a lack of information on the use of originator and generic medicines among patient-consumers and the general public.

For this reason, healthcare institutions should make an effort to communicate and disseminate **clear, concise and objective information on originator and generic medicines, to clarify their use, their efficacy and the impact they have on healthcare systems.** Information-giving initiatives in medical centres are therefore necessary, and there is a need for pharmacists themselves to be able to inform the general public about these medicines.

In addition to these direct patient-consumer information initiatives, information and health education programmes or campaigns could be carried out through other channels. Possible initiatives include the following:

- TV and radio campaigns.
- Informative brochures/posters.
- Seminars and conferences.
- Websites and social media.
- Press releases.

These initiatives should be aimed at clarifying the doubts that exist about the use of originator and generic medicines among the general public in terms of quality, safety, and the value of medicines. They should also stress the importance of increasing competition as a key element in the sustainability of the healthcare system. Likewise, if the current reference pricing system were to be changed to a more flexible pricing system, as outlined above, it would be necessary to inform patient-consumers about the new pricing system through healthcare information campaigns.

3.2.3. Public procurement systems

Public procurement of medicines involves the implementation of procedures in which a regulatory body or entity assumes responsibility for the procurement. In Spain, the National Institute of Health Management (INGESA) has been responsible for the management of centralised procurement framework agreements for medicines to be dispensed in hospitals. The aim of this initiative is to achieve greater savings and efficiency in medicine procurement, and improved cohesion of the SNHS. The Autonomous Communities, in compliance with Law 9/2017, of 8 November, on Public Sector Contracts, also tender public

procurement for the highest-consumption active ingredients in which pharmaceutical laboratories offer prices below the reference price in exchange for exclusive contracts[312].

Although this system results in lower prices, it has rarely been used for the supply of medicines to pharmacies. The only experience to date is that of the **Andalusian Health System (AHS)**, which between 2012 and 2019 introduced a **medicine selection system at pharmacy level** which, while not a public procurement programme, was a tendering programme at Autonomous Community level for the dispensing of medicines in pharmacies.

The AHS medicine selection system was introduced by Decree Law 3/2011 of 13 December, which approved the medicines selection system of the Andalusian Health Service. The medicine selection **process** in this system was designed as follows: (i) the AHS published the call for applications with the list of active ingredients; (ii) the pharmaceutical companies offered discounts on the proposed price; (iii) the pharmaceutical company with the highest proposed discount was selected to distribute the medicine exclusively for a period of two years in the Autonomous Community (or in the assigned area in the case of high-consumption medicines, which were distributed in batches by area).

The Andalusian system was an innovation in pharmaceutical policy. It was a procedure for selecting medicines with the same active ingredient, which obliged Andalusian pharmacies to dispense the selected drugs, as long as they were prescribed by active ingredient.

The most typical type of pharmaceutical laboratory selected in this system was a **small or medium-sized laboratory.** The large laboratories, with some exceptions, opted not to compete, some of them publicly opposing the system[313].

At the dispensing level, the price of the medicines did not change, remaining the same as in the rest of Spain. The difference between the reference price of the medicine and the discount offered by the winning pharmaceutical company was

[312] Spending Review – Estudio Medicamentos dispensados a través de receta médica, AIReF (2019).

[313] See, among others:
https://elpais.com/sociedad/2012/03/23/actualidad/1332501826_632462.html;
https://www.abc.es/sociedad/abcp-andalucia-laboratorios-para-subasta-201203240000_noticia.html;
https://www.diariofarma.com/2015/06/01/la-conviccion-de-no-acudir-a-las-subastas-le-cuesta-a-cinfa-87-millones;
https://www.consalud.es/autonomias/andalucia/las-subastas-de-medicamentos-cronica-de-una-muerte-anunciada_60018_102.html;
https://www.diariofarma.com/2020/12/10/aeseg-ve-lesivas-las-nuevas-subastas-andaluzas-e-insta-a-esperar-al-plan-de-genericos-del-ministerio-de-sanidad

paid into the public treasury on a monthly basis, which meant **significant cost savings** for the Autonomous Community of Andalusia.[314]

However, the system had its **critics**. The issues included shortages and problems of access to medicines, along with the risk this could pose to the sustainability and capillarity of the pharmacies in Andalusia.

Nevertheless, according to an analysis conducted by the Independent Authority for Fiscal Responsibility (AIReF), the **shortages** between the medicines selected by the Andalusian system and those not selected were similar, with Andalusia being above the national average, which could suggest that the reason for the higher incidence of shortages in Andalusia was not linked to the medicine selection system.[315]

As for the risk to the **sustainability and capillarity of pharmacies in the Autonomous Community of Andalusia**, deriving from the reduced retail margins for pharmacies, AIReF also found that the drug selection system did not affect either the capillarity or the sustainability of pharmacies.

Finally, **from a competition standpoint**, although the system allowed competition between laboratories during the tendering procedure, once the tender had been awarded, it granted a **temporary monopoly** (2 years) to the winning laboratory.

For this reason**, the CNMC considers that the best mechanism for promoting price competition for medicines dispensed through pharmacies is a reform of the reference pricing system and prescription and dispensing rules**, as proposed in previous sections. If these reforms were implemented, it would not be necessary to resort to generalised public procurement systems, such as the one implemented in Andalusia.

However, until the reference pricing system and the prescription and dispensing rules are reformed, the Andalusian experience allows us to draw some conclusions**:**

- On the one hand, the implementation of a public tendering system similar to the system used in Andalusia could yield **significant savings for the SNHS** by allowing for a broad aggregate demand in the public sector. Through successive tenders, prices would be adjusted to costs, largely mitigating the problem of asymmetric information and inefficient pricing, to

[314] AIReF puts the savings at 560 million euros for the period 2012-2017. Spending Review – Estudio Medicamentos dispensados a través de receta médica, AIReFf (2019).

[315] Spending Review – Estudio Medicamentos dispensados a través de receta médica, AIReF (2019).

the benefit of patients, smaller operators and new players, and the SNHS as a whole.

- However, these systems are not risk-free: if poorly managed or designed, **they can reduce the effective competition in the market**. To limit these potential pitfalls, **such selection procedures should not be used in a massive and systematic way**, but only for a **limited number of medicines and ensuring a robust and scrupulous tender design**. These drugs should be carefully selected, have a high cost impact and clinically proven therapeutic value.

To achieve all of the above, competitive procurement procedures would need to include the following **criteria**:

i. **Concession term:** in order to promote competition in the market, it is advisable to launch frequent tenders, where new entrants can compete on equal terms. Long-term tenders should be avoided as they fossilise the market and increase the risk of economic operators being forced out, thereby limiting the supply of potential products on the market and effective competition.

ii. **Single price offer per pharmaceutical company**: this measure reduces the complexity of the procedure and increases the bidding capacity of smaller companies, which are less able to make multiple offers conditional on different criteria (volume, sales, discounts, etc.).

iii. **Number of operators per tender:** whenever possible, a minimum number of operators should be included per tender, selected for the supply of the medicine. With regard to the number of bidders, it is advisable to broaden and diversify participation, as a larger number of bidders has a preventive effect against collusion, and increases uncertainty among bidders as to the number and identity of their potential competitors[316]. This would mitigate the risk of shortages in the system, ensure a sufficient level of competition between market players, and eliminate the creation of temporary monopolies for the duration of the contract.

iv. **Batch tendering:** it is advisable to divide tenders into batches by configuration (tablet, capsule, sachet, etc.), dosage (milligram or other unit) or volume. This favours patient access to different types of medicines and increases the potential number of operators that can supply the market with such batches.

[316] Guide on Contracting and Competition, CNMC, February 2011.

v. **Predictable, harmonised and transparent procurement processes/administrative procedures**: to ensure the participation of multiple manufacturers. In addition, it is recommended that they include delivery times to reduce the risk of medicine shortages, as well as the sanctions to be imposed if these delivery times are not met, as well as the criteria for imposing sanctions.

3.3. Biosimilar Medicines

A biosimilar medicine is a biological medicine equivalent in quality, efficacy and safety to the original reference biological medicine. According to the EMA, evidence acquired over years of clinical experience demonstrates that EMA-approved biosimilars can be used safely and effectively in all authorised indications, just like other biological medicines[317].

Many of the pharmaceutical policies of Spain's neighbouring countries and international organisations, such as the WHO, OECD, European Medicines Agency and European Parliament, include **promoting the use of biosimilars in healthcare systems**[318]. This is because biosimilar medicines can generate significant savings for healthcare systems, without any loss of benefit for patients, while also encouraging competition with reference biological medicines and promoting prices closer to marginal production costs.

In Spain, in 2019, there were 55 biosimilar dosage forms funded by the SNHS, corresponding to 7 active ingredients, but only 3 of these were dispensed through pharmacies.[319] However, **market shares remain very low**. Of the more than 11.2 billion euros in annual sales of funded medicines dispensed in pharmacies in 2019, biosimilars accounted for just 38.64 million euros (0.4% of the total in value and 0.088% in volume of packages dispensed).[320] Spain ranks approximately 10th in Europe in terms of the use of biosimilar molecules[321].

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[317] European Medicines Agency (EMA)

[318] See: *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, World Health Organisation, 2015; *Pharmaceutical Innovation and Access to Medicines,* OECD Health Policy Studies; and *Biosimilars medicines: Overview*, European Medicines Agency (EMA) 2020. Resolution of the European Parliament, of March 2, 2017, *on The Union's options for improving access to medicines*.

[319] Information provided by the MS in response to a request for information made by the CNMC.

[320] Information provided by the MS in response to a request for information made by the CNMC.

[321] Intervention by Patricia LaCruz, Director of the General Directorate for the Common Portfolio of Services of the National Health and Pharmacy System, at the Conference on Biosimilars organised by Biosim in December 2020.

Among the **barriers to the development of the biosimilars market** are doubts regarding interchange or *switching* policies related to biological medicines and biosimilars, and there is a lack of incentives and information for healthcare professionals and patients about these medicines. The responses of the market players who responded to the Public Consultation on medicines launched by the CNMC at the beginning of 2021 were along these lines.

Despite the low penetration of biosimilars in Spain, the **savings** generated by their use is **significant**. A recent study on the budgetary impact of biosimilars estimated savings of more than 5.000 million euros for the period 2009-2022, broken down as follows: savings reached 2.306 million euros by 2019 and are estimated to be in the region of 2.856 million between 2020 and 2022[322].

There are a number of ways in which the use of biosimilar medicines can be promoted through healthcare policy, including: (i) **fostering the entry** of biosimilars when originator medicines lose their exclusivity; (ii) promoting **switching *or interchange policies*** between biological and biosimilar medicines, where possible; (iii) providing **incentives and information for prescribers, pharmacists and patients**; and (iv) introducing a **pricing system** that promotes competition among operators. In this regard, the Ministry of Health's Action Plan to promote the use of generic and biosimilar medicines includes certain measures along these lines, such as: to establish, as a priority at the start of the dossier, a national stance in terms of interchangeability or encouraging the prescription of biosimilars, both at the start of treatment and during it. It also plans to develop information and training activities for professionals and a health education campaign on both generic medicines and biosimilars. The CNMC welcomes these initiatives.

The use of biosimilars can also be promoted through **profit-sharing agreements** between manufacturers and healthcare services or facilities.

These measures encourage the penetration of biosimilars, increase effective competition in the market, contribute to the sustainability of health systems and are essential to improve the access of patients to therapies and treatments with biological medicines. Each of these measures will be further developed below.

3.3.1. Switching or exchange policies between biologicals and biosimilars

One of the main barriers to entry for biosimilar medicines is the **lack of direct interchangeability** between the original biological medicine and its biosimilar. In

[322] *Budget impact of biosimilar medicines*, Professor Manuel García Goñi – Universidad Complutense de Madrid, 2020.

Spain, as in other European countries, the exchange of a biological medicine for a biosimilar must be performed under the responsibility of the clinician, who must prescribe this switch[323].

This is because biosimilar medicines are not considered to be generic forms or substitutes for biological medicines, due to the natural variability and the greater complexity of the production process in this type of medicine, which does not allow for an exact replication of the molecular microheterogeneity[324].

De facto, when the EMA scientifically reviews a biosimilar, the assessments ensure that **small differences between biosimilars and reference biological medicines do not affect the safety and efficacy of the medicine**, but this agency does not include recommendations on whether the biosimilar is interchangeable with the reference medicine, or whether the reference medicine can be substituted for the biosimilar at the prescription level.[325] Decisions on the interchangeability of reference biological medicinal products with biosimilars in prescriptions are taken at national level, at the request of the prescriber. The substitution of one biological medicine for another (biological or biosimilar) when dispensing is prohibited in all EU countries.

This is not the case in other jurisdictions. In the United States, the *Food and Drug Administration* (FDA) does contemplate the possibility of authorising the interchangeability of a biological medicine with a biosimilar in its authorisation dossier. In other words, the FDA can designate, at the request of the laboratory concerned and subject to further scientific evidence, a biosimilar drug as being interchangeable with its reference biological medicine. This implies the possibility of substitution by the pharmacist without the intervention of the prescribing physician. This dual classification, as an interchangeable or non-interchangeable biosimilar, is not possible in the European Union, where the EMA does not rule on the interchangeability of biosimilars in prescribing. This lack of judgement by the European agency on interchangeability has historically raised concerns among clinicians and patients.[326]

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[323] The regulation provides for the prescription of biological medicinal products by brand name and on the basis of their active substance. Single article of Order SCO/2874/2007, of September 28, which establishes the medicines that constitute an exception to possible substitution by the pharmacist in accordance with Article 86.4 of Law 29/2006, of July 26, on guarantees and the rational use of medicines and health products.

[324] More studies are therefore necessary to approve biosimilar drugs than for generic drugs, in order to guarantee that any small differences do not affect the safety or efficacy of the drug.

[325] *Biosimilars in the EU - Information guide for healthcare professionals* Prepared jointly by the European Medicines Agency and the European Commission, 2019.

[326] Biosimilars in the EU - Information guide for healthcare professionals. Prepared jointly by the European Medicines Agency and the European Commission, 2019.
Zozoya & Gonzalez (2018).

However, as indicated in the Ministry of Health's Action Plan to promote the use of regulatory medicines in the SNHS: biosimilars and generics, *"There is increasing evidence supporting the interchangeability between reference medicines and their biosimilars. Given the characteristics and approval process of any biosimilar medicine in Europe, some European regulatory agencies (Dutch, Finnish, Scottish, Irish and German) have taken national positions on the interchangeability of biosimilars. They consider that due to the high similarity between the reference drug and the biosimilar, there is no reason for the immune system to react differently to an exchange between the reference drug and the biosimilar and therefore any switch between them can be considered safe. Studies such as Nor-Switch*[327] *and its long-term extension support this situation*"[328].

The evolution of the biosimilars market depends, to a large extent, on the **legal framework and the resolution of existing uncertainties**, of which **interchangeability** between biologics and biosimilars is the most important. For this reason, the Spanish authorities are urged to make an effort to analyse the existing evidence on the effect of biosimilars on health, and on their interchangeability with biological medicines in the prescription stage, in order to be able to determine the safety of switching the two drugs based on clinical evidence, given the **importance of the *switching* policy as an essential element and facilitator of competition in the market for biological and biosimilar medicines.** In this way, and in the event that the existing evidence supports treatment interchangeability, it is recommended that a **formal stance** be taken in favour of the interchangeability of biological and biosimilar medicines in prescriptions. The aim is to standardise the different actions in the National Health System, increase competition in the market, promote the sustainability of the Spanish health system and guarantee access to affordable and effective biological medicines for patients who require them.

In this regard, the Ministry of Health's Action Plan to promote the use of market-regulated medicines in the Spanish National Health System: biosimilars and generics, includes as one of its lines of action the definition of a national position on the interchangeability of biosimilar medicines in order to standardise the

[327] Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, et al; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomized, double-blind, non-inferiority trial. Lancet. 2017 Jun 10;389(10086):2304-2316.

[328] Goll GL, Jørgensen KK, Sexton J, Olsen IC, Bolstad N, et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: Open-label extension of the NOR-SWITCH trial. J Intern Med. 2019 Feb 14. doi: 10.1111/joim.12880.

different actions in the SNHS (action 1 of line 2). The CNMC takes a positive view of this line of action.

Finally, it should be noted that, although at present a stance on interchangeability would have a limited impact on the retail channel due to the small number of biosimilar medicines marketed in the distribution channel through pharmacies, the presence of biosimilars in this channel will increase in the coming years as new biological medicines reach the market and their use is extended to the out-of-hospital channel.

Likewise, until such a position is adopted, it would be advisable to introduce **prescription programmes** that encourage the use of biosimilar drugs in *naïve* patients (or those who have received no treatment with biological drugs). In this regard, one of the actions included in the Ministry of Health's Action Plan, in addition to promoting interchangeability between biological and biosimilar medicines, is the development of policies for biosimilar use that promote the prescription of the biosimilar medicines at the start of treatment requiring biological treatment.[329]

This would encourage greater penetration of biosimilar medicines, which currently represent less than 1% of all medicines, and would maintain the interest of the biosimilar industry in our market.

3.3.2. Incentives for prescribers and patients and training and information programmes

To promote the use of biosimilar medicines, incentives for healthcare professionals need to be aligned with the objectives of the SNHS and patients.

One of the incentive models that has proven to be most successful internationally, in terms of efficiency, patient focus, and quality of service, is the use of gainsharing agreements. Gainsharing agreements are those where the benefits associated with the more efficient use of medicines are shared between the parties involved: the healthcare provider (care service or hospital) and the clinical commissioning group (or payer).

Most international experiences with these agreements focus on the management and dispensing of medicines in hospitals (see Box 9) and have resulted in improved resource efficiency for health systems, facilitating reinvestment and improving patient care. The basis of their success is that all these initiatives were supported by the health authorities, there were clear conditions in terms of the

[329] Action 3 of Line 2 of the Action plan to promote the use of market regulatory medicines in the SNS: biosimilar and generic medicines.

interchangeability of biological with biosimilar medicines, and the savings were shared between the health provider and the payer. This distribution must be defined in advance, in a consensual and transparent manner in the gainsharing agreement. The participation of multidisciplinary teams, transparency and constant communication with the patient, in addition to the follow-up and monitoring of the results obtained, both clinical and economic, are also important.

Box 9- INTERNATIONAL GAINSHARING AGREEMENTS

At the international level, there are several interesting examples of such programmes:

Gainsharing agreement in Southampton, UK[330]

A gainsharing agreement was implemented that involves sharing the savings achieved from the use of biosimilars, 50/50 between the trusts and hospitals (service providers) on the one hand, and the clinical commissioning groups (payer) on the other. The agreement was associated with a *switch* programme where biological medicines were exchanged for biosimilars in the case of infliximab. Available biosimilars were estimated to be 20% to 50% cheaper than the original infliximab, which could translate into potential procurement savings of £300,000 to £800,000 annually. This resulted in reduced in drug acquisition costs, and significantly increased the use of infliximab.

Gainsharing agreement in Italy

Campania Decree 66/2016 was the first regional experience of gainsharing agreements in Italy. 50% of the savings from the use of lower-cost biosimilars was used to purchase other innovative medicines; with 5% of the savings generated being reinvested into improving the quality of care at the prescribing centre that generated the savings. The use of biosimilars also increased significantly in the Campania region as a result of the agreement.

Gainsharing Agreements in France

In France, a national initiative was implemented in 2018 through instruction DSS/1C/DGOS/PF2/2018/42 on incentivising hospital prescribing of biosimilar medicines. 20% of the savings generated go directly back to the hospital, specifically to the clinical services generating them. The national target is an 80% penetration of biosimilars by 2022. Hospitals can join the initiative on a voluntary basis.

Although to date this type of agreement has mainly been used in the hospital setting, the CNMC considers it advisable for healthcare authorities to explore this type of profit-sharing agreement for biosimilar medicines not only in hospitals, but also at the out-of-hospital level. Biological and biosimilar medicines will have an increasingly important role to play in primary care, as new medicines come onto

[330] Gestión Clínica Incentivos y Biosimilares, Félix Lobo e Isabel del Río, 2020.

the market[331]. For the implementation of this type of agreement to be successful, it is necessary to include incentives at the therapeutic level, returning a percentage of the resources saved through the agreements to the unit or service that generates them. These resources could be used to improve quality of care, through reinvestment in equipment, staff recruitment, additional IT services, the purchase of innovative drugs, and so on, in a way that does not produce a conflict of interest, but stimulates healthcare professionals.

Finally, it is necessary to boost the **knowledge of clinicians and patients in terms of biological and biosimilar medicines**. It is essential to invest in **information and training programmes**, aimed at both prescribers and patients. If not, there could be an unjustified bias favouring the use of one medicine over another, hindering the prescription of these medicines, and generating doubts among patients. These initiatives should be conducted in a transparent manner using objective and contrasted information. In particular, communication between patients and clinicians about the use of biological/biosimilar medicines must be fluent, frank, and comprehensive. Ultimately, it is the patient who must receive the treatment and, therefore, they must be duly informed of the risks and benefits of the treatments prescribed.

The Ministry of Health's Action Plan to Promote the Use of Regulatory Medicines in the SNHS: biosimilars and generics includes among its general objectives the need to "*strengthen evidence-based information and scientific knowledge on regulatory medicines for both health professionals and the general public, generating knowledge and minimising uncertainty*", and to "*generate confidence in their use among professionals and the general public*". To this end, it proposes the development of health education programmes (action 2).

3.3.3. Pricing System for Biosimilar Medicines

As with chemically synthesised medicines, when a biosimilar medicine is first marketed, a **reference set** of the originator medicine and its biosimilars is created and the rules of the Reference Pricing System are applied. As in the case of generics, the initial reference pricing for biosimilar medicines is calculated on the basis of the price of the innovator biological medicine, with a 20-30% discount being applied to biosimilars when they enter the RPS.

[331] According to data from Biosim, in 2020 the penetration share of biosimilars in Spain in pharmacies it was 14% (i.e., they represented 14% of the dispensed containers of biologically synthesised medicines). A growth of more than 300% was observed in 2020 compared to 2018 in Primary Care, when penetration was 4%.

The **main difference** in the RPS between chemically synthesised medicines and biologically synthesised medicines is that the **system of homogeneous groupings does not apply to biological and biosimilar drugs** because they are not interchangeable at the dispensing level (a requirement to be part of these groupings), so the **dynamics of voluntarily lowering the prices** ("lower prices" and "lowest prices") of the dosage forms to gain market share through the dispensing rules **do not apply to these medicines.**[332] For this reason, in the case of biologically synthesised medicines, **there are very limited incentives for price competition.**

In this sense, the proposal to modify the current RPS, made in Section 3.2.1, and to replace it with a system based on flexible pricing and patient-consumer choice in dispensing, under the guidance of the pharmacist and with the possibility of avoidable co-payment, would not have a substantial impact on competition between biological and biosimilar medicines at present.

Furthermore, given the largely hospital-based nature of biological medicines, the ability of the RPS, applicable to distribution through pharmacies, to generate savings for the SNHS and foster competition in the retail channel is limited.

However, there are three types of measures that could be applied, given the current modest presence of biological and biosimilar medicines in the out-of-hospital channel, to **boost competition** between them:

- As long as the presence of biological and biosimilar medicines remains limited in the pharmacy setting, it would be advisable to explore the possibility of a **public procurement system in the out-of-hospital channel**, drawing on the experience of the hospital setting. In the hospital setting, both originator medicines and biosimilars are usually acquired through public procurement procedures. Such procurement procedures are common in other European countries, like Norway, where public tenders have increased the market share of biosimilars such as infliximab and etanercept by 95% and 82%, respectively.[333] If such procedures are chosen, the caveats outlined in Section 3.2.3 should be taken into account.
- To facilitate the entry of new biosimilar operators once patents expire and to achieve an adequate level of penetration and effective competition in the market, it would be advisable to introduce **differentiated pricing**

[332] Single article of Order SCO/2874/2007, of September 28, which establishes the medicines that constitute an exception to possible substitution by the pharmacist in accordance with Article 86.4 of Law 29/2006, of July 26, on guarantees and the rational use of medicines and health products.

[333] Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilar and generic medicines.

mechanisms between biological and biosimilar medicines for an initial period of time, delaying the creation of reference pricing sets. This would offset the market power that the originator medicine carries over from its previous period of exclusivity, allowing the biosimilar medicine to more quickly gain market share from the biological drug.

3.4. Notified prices

When a medicine is no longer funded by the SNHS, it leaves the RPS and enters the **notified price system**, whereby those responsible for these medicines are obliged to inform the DGCYF of the prices at which they will be marketed, as well as any subsequent variations, and the DGCYF may oppose these price changes. In this case, the matter must be referred to the CIPM, with the maximum industrial price (the price in force before the intention to change the price was communicated) remaining unchanged in the meantime. The request for a price change may be rejected on the **grounds of public health protection, equal access to medicines, or actual or potential harm to the interests of disadvantaged groups.**[334]

The particularity of the notified pricing system is that the defunded medicines to which it applies compete in the market with medicines which have never been funded by the SNHS and for which the prices are unregulated, unless they voluntarily opt-in to the notified pricing system[335]. As this system introduces a restriction on the ability of laboratories to freely set the prices of their medicines, it is highly unlikely that they will opt in voluntarily.

The notified pricing system therefore subjects defunded medicines to administrative control whereas their competitors are free to set their own prices. The requirement for defunded medicines to be subject to the system of notified prices limits the freedom of laboratories to set the price of these medicines and can lead to market distortions.

The Consolidated Text justifies this restriction of prices for defunded medicines by the authorities, by establishing the grounds on which the proposed price increase may be denied: (i) the aim is to protect public health; (ii) provide equal access to medicines for patients; and (iii) avoid actual or potential harm to the interests of disadvantaged groups. It is understood with this caveat that the public sector aims to prevent the price of defunded medicines from rising so high that it limits access to them by patients who need them, especially the most vulnerable, thus harming their health.

[334] Articles 93.4 and 93.4 of the Consolidated Text.
[335] Articles 94.4 and 94.5 of the Consolidated Text.

From a theoretical point of view, as long as there are competing medicines on the market, excessive price increases would not necessarily occur, as competitive dynamics would constrain companies, preventing them from making price increases that do not respond to cost increases or changes in market conditions. However, in practice, the peculiarities of the pharmaceutical market and existing market failures mean that this mechanism may not be truly effective:

- In the medicine market there are problems of **asymmetric information**. Consumers do not always have a comprehensive knowledge of all existing alternatives for treating their condition, of the availability of interchangeable medicines, nor of their respective prices. They are therefore likely to ask for the most well-known medicine, which is usually the one that has been on the market the longest (often drugs that have been previously funded by the SNHS) and/or the one with the best-known brand name (being loyal to the one they have used before, or the one with the most advertising activity), without considering alternatives that in many cases have the same composition and a lower price.
- The demand for medicines is, to a large extent, an **induced demand:** often, patient-consumers buy the medicines recommended by their doctor, so there is no real choice.
- Medicines are necessary and in many cases indispensable, so **demand is inelastic**, and price increases do not necessarily translate into reductions in demand, especially if alternatives are not known to exist, making this a "captive" market.
- The regulation of pharmacy margins generates **perverse incentives:** the pharmaceutical dispensing margin is a percentage of the price of the medicine, so that the pharmacist has an incentive to sell the more expensive product in order to increase their profit.

This may mean that, despite the existence of alternatives in the market, in practice effective competition is not intense and certain operators may have market power.

However, medicines that are defunded and therefore under the notified price regime are in competition with medicines that can fix their own price, which are interchangeable and substitutable with the former, and which, because they have never been funded, are not subject to the notified price regime. The previous arguments in favour of intervention also apply to other medicines which, however, are not subject to the same regulation. The consequence is a **dual system** where marketers of interchangeable medicines are not on an equal footing in terms of competition, creating a **regulatory asymmetry** between defunded medicines

and their unfunded competitors, leading to a distortion of competition in the market.

Moreover, **the regulation does not establish a fixed period of time** for defunded medicines to be subject to the notified price regime; instead it is effectively permanent, perpetuating these regulatory asymmetries between competing medicines.

With regard to the **practical application** of the notified price system, the CNMC has learned that, in 2012 and 2013, the DGCYF and CIPM denied marketing price increases requested for defunded medicines.[336] These denials were justified on the grounds that the requested price increases were higher than the evolution of the CPI and it was therefore considered that they could hinder equal access to medicines for patients.

The CNMC considers that the **systematic rejection of price changes based on the evolution of the CPI is not appropriate** and urges the DGCYF and CIPM to analyse each price change proposal individually, in accordance with the particular circumstances of the medicinal product, and to provide sufficient reasons for its decision. Not all medicines for which price changes are requested will be in the same position (they will not have the same market conditions, nor will they suffer the same cost shocks). For example, some of the medicines for which price variations were denied in 2019 and 2020 requested price increases of 2%, while others requested price increases of more than 100%; some had increased their price by more than 200% since they were defunded, while others had increased their price by 25%; some faced cost increases because they had to increase their production, and so on. In addition, it should be borne in mind that limiting price variation according to the CPI could trigger an "anchor" effect that encourages systematic requests by operators for price increases for these medicines according to the index, and/or acts as a price coordination mechanism.

Finally, the CNMC considers that other public interventions that could help to **solve the root of possible problems of price increases for defunded medicines should be assessed.** Specifically:

- **To encourage the provision of information to patients**, complemented by the generation of **appropriate incentives for medicine dispensers**, whose interests should be aligned with those of the patient, in order to stimulate competition through more informed demand.

[336] The CNMC has obtained, through a request for information from the Ministry of Health, the Resolutions of the DGCYF issued under Article 93.4 of the Consolidated Text since 2019.

- To eliminate the perverse incentives that the regulation of retail distribution margins generates by **regulating pharmacy margins in proportion to price** (which will be analysed in more detail later).
- To consider the possibility of increasing public funding or direct subsidies in cases where the price problem particularly affects identifiable vulnerable patient groups (e.g., in cases of chronic patients and/or those with limited economic capacity).

3.5. Wholesale and retail distribution margins

The current regulation of wholesale and retail distribution margins in Spain results in margins being calculated as a **function that is almost linear to price**, except for high-cost medicines (although, as shown in Section 2.2.5, these accounted for only 0.51% of the units dispensed by pharmacies to the public in 2019).[337]

This way of determining margins is **inefficient** for various reasons:

- The costs associated with the wholesale and retail distribution of medicines (transport, storage, conservation, dispensing, etc.) are not necessarily higher for higher-priced medicines and, therefore, the current remuneration obtained by wholesale distributors and pharmacies is **not adjusted to the costs** incurred for the provision of their services.
- The current regulated remuneration **is not related to the quality of the services provided** by distributors (wholesale or retail), which discourages competition in this variable, with a particularly relevant impact on the retail segment, given that the regulations prohibit pharmacies from providing discounts on the RP of prescription medicines and, therefore, the quality of the service provided is one of their main competitive variables.[338]
- Although laboratories and wholesale distributors apply **discounts** throughout the supply chain, these **do not reach the patient-consumer and are not passed on to the SNHS** (due to the aforementioned ban on discounts on the RP of prescription-only medicines). These discounts, which can be as high as 40% according to some estimates (see Section 2.2.5.), remain in the distribution channel as a higher margin for wholesale distributors or pharmacies.[339]

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[337] Information provided by the General Council of Official Pharmaceutical Associations (Consejo General de Colegios Oficiales Farmacéuticos) in response to a request for information from the CNMC.

[338] Article 91.3 of the Consolidated Text.

[339] Puig-Junoy (2009).

- In the retail segment, the fact that a percentage margin is obtained on the price of each medicine dispensed generates **perverse incentives**, as pharmacies increase their profits the more medicines they dispense and the more expensive these are, misaligning the interests of pharmacists with the SNHS and, particularly, patient-consumers, who are at a disadvantage due to the information asymmetry that exists between the two parties.

For all these reasons, the current system of margins does not efficiently determine remuneration, especially at the retail level, as there is no competition in the price of prescription medicines between pharmacies and it generates perverse dispensing incentives, not favouring efficiency and quality gains, nor allowing the SNHS or patients to take advantage of benefits that exist within the chain. These issues are discussed in more detail below and alternatives are proposed.

3.5.1. Alternative system to wholesale margins and a clawback mechanism

In Spain's neighbouring countries, margins take different forms, including regressive margins, proportional margins and flat rates, with regressive margins being the most common in the EU, although several countries use a mixed system: margins as a linear function of prices that become fixed from a certain price (LSP) onwards.[340] This is the case in Spain, where the wholesaler's regulated margin is 7.6% of the distributor selling price, or DSP, (equivalent to 5.48% of the RP) for all medicines with an LSP of 91.63 euros or less (equivalent to a pre-tax RP of 137.54 euros).[341] Above this price, wholesalers receive a fixed margin of 7.54 euros per pack.[342]

According to FEDIFAR, almost 50% of the operations carried out by "full-range" pharmaceutical distribution companies (which work with the full range of medicines marketed in Spain) are loss-making, i.e., the margin they obtain is

[340] "Political Regulation of Wholesalers' and Pharmacists' Margins for Prescription-Only-Medicines in Europe: An analysis of different markup schemes and their potential rationale", Hamburg University of Applied Sciences, 2017, and European Commission, contribution to the roundtable on competition issues in the distribution of pharmaceuticals., OECD, 2014.

[341] With one exception, as the margin for distributing industrially manufactured medicinal products for human use in clinical packaging (medicinal products intended for the hospital setting) is 5% of the distributor's selling price excluding tax (Article 1 of Royal Decree 823/2008).

[342] The regulation of Royal Decree 782/2013 establishes distribution margins referenced to the distributor's sales price excluding taxes in its proportional band (7.6% of the DSP) and in a fixed amount if the LSP of the medicine exceeds a threshold (7.54€ if the LSP exceeds 91.63€). To clarify, simplify and graphically represent the information, thresholds and distribution margins are also referenced to the RP in this study, so that they have a common reference. The calculations for finding the equivalences are explained in Annex I.

lower than their distribution cost.[343] The distribution model of these companies is based on a **system of cross-subsidies** whereby operations that are not profitable (distribution of very cheap pharmaceutical products, with low turnover or in hard-to-reach locations) are compensated by the resources obtained from those that are profitable (distribution of expensive pharmaceutical products, with high turnover or supply to pharmacies in large cities).[344]

The main drawback of the current remuneration system for the wholesale distribution of pharmaceuticals is that it is **not based on the costs, characteristics or quality of the service provided.** The wholesale remuneration system **should be independent of medicine prices** and at least partially based on medicine distribution services (in terms of safety, efficacy, speed and control of medication, or distribution to rural and depopulated areas), as well as on the logistical features of the products distributed (boxes, injectables, solutions, fragile products, cold storage, etc.). Otherwise, inefficiencies are generated, such as the cross-subsidies described above, which could potentially lead to other problems, such as shortages.[345]

On the other hand, although the regulation sets the margins, in practice the effective wholesale distribution margins may differ, as distributors may apply **discounts** to pharmacies (against their own margin) and may themselves benefit from discounts from pharmaceutical laboratories (gaining margin), so that the wholesaler's effective margin may be higher or lower than that foreseen in the regulations. The regulation only allows discounts from distributors to pharmacies for prompt payment and for volume of purchases, as long as these do not encourage the purchase of one product over that of its competitors, and these must be reflected in the invoice. In the case of medicines funded by the SNHS, the regulation establishes that these discounts may be applied provided that a **monthly record of discounts** is kept in the title-holding companies and distribution entities, to be remotely interconnected with the Ministry of Health.

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[343] FEDIFAR is the Federation of Pharmaceutical Distributors (Federación de Distribuidores Farmacéuticos), the employers' association that brings together full-range pharmaceutical distribution companies operating in Spain. It comprises nine associations, representing 19 distribution companies, which have 140 warehouses and a 97% market share in the national pharmaceutical distribution sector.

[344] FEDIFAR (2020): http://fedifar.net/que-hacemos/modelo-solidario-distribucion/.

[345] Nearly all of the stakeholders that responded to the Public Consultation on the medicines market launched by the CNMC in February 2021 indicated that the remuneration system is not adequate and should be reformed, although the majority did not propose an alternative system beyond a reduction or increase in margins. Some stakeholders did advocate for a change in the remuneration system based on the commodity distributed rather than the price of the medicine. It should be noted, however, that the vast majority of respondents found the service provided by distributors to be good and fast, despite the fact that their remuneration bears no relation to the quality of the service provided.

However, the CNMC is not aware that this record exists, so the Ministry does not appear to have this information at its disposal.[346]

As pharmacies are prohibited from offering discounts on prescription-only medicines, the price reductions resulting from the competitive dynamics within the distribution chain do not reach the final link: they neither benefit patients as final consumers and partial funders (through co-payment) nor reduce the cost to the SNHS[347]. As a result, **discounts applied within the distribution chain remain internal to the chain** in the form of higher margins for the operators who receive them.

Establishing a ***clawback mechanism***, whereby part of the discounts offered to pharmacies in the distribution channel for funded medicines would be passed on as a lower cost to the SNHS, would help to reduce the public cost of pharmaceutical provision, free up resources to fund other treatments and benefit end-consumers. This system has been successfully introduced in other countries, such as the UK.[348]

One such initiative is contained in the Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilars and generics approved by the Standing Committee on Pharmacy of the SNHS Interterritorial Council.[349].

The **CNMC** published a report (INF/CNMC/059/19) on the draft of this plan and **assessed the proposed clawback positively**, but warned that it should be designed with caution in aspects such as commercially sensitive information to which operators may have access, due to the high risks of coordination and the existence of previous sanctioning proceedings.[350]

Moreover, to favour a competitive dynamic, a full clawback of discounts should not be established, as the incentives to offer discounts would be diluted or eliminated. Thus, the design of the clawback should be such that the SNHS only receives part of the discounts obtained in the medicine chain, so pharmacies are not discouraged from negotiating these discounts. To this end, the "interconnected discount register", which is included in the regulation but which has not yet been created, should be set up so that the competent authorities can

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[346] Article 4.6 of the Consolidated Text.

[347] Article 91.3 of the Consolidated Text.

[348] CNMC (2015). More information available at https://psnc.org.uk/dispensing-supply/endorsement/discount-deduction/. Currently, in the UK the average level of "clawback" on all products to which this system applies is approximately 8% (calculated on the monthly value of medicines dispensed).

[349] Line of Action 4, Action 2: "Introduce a clawback mechanism for pharmacy discounts".

[350] In the market for health products dispensed in pharmacies (urine incontinence pads; AIO) Resolution of the Council of May 26, 2016, confirmed by the National High Court. File: S/DC/0504/14 - AIO.

collect information on the discounts obtained by each pharmacy. In this sense, the potential difficulties of implementing a clawback mechanism should be taken into account. Control mechanisms need to be introduced, either beforehand or afterwards, to ensure that the discounts offered are properly recorded.

Furthermore, the clawback should also apply to discounts obtained by wholesale distribution operators from pharmaceutical companies, as long as these have not been passed on "downstream" to pharmacies.

If a clawback were to be applied, these discounts would end up partially resulting in lower costs for the SNHS.

3.5.2. Alternative system to retail margins

Retail distribution margins in Spain are regulated as a linear function of price for medicines whose RP before tax is less than 137.54 euros (specifically, the remuneration is 27.9% of the RP). Above this price, pharmacies receive a fixed retail margin, the amount of which depends on the price of the medicine dispensed (the regulation establishes three price brackets).[351] In 2019, 99.49% of the units dispensed by pharmacies in Spain had an RP of less than 137.54 euros and were therefore in the variable retail margin bracket.[352]

However, the existence of discounts in the distribution chain implies that **the regulated retail margin for pharmacies acts as a floor.** As the monthly recording of discounts foreseen by the regulation does not seem to be in place at present, the Ministry of Health cannot trace the discounts made within the distribution channel.[353] Nevertheless, some estimates of pharmacy retail margins for 2019 showed increasing figures depending on the level of turnover, ranging from 28.7% for those with lower turnover (less than 300,000 euros per year) to 32% for those with a turnover of over 2 million euros.[354] A 2009 study commissioned by the Catalan Competition Authority revealed the existence of average discounts of 40% on the LSP of generic medicines offered to pharmacies by pharmaceutical laboratories.

The current retail margin remuneration system has several **issues**:

- Remuneration is associated with the prices of medicines and **not to the act of dispensing or the quality** of the service offered.

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[351] Article 2 of Royal Decree 823/2008.

[352] Information provided by the General Council of Official Pharmaceutical Associations (Consejo General de Colegios Oficiales Farmacéuticos) in response to a request for information from the CNMC.

[353] Article 4.6 of the Consolidated Text.

[354] Aspime (2019).

- It generates **perverse incentives** to dispense higher-priced medicines. This, moreover, occurs in a context of asymmetric information between pharmacists and consumers.
- **Additional or complementary health services are not remunerated.**[355]

On previous occasions, the CNMC has favoured more patient-oriented systems. In INF/CNMC/059/19, it recommended assessing fees based on the health value provided in dispensing, such as *dispensing fees*, in line with the recommendations of the Council of Europe back in 2001:[356] the pharmacist's remuneration system should be re-examined so that it is not based on profit margins or sales volumes, but on the professional service provided. Furthermore, in Study E/CNMC/003/15 on the retail distribution market for medicines, the CNMC found that an efficient financing system for pharmacies should **link the income derived from the dispensing of medicines to the health benefits it provides** (patient-oriented system), and cited the alternative system proposed by Meneu (2006), a **mixed system combining a fixed dispensing fee with partial or full reimbursement of the price of the medicine by the SNHS and remuneration for certain services defined by the SNHS that contribute to the health of the population.** Thus, the CNMC recommended moving from a purely product-oriented system to a mixed, more patient-oriented system.

With regard to partial or total reimbursement of drug prices, and taking into account the modification of the reference pricing system proposed above, it is necessary to introduce a system of medicine reimbursement by the SNHS to pharmacies that encourages pharmacists to dispense those medicines with a lower price within the reference sets or homogeneous groupings. Thus, in addition to reimbursing the sale price (LSP) of medicines, there is the possibility of introducing partial reimbursement (%) of the difference between the sale price (LSP) and the reimbursement price (reference pricing) set by the authorities for those medicines sold at a price lower than the reimbursement price of the group or group of medicines.

[355] In the responses to the Public Consultation on the medicines market launched by the CNMC in February 2021, most stakeholders consider it necessary to modify the current retail remuneration system. They argue that the system generates potentially perverse incentives in terms of dispensing and does not remunerate the act of dispensing itself nor the possible services offered by pharmacists. Some stakeholders also criticise the existence of ceilings on margins (but no minimums) and the constant reduction of margins.

[356] Council of Europe (2001). Resolution ResAP (2001) 2 on the role of pharmacists in the framework of health security.

Box 10

SYSTEM INVOLVING PARTIAL REIMBURSEMENT OF THE REFERENCE PRICE

Example of a reference set with 1 originator medicine and 4 competing generic medicines with a reimbursement price of 59 euros and the following LSP:

i. Originator LSP = 65 euros.
ii. Generic_1 LSP = 62 euros
iii. Generic_2 LSP = 60 euros
IV. Generic_3 LSP = 57 euros
v. Generic_4 LSP = 53 euros

Under the proposed new system, the pharmacist would only be able to dispense those medicines that are below the reimbursement price of the set, i.e.: generic_3 and generic_4. To encourage the dispensing of the lower-priced medicine, the CNMC proposes incentivising pharmacists through a system that reimburses a percentage (%) of the difference between the LSP and the reimbursement price: In this case:

- Generic_3: a % of the difference between 59 and 57 euros (i.e., a percentage of the 2 euro saving generated for the SNHS by the sale of the medicine would be returned to the pharmacy).
- Generic_4: a % of the difference between 59 and 53 euros (i.e., a percentage of the 6 euro saving generated for the SNHS by the sale of the medicine would be returned to the pharmacy).

As the percentage to be applied would always be the same, the pharmacist would have an incentive to dispense those medicines for which the difference between the LSP and the reimbursement price is greater, i.e., the lowest price (generic_4).

Also, to help ensure adequate care in small population centres, a selective fixed payment based on certain agreed community services or a minimum guaranteed income could be added[357].

In relation to the **added services that pharmacies either offer or could offer**, the responses to the Public Consultation on the medicines market launched by the CNMC in February 2021 place particular emphasis on these, indicating that community pharmacies could not only make a greater contribution to people's

[357] The responses to the Public Consultation on the medicines market launched by the CNMC in February 2021 are along the same lines. Specifically, the stakeholders propose a series of alternatives to the current remuneration system for the retail sector:

i. Remuneration for the act of dispensing.
ii. The use of a mixed remuneration system: payment per drug unit + payment per professional act (custody and pharmaceutical care).
iii. To provide for a complementary payment, in the form of incentives, for health outcomes of patients served, when a medicine is not dispensed due to duplication or contraindication, or for the provision of additional services.
iv. To consider special remuneration for pharmacies in rural areas or for pharmacies whose economic viability is compromised.

health and to the SNHS itself, but could also be a tool for decongesting (or helping) health systems at a structural level, not only occasionally in times of health crises such as the COVID-19 pandemic. Participating consumers, experts, public institutions and pharmaceutical companies highlighted, among other things, the following complementary services:

- Quitting smoking.
- Fast analytical controls.
- Development of training plans for patients/society.
- Disease screening.
- Vaccination or testing aid.
- Monitoring of medication, contraindications and treatment adherence.
- Pharmacovigilance.
- Participation in pharmaco-epidemiological studies.
- Health prevention and promotion programmes.

3.6. Restrictions on the vertical integration of distribution entities and pharmacies

To guarantee the independence of pharmacists, the Consolidated Text **prohibits vertical integration** between pharmacies and distribution entities, except for those pharmacists who are part of, or become part of, cooperatives with a minimum of 20 cooperative members or commercial companies with a minimum of 100 shareholders or partners, in both cases made up exclusively of pharmacists and already existing at the entry into force of Law 29 /2006, of July 26[358].

In practice, the **exceptions provided for in the regulation** mean that most wholesale distribution operations in Spain are owned by pharmacists who own pharmacies, vertically integrated into cooperatives (mainly) or companies. As indicated in Section 2.2.4, nine out of the ten largest wholesale pharmaceutical distribution companies in Spain are made up of pharmacists (eight cooperatives and one limited company); however, pharmacists with a pharmacy cannot join new cooperatives or distribution companies founded after 28 July, 2006, and which do not meet the other requirements mentioned above.

In the past, the CNMC pointed out that vertical integration between different agents in the medicine chain can lead to efficiencies, as there are economies of

[358] Article 4.2 of the Consolidated Text.

scale and scope between the different activities that could lead to reduced supply and marketing costs for pharmacies, lower transaction costs and help them obtain better information on their end consumers, thereby enabling them to better meet their needs.[359]

On the other hand, the **existence of an exception to the prohibition of vertical integration generates a regulatory asymmetry in favour of pre-existing cooperatives and trading companies** and means, in practice, a closure of the market in favour of these incumbent companies, to the detriment of pharmacists who want to vertically integrate with the wholesale segment. It also restricts the integration of companies with a small number of partners, discriminating against them without clear justification, and the requirement that all partners must be pharmacists does not seem necessary to protect the independence of pharmacists who wish to join.

Similarly, the Consolidated Text prohibits pharmacists from entering into partnerships with pharmaceutical laboratories, with the exception of pharmacists who had direct economic interests in laboratories prior to 28 July, 2006, who may maintain this relationship until the authorisation expires or the laboratory is transferred.[360] This time limit seems, as in the previous case, arbitrary and generates a regulatory asymmetry that does not appear to be justified.

For all these reasons, **the CNMC believes that a review of the regulations on the vertical integration of the market is necessary.** In the CNMC's view, such exceptions are discriminatory, impede the proper functioning of the market by introducing a restriction or prohibition of vertical integration only applicable to some operators, while others benefit from the possibility of being able to do so, and therefore distort the market.

[359] Study E/CNMC/003/15.
[360] Second transitory provision of the Consolidated Text.

4. CONCLUSIONS

The distribution and marketing of medicines, due to their special characteristics, are heavily regulated activities, and this intervention is based on the necessary safeguarding of public health, the existence of market failures and the impact on public finances that pharmaceutical provision entails.

The CNMC, while assuming the necessary protection of the public interest, inherent to the regulation of this market, in terms of safety and access to medicines, stresses that it is also essential in the defence of the general interest that the regulation complies with the principles of necessity and proportionality and avoids introducing or maintaining restrictions on competition that unjustifiably prevent greater efficiency in the functioning of the market, or an improvement in general welfare.

During the preparation of this study, a number of areas have been identified where improvements in health regulations and policies could be made to boost the level of effective competition in the market.

4.1. There is a need to ensure proper pharmaco-economic assessment for funding and pricing decisions for innovative medicines.

Currently, the TPRs used by the DGCYF to support its funding decisions, barely address economic issues. It would be advisable to include a pharmaco-economic analysis or evaluation of medicines in these reports, to facilitate subsequent price fixing by the CIPM, to increase the transparency and predictability of the price-setting mechanisms for innovative medicines, and as a mechanism to improve the control of public action.

In this regard, the CNMC welcomes the reform of the TPRs outlined in the Plan for the consolidation of Therapeutic Positioning Reports, developed by the Standing Committee on Pharmacy of the SNHS Interterritorial Council and approved in 2020.

4.2. There is scope for the use of big data in the long-term therapeutic and economic evaluation of innovative medicines.

The therapeutic and economic evaluation of innovative medicines in the long term is carried out through follow-up, or Phase IV studies. The SNHS should complementarily develop, either alone or in collaboration with academic institutions or independent experts, its own tools for economically assessing medicines over time. This requires databases and the use of big data to generate economic information and data on the therapeutic effectiveness of medicines over time. The evidence generated by using big data in the evaluation and

oversight of medicines has enormous potential, allowing for a more expeditious, complete and real-time therapeutic and economic assessment of medicines. This information could be used to help make funding decisions, optimise drug use recommendations and adjust prices.

If Valtermed becomes a benchmark in the healthcare field, it could provide information that is crucial for optimising treatments, funding, adjusting prices and sharing risk between the authorities and operators in almost real time. The end patient would benefit from this improvement in healthcare management and it would boost the sustainability of the healthcare system.

4.3. The current system of reference prices does not adequately promote competition

The interaction between the RPS, the Homogeneous Grouping System and the rules for dispensing medicines, in addition to being confusing, means that the incentives for laboratories to voluntarily lower prices are very low or even non-existent. As a result, all medicines in the same homogeneous grouping (the originator medicine and its generics) have strong incentives to set the same price, effectively eliminating price competition.

The system thus functions as a price cap system (through the reference price) with limited incentives to lower prices, leaving no room for competition and no greater margin of choice for the consumer, who is given the lowest-priced medicine without the option to choose another.

4.4. Promoting competition between originator and generic medicines requires changes in dispensing as well as information and health education programmes

A reform of the RPS alone is not sufficient to boost competition between originator medicines and their generics. When prescribing by active ingredient, current regulations oblige pharmacists to dispense the lowest priced medicine in the homogeneous grouping. Mandatory substitution increases the risk of creating a temporary monopoly during the period of time that the medicine in question has the lowest price, as well as price alignment around the lowest price offered. This entails two risks: (i) the general loss of incentive to lower prices, for fear of triggering a price war between competing laboratories, encouraging price alignment around a price above that which would be derived in a competitive market; and (ii) larger laboratories may be inclined to offer the drug at very tight margins in order to drive their smaller competitors out of the market, as these would incur losses if they bid at that price, thus enabling larger players to take

over the entire market. In the short term this would be beneficial in terms of savings for the SNHS, but in the medium to long term the monopoly laboratory could raise drug prices above the initial level, to the detriment of the SNHS and general welfare.

One alternative is to modify the pharmacist's obligation to substitute medicines with indicated alternatives and, in the case of medicines priced below the fixed reimbursement price, the pharmacist would be obliged to dispense one of the medicines below that price. This would redress the dispensing of a single medicine, increasing the variety of medicines dispensed together with the level of competition. This does not preclude the possibility that, in the event the medicine dispensed has a higher price than the maximum reimbursement price (reference price), because there are no alternatives below the reimbursement price, consumers would have to pay the difference out of their own pocket (avoidable co-payment).

However, for the consumer to be able to make an informed choice, information and health education programs are also necessary. Health institutions should make an effort to communicate and disseminate clear, concise and objective information on originator and generic medicines in order to clarify their use, efficacy and the impact they have on healthcare systems.

Furthermore, it is necessary to reflect on the possibility of adapting medicine dispensing to the treatment needs of each patient-consumer, by implementing personalised and automated dispensing systems that allow medication to be repackaged in single-dose or multi-dose systems. This would improve efficiency and increase competition in the pharmacy retail channel.

4.5. Currently there is no formal stance on the interchangeability of biological and biosimilar medicines in Spain

A policy of switching or a formal stance on the interchangeability of prescribed biological and biosimilar medicines, when there is sufficient favourable clinical evidence, would encourage greater penetration of biosimilar drugs in Spain. The aim is to standardise the different actions in the National Health System, increase competition in the market, promote the sustainability of the Spanish health system and guarantee access to affordable and effective biological medicines for patients who require them. The competent authorities should conduct an analysis of the clinical evidence on the interchangeability of biosimilars with biological medicines when prescribing, in order to determine the safety of drug interchangeability.

4.6. The current system of wholesale and retail mark-ups does not recognise the quality of services and generates perverse incentives

The current regulation of wholesale and retail distribution margins in Spain results in margins being calculated, practically, as a function of price, except for high-cost medicines. This type of remuneration is inefficient because it is not related to the costs, characteristics or quality of the services provided, either at wholesale or retail level. This discourages competition, particularly in the retail sector, given that the regulations prohibit pharmacies from offering discounts on the RP of prescription medicines and, therefore, the quality of the service provided is one of their main competitive variables. Moreover, the remuneration system generates incentives to dispense higher-priced medicines in an environment of asymmetric information between patient-consumers and pharmacies.

4.7. Neither the SNHS nor patient-consumers benefit from discounts within the distribution chain

In practice, wholesale and retail distribution margins may differ from those fixed by the regulations, as wholesale distributors may give discounts to pharmacies (against their own margin) through which pharmaceutical laboratories benefit (gaining margin). In this way, the wholesaler's effective margin may be higher or lower than the regulated margin. In the case of pharmacies, the existence of discounts in the distribution chain means that the regulated retail margin is just a floor.

However, as pharmacies are prohibited from offering discounts on prescription medicines, the price reductions resulting from the competitive dynamics within the distribution chain never reach the final link: they do not benefit patients as final consumers and partial financers (through co-payment), nor do they reduce the cost to the SNHS[361]. Consequently, the discounts applied within the distribution chain, which can be as high as 40% according to some estimates (see Section 2.2.5), result in higher margins for wholesale and retail distributors (whose regulated margins, as indicated in Conclusion 4.6, are inefficient and should be reviewed).[362]

Furthermore, although the regulation establishes that discounts may be applied provided that a monthly register is kept in the companies holding the discounts and in the distribution entities, interconnected electronically with the Ministry of Health, the CNMC has no evidence that such a register exists, so that the Ministry does not seem to be able to trace the discounts made within the distribution

[361]Article 91.3 of the Consolidated Text.
[362]Puig-Junoy (2009).

channel[363]. The creation of a monthly discount registry, electronically interconnected with the Ministry of Health, is recommended.

4.8. There are regulatory asymmetries that generate distortions in the market

Firstly, defunded medicines are subject to the notified price regime under which there is an administrative price control that does not apply to drugs that have never been funded and which have unregulated prices.[364] This implies that they can enter into competition with interchangeable and substitutable medicines, as well as those that have unregulated prices, thus creating a dual system in which marketers of interchangeable drugs are not subject to the same competition conditions. This generates a regulatory asymmetry between defunded medicines and their never-funded competitors, causing a distortion of competition in the market. The arguments in favour of this price intervention for defunded medicines, cited by the regulation itself, are: the protection of public health, equal access to medicines, and the real or potential harm to the interests of disadvantaged groups[365]. These arguments could well be applicable to other medicines that, however, are not subject to the same regulation.

Moreover, the regulation does not provide for a specific period of time during which defunded medicines must be subject to the notified price regime; instead, this is a permanent situation, perpetuating these regulatory asymmetries between competing drugs.

Secondly, Royal Legislative Decree 1/2015, of July 24, approving the Consolidated Text of the Law on guarantees and the rational use of medicines and medical products prohibits vertical integration between pharmacies and distribution entities to guarantee the independence of pharmacists[366]. However, it does permit this for pharmacists who are part of, or become part of, cooperatives with a minimum of 20 cooperative members or commercial companies with a minimum of 100 shareholders or partners, in both cases made up exclusively of pharmacists and already existing at the entry into force of Law 29 /2006, of July 26. In practice, these exceptions mean that the majority of wholesale distribution operators in Spain are owned by pharmacists who are also pharmacy owners, vertically integrated into cooperatives (mainly) or companies.

[363] Article 4.6 of the Consolidated Text.
[364] Articles 93.4 and 93.4 of the Consolidated Text.
[365] Articles 93.4 and 93.4 of the Consolidated Text.
[366] Article 4.2 of the Consolidated Text.

The existence of these exceptions to the prohibition of vertical integration generates a regulatory asymmetry in favour of pre-existing cooperatives or trading companies and, in practice, means a closure of the market in their favour and to the detriment of pharmacists who want to vertically integrate with the wholesale segment. It also restricts the integration of companies with a small number of partners, discriminating against them without clear justification, and the requirement that all partners must be pharmacists does not seem necessary to protect the independence of pharmacists in this situation.

Finally, in a similar way, the Consolidated Text prohibits the affiliation of pharmacists with pharmaceutical laboratories, with the exception of pharmacists who had direct economic interests in laboratories prior to 28 July, 2006, who may keep such interests until the expiry of the authorisation or transfer of the laboratory.[367] This time limit seems, as in the previous case, arbitrary and generates a regulatory asymmetry that does not seem to be justified.

[367] Second transitory provision of the Consolidated Text.

5. RECOMMENDATIONS

The analysis of the market for the commercialisation and distribution of medicines in Spain carried out in this study has identified a series of restrictions that are inefficient and detrimental to competition and the general interest. To alleviate this situation, the following recommendations are proposed, addressed to the competent administrations at both the national and regional levels.

FIRST. Strengthen Therapeutic Positioning Reports (TPRs) as a comprehensive and transparent reference document to support financing and pricing decisions for innovative medicines

Although the TPRs have marked a turning point in medical evaluation since their creation in 2013, the CNMC considers that there is room for improving and strengthening them further as a reference document for aiding decision-making in terms of the financing and pricing of innovative medicines.

Specifically, they should include a comprehensive pharmaco-economic analysis of medicines, in addition to a clear analysis of therapeutic positioning that is neither ambiguous nor incomplete.

In this regard, the Plan for the Consolidation of Therapeutic Positioning Reports, drafted by the Advisory Committee for the Funding of the SNHS Pharmaceutical Service and published by the Ministry of Health in 2020, provides a solid basis by including measures aimed at correcting the current shortcomings of the TPRs. However, the CNMC recommends improving the following aspects of the Plan:

- The most substantial modification to the reform proposed by the Ministry of Health is including pharmaco-economic information on the medicine in the TPRs, as well as improving the critical reading of the clinical evidence and its limitations. Although the Plan describes the method to be used in the economic evaluation, it does not go deeply enough into its different aspects. Nor does it explain how the economic evaluation will be carried out when insufficient evidence is available, or there are no valid comparators, which could occur in the case of disruptive drugs. For this reason, it is necessary to further develop the different aspects included in the Plan in relation to the economic evaluation, in order to clarify the method to be used and to add transparency to the economic evaluation process.
- As regards the procedure for drawing up the TPRs, the CNMC welcomes the creation of the Medicines Evaluation Network (REvalMed), although it is necessary to improve the transparency of REvalMed's internal organisation, its decision-making, its independence and the members that comprise it.

- Finally, the reform also envisages streamlining the overall time taken to prepare TPRs. The CNMC supports this streamlining, although it also considers it desirable that draft TPRs are circulated to the various stakeholders, including patient associations, clinical specialists, and so forth, for comment.

SECOND. Implement continuous and repeated therapeutic and economic evaluation of innovative medicines over time through the use of new technologies and big data.

It is necessary to improve the assessment of the medium- and long-term therapeutic effectiveness of funded medicines, where effectiveness is understood as the efficacy of a medicine in real conditions or clinical practice in patients, in order to both optimise clinical practice and adjust medicine pricing over time. To this end, it is recommended that therapeutic and economic evaluation be carried out continuously and repeatedly over time, especially for medicines with a significant budgetary impact.

New technologies and big data provide a unique opportunity for generating economic data and real therapeutic effectiveness in clinical practice in a more expeditious, comprehensive and real-time manner. This information could be used to help make funding decisions, optimise drug use recommendations and adjust prices. In this regard, it is important to take advantage of the framework provided by the Digital Health Strategy approved by the Ministry of Health in November 2021, which includes as one of its strategic lines the strengthening of data analytics and the exploitation of information for the 'business intelligence' of the SNHS, linked to the creation of a Health Data Space. Such a Health Data Space could also facilitate data sharing between different information systems and thus facilitate access to relevant information and its processing to draw conclusions.

Along these lines, if the Ministry of Health's recently created Valtermed registry becomes a benchmark in the healthcare field, it could provide crucial information for optimising treatments, financing, price adjustment over time and risk sharing between the authorities and operators in almost real time. This improvement in healthcare management would provide benefits for the end patient and boost the sustainability of the healthcare system. However, for this to happen, it must be developed by the Ministry of Health by including a large number of new medicines in the registration platform (currently, data on only 11 high-impact drugs is recorded) and implementing an adequate information system that allows the data on the therapeutic effectiveness of these medicines to be extracted in an easy and comprehensive way.

Furthermore, all the information included in Valtermed should be accessible to health professionals (at present, hospitals have access to their own data; the Autonomous Communities to the data of their entire community, but not to that of others; and the State to all the information). Access to the therapeutic assessment of a large number of patients and different profiles would enable the identification of problems in clinical practice and clinical subgroups with less or greater effectiveness, characterise the uncertainty or long-term outcome of treatments by patient type, and facilitate a host of other potential benefits. If access to the information could generate problems in terms of data confidentiality, anonymised or aggregated access to the information could be achieved.

Finally, the data records and information contained in Valtermed, or information generated through other software tools, could be useful for more efficiently implementing risk-sharing arrangements, especially, but not only, for medicines with a high budgetary impact. It should be stressed that the functionality of registries, such as Valtermed, depends on the information entered by healthcare professionals. It is therefore recommended that these systems simplify the collection of information as much as possible, and coordinate with existing health information sources to minimise any additional data collection burden.

THIRD. Reform the Reference Price System (RPS) to encourage real price competition

We propose implementing a more flexible RPS, allowing laboratories to freely set the wholesale price of the medicine (LSP), with the maximum reimbursement price being fixed through the reference price. In the event that the price set by the laboratory is below the reference price, the SNHS would reimburse this lower price and this lower price would be taken into account when calculating the patient's co-payment. In the opposite case, for medicines priced above the reference price, the reference price would be reimbursed, with the consumer paying the difference between the reference price and the price set by the laboratory (avoidable co-payment).

This system of flexible pricing would favour the entry of new generic operators and is key to achieving an adequate level of effective competition in the market.

This change in general intervention mode does not preclude the possibility, in areas and circumstances where market shortcomings are detected or where there are other overriding reasons of general interest, of adopting, structurally or temporarily, more intensive intervention measures, including the establishment of maximum prices when this is necessary and proportionate in accordance with overriding reasons of general interest, such as the protection of public health, equal access to medicines, or the protection of certain disadvantaged groups.

For this aforementioned reform of the Drug Pricing System to promote real competition, it must be accompanied by changes to prescription and dispensing policies, as discussed in the following recommendation.

In addition, it is advisable to clarify the terminology used in the reference pricing and homogeneous grouping systems, as it is confusing, misleading and there is an overlap between the terms used. To do this, it would be necessary to review both systems with a view to avoiding confusing dynamics, clarifying concepts and determining how these systems work.

FOURTH. Modify prescribing and dispensing policies to encourage competition between originator and generic medicines, promoting patient choice

It is recommended that Article 87 of Royal Legislative Decree 1/2015 of 24 July, 2015, approving the Consolidated Text of the Law on Guarantees and Rational Use of Medicines and Medical Devices, is amended so that, in general, medical products are prescribed by active ingredient, except for those medicines that cannot be substituted in pharmacy dispensing. This would favour the introduction of generic medicines into the market, encourage price competition, promote innovation and transparency, mitigate conflicts of interest between doctors and industry, and improve patient information. This is one of the measures included in the Ministry of Health's Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilars and generics.

We also recommend changing the pharmacist's obligation to replace the prescribed medicine with a lower-priced one for an indicated substitution. Under this system, the pharmacist would be obliged to inform the consumer about the price alternatives and medicines available on the market. In the case of medicines priced below the reimbursement price set for their group, the pharmacist should dispense one of the medicines below that price. This would correct the dispensing of only one medicine (that with the “lowest price”), increasing the variety of medicines, consumer choice, and the level of competition. This does not preclude the possibility that, in the event the selected medicine has a higher price than the maximum reimbursement price (reference price), because there is no alternative with a lower price, consumers would have to pay the difference out of their own pocket ("avoidable co-payment"). Also, it should be noted that in these cases, the authorities may intervene in the price of medicines where this is excessive. Any intervention must be justified, time-limited, and based on reasons of public health protection, equal access to medicines, or actual or potential harm to the interests of certain disadvantaged groups.

Finally, it is necessary to reflect on the possibility of personalising drug dispensing in pharmacies. This personalised dosage could be implemented either manually or automatically by using drug dispensing robots that allow medication to be repackaged into single-dose or multi-dose systems.

This type of personalised and automated dispensing would not only limit the over-sale of medicines in the retail pharmacy channel, but would also improve patient-consumer service, especially for particularly vulnerable groups, such as the elderly or polymedicated persons, for whom a grouped dosage of medication would limit human error and facilitate treatment adherence. Similarly, introducing this kind of dispensing robots would improve dispensing efficiency and increase competition in the retail pharmacy channel.

Finally, the prescription aid systems that the health services in the Autonomous Communities make available to healthcare professionals to assist them in their clinical activity could incorporate criteria that encourage efficient prescribing. For example, these systems could introduce a medicine indicator or ranking scheme that would help healthcare personnel identify the most appropriate medicines for the patient's treatment and those with the best cost-effectiveness conditions, boosting the quality of treatments, as well as the economic sustainability of the SNHS.

FIFTH. Define the reference sets of the Reference Pricing System as pro-competitively as possible

Where clinically appropriate, reference sets should be defined as broadly as possible to encourage competition between the different medicines in the set. This does not preclude the creation of more limited sets where this is therapeutically appropriate for medicinal products that cannot be considered equivalent in clinical practice. In these cases, exceptional sets should be applied in accordance with the appropriate clinical criteria, whether this is the ATC5 level, the active ingredient, or another appropriate designation.

The proposal included in the Ministry of Health's Action Plan to promote the use of generic and biosimilar medicines is along these lines. According to this, once the reform has been adopted, reference groups may be made up of dosage forms of funded medicines that all have the same ATC4, defined daily dose (DDD), same pharmaceutical configuration or grouping of configurations and identical administration route, subject to the agreement of the Standing Committee on Pharmacy in those indications where it is considered cost-effective. It would therefore appear that, as far as possible, and always under clinical and cost-effectiveness criteria, the Ministry is considering the option of defining broader groupings at the ATC4 level.

The CNMC welcomes this measure, and recommends, whenever possible, considering extending the reference sets to a broader scope (ATC4 or beyond) than the current level (ATC5), at least for certain therapeutic indications in which it is feasible or indicated both clinically and economically. The broader the groupings, the more medicines will be included in them and the more competition there will be between the different medicines in the pool.

SIXTH. Establish a formal stance on the interchangeability of biological and biosimilar medicines when there is favourable clinical evidence

The policy of switching or interchange is an essential element and facilitates competition between biological and biosimilar medicines. For this reason, the competent authorities are urged to conduct an analysis of the clinical evidence on the interchangeability of biosimilars with biological medicines when prescribing, in order to determine the safety of the drug interchangeability.

In the event that the existing evidence supports prescription interchangeability, it is recommended that a formal stance be taken in favour of the interchangeability of biological and biosimilar medicines. The aim is to standardise the different actions in the National Health System, increase competition in the market, promote the sustainability of the Spanish health system and guarantee access to affordable and effective biological medicines for patients who require them.

SEVENTH. Develop informative and health education campaigns on generic and biosimilar medicines

It is necessary to continue developing informative and health education campaigns on the use of medicinal products, both chemically synthesised (originator and generic) and biological and biosimilar medicines, so that the recommendations made above are truly effective.

For chemically synthesised medicines, information and health education programmes aimed at the general public are recommended, given that there is still a lack of information on the use of originator medicines/generics among patients/consumers and the general public. Health institutions should make an effort to communicate and disseminate clear, concise and objective information on these medicines in order to clarify doubts about their use, efficacy, safety, quality and their impact on healthcare systems.

With regard to biological and biosimilar medicines, it is essential to continue with information and training programmes, for both patients and prescribers. Otherwise, there could be an unjustified bias favouring the use of one or other medicine, hindering the prescription of these medicines and generating doubts

among patients. These initiatives should be conducted in a transparent manner using objective and contrasted information. In particular, communication about the use of biological/biosimilar medicines between patients and clinicians must be fluent, honest, and complete.

EIGHTH. Reform the current system of distribution margins proportional to price, to one linked to the services provided

In the case of wholesale distribution margins, the remuneration system should be based, at least partially, on the medicine distribution services (in terms of safety, efficacy, speed and control of medication, or distribution to rural and depopulated areas) and on the logistical specifics of the products distributed (boxes, injectables, solutions, fragile items, cold storage, etc.), ensuring fair remuneration for all medicines and an adequate supply to the most remote and depopulated rural areas.

In relation to retail distribution margins, the CNMC recommends moving from a purely product-oriented system to a mixed, but more patient-oriented system (this recommendation was already made by the CNMC in E/CNMC/003/15 on the retail distribution market for medicinal products and in INF/CNMC/059/19). In particular, a mixed remuneration system should be considered, combining a fixed fee for dispensing, and remuneration for certain services defined by the SNHS that contribute to the health of the population.

We also recommend the introduction of a system of incentives for pharmacists to encourage the dispensing of lower-priced medicines within the homogeneous groups of the reference pricing system. In this way, the possibility is raised of introducing partial reimbursement (%) of the difference between the wholesale price (LSP) and the reimbursement price (reference price) set by the administration for those medicines sold at a lower price than the reimbursement price for their set or group.

Also, to help ensure adequate care in small population centres, a selective fixed payment based on certain agreed community services or a minimum guaranteed income could be added.

NINTH. Introduce a return, or clawback system

The establishment of a clawback mechanism, whereby a portion of the discounts offered to distributors and pharmacies in the funded medicine distribution channel would be passed on as a lower cost to the SNHS, would help to reduce the public cost of pharmaceutical provision, free up resources to finance other treatments and benefit end consumers.

The CNMC welcomes the fact that the Action Plan to promote the use of market-regulated medicines in the SNHS: biosimilars and generics, approved by the Standing Committee on Pharmacy of the SNHS Interterritorial Council includes an initiative along these lines. However, for the clawback mechanism to be successful, it must be designed with caution in aspects such as operator access to commercially sensitive information, due to the high risks of coordination and the existence of prior sanctioning proceedings. In this regard, it is recommended that intermediate operators in the chain should not be able to consult the data of third party operators, which should appear in an aggregated and confidential format.

Furthermore, to encourage a competitive dynamic, a full clawback of discounts should not be designed, as the incentives to offer discounts would be diluted or eliminated. Hence, the design of the clawback mechanism should be such that the SNHS receives a share of the discounts obtained in the medicines chain, so as not to discourage pharmacies from negotiating these discounts.

Lastly, the interconnected register of discounts referred to in Article 4.6 of the Consolidated Text should be set up so that the competent administrations can obtain information on the discounts obtained by each pharmacy.

TENTH. Review the notified price system

The notified price system generates a regulatory asymmetry between defunded medicines and their competitors that were never financed by the SNHS, by subjecting the former to a price control for a series of reasons that could well be applied to the latter (protection of public health, equal access to medicines or real or potential harm to the interests of disadvantaged groups). Moreover, defunded medicines are subject to permanent administrative control, as the regulations (Articles 93.4 and 93.4 of the Consolidated Text) do not establish any time limit.

The CNMC recommends reviewing this system to assess its necessity and proportionality, both in relation to the medicines that are subject to it and in terms of the time during which it is considered necessary to subject them to administrative control.

With regard to the practical application of the notified price system, the CNMC has learned that in 2012 and 2013, the DGCYF and the CIPM denied marketing price increases requested for defunded medicines. The refusal decisions state that the requested price increases were higher than the evolution of the CPI and, therefore, were considered to potentially hinder equal access to medicines by patients.

The CNMC considers that the systematic rejection of price changes based on the evolution of the CPI is not appropriate and urges the DGCYF and the CIPM to analyse each price change proposal individually, in line with the particular circumstances of the medicinal product in question, and to provide sufficient reasons for its decision.

Finally, the CNMC considers that other public interventions that could help to **solve the root of possible problems of excessive prices for defunded medicines should be assessed.** Specifically:

- **Boosting patient information**, complemented by the generation of **appropriate incentives for medicine dispensers**, whose interests should be aligned with those of the patient, in order to stimulate competition through more informed demand.
- Eliminating the perverse incentives that the regulation of retail distribution margins generates through **the regulation of pharmacy margins that are proportional to price.**
- Assessing the possibility of increased public funding or direct aid in cases where the price problem particularly affects identifiable patient groups (e.g., in the case of chronic patients and/or those with reduced economic capacity).

ELEVENTH. Review the regulations on vertical integration between the wholesale and retail distribution channels

It is recommended that the regulation on vertical integration between the wholesale and retail distribution of medicines (Article 4.2. and the second transitional provision of the Consolidated Text) be reviewed on the grounds that it introduces a restriction or prohibition on vertical integration that only applies to some operators (cooperatives or pre-existing commercial companies), while others benefit from the possibility of being able to do so. This asymmetry distorts the market and means, in practice, a closure of the market in favour of the incumbent operators.

ANNEX I. CALCULATION OF MARGINS FOR THE DISTRIBUTION AND DISPENSING OF MEDICINAL PRODUCTS

For the purposes of clarifying and simplifying the information, as well as to represent it graphically, it is convenient to relate all the distribution and dispensing margins, as well as the thresholds established by the regulation, to a single reference (the RP). This annex shows the succession of calculations carried out to achieve this objective, the results of which are already included in Sections 2.2.4 and 2.2.5 of this study.

Throughout the annex, the following abbreviations are used:

LSP: Laboratory sale price

WDM: Wholesale distribution margin

DSP Distributor sales price = LSP + WDM

RDM: Retail distribution margin

RP: Retail price = LSP + WDM + RDM

Wholesale distribution margin on the LSP:

According to Article 1 of RD 823/2008, the margin corresponding to the distribution of industrially manufactured medicinal products for human use for dosage forms of medicinal products whose laboratory selling price is equal to or less than 91.63 euros is set at 7.6% of the distributor's selling price excluding tax. The margin for the distribution of industrially manufactured medicinal products for human use for presentations of medicinal products whose laboratory selling price is greater than 91.63 euros is set at 7.54 euros per pack.

Therefore:

$$If\ LSP \leq 91.63€ \rightarrow WDM = 0.076\ DSP = 0.076\ (LSP + WDM) \rightarrow$$
$$\rightarrow WDM = \frac{0.076\ LSP}{0.924} = 0.082251\ LSP$$

$$If\ LSP > 91.63€ \rightarrow WDM = 7.54€$$

The wholesale distribution margin is approximately 8.23% of the LSP when the LSP is less than or equal to 91.63 €, and 7.54 € when it is higher.

Retail distribution margin on the LSP:

According to Article 2 of RD 823/2008, pharmacy margins for dispensing and retail sales of industrially manufactured medicinal products for human use, for

those medicinal products whose industrial price is equal to or less than 91.63 euros, are set at 27.9% of the retail price excluding taxes.

$$\boxed{\begin{gathered} If\ LSP \leq 91.63€ \rightarrow RDM = 0.279\ RRP = 0.279\ (LSP + WDM + RDM) \rightarrow \\ \rightarrow RDM = 0.279\ (LSP + 0.082251LSP + RDM) \rightarrow \\ RDM = \frac{0.301948LSP}{0.721} = 0.41879061LSP \end{gathered}}$$

Therefore, the retail margin is approximately 41.88% of the LSP when the LSP is 91.63 € or less.

Pharmacy margins for the dispensing and sale to the public of industrially manufactured medicinal products for human use whose industrial price is greater than 91.63 euros and equal to or less than 200 euros, is set at 38.37 euros per pack; [...] for those medicinal products whose industrial price is greater than 200 euros and equal to or less than 500 euros, it is set at 43.37 euros per pack; [...] for those medicinal products whose industrial price is greater than 500 euros, it is set at 48.37 euros per pack.

$$\boxed{If\ 91.63€ < LSP \leq 200 \rightarrow RDM = 38.37€}$$

$$\boxed{If\ 200€ < LSP \leq 500 \rightarrow RDM = 43.37€}$$

$$\boxed{If\ LSP > 500 \rightarrow RDM = 48.37€}$$

LSP - RP equivalences:

Based on the above calculations, and taking into account the fact that

$$RP = LSP + WDM + RDM$$

it is possible to find the breakpoints (or thresholds) of the piecewise functions of the margins (wholesale and retail), which are regulated in terms of the RP of the medicine:

$$\boxed{\begin{gathered} If\ LSP \leq 91.63€ \rightarrow RP = LSP + WDM + RDM \rightarrow \\ \rightarrow RP = LSP + 0.082251LSP + 0.41879061LSP \rightarrow RP = 1.50104169LSP \end{gathered}}$$

Therefore,

$$\boxed{If\ LSP = 91.63€ \rightarrow RP = 1.50104169LSP = 137.54€}$$

Where,

$$\boxed{\begin{gathered} If\ LSP = 91.63001€ \rightarrow RP = LSP + WDM + RDM \rightarrow \\ \rightarrow RP = 91.63001 + 7.54 + 38.37 \rightarrow RP = 137.54€ \end{gathered}}$$

The margin function for a LSP of 91.63 euros is continuous (no jumps or discontinuities), as can be seen in Figures 12 and 14, and unlike the other thresholds, as shown below:

$$If\ LSP = 200€ \rightarrow RP = LSP + WDM + RDM \rightarrow \\ \rightarrow RP = 200 + 7.54 + 38.37 \rightarrow RP = 245.91€$$

$$If\ LSP = 200.0001€ \rightarrow RP = LSP + WDM + RDM \rightarrow \\ \rightarrow RP = 200.0001 + 7.54 + 43.37 \rightarrow RP = 250.91€$$

$$If\ LSP = 500€ \rightarrow RP = LSP + WDM + RDM \rightarrow \\ \rightarrow RP = 500 + 7.54 + 43.37 \rightarrow RP = 550.91€$$

$$If\ LSP = 500.0001€ \rightarrow RP = LSP + WDM + RDM \rightarrow \\ \rightarrow RP = 500.0001 + 7.54 + 48.37 \rightarrow RP = 555.91€$$

Wholesale distribution margin on the RP:

Given that

$$If\ LSP \leq 91.63€$$

$$\rightarrow\ WDM = 0.082251 LSP\ and\ RP = 1.50104169 LSP$$

Substituting we obtain:

$$\rightarrow WDM = 0.082251 * \frac{1}{1.50104169} RP = 0.0547959 RP$$

Therefore, the distribution margin is approximately 5.48% of the RP (equivalent to 8.23% of the LSP) when the RP is less than or equal to 91.63 €.

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