PPRI
Pharmaceutical Pricing and Reimbursement Information

PPRI Pharma Brief: Italy 2021

Pharmaceutical Pricing and Reimbursement Information (PPRI) Pharma Briefs Series

Commissioned by the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection

Gesundheit Österreich GmbH

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This report contributes to the implementation of the 2030 Agenda for Sustainable Development, in particular to Sustainable Development Goal (SDG) 3 "good health and well-being" and its target 3.8: Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.

About PPRI Pharma Briefs

This concise report on the pharmaceutical pricing and reimbursement policy framework in Italy is part of the series of PPRI Pharma Briefs launched by the Pharmaceutical Pricing and Reimbursement Information (PPRI) Secretariat in 2019.

PPRI networks

The PPRI network is a collaboration of **pharmaceutical pricing and reimbursement authorities** of 52 – mostly European – countries (as of October 2021) as well as international and European institutions (e.g. European Commission, OECD, World Health Organization). The aim of this network is to facilitate exchange between public officials, supported by scientific evidence and a common understanding of pharmaceutical policy issues. Under the framework of PPRI, further regional PPRI networks (e.g. in Central Asia) and thematic PPRI networks (e.g. on medical devices) have been established. PPRI networks are coordinated by the PPRI Secretariat which is hosted at the Pharmacoeconomics Department of the Austrian National Public Health Institute (Gesundheit Österreich GmbH / GÖG).

PPRI
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PPRI contributes to the international scientific evidence base, in particular in the areas of (comparative) **pharmaceutical systems research** and pharmaceutical policy analysis, by providing country information that is usually not published in other literature. This is of interest for policy-makers who want to cross-learn and benchmark as well as for researchers who perform policy analyses and require contextual information on national pharmaceutical systems.

PPRI country information

Well-established publications that offer pharmaceutical pricing and reimbursement information on a single PPRI country are the **PPRI Pharma Profiles** that are available as in-depth reports as well as short reports, see https://ppri.goeg.at/ppri_pharma_profiles. Furthermore, one-page graphical abstracts are provided in the **PPRI Posters**, see https://ppri.goeg.at/ppri_posters.

The new series **PPRI Pharma Briefs** responds to the interest and needs expressed by policy-makers and technical experts in public authorities responsible for the pricing and reimbursement of medicines to read concise reports of the pharmaceutical policies in other countries.

The PPRI Pharma Briefs draw upon the information and data that have been provided by the PPRI network members, in addition to literature and relevant documents, such as legal provisions.

For requests and comments, please contact ppri@goeg.at.

Key data at a glance

General and economic data

Population (1 January 2021)	59,257,566 (provisional value)
Country size (2021)	302,068.2564 km²
Gross domestic product / GDP (2019)	GDP per capita: € 27,818
Health expenditure / HE (2020, provisional values)	HE per capita: € 2,690.5, USD PPP 3,819.4 HE in % of GDP: 9.7% Public HE as % of total HE: 76.3%
Pharmaceutical expenditure / PE (2020)	PE per capita: € 348 Public PE as % of total PE: 76.5% Public PE in % of public HE: 18.9%

GDP = gross domestic product, HE = health expenditure, PE = pharmaceutical expenditure, PPP = Purchasing Power Parties, USD = United States dollars

Sources: population – Eurostat [1], country size – ISTAT [2], GDP – Eurostat [3], health expenditure – OECD Health Expenditure Indicators [4], pharmaceutical expenditure: AIFA 2020 report on use of medicines [5]

Provision of pharmaceuticals

Community pharmacies (March 2019)	19,331 community pharmacies (thereof 17,656 private and 1,675 public pharmacies)
Dispensing doctors	No dispensing doctors
Wholesale (year not specified)	Number of wholesale companies: 60 Number of total outlets: 193
Pharmaceutical industry (2021)	200 companies (Italian and foreign companies)

Pharmaceutical industry – Data relate to the members of the industry association

Sources: pharmacies – Federfarma [6], wholesale – ADF [7], pharmaceutical industry – Farmindustria [8]

Pharmaceutical market

Pharmaceutical market (2019)	€ 34 million
Medicines (2020)	19,160 package presentations of medicines authorised and marketed in 2020 (counted including different pharmaceutical forms and dosages) 11.845 medicines (counted including different pharmaceutical forms and dosages) included in the outpatient reimbursement list (December 2020, year)
Generic market shares (2020)	14.5 % in value (reimbursement segment) 22.46% in volume (outpatient sector)

Sources: production – Farmindustria [9], data on medicines authorized, marketed and reimbursed – provided by AIFA, market shares – Egualia [10]

Key technical terms are defined in the glossary in Annex 3.

Pharmaceutical pricing (2021)

Price regulation	In place for reimbursable medicines. i.e. medicines prescribed at the expense of the National Health Service (Servizio Sanitario Nazionale / SSN) in the outpatient and inpatient sectors
Pricing authorities	**Outpatient and inpatient**: Italian Medicines Agency (Agenzia Italiana del Farmaco / AIFA)
Key pricing policies	**External price referencing**: no specific external price referencing policy but supplementary pricing policy for reimbursable medicines in outpatient and inpatient sectors (prices in other European countries are, among others, considered to inform price negotiations) **Value-based pricing**: no fully-fledged value-based pricing policy, but value-based pricing elements are key components in pricing and reimbursement decision for reimbursable medicines in outpatient and inpatient sectors **Price negotiations**: key pricing policy for reimbursable medicines in outpatient and inpatient sectors, conducted between AIFA and the pharmaceutical company **Managed-entry agreements (MEA)**: significant number of MEA concluded for reimbursable medicines with high budget impact in outpatient and inpatient sectors; use of financially-based MEA, performance-based MEA and "appropriateness agreements" supported by the AIFA Monitoring Registries system **Tendering**: done by users (hospitals) and by regions, supported by the dynamic purchasing (DPS) system (e-procurement) of the national procurement agency **Cost-plus pricing**: no **Generic price link**: in place for reimbursable medicines in outpatient and inpatient sectors (generics and originator medicines to reduce the price by at least 20%) **Biosimilar price link**: in place for reimbursable medicines in outpatient and inpatient sectors (biosimilars and originator medicines to reduce the price by at least 20%)
Pricing in the supply chain	**Wholesale:** statutory linear wholesale margin for all outpatient medicines (different rates for originators and biosimilars than for generics) **Pharmacy**: statutory linear pharmacy margin for all outpatient medicines (different rates for originators and biosimilars than for generics) **Value-added tax**: 10% for medicines (standard VAT: 22%)

Source: overview provided by PPRI Secretariat, validated by AIFA

Pharmaceutical reimbursement (2021)

Reimbursement authorities	**Outpatient and inpatient:** Italian Medicines Agency (AIFA) to decide on the inclusion of a medicine into reimbursement, regions to fund reimbursed medicines
Reimbursement lists	**Outpatient and inpatient:** national positive list (Prontuario Farmaceutico Nazionale, PFN), additional regional positive lists; two "innovation funds" (one for innovative oncology medicines and one for innovative non-oncology medicines) **Inpatient:** hospital or regional pharmaceutical formularies
Reimbursement criteria	**Positive list ("Prontuario") – outpatient and inpatient**: HTA performed by AIFA and appraised by AIFA advisory committees; criteria: added therapeutic benefit, unmet medical need risk/benefit ratio, budget impact on SSN and cost/efficacy ratio, therapeutic benefit, expected market share, prices in other countries **"Innovation funds":** unmet medical need, added therapeutic benefit, quality of evidence
Co-payments for medicines	**Outpatient:** prescription fee in several Regions **Inpatient:** no co-payments in place
Demand-side measures to enhance the uptake of off-patent medicines	**Reference price system:** at ATC-5 level in place **Prescribing by International Non-Proprietary Name (INN):** voluntary **Generic substitution:** mandatory (unless exclusion of substitution indicated by prescribing doctor); **biosimilar substitution at pharmacy level**: not allowed

Source: overview provided by PPRI Secretariat, validated by AIFA

Summary

Health care in Italy is based on a National Health Service (called Servizio Sanitario Nazionale / SSN). The SSN works through the central government, regionally and locally (local health authorities ASL and "Independent Hospitals" AO). Health care is a matter of shared jurisdiction between the central Government and the regions, and in the regions, the respective ASL are responsible for the health of the entire population in their area. The Italian SSN is mainly financed by national and regional taxes; some patient co-payments also apply. Funds are assigned to the regions which are intended to cover the provision of the so-called Essential Care Levels (LEA) which define a minimum of health care services provided by the governments. Thus, the regions are the public funders for medicines.

The key public institution in the pharmaceutical sector is the Italian Medicines Agency (Agenzia Italiana del Farmaco / AIFA). It is responsible for all matters regarding the medicines for human use, including market authorisation, pharmacovigilance, pricing and reimbursement and pharmaceutical expenditure monitoring.

AIFA is in charge for setting the price of a medicine and its inclusion into reimbursement in one joint process. AIFA is supported by two advisory committees, which both have representation of national and regional public institutions: the Scientific Technical Commission (Commissione Tecnico Scientifica / CTS) provides opinions regarding the classification of new medicines towards their reimbursement status, and the Pricing and Reimbursement Committee (Comitato Prezzi e Rimborso / CPR) offers technical advisory support concerning the price negotiation for publicly funded medicines.

Upon receipt of the company's application, AIFA evaluates the medicine based on an assessment of several criteria, including unmet medical need, added therapeutic benefit and risk/benefit ratios, budget impact, cost/efficacy and prices in other countries, and negotiates the price. For several new high-priced medicines, managed-entry agreements (financially-based such as capping, price-volume, cost sharing, confidential discounts or performance-based ones such as Payments by Result, Risk Sharing and Payment at Results) and "appropriateness agreements" that monitor prescribing appropriateness through AIFA Monitoring Registries.

If medicines are considered eligible for reimbursement, they are included in the national positive list (Prontuario Farmaceutico Nazionale, PFN), either in Class A (for outpatient use) or in Class H (inpatient use). The price of medicines included in the PFN is always fully covered by the SSN (no percentage co-payments); in several Regions patients have to pay prescription fees for medicines for outpatient use. No co-payments are applicable for medicines in inpatient use. While medicines for outpatient use are reimbursed per product, medicines used in hospitals are funded through the diagnosis-related group (DRG) system. In addition to the national reimbursement list, hospitals have their own hospital pharmaceutical formulary to select the medicines for their use. Purchasing of medicines for inpatient use is done by hospitals and sometimes by regions. For some medicines, the national procurement agency CONSIP runs centralised purchases through the "Dynamic Purchasing System" (DPS) by offering an e-procurement platform.

Pharmaceutical companies are obliged to grant to the SSN a cumulative 5% + 5% mandatory manufacturer discount on the ex-factory price of reimbursed medicines. Pharmaceutical companies are allowed to suspend the 5% price reduction for the medicines of which they hold a marketing authorisation against payment (pay-back) of the related countervalue to specified current accounts indicated by the Regions.

In Italy an expenditure governance system is in place according to that in case of overspending the national budget ceilings, which are defined on an annual basis, companies have to contribute to paybacks.

For medicines which are not included into reimbursement, manufacturers can freely set the price.

Prices of reimbursable medicines used in the outpatient sector are regulated throughout the supply chain, with linear margins being applied for wholesalers and community pharmacies. Margin rates for reimbursable originator and biosimilar medicines differ from those for reimbursable generic medicines. Community pharmacies are requested to pay discounts to the SSN based on their location and annual sales. For non-reimbursable medicines, wholesale and pharmacy margins are not regulated.

In 2017, Italy introduced two funds for innovative medicines, each of them 500 million euro. Cancer medicines and other innovative medicines that meet the defined criteria (unmet medical need, added therapeutic benefit and quality of evidence) are eligible for separate funding of these funds, with immediate access to the regional markets and an exemption from the mandatory 5% + 5% discounts of pharmaceutical companies to the SSN.

When treating a patient for the first time for a chronic disease and for a new episode of a non-chronic disease, doctors indicate the International Non-Proprietary Name (INN) or the trade name (voluntary INN prescribing). Doctors may indicate "non-substitutability" on a prescription. In absence of exclusion of substitution by the prescribing doctor, the community pharmacist substitutes the prescribed medicine by one with a lower price (e.g. generic version). However, biosimilar substitution at pharmacy level is not allowed. In the off-patent medicines market, Italy has a reference price system for equivalent medicines at ATC-5 level.

Italy was co-founder of the cross-country collaboration "Valletta Declaration" and promoter of the "Transparency Resolution" at the World Health Assembly in 2019. In 2020, it changed legislation to implement more transparency in the pricing and reimbursement negotiations.

Keywords

Pricing, reimbursement, pharmaceutical policies, pharmaceutical system, Italy

Sintesi

In Italia, il sistema assistenziale-sanitario è basato su un Servizio Sanitario Nazionale (SSN). Il SSN opera attraverso organi e strutture centrali dello Stato, regionali e territoriali (Aziende Sanitarie Locali / ASL e Aziende Ospedaliere / AO). La Costituzione prevede, per la tutela della salute, competenze legislative dello Stato e delle Regioni, e le ASL hanno lo scopo di erogare i servizi sanitari nei propri ambiti territoriali di competenza. Il SSN italiano è finanziato principalmente da tasse nazionali e regionali; tuttavia, per alcune categorie di pazienti, si applicano oneri addizionali a carico dell'assistito chiamati "ticket". I fondi sono assegnati alle Regioni per garantire i Livelli Essenziali di Assistenza (LEA) che definiscono i servizi sanitari gratuiti garantiti a tutti i cittadini. In questo modo le Regioni finanziano i farmaci sovvenzionati pubblicamente.

L'ente pubblico chiave nel settore farmaceutico è l'Agenzia Italiana del Farmaco (AIFA). È responsabile di tutte le materie riguardanti i farmaci per uso umano, tra cui l'Autorizzazione all'Immissione in Commercio (AIC), la farmacovigilanza, i prezzi e la rimborsabilità e il monitoraggio della spesa farmaceutica, ai fini del rispetto dei "tetti" definiti annualmente.

Il prezzo e la rimborsabilità di un farmaco sono definiti attraverso una procedura di negoziazione congiunta, in cui AIFA è supportata da due organi consultivi, composti da rappresentanti di istituzioni pubbliche centrali e regionali: la Commissione Tecnico Scientifica (CTS) che esprime il parere consultivo sulla classificazione dei farmaci nuovi ai fini della rimborsabilità e il place in therapy, e il Comitato Prezzi e Rimborso (CPR) che svolge funzioni di supporto tecnico-consultivo ai fini della contrattazione dei prezzi dei farmaci rimborsati.

Ricevuta la domanda di rimborsabilità e prezzo, l'AIFA procede all'istruttoria del farmaco ai fini della negoziazione del prezzo e altre condizioni negoziali con l'azienda produttrice. La valutazione è condotta attraverso diversi criteri, tra cui il valore terapeutico aggiunto il bisogno terapeutico e il rischio/beneficio, l'impatto sul budget, il rapporto di costo/efficacia e i prezzi applicati in altri paesi. Per numerosi nuovi farmaci ad alto costo sono stati stipulati accordi negoziali di rimborso condizionato (accordi di carattere finanziario come Capping, prezzo-volume, cost sharing, sconti confidenziali, etc., oppure accordi Outcomes Based come i Payments by result (PbR), il Risk Sharing e il Payment at Results) e accordi per il monitoraggio per l'appropriatezza prescrittiva attraverso il sistema dei Registri di Monitoraggio AIFA.

Se i farmaci sono considerati rimborsabili, sono inclusi nel Prontuario Farmaceutico Nazionale (PFN) in classe A o in classe H (farmaci di esclusivo uso ospedaliero). Il prezzo dei farmaci nel PFN è sempre interamente erogabile a carico del SSN (nessuna percentuale di ticket); in numerose Regioni i pazienti devono pagare un ticket per i farmaci di uso ambulatoriale. I ticket non sono mai applicati per i farmaci ad uso ospedaliero. Mentre i farmaci di uso ambulatoriale sono rimborsati per prodotto, i medicinali di uso ospedaliero sono finanziati attraverso il sistema dei Diagnosis Related Groups (DRG, Raggruppamenti omogenei di diagnosi). Oltre al PFN, vengono usati formulari farmaceutici regionali e anche ospedalieri negli ospedali. L'acquisto di farmaci per uso ospedaliero è competenza delle Regioni o degli ospedali. Per alcuni farmaci, la centrale acquisti

della pubblica amministrazione italiana CONSIP gestisce acquisti centralizzati mediante un sistema dinamico di acquisizione (Dynamic Purchasing System, DPS) su una piattaforma di e-procurement.

Per i farmaci rimborsati, le aziende farmaceutiche sono obbligate a concedere al SSN uno sconto cumulativo di 5% e 5% sul prezzo ex-factory. Le aziende possono richiedere sospensione della riduzione del prezzo del 5% per le specialità medicinali di cui sono titolari dietro versamento (pay-back) del relativo controvalore su appositi conti correnti indicati dalle Regioni.

In Italia vi è un sistema di governance della spesa farmaceutica che prevede che in caso di superamento dei tetti di spesa, definiti su base annuale, le aziende devono contribuire al ripiano dell'eccedenza attraverso un meccanismo di "payback".

Per i farmaci non rimborsati, il prezzo viene liberamente definito dall'azienda ("free pricing").

I margini di industrie farmaceutiche, grossisti e farmacie sui farmaci concedibili a carico del SSN sono fissati come margini lineari. Le quote di spettanza per i farmaci rimborsabili originatori e biosimilari differiscono da quelle per i farmaci generici rimborsabili. Le farmacie sono obbligate a concedere sconti al SSN in base alla loro ubicazione e al loro fatturato SNN annuale. Per i farmaci non rimborsabili, i margini dei grossisti e delle farmacie non sono fissati.

Nel 2017 l'Italia ha istituito due fondi, con una dotazione di 500 milioni ciascuno, dedicati ai farmaci innovativi oncologici e innovativi non oncologici. Il riconoscimento dello stato di innovatività di un farmaco si basa sulla valutazione di tre criteri: il bisogno terapeutico, il valore terapeutico aggiunto e la qualità delle prove scientifiche valutate attraverso il sistema GRADE. I farmaci innovativi godono di alcuni vantaggi rappresentati dall'accesso immediato nelle Regioni e dalla mancata applicazione dello sconto del 5% + 5%.

Per i farmaci il cui brevetto è scaduto, il medico che curi un paziente, per la prima volta, per una patologia cronica, ovvero per un nuovo episodio di patologia non cronica, per il cui trattamento sono disponibili più medicinali equivalenti, indica nella ricetta del Servizio sanitario nazionale la denominazione del principio attivo contenuto nel farmaco oppure la denominazione di uno specifico medicinale a base dello stesso principio attivo. L'indicazione dello specifico medicinale è vincolante per il farmacista ove nella ricetta sia inserita, corredata obbligatoriamente da una sintetica motivazione, la clausola di non sostituibilità. La sostituzione biosimilare a livello di farmacia non è consentita. L'Italia applica un "sistema di prezzi di riferimento", in cui i farmaci equivalenti a livello ATC 5 sono inseriti in liste di trasparenza.

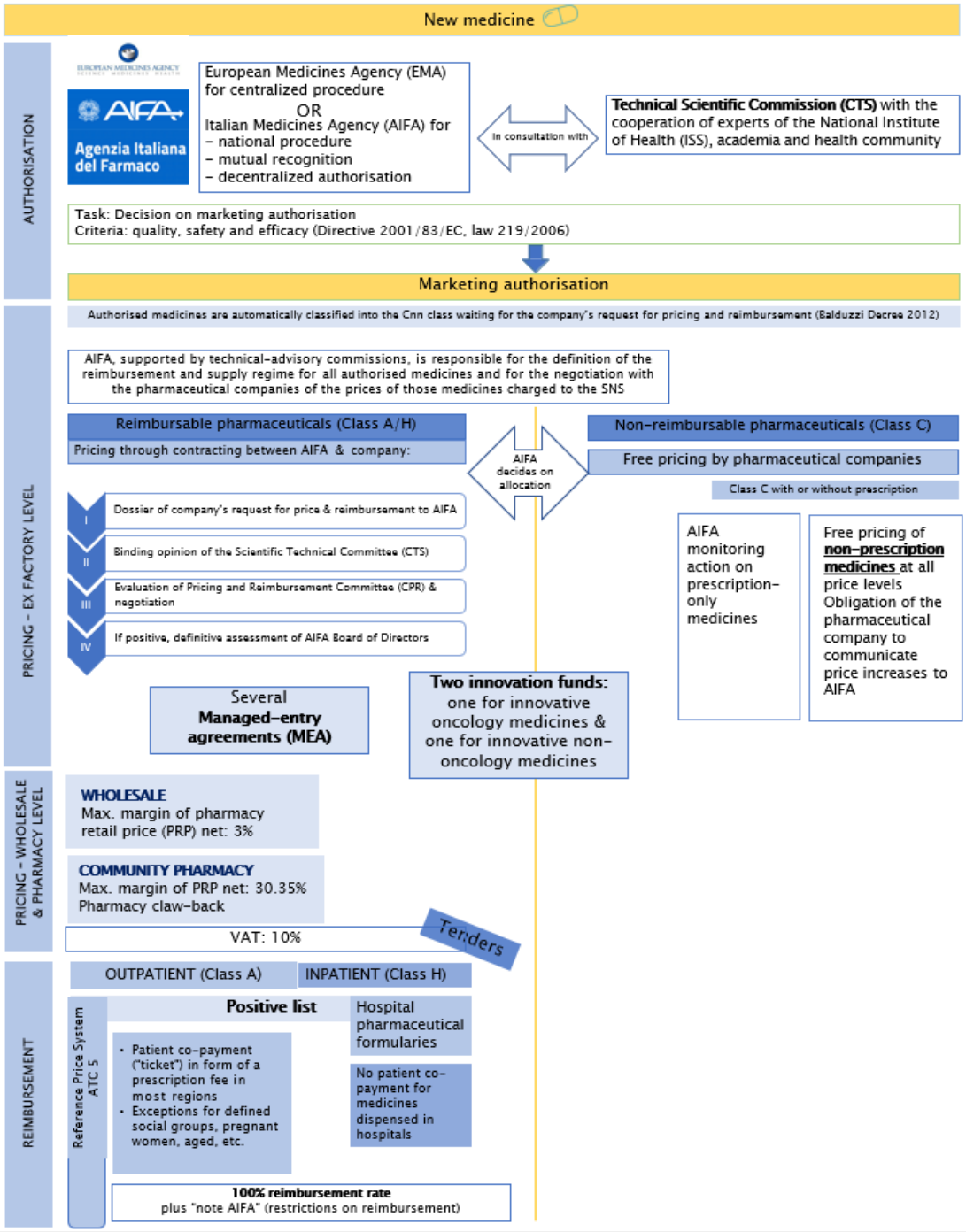
L'Italia è stata co-fondatrice della collaborazione transnazionale "Valletta Declaration" e ha proposto la "Risoluzione sulla trasparenza" all'Assemblea Mondiale della Sanità nel 2019. Nel 2020 ha cambiato la legislazione per promuovere la trasparenza nelle negoziazioni sui prezzi e sui rimborsi.

Parole chiave

Prezzi, rimborsi, politiche farmaceutiche, sistema farmaceutico, Italia

Graphical summary

Pharmaceutical pricing and reimbursement policies in the in- and outpatient sectors in Italy



Source: PPRI Secretariat, based on [11]

1 Framework

Health and pharmaceutical care in Italy is organised as a National Health Service (NHS, called Servizio Sanitario Nazionale/SSN). The SSN is established based on three tiers: the central government, 21 regional governments (the "Regions" including autonomous regions) and local health units (Aziende Sanitarie Locali, ASL) and "Independent Hospitals" (Aziende Ospedaliere, AO). Health care is a matter of shared jurisdiction between the central government and the Regions, where the respective ASL are responsible for the health of the entire population in their area.

The Italian SSN is mainly financed by national and regional taxes; patient co-payments apply for outpatient medicines in some Regions. The central government defines the economic and financial programme with a proposal for the next year's national budget and for the next three calendar years. This proposal is outlined in the annual Budget Law ("Legge di Bilancio"), which also establishes the amount to be spent by the government on health care ("spending ceilings"). Funds assigned to the Regions are intended to cover the provision of the so-called Essential Care Levels (LEA) which define minimum health care services to be provided. In the pharmaceutical sector, Regions are the key funders for medicines.

The key regulatory institution in the pharmaceutical sector is the Italian Medicines Agency (Agenzia Italiana del Farmaco (AIFA), established in 2004 based on Law no. 326/2003 [12]. It is responsible for all matters regarding the medicines for human use, including market authorisation, pharmacovigilance, pricing and reimbursement. Pricing and reimbursement decision-making processes are interlinked, and AIFA decides on the price of a medicine and its inclusion into reimbursement in one joint process. AIFA is supported by two committees:

» the Scientific Technical Commission (Commissione Tecnico Scientifica / CTS) and
» the Pricing and Reimbursement Committee (Comitato Prezzi e Rimborso / CPR).

Both committees have ten members each who have been nominated by ministries (Ministry of Health, Ministry of Economy) and regions [13]. Technical experts employed at AIFA perform Health Technology Assessment (HTA) reports that are appraised by the two committees CTS and CPR [14].

While some specificities exist for hospital medicines (e.g. special reimbursement class), pricing and reimbursement decision-process do not differ between outpatient and inpatient sectors.

In addition to the classification according to the prescription status (i.e. medicines that require medical prescription and those that do not), non-prescription medicines (farmaci senza obbligo di prescrizione medica / SOP) may be distinguished between those for which self-selection in community pharmacies is allowed (farmaci di automedicazione / AM; frequently also referred to as Over-the-Counter / OTC medicines) and those for which this is not permitted (farmaci senza obbligo di prescrizione medica / SP) [15]. In 2006, the "Bersani law" [16] introduced the liberalisation in the distribution channels of non-prescription medicines (both AM and SP), which, since then, may be sold in any shop, under the condition that a pharmacist is present and a designated space is provided. In practice, major non-pharmacy sale points of non-prescription medicines are para-pharmacies and "health corners" of super- and hypermarkets.

Information in the following sections relates to the year 2021, unless indicated differently.

2 Pricing

Pricing at manufacturer price level

Ex-factory prices (manufacturer prices) of outpatient and inpatient medicines that are included into reimbursement (i.e. funded by the Regions) are **negotiated between** the Italian Medicines Agency (**AIFA) and** the marketing authorisation holder (**MAH**). The decision on whether, or not, a medicine is granted reimbursement depends on the outcome of the price and reimbursement negotiation.

For several medicines with high budget impact, managed-entry agreements (MEA) have been included (see below the section "Agreements").

The **process for requesting reimbursement and a price** for a medicine is as follows:

» The MAH submits a dossier to AIFA. The dossier has to be prepared in line with the guidelines published by AIFA.

» The Scientific Technical Commission (**CTS**) expresses a binding opinion on the reimbursement status, based on the therapeutic benefit of the medicine, its place in therapy and supply regime as well as its possible innovativeness (the latter is relevant for the funds for innovative medicines).

» The Pricing and Reimbursement Committee (**CPR**) evaluates the dossier and, if necessary, invites the MAH to a price negotiation.

» In case of a positive opinion for inclusion of the medicine into reimbursement, the negotiation result is submitted to AIFA Board of Directors for the definitive appraisal.

The decision will be then published in the Official Journal.

According to a resolution of the Interministerial Committee for Economic Programmation as of 2001 [17], the criteria for the inclusion of a medicine into the positive list include

» a positive cost/efficacy ratio,

» a favourable risk/benefit ratio,

» the assessment of the budget impact on the SSN,

» the therapeutic benefit and impact on target population,

» the expected market share and

» the list price of the medicine in other countries.

In August 2019, following the Resolution on "Improving the **transparency** of markets for medicines, vaccines, and other health products" of the World Health Assembly (WHA) [18], Italy changed legislation, through a Decree [19] issued by the Ministry of Health and the Ministry of Economics.

The Decree established new criteria for pricing and reimbursement (to be applied from 1 March 2021 on [20]) and requested the MAH to provide information on the launch of a medicine, its consumption and reimbursement status in other countries. This should specify the conditions of the price and reimbursement, including any negotiated contract [21].

The main changes concern:

» Focus on the added therapeutic value, which implies that the MAH has to submit the documentation showing added therapeutic value. If the added therapeutic value is not proven, the company is required to submit further data deemed of interest for the SSN, in terms of economic benefit.

» The Decree also applies to the inclusion of medicines in the list pursuant to Law 648/1996 and to the purchase of specific categories of medicines of Class C (non-reimbursable medicines) and Cnn (C not yet negotiated, see below "Reimbursement") by SNN bodies for public health needs.

» The Decree established that the negotiation procedure may be started both by the company (as already provided for in CIPE Resolution of 2001) and by AIFA in the case of medicines whose reimbursement has a significant impact in terms of SNN expenditure or prescriptive inappropriateness, or in case of medicines that have never been subject to previous negotiations. The procedure may also be started by AIFA if previous negotiations had not unsuccessful and the medicine had therefore been assigned to Class C (non-reimbursable medicines).

» In case that comparators are available, the company is required to submit, together with the documentation, an economic assessment supporting the price proposal, and research and development (R&D) costs incurred.

To determine the eligibility of a medicine for funding out of one of the "innovation funds" (see the chapter on "Reimbursement"), three further criteria are applied.

The Italian pricing and reimbursement procedure contains value-based elements but it is not a fully-fledged **value-based pricing system**. Manufacturing costs do not play a role (no cost-plus pricing).

Components of the **external price referencing** (EPR) policy come into play, as the prices of the same medicine in other countries are used as a supplementary data to inform the price and reimbursement negotiation. Italy considers prices of 24 European reference countries (Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Greece, Finland, France, Hungary, Iceland, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and UK). There is no specific formula as to determine a benchmark (e.g. average) price.

Prices of the generic and biosimilar medicines are linked to the prices of the originator or reference medicines, respectively (**price link**). In principle, generic and biosimilar must be priced at least 20% lower than the originator and reference medicine. According to Decree Law n. 158/2012 [22], a generic or biosimilar medicine that is included in the same reference cluster as the originator or

reference product would automatically obtain reimbursement if the price is beneficial to the SSN. There are additional rules for tendering of biosimilar medicines (see below the section "procurement").

In October 2020, AIFA issued a new simplified procedure for pricing and reimbursement of generic and biosimilar products. In case that the MAH presents a price proposal with a discount of a certain extent (different classes of minimum discounts have been pre-defined based on SSN spending for that active ingredient in the last three years), the product will undergo an accelerated procedure for pricing, and will be automatically included in the positive list.

Italy applies a mandatory manufacturer discount of 5% on the ex-factory price of reimbursed medicines. The discount is given to the SSN at the time of procurement plus an additional 5% that the MAH can – only during the first year of marketing – decide to give either at the procurement or later in the form of a pay-back. This mandatory discount is cumulative (i.e. applied one after the other) and thus sums up to 9.75% [23]. Published prices do not show this 5% discount. Following the negotiation agreement with AIFA further hidden discounts granted to the SSN as part of a MEA can be agreed. For further industry pay-back in case of exceeding the defined expenditure ceilings see the chapter on "Reimbursement".

The price of medicines that are not reimbursed can be freely set by the MAH (**free pricing**). However, a price increase is only allowed every second year (in the odd years), and the increase must not exceed the expected inflation rate. AIFA monitors the prices of non-reimbursed prescription-only medicines to ensure compliance to these rules, and MAH of non-reimbursed non-prescription medicines are obligated to communicate to AIFA variations in the prices due to distribution.

Procurement and tendering

At a centralised level, procurement for the public sector (including medicines) is supported by the national procurement agency **Consip**, which is owned by the Ministry of Economy and Finance. In addition, regions and hospitals also perform their own procurements of medicines.

Consip applies the DPS (**dynamic purchasing system**) methodology for tendering (off-patent) medicines. DPS is a kind of "open" framework agreements. While Consip provides negotiation and tender documents on an e-procurement platform of the Ministry of Economy, it does not perform any needs assessment and aggregation, as it did in the first tender for medicines two decades ago. The needs aggregation and direct purchase is done either by the individual users (hospitals) or by the Regions for several hospitals in their area. A list of around 6,400 items is integrated on the e-procurement platform. The users (hospitals / Regions) can chose the most appropriate ones [24].

Some Italian regions have their own DPS systems [24].

In 2017, new rules for **tendering of biological medicines** (including biosimilar medicines) were introduced. If three or more medicines of an active substance have been marketed, it is no longer

allowed to choose the lowest-priced offer. Instead, the procurer has to conclude a "multi-award framework agreement" with all bidders are granted with a defined quote [25].

Pricing in the supply chain

In the outpatient sector, prices of reimbursable medicines are regulated at all supply chain levels (i.e. regulation of the wholesale prices and the pharmacy retail prices) through statutory margins. For non-reimbursable medicines, no margins have been determined.

For reimbursable originator and biosimilar medicines, the **wholesale margins** are statutorily determined at 3% of the pharmacy retail price net and the **pharmacy margins** at 30.35% of the pharmacy retail price net. The shares for reimbursable medicines for industry are thus 66.65% of the pharmacy retail price net for reimbursable originator and biosimilar medicines, and they are 58.65% of the pharmacy retail price net for reimbursable generic medicines, thus 8% lower than for originator and biosimilar medicines [26]. This 8% difference can be distributed between wholesalers and pharmacies, leading to wholesale margins of 3.65% of the pharmacy retail price net and pharmacy margins of at 37.7% of the pharmacy retail price net for reimbursable generic medicines.

The pharmacy margin is reduced by a statutory discount that community pharmacies have to grant to the SNN. The size of this mandatory pharmacy discount varies with regard to the location (urban or rural pharmacies) and the annual sales of the pharmacy on reimbursable medicines (for the scheme see Annex 2) [27].

The **value-added tax** (VAT) on medicines is 10% (except for therapeutic oxygen, which amounts to 4%), in contrast to the general VAT rate of 22%.

3 Reimbursement

Reimbursement for outpatient medicines

In Italy a positive list (Prontuario Farmaceutico Nazionale, PFN) is in place. Medicines considered eligible for reimbursement are put on the positive list, either in "class A" (for medicines used in the outpatient sector) or in "class H" (for medicines used in the inpatient sector). Non-reimbursed medicines are allocated to "class C". Non-prescription medicines are usually not reimbursed.

Furthermore, regional formularies apply (e.g. Prontuario terapeutico regionale dell'Emilia Romagna [28]).

After marketing authorisation (independent from whether it was obtained through centralised, decentralised, mutual recognition or national procedure or cases of parallel import), the medicine is automatically classified into Cnn (C non negoziati). For these medicines, the dossier of the MAH with the request for reimbursement and price is still awaited. Created by the "Balduzzi Decree in September 2012 [29], the Cnn category allows patients access to a medicine, which is not reimbursable at that time, as the pricing and reimbursement negotiation has yet to be done.

The criteria which are applied in the reimbursement decision process based on an HTA prepared by AIFA and appraised by the two advisory committees CTS and CPR were described above in the chapter on "Pricing". The Guidelines for the compilation of the request for reimbursement and pricing, which have been effective since March 2021 [21] did not only introduce the request for details on the prices, including MEA, in other countries, but also stipulated mandatory application of economic evaluation as for new substances, orphan medicines and/or extension of indications and provided a definition of indirect costs for inclusion in budget impact models and economic evaluations and made explicit reference to DALYs [30].

Reimbursable medicines are always fully funded by the regions (no percentage reimbursement rates). However, AIFA can decide to put prescription restrictions on certain medicines or therapeutic classes, which are known as "AIFA note" [31].

In 2017, Italy introduced two funds for innovative medicines [25]: each is worth 500 million €, one fund is for innovative oncology medicines and the other fund is for innovative non-oncology medicines.

Innovative medicines (i.e. those funded out of the dedicated innovation funds) must comply with the following three criteria:

» Unmet medical need

» Added therapeutic benefit

» Quality of evidence (robustness of clinical studies) with is assessed through the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology [32-35].

Medicines which are classified as fully innovative according to these criteria enjoy some advantages:

» Separate funding out of these funds

» Immediate access to the regional markets (no regional or local reevaluation)

» No application of the mandatory discount of MAH to the SSN [36]

Conditionally innovative medicines have immediate access to regional markets.

Regions can access the funds for 36 months; afterwards, they have to pay themselves.

There is no formal link between the assessment of the innovativeness and the pricing and reimbursement negotiation [36], and it is not a general definition to determine the status of innovativeness of a medicine.

Italy has defined national ceilings for public pharmaceutical spending. Overspending has to be paid back to the SSN, including Regions, by pharmaceutical industry, wholesale and pharmacy

according to their respective shares [37]. Orphan medicines are excluded from this payback mechanism regarding the pharmaceutical expenditure of budget. For 2021, the budget Law set the overall spending ceiling at 14.85%, with at 7% of total SSN spending for spending in community pharmacy) and 7.85% for spending done through direct purchases of regions [38].

Based on legislation from 2003 [39], Italy installed the so-called 5% Fund which is fed by 5% of annual expenses of pharmaceutical companies on promotional activities relating to medicines. 50% of it are used to fund orphan medicines and life-saving medicines that have not yet been authorised in Italy, and another 50% to fund independent research.

In almost all Regions (e.g. Umbria, Emilia-Romagna, Trento), co-payments for medicines used in the outpatient sector are applied in the form of fixed prescription fees. There are exemptions from the prescription fees, e.g. for vulnerable social groups, pregnant women, aged, etc.; the exemptions also differ between the regions [40]. No percentage co-payments apply; deductibles are in place.

Reimbursement for inpatient medicines

In addition to the overall national positive list "Prontuario" (with medicines used in hospitals attributable to class H), separate hospital pharmaceutical formularies (HPF) are in place at hospital level.

Most medicines included in an HPF are part of the national "Prontuario" (or a regional "Prontuario") but the HPF may also include some non-reimbursed medicines (class C).

In principle, the decision processes as to whether, or not, medicines for inpatient use are reimbursed do not differ from medicines for outpatient use. Also, there is a need for a positive opinion of the Scientific and Technical Committee CTS on the medicine before it may be used in hospitals. Funding for the medicines (inpatient and outpatient) is done by the SSN via the Regions.

The difference between outpatient and inpatient sectors concerns the funding mechanisms. While in the outpatient sector medicines are reimbursed individually, the funding for medicines used in hospitals is done through the DRG system (unless for those medicines funded out of the innovation funds).

In addition, some class A medicines are listed in the Prontuario Ospedale-Territorio (PHT) [41]. Introduced in 2004, the PHT should guarantee therapeutic continuity between therapies administered in hospital (class H) and chronic or short-term therapies in the outpatient sector (class A). Once reimbursement of a medicine in class A has been approved, AIFA decides on whether, or not, the medicine will be included in the national PHT. Every region can modify this list (and at local levels as well) and can decide which of the medicines included in PHT will be dispensed through "Distribution on behalf" (Distribuzione Per Conto, DPC). Upon the DPC mechanism, medicines are directly purchased by health authorities, but their delivery is ensured by community pharmacies [42].

Medicines included in an HPF are administered to the inpatients without any co-payments. Medicines for inpatient use are paid by the hospitals out of their hospital budgets, so they are funded by the respective regions.

Agreements

Starting in the first years of the new millennium, Italy was one of the first countries which concluded managed-entry agreements (MEA), and it is probably the (European) country with the highest number of MEA, including performance-based MEA.

There are MEA at patient level and MEA at population level. The first group comprises Payment by Result and risk sharing (both performance-based MEA) as well as cost sharing and capping models (financially-based MEA). For all these MEA at patient level, AIFA Monitoring Registries have been implemented. The rationale of monitoring registries is to ensure and manage prescribing appropriateness. In 2020, 166 monitoring registers were available at the web platform [5]. MEA at population level, which include spending caps, are monitored by SSN expenditure and consumption data.

AIFA negotiates the MEA with the MAH. Regions and hospitals do not conclude MEA on their own.

Information on which medicines are subject to a MEA, and usually also on the type of discount, is published. The discounts per se tend to be confidential and are only known to the public institutions involved (ASL and AO).

Demand-side measures

Italy has an internal reference price system for equivalent medicines: for medicines in a cluster of equivalent medicines with a pharmacy retail price (PRP) above the reimbursement price ("prezzo di riferimento") patients have to co-pay the difference between reimbursement price and PRP. This is relevant for off-patent generic medicines but not for new (on-patent) medicines. Biosimilar medicines are not included in these so-called "transparency lists" since this would imply automatic biosimilar substitution (see below). No exemptions apply for the co-payments under the internal reference price system.

For off-patent medicines, when treating a patient for the first time for a chronic disease and for a new episode of a non-chronic disease, the doctor indicates the active substance or the trade name of a specific medicine on the prescription (indicative INN prescribing). The physician can indicate "non-substitutability" on the prescription. If substitution is not excluded by the doctor, the pharmacist must dispense the lower-price medicine instead of the prescribed one (mandatory generic substitution), after having informed the patient. If the patient insists on the higher-priced medicine, s/he has to pay the remainder. Biosimilar substitution (i.e. substituting a biological original by a biosimilar or substituting a biosimilar by another biosimilar) at pharmacy level is not allowed. Prescribing biosimilar medicines, including a switch to biosimilars, by doctors is, however, recommended. In some Regions, there are also prescribing quotes [43]. In February 2021, simplified

procedures and requirements for generics and biosimilar medicines of non-reimbursed medicines were introduced [44].

4 Developments

A major reform was the implementation of the "Innovation funds" in 2017 to encourage innovation, the methodological specifications to assess new, possibly innovative medicines In July 2021, it was decided to merge, from January 2022 on, the two funds into one fund which will be assigned 1,000 million € [45].

Italy was also well-known for advocating affordable access to medicines through solidarity, collaboration and transparency. In 2017, the cross-country collaboration "**Valletta Declaration**" was established, and Italy was one of its co-founders. The Valletta Declaration which mainly comprises Mediterranean countries aims to technically collaborate in the areas of horizon scanning, HTA, joint pricing and reimbursement negotiations and information-sharing [46].

Italy has also been one of the promoters of the WHA Resolution on "Improving the **transparency** of markets for medicines, vaccines, and other health products" [18] in 2019, and in 2020 it changed legislation to increase price transparency in the pricing and reimbursement negotiations [19] followed by AIFA guidelines for implementation in March 2021 [21].

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6 Annex

Annex 1: Stakeholders

Role	Name in Italian language	Website(s)
Competent authority for marketing authorisation of medicines	AIFA – Agenzia Italiana del Farmaco	www.aifa.gov.it
Competent authority for pricing of medicines	AIFA – Agenzia Italiana del Farmaco	www.aifa.gov.it
Competent authority for reimbursement of medicines (outpatient)	AIFA – Agenzia Italiana del Farmaco	www.aifa.gov.it
Public payer(s) for outpatient medicines	Regioni italiane (regions)	www.regioni.it/regioni-online
Public payers for inpatient medicines	Regioni italiane (regions)	www.regioni.it/regioni-online
Patients organisations	Several disease-specific associations	For an overview see europaoggi.it/content/view/762/149
Consumers organisations	Several associations, e.g. Altroconsumo, Cittadinanzattiva, Confconsumatori	www.altroconsumo.it www.cittadinanzattiva.it www.federconsumatori.it
Pharmacy associations	Federfarma	www.federfarma.it
Industry associations	Farmaindustria Egualia (previous: Assogenerici)	www.farmindustria.it https://www.egualia.it
Wholesale association	ADF – Associazione Distributori Farmaceutici	www.adfsalute.it

Annex 2: Regulation of mandatory pharmacy discounts (2021)

Community pharmacies have to grant mandatory pharmacy discounts to SSN, whose extent depends on the location of the pharmacy (urban or rural) and the annual sales of reimbursable medicines (see below the table for the defined rates).

Price range in €	Urban pharmacies and non-subsidised rural pharmacies with SSN turnover of			Subsidised rural pharmacies with SSN turnover of		
	> 300.000 €	300.000 € – 150.000 €	< 150.000 €	> 450.000 €	450.000 € – 150.000 €	< 150.000 €
0 – 25.82	3.75% + 2.25%	1.5%	Exempted	3.75% + 2.25%	1.5%	Exempted
25.83 – 51.65	6% + 2.25%	2.4%		6% + 2.25%		
51.66 – 103.28	9% + 2.25%	3.6%		9% + 2.25%		
103.29 – 154.94	12.5% +2.25%	5%		12.5% + 2.25%		
> 154.94	19% + 2.25%	7.6%		19% + 2.25%		

Source: developed based on Legge 30 dicembre 2018, n. 145/2018 [27]

Annex 3: Glossary

claw-back	A policy where funds already paid by public payers to pharmaceutical companies, wholesalers or pharmacists have to be paid back to the third party payers under certain conditions (e.g. if a certain threshold is exceeded).
community pharmacies	Health care facilities which dispense medicines (prescription-only medicines and/or non-prescription medicines, reimbursable and/or non-reimbursable medicines) to outpatients.
co-payment	Insured patient's contribution towards the cost of a medical service covered by the health insurance. Can be expressed as a percentage of the total cost of the service (percentage co-payment), as a fixed amount (prescription fee) or a deductible.
cost-plus pricing	Pricing policy that determines a medicine price by taking into account production costs, promotional expenses, research & development, administration costs, overheads and a profit that is considered "reasonable".
discount	A price reduction granted to specified purchasers under specific conditions prior to purchase.
external price referencing	The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country.
free pricing	Pricing policy, in which governments allow pharmaceutical companies to determine the price of the medicine they launch.
generic substitution	Practice of substituting a medicine, whether marketed under a trade name or generic name (branded or unbranded generic), with a less expensive medicine (e.g. branded or unbranded generic), often containing the same active ingredient(s).
Health Technology Assessment (HTA)	A multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.
INN prescribing	Requirements for prescribers (e.g. physicians) to prescribe a medicine by its International Non-Proprietary Name (INN), i.e. the active ingredient name instead of the trade name.
managed-entry agreement (MEA)	An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms and are usually classified into financially-based and performance-based MEA.
marketing authorisation	A licence issued by a medicines agency approving a medicine for market use based on a determination by authorities that the medicine meets the requirements of quality, safety and efficacy for human use in therapeutic treatment.
margin	The percentage of the selling price that is profit (e.g. a wholesale margin, a pharmacy margin)

pharmaceutical expenditure	Total expenditure on pharmaceutical and other medical nondurables. This comprises medicinal preparations, branded and generic medicines, patent medicines, serums and vaccines, vitamins and minerals and oral contraceptives and other medical nondurables such as bandages, elastic stockings, incontinence articles, condoms and other mechanical contraceptive devices.
policies	Instruments, tools and approaches that allow policy-makers to achieve defined objectives.
price link policy	Practice of setting the price of a medicine (e.g. a generic or a biosimilar) in relationship to the price of another medicine (e.g. originator, biological reference medicine), usually at a certain percentage lower.
pricing (price setting)	Act of determining the medicine price which is either taken by a pharmaceutical company (free pricing) or is the competence (responsibility) of a competent authority (price control).
price negotiation	A pricing procedure, in which medicine prices are discussed and agreed (e.g. between manufacturer and third party payer).
price regulation (price control)	Pricing policies where government authorities set the price of a medicine and/or indirectly influence it (e.g. statutory pricing, price negotiations, public procurement).
procurement	A process to purchase goods and services (e.g. medicines) that involves many steps and many stakeholders based on national, or supranational, regulation, policies, structures and procedures.
reference price system	A reimbursement policy in which identical medicines (ATC 5 level) or therapeutically similar medicines (ATC 4 level) are clustered (reference group). The third party payer funds a maximum amount (= reference price), while the patient must pay the difference between the reference price and the actual pharmacy retail price of the medicine, in addition to any co-payments.
reimbursable medicines	Medicines which are eligible for reimbursement. Expenses of reimbursable medicines may be fully covered by third party payers, or only partially (a specific percentage).
reimbursement	Coverage of the expenditure by a third party payer (e.g. social health insurance/National Health Service).
reimbursement list	A list that contains medicines with regard to their reimbursement status. It may either include medicines eligible for reimbursement (positive list) or those explicitly excluded from reimbursement (negative list).
tendering	Any formal and competitive procurement procedure through which tenders (offers) are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous.

value-based pricing	Policy of authorities to set the prices of a new medicine and/or decide on reimbursement based on the therapeutic value that a medicine offers, usually assessed through health technology assessment (HTA) or economic evaluation. In a full-fledged VBP, the pricing and reimbursement systems are integrated, and the price and reimbursement decision is taken jointly based on a value assessment.
wholesale	All activities consisting of procuring, holding, supplying or exporting medicines, apart from supplying medicines to the public.

Source: Glossary of Pharmaceutical Terms [47]