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5. Market Access in Italy

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5.1 General Outlook of National Health Service and Health Policies

The Italian National Health Service (*Servizio Sanitario Nazionale* – SSN) – established with the law 833/1978 [1] – is a network of structures and facilities to guarantee health services access to all the citizens, as stated by Article 32 of the Italian Constitution [2]. The SSN operates under the direction and responsibility of the Ministry of Health (MH), which determines general healthcare policies, while the "retail sale" is planned, coordinated and managed at regional level, as a consequence of the process of devolution from State to Regions, regulated by the Constitution title V reform in 2001 [3].

The Italian Government as warrantor of health rights (article 32) [2], through MH, determines the essential levels of care (*Livelli Essenziali di Assistenza* – LEAs) that every region has to be able to provide in the public setting.

Every Region autonomously defines its strategic planning, especially in terms of financial resources and distribution on regional territory of Local Health Units (*Aziende Sanitarie Locali* – ASLs) and Hospital Units (*Aziende Ospedaliere* – AOs), as well as act as supervisors of granting procedure of private health units. ASLs and AOs operate autonomously to guarantee the organization of local health care and supply of healthcare services.

The collaboration between the various governments of SSN, i.e. State, Regions, ASLs and AOs, is a fundamental principle for ensuring uniform health conditions and guarantees throughout the national territory acceptable and appropriate levels of health services for all citizens.

The cooperation between the State, on one side, and the nineteen Regions plus the autonomous provinces of Trento and Bolzano, on the other, is promoted through *Conferenza Permanente Stato Regioni* that represents the policy place in which politic negotiation between central administration and regional autonomies occurs. It was established with the law of 12 October 1983 4].

Long-time planning is a qualifying element of SSN: the MH, as delegate of the central Government, with the cooperation of Regions establishes the National Health Plan (*Piano Sanitario Nazionale* – PSN). It describes the general targets and elements that must be reached in health matter on the national territory, taking into account the financial, demographical and epidemiological contexts, as well as new scientific and technological innovations. It has three-year validity, but it may be revised *in itinere* if needed. The PSN defines the line that all health care stakeholders must follow for guaranteeing LEAs, and how funding must be broken down by levels of care.

The LEAs are all the health services and benefits – included some pharmaceuticals – that the SSN supplies to all citizens free of charge or on payment of a prescription charge, which is independent of income or residency. The LEAs have been defined at the national level with the law of the President of the Council of Ministers of 29 November 2001 [5]. The reform of title V of the Constitution [3] has also provided for the regions the chance to use their own resources to supply additional services and benefits, but never less than those included in LEAs. This implies that LEAs could be different from region to region, provided that those defined nationally are guaranteed all over the regional territory.

The financial resources available for supporting the SSN are annually allocated by Italian Government. The national health care fund is financed by earnings deriving from prescription charge for health services, taxation (VAT, for example), and State budget. The resources are allocated to each Region and autonomous provinces for capitation share and specific criteria negotiated in occasion of *Conferenza Permanente Stato-Regioni*. The Regions assign the funding to ASLs, AOs and private health care units for warranting the essential health care services defined by LEAs [5], and further resources on the basis of out-patient and in-patient health services supplied – through the payment of tariffs decided by national government and integrated with regional ones for extra health care services provided. ASLs play the double role of provider and buyer of healthcare services, whilst AOs and private health units work to reach as many patients as possible (competition) and receive reimbursements by ASL for the health services performed.

The financial crisis that has struck Italy and the consequent need to rationalize public spending has constrained legislators to review the organization of the SSN. Government and Regions signed a three-year financial and programmatic agreement on SSN expenditure and programming, which aims to improve and promote the quality and the appropriateness of the health services (*Patto della Salute* 2014-2016) [6]. According to *Patto della Salute*, the State commits to the intended funds allocation to the Regions at the beginning of the three-year period, basing on which they may initiate their mid-term planning, relying on resource certainty, and struggle the wastefulness, with the purpose to allocate the savings to improve quality of care services. In case of health over exceeding the budget allocated, regions have the task of compensating for the debt through taxation. Pharmaceuticals (may) fall within the LEAs and follow a specific regulation: the Italian Medicines Agency (*Agenzia Italiana del Farmaco* – AIFA) is the authority under direction of MH responsible for drugs regulation and guarantees access to medicines all over the national territory, ensuring unity of the national pharmaceutical system in agreement with the regional authorities, pharmaceutical industries and distributors.

5.2 Pathways of Market Access

Pricing and Reimbursement of Pharmaceuticals

Classification of drugs by supply and reimbursement regimen

Medical products in Italy are pooled in two main categories, i.e. medicinal products and medical devices.

The first ones are regulated by the law 219/2006 [7] (and successive modifications), whilst medical devices follow the law 37/2010 [8], as implementation of the Directive 2007/47/CE of European Parliament and Council. Medical devices, managed directly by Minister of Health, consist in any instrument, material or other article used alone or in combination with the purpose of diagnosis, prevention, monitoring, treatment or alleviation of either disease, any injury or handicap, or a physiological process.

Medicinal products, i.e. "any substance or combination of substances presented as having proprieties for treating or preventing disease in human being", are managed by AIFA [7].

According to the law 219/2016 [7], at the time of Marketing Authorization (MA) issue, medicinal products are classified for the prescription and supply rules (Table 1).

- Drugs subjected to medical prescription:
  - Medicinal products on renewable (RR) (not more than 10 times in 6 months) or non-renewable medical prescription (RNR).
  - Medicinal products subjected to special medical prescription (e.g. a narcotic or if there is a risk of medicinal abuse).
  - Medicinal products on restricted medical prescription, reserved for use in certain specialized areas (e.g. in a hospital environment [OSP] or prescription of a specialist [RLR and RLNR]).
- Drugs not subjected to medical prescription:
  - Over the counter (OTC).
  - Other medicinal products not subjected to medical prescription (SOP).

In general, pharmaceuticals are subjected to medical prescription when they are either administered via parenteral route, or associated to particular adverse events or when the risk of incorrect use with associated patient health risk exists. Moreover, some pharmaceuticals are administered in hospital environment or by specialist, due to high risks associated to administration, for safeguarding public health or for the innovative nature of medicinal products that require supervision by medical personnel during or immediately after administration.

Prescription type	Specification
Renewable (RR)	Not more than 10 times in 6 months
Non-renewable (RNR)	Repeated each time
Triple copy (TPC)	Prescription for narcotic drugs
Renewable w/ limitation (RRL)	For drugs prescribed only by specialist
Non-renewable w/ limitation (RNRL)	For drugs prescribed only by specialist and repeated each time
Hospital (OSP)	For drugs allowed in hospital environment only
Used by specialist limitation (USPL)	For drugs that can be used only by a specialist

Table 1. Prescription classes of medicinal products in Italy

The SSN guarantees pharmacological therapy for all citizens with acute and chronic severe diseases according to LEAs as reported in the law of the President of the Council of Ministers of 29 November 2001 [5]. Medicinal products are classified according to reimbursement regimen in drug reimbursed by SSN and drug not reimbursed by SSN.

Drug reimbursed by SSN, and listed in the National Pharmaceutical Handbook (*Prontuario Farmaceutico Nazionale* – PFN), the positive list of drugs.

- Class A: drugs dispensed by SSN for their approved therapeutic indications, as reported in the Summary of Product Characteristics (SPC), through territorial pharmacies. Regions may demand prescription charge, except for some categories of patients (e.g. low income, veterans), or decide to reimburse them only when used for specific therapeutic indications – defined by a legal act by AIFA (nota AIFA).

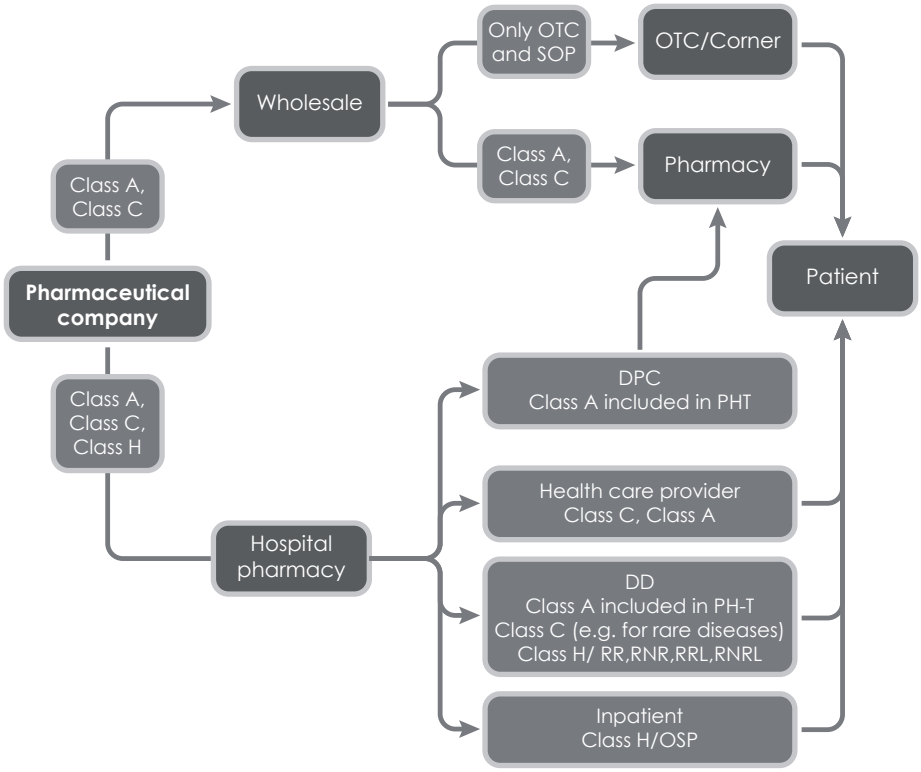

Figure 1. Drug flow based on supply and reimbursement regimen

DD = *Distribuzione Diretta* (drugs distributed directly through hospital pharmacies); DPC = *Distribuzione Per Conto* (drugs distributed by territorial pharmacies); OSP = hospital prescription; OTC = Over The Counter; PH-T = *Prontuario Ospedale Territorio*; RNR = non-renewable prescription; RNRL = non-renewable w/ limitation prescription; RR = renewable prescription; RRL = renewable w/limitation prescription

- Class H: drugs that are dispensed by SSN and distributed through public structures. These drugs may only be used in hospital, or in a structure similar to it, when prescribed with OSP prescription. If prescription occurs through either RR, RNR, RRL or RNRL prescription, the distribution takes place directly from the public structure on the order of treatment plan issued by the authorized center.

In 2004 the *Prontuario Ospedale Territorio* (PH-T) [9] was introduced. It contains a list of class A drugs for which normally the first administration began during hospital stay or in secondary care facilities. Each Region has to supply medicinal products included into the PH-T directly through hospital pharmacies (*Distribuzione Diretta* – DD) or by territorial pharmacies (*Distribuzione per conto* – DPC), under special reduction of distribution costs, in order to guarantee the therapeutic continuity from hospital to home and govern the pharmaceutical expenditure. Drugs with authorized off-label use(s), innovative and very costly drugs classified in class A are also integrated in the PH-T.

Drug not reimbursed by SSN.

- Class C: drugs that do not fall within the above classes; they are considered useful but not essential and are totally paid by patients (or by health care providers when used within a LEA). OTCs and SOPs are integrated as subcategory of class C, dispensed without prescription (class C-bis).

Figure 1 summarizes the Italian drug flow based on supply and reimbursement regimen.

Applying for Reimbursement of a New Drug: the Procedure

Determination of pricing and reimbursement (P&R) class is the unique activity regarding drugs that is not regulated at the European level, but is managed by national regulatory agencies.

The price of drugs reimbursed by the SSN is determined through negotiation between AIFA and pharmaceutical companies (according to law 326/03 [10]) on the basis of the procedures and criteria set out in Interministerial Committee for Economic Planning (CIPE) deliberation of February 2001 [11]. Marketing authorization (*Autorizzazione Immissione in Commercio* – AIC) and P&R application are procedures that have to be presented separately according to the law 189/2012 [12].

In general, the pharmaceutical companies may present the P&R application for new medicinal products only after publication of the marketing authorization on the Italian Official Gazette (GU): approved drugs are provisionally classified in the new Class Cnn – it contains all medicinal products with AIC but not yet negotiated (nn) from AIFA for the purpose of reimbursement– and may be distributed through private market or by reaching an agreement directly with Regions as long as P&R application is not evaluated and approved by AIFA. The manufacturer has to communicate to AIFA the ex-factory and retail price. This procedure is not adopted for orphan drugs, medicinal products with exceptional therapeutic relevance and drugs for exclusive hospital use (supplied through OSP prescription) for which the P&R application may occur simultaneously with the AIFA marketing authorization process.

In detail, within 60 days from publication on the European Official Gazette (GUEU) of a marketing authorization of a drug authorized through centralized procedure (via European Medicines Agency – EMA), AIFA publishes on the Italian GU a law provision, including drug details, supply class – determined after CTS (Technical-Scientific Committee) consultation – and classification in the provisional Cnn class. The manufacturer may present the P&R application to AIFA immediately after publication on GUEU of EMA drug approval. For the other registration procedures (mutual recognition, decentralized and national), the marketing authorization holder may present P&R application only after the publication on GU of decisions on marketing authorization and classification for supply. In both registration procedures, pharmaceutical company has to present an application to change reimbursement class (from Cnn to either A or H).

Figure 2 summarizes the P&R procedures for centralized, mutual recognition, decentralized and national MA application in Italy.

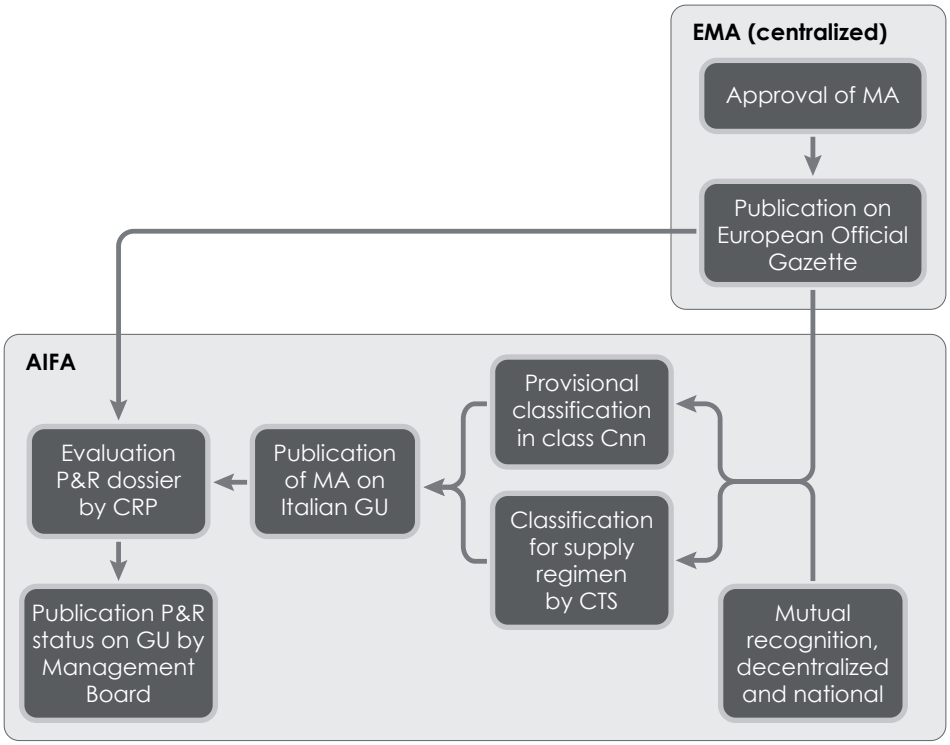

Figure 2. The P&R procedures for centralized, mutual recognition, decentralized and national MA application (modified from [13])

CRP = prices and reimbursement committee; CTS = technical-scientific committee; GU = Official Gazette; MA = Marketing Authorization; P&R = Price and Reimbursement

Initiation of the application

As first step, the pharmaceutical company has to present the P&R application, which shows either:

- a positive cost-effectiveness ratio – for medicinal products that are either innovative or provide a more appropriate response than drugs already available for the same therapeutic indications, or
- a better risk-benefit ratio compared to other drugs already available for the same indication, or
- other elements of interest for the SSN (read lower cost), if the new drugs do not present a significant clinical superiority compared to medicinal products already available but is of at least equal effectiveness and safety.

The negotiation process

AIFA, through the Prices and Reimbursement Committee (CPR), reviews reimbursement requests, also supported by consumer and spending data provided by Medicines Utilization Monitoring Centre (OSMED), an instrument for collecting data on General Practitioner (GP) prescriptions and sales data from territorial and hospital pharmacies and monitoring the prevalence of use, and expenditure for pharmaceuticals.

In particular, the criteria to define reimbursement class and price of the new drug rely on:

- Target disease and place in therapy;
- Added therapeutic value and competitor prices;
- Budget impact on SSN expenditure (the new medicinal product integrates the armamentarium or take drugs' place in the market);
- Prices in other European community countries.

The negotiation begins taking into account the daily cost of medicinal products having the same indications. A "premium price" – financed through a fund established by the Italian authorities in order to support research and development of innovative drugs – is allowed for very innovative or orphan drugs. In case of no therapeutic advantage, a lower or the same price as the cheapest drug in the same therapeutic category is fixed (therapeutic reference pricing).

The contract and publication on Italian Official Gazette

The price and reimbursement class, resulting from CPR and pharmaceutical company negotiation, have to be ratified by CTS; the final step consists in Management Board approval, followed by publication of ex-factory price with reimbursement class on Italian Official Gazette.

The price determined at the end of the negotiation procedure has 24 months of validity, save different contractual clauses. Upon expiration, the contract is renewed automatically, if pharmaceutical company or AIFA do not make request of amendments to the original contract within 90 days before expiration date.

Pricing

Containment policy of pharmaceutical expenditure

For limiting pharmaceutical spending and make resources available to promote innovation and assure SSN sustainability, the Italian Governments and AIFA (since 2004), consistent with the *Conferenza Permanente Stato-Regioni*, introduced several measures in the last 20 years. In detail, the law 405/2001 [14] established a territorial ceiling pharmaceutical expenditure (i.e. deriving from outpatients only) that had not to exceed 13% of overall health expenditure both at national and regional level. Every Region and autonomous province is responsible of spending control and corrective interventions: a fixed fee paid by patient (copayment) for prescribed and reimbursed drugs is adopted in many Regions. Furthermore, for supporting Regions to control pharmaceutical expenditure, central Government implements a reference price for drugs not covered by patent and mandatory discounts – proportional to the retail price – that every pharmacy has to apply to SSN (the payer). In 2004, the amount of pharmaceutical expenditure ceiling was incremented to 16% of the overall health expenditure and included both inpatient and outpatient pharmaceutical spending [10]. In the same year, as first responders from establishment, AIFA updates the PFN, and adopts the PH-T to guarantee prescription persistence and govern the pharmaceutical expenditure: drugs included in PH-T are bought by the SSN directly from the pharmaceutical industry at the hospital price (ex-factory price, net of mandatory and hidden discounts), and distribution costs are totally abolished or reduced. Each Region has to supply medicinal products included into the PH-T directly through hospital pharmacies (*Distribuzione Diretta* – DD) or by territorial pharmacies (*Distribuzione Per Conto* – DPC: it consists in a measure to acquire medicinal products at hospital price and deliver to the patients through the territorial pharmacies, establishing a lower distribution margin for the pharmacy). In 2005, with the aim to balance annual pharmaceutical overspending, AIFA applies a reduction of 4.4% to all refundable pharmaceuticals (i.e. classified as A and H), save blood products, vaccines, and drugs covered by patent with retail price lower than 5 euros [15]. In July 2006, AIFA increases the mandatory discount to 5%, and in September of the same year establishes a further discount of 5%, in view of overruns 2006 pharmaceutical budget [16]. The financial plan for 2007 [17], presented in December 2006, introduces the payback as alternative to the reduction of drug prices provided for by September determination. The payback consists in a direct payment to Regions equivalent to the amount deriving from the price cut: it is currently still in force. Every year pharmaceutical companies may decide to employ payback mechanism to its products on the basis of market and financial strategies.

General reform of pharmaceutical policy is in force with the law 222/2007 and promotes a synergy between Minister of Health, Minister of Economy and Finance, AIFA and Regions, and pharmaceutical companies, with the aim of regulating and developing the pharmaceutical system [18]. The outpatient pharmaceutical budget, including products supplies through direct distribution (both DD and DPC), was set at 14%, both at national and regional level, and split from inpatient pharmaceutical expenditure. The overspending of outpatient expenditure at national level is covered by manufacturers and

supply chain through measures *ad hoc* determined by AIFA, as a direct payment to Regions, with the payback mechanism, and increment of mandatory discount. Regions are stimulated at control of their own spending since they balance the overspending due to outpatient expenditure only in that case exceed locally and not at national level. Whereas inpatient pharmaceutical expenditure could not exceed 2.4% of the overall healthcare expenditure: Regions are responsible for respect of ceiling, and refund any overspending through reduction of hospital and overall healthcare resources. Moreover, for controlling the pharmaceutical expenditure, a maximum budget ceiling, based on volumes and pricing data during the previous year, is assigned to every manufacturer. It represents the amount that SSN is available to reimburse and is allocated according to resources of the national healthcare fund for pharmaceutical expenditure (determined every year with financial law), which is increased with a part (maximum of 60%) of the amount made available by savings originating drug patent expiration. Companies may increase budget allocated, within any specific therapeutic class, gaining market shares. Innovative drugs are excluded from payback procedure and have a specific fund (20% of medicine fund, increased with expired drug patent) to promote the innovation and support the companies committed to research and development. In case of overspending of this amount, all companies have to participate in the fund, in proportion of market share.

In 2010 according to disposition provided for by law 222/2007, the overspending of outpatient expenditure constrain AIFA to introduce further and provisional discounts for class A drug prices to pharmacists – in the amount of 1.82% – and companies – 1.83%, which companies remit through payback mechanism [19].

The pharmaceutical expenditure ceilings currently in force are established by law 95/2012 [20]: the outpatient expenditure limit is set at 11.35% of total healthcare expenditure, while the inpatient expenditure is not allowed to exceed 3.5%. In case of exceeding of expenditure ceilings, measures adopted remain in effect, except for the deficit of the inpatient pharmaceutical expenditure that is financed for 50% by Regions, and the remaining 50% by pharmaceutical companies, via the payback mechanism.

Price definition process: the basics

The prices of drugs classified in class C are directly determined by the pharmaceutical companies and may be increased in January of any odd year (the increment has not to exceed the annual inflation), whilst the reduction price may be performed anytime. The publication in GU is not requested, but the retail price has to be communicated to AIFA by manufacturer.

For drugs reimbursed by SSN, the prices and the margins for pharmaceutical companies, pharmacists and wholesalers are fixed by law. Ex-factory price is the 66.65% of retail price, at net of VAT (in Italy this tax for basic goods amounts to 10%), and represents the maximum hammer price paid by SSN public administrations, such as ASLs and AOs [7]. For drugs supplied through territorial pharmacies, SSN (via ASL) reimburses the retail price, which includes the margins for pharmacist and wholesaler (33.35% of retail price at net of VAT). According to the law 39/2009 [21], the ex-factory price of products never covered by a patent, is set at 58.65% of the net public price, for increasing the margin

for the distribution channel (up to 41.35%), with the aim to extend generic drug market. Drugs in class H and directly sold to the public administrations (class A included in PH-T) are privately negotiated between pharmaceutical company and hospital pharmacy, based on budget allocated for that specific pathology.

Reference pricing and alternative strategies

Italian pharmaceutical policy works for containing pharmaceutical expenditure through price negotiation, prescription monitoring, and reference pricing. The latter measure limits the pharmaceutical expenditure by fixing the maximum SSN reimbursement price to all off-patent drugs having the same active pharmaceutical ingredient, pharmaceutical form, administration route, release mode, and unit dose (generic drug). The pricing of generic drugs has a price reduction at least equal to 20 per cent relative to originator drug (with expired patent); the price of other generic products will be equal or lower to the reference price established by negotiation. The policy of reference pricing is used also for some drugs sharing therapeutic indications with equivalent efficacy and safety. This procedure is common at the regional level, where ASLs and AOs may launch tenders for pharmaceutical products in the same therapeutic area, conform to AIFA [20].

The prescription monitoring occurs via AIFA notes and therapeutic plans. AIFA notes are a regulatory tool aimed at improving the appropriateness of the drug prescription, limiting the class A drug reimbursement only for specific indications, essentially chronic diseases: for other indications, drugs remain at patient charge. Therapeutic plans, established with the law 537/1993 [22], are other instruments for limiting prescription and reimbursement only to those indications for which clinical evidence is reported, and for guaranteeing patient therapeutic adherence and appropriateness of use. AIFA lists the drugs needing therapeutic plan, which may be only delivered by specialized centers identified in each Region. Since 2007, AIFA implements AIFA Registers to verify appropriateness in prescribing: they are placed in the early phases after MA of new drugs, and in some cases for the authorized off label use, with the purpose to value real world data on safety and effectiveness – bridge a gap on clinical evidence due to poor clinical data available – apply and manage the negotiation conditions – i.e. Managed Entry Agreements (MEAs) – and consequently govern the public expenditure.

Negotiation based on future events by MEAs is a further strategy for containing SSN pharmaceutical expenditure. MEAs are arrangements between manufacturers and payers that enable the reimbursement of a medicine with specific conditions for reducing impact of uncertainty relating to clinical benefit, cost-effectiveness, and expenditure.

They may consider responding patients (outcome based) or sales volume (price/volume based). Some measures are:

- Payment by results: payback of costs for not responder patients during the first efficacy evaluation;
- Risk-sharing: discount on price (averagely 50%) for no responder patients during first evaluation of efficacy;
- Success fee: reimbursement on responder patients;

- Cost-sharing: discount on price (up to 100%) for the first course of eligible patients;
- Capping: payback of costs for overrun the budgets.

If the benefits obtained are lower then those expected, AIFA may initiate a process of re-negotiation with manufacturer, in order to reduce economic impact.

Financial Flows After the Reimbursement Decision

After publication on GU of P&R approbation, medicinal products may be delivered to the patient, according to supply regimen granted by AIFA. SSN reimburses the price of the medicinal products of class A and H at net of mandatory (and potentially hidden) discounts to the supply chain.

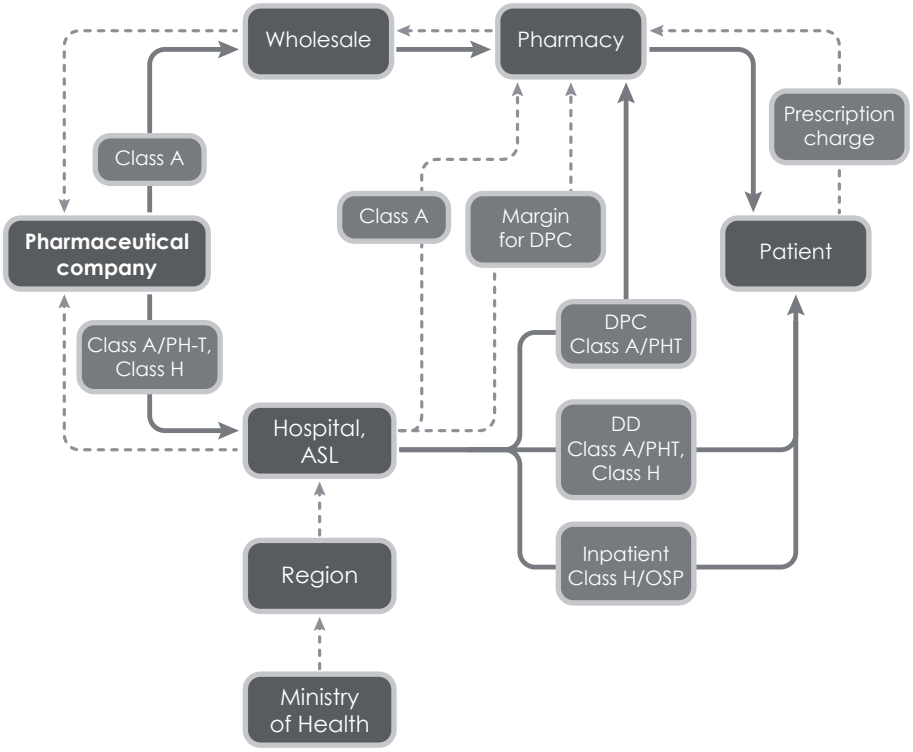

Figure 3. Financial flows for reimbursement of drug classified in class A and H. Dashed lines show the money flow for reimbursing the pharmaceutical company. Continuous lines show the flow of medicinal products based on supply and reimbursement classification
ASL = Local Health Unit; DD = *Distribuzione Diretta* (drugs distributed directly through hospital pharmacies); DPC = *Distribuzione Per Conto* (drugs distributed by territorial pharmacies); OSP = hospital prescription; PH-T = *Prontuario Ospedale Territorio*

The medicinal products sold by territorial pharmacies are reimbursed directly by ASL, which pays the reference price withholding mandatory discounts for the pharmacies and wholesales (and prescription charge paid by patient for in-patent drugs). Moreover, the ASL pays to the territorial pharmacies a margin for the distribution service of drug delivery in DPC regimen.

Pharmaceutical companies receive the reimbursement for class A and H drugs directly by hospital pharmacies (located in each ASL and AO), which acquire at hospital price (i.e. at net of mandatory and hidden discounts) both the medicinal products that are delivered via hospital and via DD and DPC.

Figure 3 summarizes the financial flows for reimbursement of drug classified in class A and H.

5.3 Mapping and Structure of Decision Makers

Minister of Health

It was established in 1958 and it is the core of SSN. It decides the policy line for warranting the health to all citizens.

The duties of the MH are focused for:

- Guaranteeing quality, transparency, equity and efficiency of SSN through appropriate communication to population;
- Resolving disparity and inequity;
- Collaborating with regions to increase the efficiency of SSN;
- Taking and drawing a line in case of emergency for public health.

Secretary of MH trusts on three departments:

- *Dipartimento sanità pubblica e innovazione*, which coordinates and monitors health conditions and safety of persons at work, promotion and development of research, funding and supervision of IRCCS and other national bodies;
- *Dipartimento della programmazione e dell'ordinamento del SSN*, which coordinates and monitors activities of healthcare planning, administrative organs that assurances the SSN quality, Italian health care abroad, information and statistical systems of SSN, trainings of SSN staff, territorial organization of pharmaceutical assistance and clinical risk;
- *Dipartimento di sanità pubblica veterinaria, sicurezza alimentare e organi collegiali per la tutela della salute*, which coordinates and monitors on veterinary medicine, nutrition and alimentary safety.

Moreover, MH avail oneself of technical and scientific consultation of authorities, as:

- AIFA that decides on pharmaceutical field;
- *Consiglio Superiore di Sanità* (CSS) that provides opinions on health field (i.e. during epidemic);
- *Istituto Superiore di Sanità* (ISS) that provides opinions to MH carrying out research, monitor, documentation and training to SSN administrations.

AIFA

AIFA was established with the law n. 326 of 24/11/2003 (article 48) [1]: it is a public body having legal position and administrative, organizational, patrimonial, financial and management autonomy, under the direction of the Ministry of Health and under the vigilance of the Ministry of Health and the Ministry of Economy. According to the law 245/2004 [2], the management of AIFA consist of a General Director, a Management Board and a College of Auditors of Account. General Director is the Agency's legal representative: he is designated by Minister of Health with the State-Regions Conference support, with a 5-years mandate, that is renewable. Management Board, in charge for 5 years, consists of 1 chairman, appointed by the Ministry of Health together with State-Regions Conference, and 4 members, 2 appointed by Ministry of Health and 2 by State-Regions Conference. College of Auditors of Accounts, in charge for 5 years too, is formed by 3 members: 1 chairman appointed by the Ministry of Health, 1 by the Ministry of Economy and 1 by the State-Regions Conference.

The AIFA is subdivided in 6 functional Areas, 5 technical and 1 with administrative tasks:

- Pre Authorization: competences on clinical trials of medicines, Good Clinical Practice (GCP), independent research funded by AIFA;
- Registration: responsibilities on registration process of medicinal products for human use, according to official regulations at national and European level (Mutual Recognition, Decentralized Procedure);
- Post-Marketing Surveillance: responsibilities on drugs safety after their commercialization;
- Pharmaceutical Strategy and Policy: competences on price and reimbursement of medicines, supervision on pharmaceutical expenditure at national and regional level, through the OSMED; it studies the national and international scenario in the field of pharmaceutical policy and may suggest new models and procedures to foster the development of the sector;
- Inspections and certification: tasks of control activities, inspection and issuing of permits for the production of medicines, medicinal gases and raw materials;
- Administrative Affairs: tasks of ensuring the unity and integrity of administrative, legal, regulatory and business affairs of regulatory agency.

AIFA is supported by four technical-scientific committees' activities [3], constituted by experts having documented knowledge in their field.

- Technical-Scientific Committee (CTS) evaluates and gives consultative opinions on national and communitarian applications; it classifies medicinal products for reimbursement and gives technical-scientific advice. CTS is set up by a Ministry of Health decree and it is constituted by 10 members, i.e. General Director of Agency, ISS's chairman and by 8 experts, appointed by Ministry of Health (3 members), Ministry of Economy (1 member) and State-Regions Conference (4 members). The 8 members stay in charge for 3 years.
- Prices and Reimbursement Committee (CPR) performs negotiation activities with pharmaceutical companies in order to define the price of medicinal products that are reimbursed by National Healthcare System (SSN). CPR is set up by a Ministry of

Health decree and it is constituted by the AIFA General Director, ISS's chairman and 8 experts appointed by Ministry of Health, State-Regions Conference and Ministry of economy. As for CTS, the members of CPR, excluding AIFA General Director and chairman of ISS, are in charge for 3 years.

- Agency-Regions Liaison Center assures a close collaboration between AIFA and the Regions. It analyses the pharmaceutical expenditure trend at a national level, promotes generic drugs and analyses the drug distribution and reimbursement at regional level. It is constituted by 10 members, appointed every 5 years.
- Research and development promotion Committee promotes public scientific research in the welfare strategic sections and supports private investments on the national territory. It is constituted by 10 members in charge for 5 years.

The main AIFA tasks are:

- to authorize marketing of medicinal products by national or European procedures according to quality, safety, and efficacy criteria;
- to continuously monitor adverse reactions using the national pharmacovigilance network that links together all the pharmacovigilance services in Health Local Units (ASL), hospitals (AO), Regions and pharmaceutical companies;
- to inspect pharmaceutical companies manufacture sites in order to guarantee the medicinal products and starting materials manufacturing quality (GMP);
- to verify the enforcement of GCP during clinical trials.

Regions: ASLs and AOs

Above it has been presented who guarantees the public health and determines the essential levels of care, MH, and who regulates the pharmaceutical market, AIFA. The nineteen Regions and autonomous provinces of Trento and Bolzano are the public administrations that decide the local health politics inside its jurisdiction, establishing legislative and administrative functions: they autonomously plan the *Piano Sanitario Regionale* (PSR), following the indication of PSN promulgated by MH, and govern the resources obtained by national and local taxation, allocating to ASLs, AOs and private health units for pharmaceutical, ambulatory, rehabilitative and hospital assistance (i.e. LEAs). AOs are hospital chosen by region with a high level of specialization, financial and administrative autonomy and provide healthcare services to patients regardless of regional provenance: patient residence ASL pays by tariff the health care service supplied by AO. MH defines maximum tariffs, but every region may decide to integrate the health supply based on financial availability.

5.4 Challenges and Catalyzers for Market Access

Health and Pharmaceutical Expenditure and New Health Policy

An Italian study observed that 13% of patients use 55-60% of health resources [23]: these patients had an age between 60 and 85 years and were simultaneously interested

by 1-4 chronic diseases. In the next future (about 25-35 years), the population with more than 60 years old will increase at least of 10%, with consequently increment of patients that need more health resources. The control of health expenditure is fundamental for the sustainability of Italian SSN. In 2015, the pharmaceutical expenditure, which included drugs reimbursed by SSN and these payed by patients, was of 28.9 billions of Euros (1,9% of Italian GDP), of which 76% at the expense of SSN, due to innovative medicines, in particular for treating hepatitis C [24]. In 2016, the overall health spending was estimated to € 113 billions, about 6.8% of Italian GDP, with a rise expectation in the short and mid term, and simultaneously with a minor impact on PIL, which is expected to grow according to the latest forecasts [24]. The pharmaceutical expenditure exceeded the allocated budget, both for inpatient and outpatient: in particular, inpatient expenditure overcame the ceiling of 3.5% in all regions, and reached 5.1% at national level, with an extra expenditure that amount at 1.2 billions of Euros. Outpatient expenditure was about 0.6% over the ceiling of 11.35%: innovative drugs via PH-T were the main responsible, with an increment of 23% versus the same period of 2015. The overall healthcare expenditure will increase, driven by pharmaceutical expenditure, but with a minor impact on GDP: this scenario may allow to free resources for improving the healthcare.

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