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Italy – a study case of medicines pricing and reimbursement

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Abstract

The Italian National Health Service (*Servizio Sanitario Nazionale*, SSN) is structured at comprehensive levels such as collective prevention and public health, cure and rehabilitation assistance, and pharmaceutical services, with the primary objective of guaranteeing universal access of all Italian citizens, on equal terms, to equitable provision of health services. Italy was used as a case study to explore their healthcare system and their economic regulation and reimbursement of pharmaceuticals. The Italian Medicines Agency (*Agenzia Italiana del Farmaco,* AIFA) is responsible for regulation related to efficacy, safety and quality, pricing and negotiations for reimbursement of medicines. Among the various negotiation criteria defined in specific legislation, biosimilars and generics enter the Italian market with a discount of at least 20% to the reference medicine. Price review occurs in a periodical basis and upon the emergence of new evidence of efficacy and safety arising from pharmacovigilance or upon request of changes in the therapeutic indications and/or dosage. In addition, conducting the monitoring and analysis of pharmaceutical consumption and expenditure contributes for planning health policy interventions, since it allows for prompt identification of emerging phenomena, framing prescription behaviours, and verifying the effectiveness of regulatory interventions at regional and national levels. Efficacy, safety, and cost-effectiveness analyses are conducted before the introduction of the medicines in the Italian market. It continues to be performed when the drug in on the market with health technologies assessment, constituting a process of permanent investigation of the clinical, economic and social consequences of the medicine's utilisation. In addition, it allows controlling expenses and identifying avoidable costs.

Keywords: drug price, health technology assessment, reimbursement mechanisms, health systems plan, universal health insurance.

Itália – estudo de caso sobre precificação e reembolso de medicamentos

Resumo

O Serviço Sanitário Nacional (*Servizio Sanitario Nazionale*, SSN) na Itália está estruturado em níveis abrangentes de saúde coletiva como a prevenção, assistência para cura e reabilitação e assistência farmacêutica, com o objetivo primordial de garantir acesso universal a todos os cidadãos italianos em condições de igualdade e prestação equitativa de serviços de saúde. A Itália foi usada como um estudo de caso para análise do sistema de saúde, da regulação econômica e reembolso de medicamentos. A Agência Italiana de Medicamentos (*Agenzia Italiana del Farmaco,* AIFA) é responsável pela regulação sanitária relacionada à eficácia, segurança e qualidade, assim como pela análise de preço e negociações para reembolso dos medicamentos pelo SSN. Entre os diversos critérios de negociação definidos em legislação específica, os biossimilares e genéricos entram no mercado italiano com um deságio de 20%, no mínimo, em relação ao medicamento referência. A revisão de preços ocorre em períodos pré-definidos e em situações de novas evidências de eficácia e segurança decorrentes da farmacovigilância, ou por solicitação de alterações nas indicações terapêuticas e/ou posologia. O monitoramento e análise do consumo e das despesas farmacêuticas contribuem para o planejamento das intervenções das políticas de saúde pois permitem identificar prontamente fenômenos emergentes, enquadrar comportamentos prescritivos e verificar a eficácia das intervenções regulatórias em nível regional e nacional. As análises de eficácia, segurança e custo-efetividade ocorrem de maneira previa à introdução de cada medicamento no mercado italiano, e contínua para manutenção da comercialização; esse processo configura a avaliação de tecnologias em saúde devido a permanente investigação das consequências clínicas, econômicas e sociais da utilização do produto, além de permitir o controle das despesas e análise de custos evitáveis.

Palavras-chave: preço de medicamento, avaliação de tecnologias em saúde, mecanismos de reembolso, planos de sistemas de saúde, cobertura universal do seguro de saúde.

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Introduction

In 2020, Italy had an approximate population of 59.6 million inhabitants, which corresponded to 13.3% of the total population of the 27 Member States of the European Union. Currently, most of the population is aged from 40 to 59 years old. There is a growing trend for the population aged up to 79 years old up to 2040, due to an increased life expectancy at birth, which in 2019 was approximately 85.4 years old for women and 81.1 years old for men. In 2019, the birth and mortality rates per 1,000 inhabitants were in the order of 7.0 and 10.6, respectively[1–3].

Due to the covid-19 pandemic, between March and December 2020, there were an excess of 108,178 deaths in relation to the media of the same period between 2015 and 2019, a 21% increase. January and February were not considered in this calculation because the first reports of positive tests for covid-19 dated from the last week of February, and the mortality rates for these two months in 2020 were lower than the mean recorded between 2015 and 2019. The increase in the number of deaths among the population aged 80 years old and over explains 76.3% of the overall mortality excess. The age group between 65 and 79 years old explains another 20% of the excess deaths with the mean for the 2015-2019 period[1].

In economic terms, Italy had the fifth-highest Gross Domestic Product (GDP) among the 37 countries that comprise the Organization for Economic Cooperation and Development (OECD) in 2019. Between 2018 and 2019, there was a 0.6% increase, rising from 41.9% to 42.4%[2]. However, in 2020, due to multiple factors, including those related to the covid-19 pandemic, the sum of all goods and services produced in Italy was 8.9% lower than that observed in 2019. The GDP per capita in 2019 was € 27,818[4]. That is to say, the Italian GDP variation in 2020 was negative at a rate of 8.9%[3], but with the projection of upward of 4.1 in 2021 and 4.0 in 2022[5].

Among the several indicators that show the interface between economy and health, health expenses, both *per capita* and as a percentage of the GDP, summarize the overall availability of resources. It is to be noted that the sufficiency of health resources does not automatically translate into better health results, as does expenditure efficacy. In this sense, investments in quality of care, in access to health services, in hiring health care professionals, and their continuing education can be translated into a good country performance when these dimensions are associated with some variable or outcome of interest, such as increased life expectancy or avoidable deaths (preventable or treatable)[6].

In 2020, Italy's health expenditure (HE) *per capita*, public and private, was € 2,690.5 (US$ 3,819.4 Purchasing Power Parity, PPP), representing 9.7% of the GDP. Public HE corresponded to 76.3% of total HE. The pharmaceutical expenditure (PE) per capita was € 348, with public PE as 76.5% of total PE[4]. The country stood out for having one of the lowest rates of avoidable mortality, as well as an increased life expectancy at birth, and even one of the highest survival rates for breast cancer[6].

In this context, it is important to remember that the gearing that moves the health services is composed by a legal framework, permeated by technical and economic parameters.

Italy was used as a case study to explore the technical, economic, and legal structure of their health system, focusing on the economic regulation and reimbursement of medicines.

Characterisation of the National Health Service in Italy

The National Health Service (*Servizio Sanitario Nazionale*, SSN) was instituted in 1978 through Law No. 833, based on the Constitution of the Italian Republic. Some characteristics of the SSN it is like in Brazil, as the decentralised system, with competencies and duties of the State, regions, municipalities, and companies regarding the health structure and planning of the SSN; the fundamental values, such as universality, equality and equity, and the primary objective of the System's organisational structure, in guarantee universal access of all Italian citizens, on equal terms, to equitable provision of health services[7].

The health service network is organized according to its nature (public and private) and structured by type of health care provided: primary care, hospital care, specialized outpatient care, home and semi-home care, and rehabilitation care, as well as other types of care. These assistance structures have been changing over the years, and an analysis conducted in the 2016-2019 evidenced a 1.4% decrease in structures with public coverage and a 1.0% in structures with private accreditation. In specialized outpatient care, a reduction was observed in public structure (1.3%) and an increase in private accredited network (0.1%). In the scope of rehabilitation care, an increase was observed in public (0.1%) and private (1.2%) structures[8].

In 2019, hospital care and other types of assistance were mostly public, with 51.9% and 87.0%, respectively. Conversely, private structures were predominant in the provision of specialized outpatient care (60.4%), home care (83.2%), semi-home care (71.1%), and rehabilitation care (78.4%)[8]. In March of 2019 there were 19,331 community pharmacies (17,656 private and 1,675 public pharmacies). In 2021 the members of the industry association informed that there were 200 pharmaceutical companies, between Italian and foreign companies[4].

The means through which Italian citizens access the health services, as well as they route through the different care structures and can be insert in a social and health integrate care, is coordinated and validated by a general physician or paediatrician affiliated to the SSN[8].

To serve the three major structural levels of the SSN, there are basic organizational principles and health planning. The Essential Assistance Levels (*i Liveli Essenziali di Assistenza*, LEA) correspond to actions and services that the SSN is obliged to provide to all citizens, either free of charge or through the payment of a participation fee (ticket), with public resources collected from taxes. In 2017 a Decree (*Decreto del Presidente del Consiglio dei Ministri,* DPCM) updated the activities, services, and benefits ensured to Italian citizens with the public resources made available to the SSN. This decree redefined and updated the list of rare and chronic disabling diseases that give patients the right to waive from the ticket, as well as the names of the outpatient care and prosthetic assistance specialties, introducing technologically advanced services and excluding obsolete ones. In addition, each region is allowed to guarantee services and varied activities from those included in the LEA, provided it is with its resources[7,9,10].

Pharmaceutical services and medicines offered in the SSN

In the context of the services provided by the SSN, pharmaceutical services represents the most susceptible to change because it strictly depends on the provisions from the financial legal framework, based on monitoring the flow of medicines distribution, prescription, and procurement[8,11].

The OsMed (*Osservatorio sull'impiego dei Medicinali*) is an official reference structure of the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) which, among other activities, is responsible for systematically and continuously monitoring information flows on medicines distribution, prescription, and procurement. Each body from the SSN structure has access to an electronic platform in which all the medicines-related transactions are recorded[11]. Management of the electronic registry platform is articulated through a network consisting of nearly 3,500 health structures, 52 regional managers, 963 health directors, 32,857 physicians, and 2,318 pharmacists. This network makes it possible to regulate the organization of pharmaceutical care throughout the territory[12].

Reports are published in the AIFA website with an overview about the expenses of the SSN recorded in the previous three years through the OsMed flow for the agreed-upon pharmaceutical expenses, the traceability flow of medications for direct distribution and hospital expenses, for the molecules whose patents expire in the current year and in the two subsequent civil years. The transparency provided with this publication serves as an essential premise of the activity of planning pharmaceutical services in Italy, as well as supports companies that intend to request medicines entry in the Italian market, such as that of generics and biosimilars, which are conditioned to the expiration date of patent protection of the reference medicine. In addition to that, this economic information from this legal framework, is a basis for the pricing model with internal referencing[11–13].

All medicines that receive authorisation for entry into the Italian market are distributed into three large lists, or classes, which distinguish medicines reimbursable by the SSN from those that are entirely paid by the patient out of pocket. The list of reimbursable medicines is divided into Lists A and H. Some of the country's regions have specific regulation instructing a co-payment the citizens for these medicines. List C covers the non-reimbursable medicines; however, reimbursement is granted to people below the poverty threshold, to those having very serious diseases and to holders of lifelong war pensions who provide a medical certificate proving the therapeutic usefulness of the medicines from this list[12,14,15].

List A includes essential medicines, generally for chronic diseases. It contains the medicines from AIFA's transparency list, as well as patent-protected medicines and those that, even if not protected by patents, are not expected to be substituted. In addition to that, some medicines have prescribing restrictions, i.e., they can only be prescribed in List A to patients with certain pathologies; otherwise, they fall into List C[12,14,15].

List H includes medicines for exclusive in-patient or specialized health units use[12,14,15].

List C encompasses medicines for minor diseases, considered non-essential. This list is divided into medicines with or without mandatory medical prescription. In turn, the non-prescription medicines are subdivided into those allowed and not allowed to be advertised (List C-bis-SOPs)[12,14,15].

According to the SSN pharmaceutical services, and its monitoring in 2019, it was possible to identify of 564,109,389 prescriptions (RXs), accounting for a total value of almost nine billion euros and a mean cost of 15.06 euros per prescription. The mean cost per prescription is highly variable across the national territory, depending on the regional demographic, geomorphological, and epidemiological characteristics, which made this cost vary from a minimum of 11.94 euros to a maximum of 20.51 euros[8].

The monitoring and analysis of pharmaceutical consumption and expenditure is the necessary instrument for planning the health policy interventions, since it allows for prompt identification of emerging phenomena, framing prescriptive behaviours, and verifying the efficacy of regulatory interventions at the regional and national levels[11].

Pharmaceutical market

In 2019, the pharmaceutical market corresponded to € 34 million. The pharmaceutical expenditure corresponded to 19.2% of the health expenditure in Italy. In 2020 there were 19,160 package presentations of medicines authorised and marketed (including different pharmaceutical forms and dosages) and 11.845 medicines (including different pharmaceutical forms and dosages) included in the outpatient reimbursement list (December 2020, year). In the same year, the generic market share corresponded to 14.5 % in value (reimbursement segment) and 22.46% in volume (outpatient sector)[4].

Regulation of the pharmaceutical market: marketing authorisation, pricing, and reimbursement

The AIFA is responsible for market authorisation, pricing, reimbursement, pharmacovigilance. For the decision-process of pricing and reimbursement, this institution is supported by two advisory committees: Pricing and Reimbursement Committee (*Comitato Prezzi e Rimborso*, CPR) and Scientific Technical Commission (*Commissione Tecnico Scientifica*, CTS). Health Technology Assessment (HTA) reports, elaborated by technical experts, are appraised by both advisory committees before the final decision of pricing and reimbursement[4].

Marketing authorisation

The marketing authorisation for entry in the European Union (EU) market can occur through three different routes. This analysis is specifically based on the medicine's conditions of quality, safety, and efficacy[16–18].

The centralised procedure is based on a technical-scientific evaluation, unique in the EU, performed by the European Medicine Agency (EMA) upon request of the interested company. Mandatory marketing authorisation through this route encompass medicines for rare diseases and almost all new molecules[17,18]. The decentralised procedure occurs when the company requests the simultaneous authorisation in more than one EU Member State if the medicine has not yet been authorised in any EU country. The third possible route is through the mutual approval procedure, which occurs when a medicine is authorised in some EU country and the company requests authorisation in another countries. This process requires reliance in the scientific evaluations performed by other Member States. However, EMA can decide on any issues that have been mandatorily or optionally referenced to it in the context of the procedures to assess and authorise medicines[17,18].

Once marketing authorisation is granted, decisions on pricing and reimbursements will be taken at the level of each Member State and depend on the submission of a request by the company. In Italy, these analyses fundamentally consider the therapeutic added value and the cost-effectiveness relationship of each medicine in the context of the national health system of the concerned country[17,18].

Pricing

When applying for marketing authorisation to AIFA, companies must include the intended price and classification within the reimbursement lists[15]. The pricing and negotiations in the cases of medicines suitable for reimbursement occur simultaneously and do not differ between outpatient and inpatient sectors[4,19]. The CTS appraise the HTA report and expresses opinion about a possible innovativeness, the therapeutic benefit (figure 1) and the place in therapy of the medicine, as well as to classify them into the reimbursement lists[4].

Figure 1. Criteria for defining therapeutic need and therapeutic value

In this context, the safety and efficacy studies are considered, as well as the quality of evidence for this material.

1. Therapeutic need:

- the efficacy and safety of the medicine are reviewed in relation to other available medicines in the market for the same pathology and population.

2. Therapeutic value:

- is determined by the magnitude of the clinical benefit when compared with the available alternatives, based on clinically recognised, relevant, and validated outcomes for the pathology in question;

- is defined as: maximum, important, moderate, scarce, and absent.

3. Quality of the evidence:

- the scientific studies presented by the company are reviewed according to GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method and allows classifying the quality of the evidence as high, moderate, low, or very low.

* In this sense, the score obtained for each basic element assessed enables to classify the product as follows: innovative, conditional (or potential) innovation, or non-innovative[20–22].

* This kind of analysis are used for all application or all categories submitted by the company, be it an orphan drug, or a suggestion of innovation due to the addition of indication or change in dosage[23].

New criteria for pricing and reimbursement begun to be applied in 2021 after the publication of the Decree, following the Resolution of the World Health Organisation (WHO) about "improving the transparency of markets for medicines, vaccines, and other health products". Some changes are: the marketing authorisation holder (MAH) has to show the documentation about the added therapeutic value and has to provide information about consumption and reimbursement status in other countries[4].

The external reference price (ERP) is used as a supplementary data and Italy considers prices of 24 European countries as a guide for pricing and reimbursement negotiation[4]. Additional information, such as sales volume and availability of the product to the SSN that may be achieved in the specific segment within 24 subsequent months, may be required[20]. In other words, medicines pricing in Italy takes into account internal and external reference pricing[21].

Generic and biosimilar medicines enter into the Italian market with a price at least 20% lower than the originator[4].

Marketing authorisation for the Italian market, or extension of a therapeutic indication, determine if a given product will be monitored concerning the prescriptions and dispensing at the SSN level, and will have its efficacy and safety continuously reassessed for renegotiation purposes, to control expenses and analyse avoidable costs[12]. AIFA performs the inspection of non-reimbursed prescribed medicines verifying compliance with two conditions: the medicines price, that can be increased every two years, only in odd years, and this increase cannot exceed the predicted inflation[15]. About the non-reimbursed non-prescription medicines, the company is obliged to communicate to AIFA variations in the prices due to distribution[4].

An exception for commercialisation of medicines, of those with exceptional therapeutic and social relevance, or exclusive for inpatient use, was established in 2012. After marketing authorisation, and during the period of appraisal and decision of pricing and reimbursement, the medicines will be classified into List Cnn (List C-not negotiated) until the results of the analyses are published. During this period, the medicines are not reimbursable. However, the company must inform ex-factory and retail selling prices of these medicines to AIFA, in addition to the date of entry into the market, before the beginning of commercialisation; these requirements also apply to the parallel import medicines[15,19].

The maximum consumer's price (retail price) comprises the ex-factory price, with the addition of the value-added tax (VAT) and of aliquots and margins that vary according to the distribution channel and are established in specific legislations[4,22].

In the Italian regulation there is no definition for innovation of a medicine, that is, there is no relationship between price and reimbursement value with innovation status[4].

Reimbursement

Reimbursable medicines are those used for severe pathologies, both chronic and acute, which are considered essential to guarantee the predicted treatments at the essential health care levels, whether at the outpatient or inpatient level[14,23]. Medicines are put in the positive list (Prontuario Farmaceutico Nazionale, PFN) if they are considered for reimbursement, either in Class A (outpatient) or Class H (inpatient). Non-prescription medicines are usually not reimbursed[4].

The reimbursement prices by the SSN are determined through a negotiation between Pricing and Reimbursement Committee (CPR) and the manufacturers. The negotiation criteria consider pharmacoeconomic studies, as well as the quality of evidence for this material (figure 2) and market criteria like: the reimbursement price in the EU Countries (if it exists), the prices of other products eligible for reimbursement and that is part of the company's portfolio but have not been object of negotiation, in addition to the compared efficacy in relation to other products already commercialised for the same clinical condition. If the product's efficacy is equivalent to products already commercialised for the same indication, the negotiated price should consider the already negotiated prices, weighted by the data on presumed consumption, historical trend of the medicine's therapeutic, supplemented by the effects of epidemiological estimations and/or predictions; this criterion is based on the market substitution effect[24].

Figure 2. Criteria for defining reimbursement

To carry out a comparative and critical analysis with the studies sent by company, the following procedures are conducted:

1. Evidence searching to identify published pharmacoeconomic and budget impact analysis studies related to the national or international context;

2. identification of recommendations and decisions taken by other countries in relation to the medicine in question;

3. analysis of treatment cost compared to other therapeutic alternatives[24].

The quality of the evidence:

- the scientific studies presented by the company are reviewed according to ISPOR *(International Society of Pharmacoeconomics and Outcomes Research)* recommendations regarding the quality and robustness of the studies.

* For reimbursement is possible to access treatment with a medicine regularly on the market but for an indication other than that for which it was authorised (Law 94/98 art.3, paragraph 2 - ex Di Bella Law), even in the presence of regularly authorised therapeutic alternatives. In this case, however, the therapy is the responsibility of the patient or the responsibility of the health company in case of hospitalization. All of these early access routes take place under the responsibility of the prescribing physician[26].

* It is worth highlighting that an open and editable format of the pharmacoeconomic and budget impact analysis studies is required for orphan drugs, new molecules, an extension of indication or change in dosage, change in unit dosage, and renegotiation of prices[12,27].

The negotiated and agreed-upon price represents the SSN maximum transfer price for local hospitals and health authorities. A confidential discount is usually negotiated between AIFA and the manufacturer. Based on this net price, each body may negotiate commercial discounts, applying their procedures[24].

In case of failure to reach an agreement on the medicines price, or on the exclusion of a medicine previously available by the SSN, the medicine is included in Class C and communication to the population and health care professionals will occur via the Ministry of Health bulletin and through other appropriate means[19,24].

For reimbursement there are regional price negotiations that take into account the expected sales volume and annual SSN mean expenditure with all the comparators with regulated prices. The price negotiation by tendering can allow 99% off discount[15,16,19,25–27].

Between 2017 and 2021, there was a variation in the number of dossiers analysed by the AIFA in relation to the type of negotiation. For dossiers with extension of indications and orphan medicines there was an increase in the amount analysed, from 24,3% to 34,5% and from 42,1% to 100%, respectively. For dossiers with new active drugs there was a reduction, going from 72,7% to 48,8%[28].

Price review

Review of negotiated prices can occur at any time, whether due to new evidence of efficacy and safety arising from the pharmacovigilance system or upon request for changes in the therapeutic indications and/or dosage. Therefore, the benefits of the reimbursement classification may be changed and, consequently, a new negotiation of prices and reimbursement conditions will begin[20–22,24].

The established legal period for price review is by default 24 months, 36 months for innovative medicines and 18 months for conditionally (or potentially) innovative medicines[20–22,24].

It is worth noting that the Balduzzi Decree established the mandatory price review of all products from the reimbursable list through a reorganisation and equalisation of prices according to the therapeutic indications and classes, separating protected and non-patent-protected medicines. The purpose of this Decree was to reduce SSN expenses through renegotiations with companies through the selective application of price reductions[29].

The efficacy, safety, budget impact and cost-effectiveness analyses occurred before the medicine introduction into the Italian market. Continuous monitoring is performed while the drug on the market, using HTA, for investigating clinical, economic and social consequences of using the product[30].

Conclusion

The organisational structure of the health systems in Brazil and Italy are similar, as both legal basis and fundamental values guarantee their citizens, under equal conditions, universal access to the equitable provision of health, including pharmaceutical services.

In relation to the drug pricing and reimbursement, both are conducted by the health regulatory authority and are based on HTA components, having the therapeutic benefit guiding the pricing. They use external and internal reference pricing, just as in Brazil. The internal reference pricing considers, among other items, the prices and sales volumes of other competing drugs, from the same company and from the market. External reference pricing considers prices, consumption and reimbursement conditions in other countries.

When carrying out this case study on the pricing and reimbursement of medicines in Italy, two components can be considered as special interest, the classification of the added therapeutic benefit, namely innovative, conditional (or potential) innovation, or non-innovative, as well as the periodic review of prices. It is noteworthy that price reviews, whether encouraged by new evidence of effectiveness, efficacy and safety arising from the pharmacovigilance system, either by requesting changes in therapeutic indications and/or dosage or unit dosage and the continuous evaluation of the clinical, economic, and social benefits of using medicines based on HTA with a life cycle perspective can be beneficial for the society, ensuring the medicines are always assessed based on the best available evidence and affordable prices.

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Conflict of interest declaration

The authors declare that there are no conflicts of interest in relation to this article.

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