Scope of vignette:
- authorised medicinal products (with marketing authorisation)
- decision process about routine use (and not individual requests for reimbursement)
- submissions for P&R made by manufacturers

Green = related to/any special considerations for rare disease and ultra-rare disease treatments

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
Overview of health system and P&R/HTA process	Tax based health care system [1] Since 2004 [2], the national authority responsible for the regulatory, pricing & reimbursement and HTA activities on pharmaceuticals, is the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). AIFA is supported by two Advisory Committees[i][3]: **1- Technical Scientific Committee** (Commissione consultiva Tecnico - Scientifica, **CTS**): defines the place in therapy of new medicinal products; provides binding opinions on clinical trials/pharmacovigilance activities and on the therapeutic value of medicines by defining the place in therapy (the role of the medicine in its specific therapeutic context); defines drug class for reimbursement; gives technical opinions on definition of eligible population as eventual national data collection (registry or therapeutic plan) and parameters for possible application of performance-based risk-sharing agreement (PBRSA). **2- Pricing & Reimbursement Committee** (Commissione consultiva Prezzo e Rimborso, **CPR**): carries price negotiations, provides opinions regarding the price of medicines at the expiration of the negotiation agreement. [3] Each committee is composed of ten members: three assigned by the Ministry of Health, one by the Ministry of Economy and Finance and **four by the State-Regions Conference**. The general director of AIFA and the president of the National Institute of Health (Istituto Superiore di Sanità) are added as members by law. The validity of committees is three years, renewable consecutively only once. Positive drug list used [7]. The medicinal products with positive innovativeness' recognition (full) are automatically included into the regional formulary[ii]. For all other drugs [class A[iii] + PTH[iv] (Hosp-territory formulary)], the regions make their own decisions and assessment of whether to include a drug into a formulary and/or other limitations (eligible population).	
Differentiation of rare disease treatments in the P&R system	In order to facilitate OMPs access, several regulations were issued https://www.aifa.gov.it/en/farmaci-orfani: **1- Economic protection:** The **Stability Act**[v,vi] has introduced a mechanism of economic protection for OMP Market Authorisation Holders (MAHs). These are exempt from the national	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	pharmaceutical payback mechanism, which is conversely distributed among all other MAHs in proportion to their pharmaceutical sales volumes. AIFA recognizes that certain OMPs benefit[vii] from the **2013 hospital pharmaceutical expenditure legislation** [11]. Law 145/2018 (2019 Stability Law - Article 1 paragraphs 574-585) has modified since 2019 the AIFA list of orphan drugs because it will contain only those authorized by EMA with AIFA reimbursement class A and H and which have not yet exhausted the market exclusivity benefit. The **2019 Budget Law** (Law no. 145 of 31 December 2018) amended the methods used to break down the ceiling for pharmaceutical expenditure for direct purchases by the NHS structures (so-called payback), providing that the distribution of the Spending overhead is spread over all pharmaceutical companies that contribute to the cost of direct purchases based on market shares. It also predicted that the orphan drugs that will benefit from the exclusion from the shelf procedures will be only those authorized by the EMA, excluding the so-called Orphan Likes, the drugs included in the Orphanet register and all the drugs that were authorized as Orphans by the EMA but that they have exhausted the period of market exclusivity. Medicines not present in the so-called EU list of orphan drugs (Community Register of designated orphan drugs) will no longer be considered as such in Italy. The AIFA makes available the list of orphan drugs prepared in application of the new discipline[viii]. **2- Fast track procedure** OMPs, hospital or exceptionally therapeutic and social medicinal products are evaluated as a priority. Furthermore, for these drugs, the current allows the company to submit the request for classification and price before marketing authorization is granted. In order to increase the availability of orphan drugs nationwide, the so-called Balduzzi Law (Law n. 189 of 2012, Article 12, paragraph 3) allows the MAH to apply to AIFA's PR procedures as soon as the CHMP positive opinion is released and therefore, before the marketing authorization is formally granted by the European Medicines Agency. Moreover, following Decree Law n. 69 of June 21, 2013, and Law n. 98 of August 9, 2013 (Article 44), AIFA prioritizes the pricing and reimbursement dossiers of orphan drugs (together with those concerning medicines of exceptional therapeutic relevance) over other pending applications. In such cases, the assessment period is reduced from 180 days to 100 days (so-called "fast track authorisation"). **3- Early access** Access to treatment for patients suffering from a rare disease is guaranteed by means of various legislative instruments. The centralised procedure represents the standard access way; whenever an orphan drug has no marketing authorisation, patient access is ensured access through the following rules: - Law n. 648 of 1996, allowing the use of a medicine on a national basis[ix]	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	- Law n. 326 of 2003, Article 48 (also known as 5% AIFA Fund) and the Ministerial Decree of 94 of 1998 (former Legge Di Bella) that, unlike Law n. 648, regulate pharmaceutical prescription for individual patient on a nominal basis. **4- Independent research on orphan drugs funded by AIFA** AIFA was the first European regulatory agency to include among its institutional objectives the promotion of independent scientific research, also encouraging the development of orphan drugs through the financing of non-profit clinical studies. The Independent Research promoted by AIFA represents a tool able to produce results and knowledge with particular regard to those pathologies which, given their reduced incidence, often do not arouse commercial interest. The results of projects funded by the AIFA, in the field of Independent Research, aim to generate evidence with a significant impact on the NHS and on the appropriateness of the use of drugs, guaranteeing adequate effects of scientific results. The Independent Research is financed through the 5% Fund (Law n. 326/2003) and is addressed to all Italian researchers of public and non-profit institutions.	
Eligible medicinal products	All newly licensed drugs (first P&R negotiation and re-negotiation) From May 2017: more detail also drugs with innovativeness recognition status (in a second stage)	All newly licensed OMPs (first P&R negotiation and re-negotiation). 100-day fast track procedure for OMPs [8] From May 2017: OMPs with innovativeness recognition status.
Process	Pharmaceutical company submits dossier to AIFA, offices and advisory committees conduct a preliminary assessment to evaluate/establish place in therapy, reimbursement class of the pharmaceutical product and provision systems. At the end of the decision-making process, once the CPR has concluded the negotiation procedure, the final decision concerning reimbursement is made. The P&R process occurs in four stages: 1- Pharmaceutical company applies for P&R procedure by submitting the dossier to AIFA; 2- CTS provides its binding opinions place in therapy and therapeutic value of medicines, provision systems for medicinal products;	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	3- CPR assesses the dossier and then meets the pharmaceutical company for the negotiation procedure; 4- Result of the negotiation is submitted to the Board of Directors for a final evaluation Within 180 days from the application, CTS and CPR express their advice (opinion) and the ex-factory price is published in the Official Journal (Gazzetta Ufficiale). Regarding the innovation's assessment, AIFA has launched two models over the years: **1- Algorithm 2007**, AIFA adopted its own set of criteria "Criteria for ranking therapeutic innovation of new drugs and elements for supplementing the dossier for admission to the reimbursement system" as the result of a joint AIFA-industries association Working Group [10]. The score of therapeutic innovation is assessed on the base of: *(a) the availability of previous treatments, and,* *(b) the extent of the therapeutic effect.* The algorithm considered the following therapeutic categories: A) *therapeutic agents for serious diseases (a disease is serious if it meets one of the following criteria: it is fatal, it requires hospitalisation, it is life-threatening or heavily disabling);* *B) risk factors for serious diseases (e.g. hypertension or obesity);* *C) non-serious diseases (e.g. allergic rhinitis).* At a later stage, according to the Resolution n. 27 of December 18, 2009 of the Board of Directors, the CTS was conferred competence as regards the issuing of the place in therapy and the degree of innovation, both from a scientific and from a therapeutic point of	Regarding the attribution of the degree of innovation (Algorithm 2007) to various types of drugs specifically for the "Important therapeutic innovation (A)" the algorithm reported that "*This category includes orphan drugs for rare diseases. The important innovation is based on the consideration that these diseases are by definition serious and, in the majority of cases, without adequate treatment* *[A (severity of the disease) + A (availability of standard treatment) + A (extent of the therapeutic effect)].* *The marketing of these drugs makes a first therapeutic option available for these diseases.*"

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	view. In fact, the concept of innovation of a medicine was widened and its evaluation more detailed. **2- New Scheme 2017 [4]** (Deliberation 519/2017) includes: <u>I) Therapeutic Need</u> - *Maximum* (lack of therapeutic options), - *Important* (presence of clinical alternatives, no impact or unvalidated), - *Moderate* (presence of clinical alternatives, but little impact evidence), - *Low/ Poor* (presence of one or more alternative treatments being evaluated with high impact) and, - *Absent* (presence of alternative treatments for the indication in able to modify the natural history of the disease and with a favourable safety profile) <u>II) Added therapeutic value</u> - *Maximum* (greater efficacy demonstrated on clinically relevant outcomes than alternative treatments (if available), - *Important* (greater efficacy demonstrated on clinically relevant outcomes, or ability to reduce the risk of disabling or life-threatening complications, or better risk/benefit ratio (R/B) than the alternatives, or ability to avoid the use of clinical procedures at high risk) - *Moderate* (greater efficacy in the moderate or demonstrated in some subpopulations of patients or surrogate outcomes, and with limited effects on QoL), - *Low/ Poor* (More effective, however, it has been demonstrated outcomes of medically relevant or is minor) and, - *Absent* (no added clinical benefit compared with alternatives)	The assessment on Innovativeness' recognition [4] is relevant for rare disease treatment, in that assessment of quality of the evidence will take into account the difficulty of conducting clinical trials. In these cases, when there is a high unmet medical need and strong indications of an added therapeutic benefit, Innovativeness can be attributed, even when evidence quality is 'Low'.

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	III) Robustness of clinical trials (GRADE scores): - *High,* - *Moderate,* - *Low,* - *Very low.* Medicinal products which have been recognized as having a therapeutic need and added therapeutic value both at the "Maximum" or "Important" level and a "High" quality of evidence may be considered innovative. On the other hand, innovation cannot be recognized in the presence of a therapeutic need and/ or an added therapeutic value judged as "poor" or "absent", or of a quality of CTs judged to be "low" or "very low". [4] Intermediate situations will be evaluated case by case, taking into account the relative weight of the individual elements considered. At the end of the process, the CTS will prepare a brief report, in which the assessments relating to each of the three areas considered will be described, and the relative final judgment will be expressed. The possible results of the evaluation are: - **recognition of innovation**, which will be associated with the inclusion in the Fund of innovative drugs, or in the fund of innovative oncology drugs, the expected economic benefits by article 1, paragraph 403, Law 11 December 2016, n. 232 (Budget Law 2017) and inclusion in the Regional Therapeutic Manuals in accordance with the terms established by current legislation (Chapter III, article 10, paragraph 2, Law 8 November 2012, n. 189); - **recognition of the conditioned (or potential) innovativeness**, which only entails the inclusion in the Regional Therapeutic	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	Manuals in the terms provided by the current legislation (Chapter III, article 10, paragraph 2, Law 8 November 2012, n. 189); - **failure to recognize innovation**.	
Disease specific expert input (e.g. clinicians or patients in any stage of the process)	Clinicians or scientific associations (specific questions or auditions during CTS meetings) could be involved during the Stage 2 [i.e. opinions by CTS provides on place in therapy, therapeutic value, and provision systems] specifically (AIFA Declaration Of Interest included): it regards items for which the CTS usually has the information: but there are cases - and it is that of rare diseases - where this involvement is more necessary and, at times, mandatory. Clinicians are also included during the discussions on eligible population definition for AIFA registries or on therapeutic plans and the set-up of follow up measures.	
Key domains in assessment	- Clinical efficacy - Cost-effectiveness - Budget impact - Innovativeness' recognition	
Evidentiary requirements	RCTs preferred	Although there is general concern around the limited clinical evidence available for OMPs, Italian decision makers have occasionally relied on sources of evidence other than RCTs, including literature reviews, cohort studies and Phase II clinical trials results.
PROMs	None. Assessing the added value through its innovativeness' recognition scheme [4], AIFA mentions the "quality of life" without however specifying PRO or PROMs. No specific guidelines.	
Appraisal framework	It consists of final opinion from CTS based principally (from 2017) on innovativeness' recognition scheme. In addition to the key domains, the following criteria are considered: - place in therapy - comparator - study design - added clinical value	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	- primary endpoint (surrogate or not) - safety profile - clinical trial design (GRADE methodology). The final CTS opinion is a detailed report on the recognition of innovation (see Report di valutazione dell'innovatività or Innovation value-framework: https://www.aifa.gov.it/en/web/guest/farmaci-innovativi) and an opinion on reimbursement (Yes/ No). In case of Yes, it provides information on the reimbursement classification (Class H or A[x]) and supply regime. It also specifies the indications for which to include a PBRSA or suggestions for CPR to implement a FBA. Furthermore, the CTS opinion also specifies which therapeutic indication to reimburse (which is not necessarily the same as the label approved by the EMA). Therefore, the opinion also contains details on the limitations and possible inclusion & exclusion criteria (if AIFA registry, these elements are fundamental for the data collections at national level).	
Reimbursement decision	Pricing and reimbursement are decided following a negotiation between AIFA (CTS + CPR) and the pharmaceutical company. The medicinal product could receive a positive decision and be reimbursed under National Health System (SSN) as H (hospital) or A classification, or be denied reimbursement (C classification). A positive decision may also include limitations on the EMA indication with some restrictions on target population. If needed, national registries and therapeutic plans are used to monitor drug expenditures and efficacy/safety issues, and entry agreements may be implemented.	
Pricing process	The pricing process begins after the clinical assessment (after the CTS opinion). Since January 1st, 2004, prices of all medicines reimbursed by the NHS are established through a negotiation procedure between AIFA and the pharmaceutical company, in	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	accordance with methods and criteria previously adopted only for medicines approved with European procedures. During negotiations, parameters taken into account are those defined by the CIPE Resolution n. 3 of 2001 (CIPE - Comitato Interministeriale per la Programmazione, Interministerial Committee for Economic Planning): - Economic impact on the NHS - Prices in other EU countries - Cost of treatment per day compared to the cost of medicines with similar effectiveness - Benefit/risk ratio compared to medicines with the same therapeutic indication - Cost/effectiveness ratio when other treatment options are available - Innovativeness' recognition (Yes/ No. If Yes, full, potential or conditional innovation score) [4]. **Consideration of AIFA economic evaluation** Includes evaluating the cost-effectiveness and sustainability profile of the medicines as part of the process of defining the reimbursement and the price charged to the NHS. The pharmacoeconomic analyses are of particular importance for the negotiations conducted by the CPR with pharmaceutical companies, in particular in the case of medicines that are innovative with respect to the treatments already available and in the case of orphan drugs for the treatment of rare diseases. To this end, AIFA writes non-mandatory and non-binding opinions for the CPR, which constitute a support tool in the decision-making process for the definition and reimbursement of the price of a drug. The preliminary investigation includes the following phases: a) critical evaluation of the pharmacoeconomic studies presented by pharmaceutical companies within the PR dossier, b) revision of the pharmacoeconomic model where transmitted by the company in an open and editable format, c) literature review for the identification of further published pharmacoeconomic studies relating to the national or international context, d) identification of recommendations and decisions made in other countries regarding the medicinal product in question, e) analysis of treatment costs with respect to therapeutic alternatives, f) economic and financial impact assessment. The critical evaluation of the pharmacoeconomic studies presented by pharmaceutical companies is carried out by verifying compliance with the standards developed by the ISPOR Task Force for CEA and BIA (Husereau *et al*., 2013; Sullivan *et al*., 2014); for the evaluation of the quality and robustness of the studies AIFA uses instruments recognized and validated at an international level, example.g., the check-lists of Drummond *et al*. 2015 and Philips *et al*., 2004. The final opinion is sent to the HTA Secretariat for discussion in the plenary and subsequently to the members of the Commissions within the preliminary documentation.	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	The new guidance to applicants for the submission of pharmacoeconomic analyses within the Pricing and Reimbursement Dossier [4] intends to provide companies with detailed instructions for completing chapter 9 of the dossier to support the request for reimbursement and price envisaged by the CIPE Resolution of 1 February 2001. Although the presentation of pharmacoeconomic analyses by companies is not mandatory, it is highly recommended for some types of negotiations, e.g.: • orphan drugs, including any extensions of indications; • new active ingredients, including reclassifications of active ingredients already negotiated but not reimbursed, and combinations that contain at least one new active ingredient; • extension of the therapeutic indications of drugs subject to patent coverage, except in the case where it is an extension of the population of the indication already authorized and reimbursed. On August 1, 2019, the Ministry of Health announced the approval of a Ministerial Decree [5], issued in agreement with the Ministry of Economy and Finance, which sets new criteria for the price negotiation procedure between the MAH and AIFA in order to establish the price for medicines that will be reimbursed by the NHS. The Ministerial Decree was published in the Italian Official Gazette in August 2020 [6] and replaces the previous CIPE Resolution no. 3 of February 1, 2001. The approval of this Ministerial Decree[xi] aims to achieve transparency in price negotiation and update the criteria established by the CIPE Resolution 3/2001. In particular, more emphasis has been put on the requirement for the added therapeutic value of the medicines that are under negotiation. **Within 30 days from the date on which the Decree enters into force, AIFA will have to issue a Resolution providing more detailed indications on the negotiation application; therefore, until such a measure is adopted, the new procedure cannot be fully operational.**	
Managed entry agreements	MEAs are part of the overall assessment and part of PR contract signed from AIFA and pharmaceutical industry whereby: Performance-based risk-sharing agreements (PBRSA) (Payment by result) are the CTS' responsibility and Financial-based agreements (FBA) (Cost-sharing, Price/ volume, Cap ceiling) are part of the CPR opinion done during the negotiation phase. PBRSAs are implemented only through the AIFA registers. Case by case decisions and occasionally a MEA is discussed collegially by the two Committees (e.g. Chronic Hep C or the incoming CAR T - cell therapy) If the product is recognised as fully innovative, the data collection is mandatory by Law [5]. There are exceptions, especially for orphan drugs with an important safety profile such as ATMPs. In these cases, the data collection (AIFA registries) are mandatory even the innovativeness isn't recognised by AIFA.	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
	Exception for OMPs: early access tools [8] are present and, for 648/96 Law (in very few cases) PBRSA (only with AIFA registry) could be possible. In this case the Committee involved is only CTS.	
Main challenges in appraising medicines for rare diseases	- Surrogate endpoints - Very often, little knowledge of the rare disease - Lack of good quality clinical data - Lack of comparator (lack of therapeutic alternative): country clinical practice specific - Lack of epidemiologic (historical) data - Lack of disease-based data (registry) - Difficulties on monitoring treatment efficacy/ safety - Making arrangements to work for all stakeholders: sharing data/ platforms - Lack of long-term meaningful clinical outcomes - High price and costs	
Impact of special processes	Shorter timing of evaluation (100 days) Innovativeness can be attributed, even when evidence quality is 'Low'. [4]	
Proposed policy change	- Making arrangements work for all stakeholder especially sharing results of the decision-making. - Transforming AIFA registries into prospective observational studies. Looking with the EMA vision (patient registries strategy[xii]) and EUnetHTA PLEG[xiii] strategy (post-lunch evidence generation). - Generating the AIFA platform registries directly linking the hospital and regional data sources to avoid duplication of data entry and be useful for administrative local/ regional pharmaceutical planning. - Generating long-term meaningful outcomes (clinical and socioeconomic) at patient and/ or population level (if needed for PBRSA and/ or FBA implementation) - Involving patient perspective including PROs or PROMs (endpoint in an observational study) - Sharing transparent access data for research purposes as academia, scientific associations and industry. - Explore the potential applicability and impact of 'extremely large datasets" (big data) into drug regulatory & HTA/PR process.	
Joint initiatives	Valletta declaration, EUnetHTA [6]	
SOURCES		
1	https://international.commonwealthfund.org/countries/italy/	

Italy	Standard process (non-orphan drugs)	Standard process (orphan drugs - different criteria)
2	https://www.aifa.gov.it/en/web/guest/l-agenzia L'uso dei Farmaci in Italia. Rapporto Nazionale Anno 2018: https://www.aifa.gov.it/documents/20142/0/Rapporto_OsMed_2018.pdf/c9eb79f9-b791-2759-4a9e-e56e1348a976 National Report on Medicines Year 2017: https://www.aifa.gov.it/documents/20142/241052/OsMed_2017_eng.pdf/543aebd9-502e-ec61-7ceb-3cc16fd920d9	
3	https://www.aifa.gov.it/en/web/guest/commissioni-tecnico-consultive https://www.aifa.gov.it/documents/20142/516919/Regolamento_CTS_CPR_102014.pdf/94026b0b-9c4f-d111-f135-e55b156e93b7	
4	https://www.aifa.gov.it/documents/20142/1028586/Guidance_pharmacoeconomic_analyses_UVE_24.7.2020.pdf/98f7b3fc-b705-fc81-5a45-31bf9cc513e8	
5	http://www.salute.gov.it/imgs/C_17_notizie_3848_listaFile_itemName_0_file.pdf	
6	https://www.gazzettaufficiale.it/eli/id/2020/07/24/20A03810/sg	
8	http://www.aifa.gov.it/sites/default/files/Determina_criteri_classificazione_farmaci_innovativi.pdf	
9	Xoxi et al., 2012; Morel et al., 2013; Montilla et al., 2015	
10	http://www.infarmed.pt/documents/15786/2835945/Paola_Testori_Coggi.pdf/2388762b-7506-4a78-9533-7422ea480c55 https://eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/ https://eunethta.eu/ja3-archive/work-package-7-national-implementation-and-impact/	
11	https://www.aifa.gov.it/en/web/guest/liste-farmaci-a-h	
12	https://www.aifa.gov.it/en/web/guest/accesso-precoce-uso-off-label	
13	https://www.gazzettaufficiale.it/eli/id/2012/11/10/012G0212/sg	
14	Italian Medicines Agency WGoID. Criteria for ranking therapeutic innovation of new drugs and elements for supplementing the dossier for admission to the reimbursement system. 2007. Available from: http://www.agenziafarmaco.it/allegati/integral_document.pdf	
15	Article 15, paragraph 8, letters i and i-bis of Law n. 135 of 2012, amended by Law n. 147 of December 27, 2013	

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[i] The management of pharmaceutical expenditure involves several financial measures aimed at balancing NHS pharmaceutical expenditure and the financial resources available (i.e. planned expenditure). This task is considered a highly relevant mission, since the management of pharmaceutical expenditure ensures the stability of the economic system. Any action intended to determine the appropriate use of medicines or to restrain regional expenditure (e.g. prices granted through local tenders lowering current ones) falls under the expenditure regulation. In this context, the activity of the CPR-CTS represents a significant tool supporting pharmaceutical expenditure decisions, particularly in the context of price negotiations with pharmaceutical companies and when defining reimbursed indications. **Regions and/or Health Local Units (HLUs) also contribute to public expenditure management when setting the price of a medicinal product or when encouraging the appropriate use of a medicine.** According to Law n.222 of 2007 and Law n.135 of 2012, the control of pharmaceutical expenditure is obtained through a set of measures, notably outpatient and inpatient pharmaceutical expenditure ceilings, pharmaceutical expenditure monitoring, fixed maximum budget ceilings for companies and/or payback mechanism when budget is exceeded.

[ii] Even though **the concept of innovation appears a general connotation, recalling the State- Regions Agreement rather than Law n. 159 of 2007** (converted in Law n. 222 of 2007 and Law n. 135 of 2012), **it implies significant differences from a juridical point of view**. The status of innovative medicine entails a variety of economic benefits, defined by law, which are limited in time (usually 36 months) and that can be subject to revaluation as new scientific evidence arises. However, innovative medicines are kept on the innovative medicines list issued by AIFA even after the expiration of economic benefits, unless otherwise decided by the CTS. The regulatory distinction between the two regulations allows to discern, on one hand, the need for fast market entry of innovative medicines and timely patient access to treatment, without considering economic constraints (i.e. the Innovation fund according to Law n. 159 of 2007 converted in Law n. 222 of 2007 and, Law n. 95 of 2012 and converted in Law n. 135 of 2012). On the other hand, the need for priority inclusion and maintenance of these medicines in regional therapeutic formularies, which depend on the availability or absence of more innovative medicines approved in the meantime. This approach was later modified by the CTS. In fact, it was decided to combine the status of innovative medicines included in the Innovation fund with the inclusion in the therapeutic regional formularies.

[iii] Class A drugs are those included in the National Pharmaceutical Formulary (Handbook) and reimbursed by the NHS at national level.

[iv] The Handbook of direct distribution (DD) for the care and continuity of care Hospital (H) -Territory (T) is the list of drugs with direct distribution by public facilities. PHT aims to ensure a balance in the overall distribution of drugs, in a health improvement framework capable of also balancing the government of pharmaceutical spending. There are three areas of therapy: Area H, or intensive and exclusively hospital therapy, whose instrument is the Hospital Handbook; H-T area of care and therapeutic continuity, with the PHT Handbook; Area T of chronicity and short-term therapies, with prescriptions from general practitioners and freely chosen pediatricians through the National Pharmaceutical Handbook. The PHT does not in itself redefine the classes of reimbursement (A, C or H). (http://www.agenziafarmaco.gov.it/sites/default/files/111.23658.1138273871234fefa.pdf)

[v] **2019 Stability Act**:

553. Given that the drug is a tool for health protection and that the medicines are provided by the National Health Service as included in the essential levels of assistance (LEA), to guarantee updated criteria for the evolution of pharmaceutical policy in the negotiation phase of the price of drugs between the Italian Medicines Agency (AIFA) and the pharmaceutical company holding the

marketing authorization (AIC), by March 15, 2019, by decree of the Minister of Health, in consultation with the Minister of Economy and of finances, having heard the Permanent Conference for relations between the State, the regions and the autonomous provinces of Trento and Bolzano, the criteria and methods to which AIFA abides in determining, through negotiation, the prices of drugs are dictated reimbursed by the National Health Service.
554. From 1 January 2019, before the expiry of the negotiating agreement with the AIC pharmaceutical company, AIFA can restart the negotiation procedures to reconsider the terms of the agreement in be, in the case in which intervals of the market occur at times such as to foresee an increase in the level of use of the drug or to set up an unfavorable cost-therapy ratio with respect to the alternatives present in the national pharmaceutical formulary.

[vi] **2020 Stability Act** (work in progress)
Several measures concerning health, from the funding of 113 billion for the National Health Fund to the new calibration of pharmaceutical spending ceilings, which become respectively 6.89% (today it is set at 3.5%) for "direct purchases" and 7.96% (today it is 11.35%) for the "affiliated". And again, from the allocation of 1.920 billion in 2019 and 2.630 starting from 2018 for the public employment, up to the stabilization of precarious workers and ad hoc funds for innovative drugs, oncology and vaccines.
Art. 59 (Provisions on health care)
- *Pharmaceutical expenditure ceilings*. From 2017, the hospital pharmaceutical expenditure ceiling will be calculated gross of class A direct drug distribution and distribution by account, and is restated to 6.89 percent (now set at 3.5%) and it assumes the name of "ceiling of pharmaceutical expenditure for direct purchases". Consequently, the ceiling for territorial pharmaceutical expenditure is also changed, which will be redetermined by 7.96 per cent (today it is 11.35%) and assumes the name of "capped pharmaceutical expenditure ceiling".
- *Fund for innovative and oncological drugs*. A total of 1 billion euros for innovative drugs, of which 500 for a new ad hoc fund for oncology (in this regard it is established that the Aifa, by 31 March 2017, will have to set the criteria for the classification of innovative drugs and to conditioned innovation and innovative oncology drugs).
- *Biosimilars*. In the maneuver it is established that "Automatic substitutability between the reference biological and its biosimilar or between biosimilars is not allowed" and that "In the public purchase procedures different active ingredients cannot be put up for tender in the same lot, even if they have the same therapeutic indications".
- *Biological drugs with expired patent*. Specific rules are also envisaged to rationalize the expenditure for the purchase of biological drugs with expired patent. In particular, for the purchase tenders a single lot is envisaged, considering the specific active principle (level V ATC), the same route of administration and dosage. The auction base of the framework agreement must be the maximum transfer price of the reference biological drug to the National Health Service. In any case it is established that "the patients must be treated, with one of the first three drugs in the ranking of the framework agreement classified according to the criterion of the lowest price or the most economically advantageous offer" and that "The doctor is still free to prescribe , without the obligation of motivation, the drug (between those months in the tender, ed.) considered suitable to guarantee the therapeutic continuity to the patients ".
- *Vaccines.* A fund is established for the purchase of vaccines included in the New Vaccine National Plan (NPNV). The Fund, again within the resources of the national health fund, is equal to 100 million euros for the year 2017, 127 million euros for the year 2018 and 186 million euros starting from the year 2019.

[vii] AIFA recognizes that certain OMPs benefit from the **2013 hospital pharmaceutical expenditure legislation**

1. Medicines qualified as OMPs in accordance with Regulation (EC) n. 141 of 2000 of the European Parliament and of the Council of 16/12/1999 (including orphan drugs, whose 10-year market exclusivity expired) and Article 8 of Regulation of 31/12/2013
2. Medicines, referring to paragraph 1, are included in the list only if they hold a MA in Italy. The following are thus excluded:
   a. orphan medicinal products not reimbursed by the NHS as referred to letter c) and c bis) of Article 8, paragraph 10, of Law n. 537 of 24/12/1993
   b. orphan drug packages reimbursed by the NHS, as referred to letter c) and c bis) of Article 8, paragraph 10, of Law n. 537 of 24/12/1993
   c. any OMP previously authorized and whose authorisation was then suspended or withdrawn as of 31/12/1993
   d. any medicinal product initially inserted in the Community Register of OMPs for human use and which have lost the request or following COMP (EMA) re-evaluation.
3. Any medicinal product which pursuant with to Article 15, paragraph 8, letter I - bis of Law Decree n. 95 of 2012 converted into Law 135 of 2012, then modified by Article 1 paragraph 228, of Law n. 147 of 27/12/2013, is included in the EMA Note EMEA/7381/ 01/en dated 30/03/2001 if not excluded according to the criteria described in paragraph 2, letters a) to d)
4. Any medicinal product holding a MA for the treatment of a rare disease or condition included in the Orphanet register (http://www.orpha.net/), although not included in the Community Register of OMPs pursuant to (EC) Regulation n. 141 of 2000 of the European Parliament and of the EU Council of 16/12/1999. These are rather excluded:
   a. any product authorised for the treatment of non-rare diseases or conditions
   b. products authorized for the treatment of rare diseases or conditions, for which MAHs had not submitted as on 31/12/2013 the requests to benefit from provisions of Article 15, paragraph 8, letter i) of Law Decree n. 95 of 2012, converted into Law n. 135 of 2012 and later amended by Article 1, paragraph 228, of Law n. 147 of 27/12/2013.

[viii] AIFA list of OMPs (last update December 31st 2018): https://www.aifa.gov.it/documents/20142/842593/Lista-farmaci-orfani-31.12.2018.pdf/2fb918f0-3432-8542-815e-6e743de78402

[ix] The procedure consists in a specific request from clinicians, scientific association or industry to AIFA to include the products into the 648/96 Law List (NHS reimbursement). The requirements are: lack of alternative therapies, patient informed consent, supporting scientific documents (Phase II study positive results), physician responsibility, and data monitoring [AIFA Registry + national Observatory data and regional departments].

[x] In Italy the medicinal products of the National Pharmaceutical Formulary reimbursed by the NHS are classified as class A (or as class H when they are paid by the NHS and dispensed in hospital or in a similar structure) (Article 8, paragraph 10, letter a, L. December 24, 1993, No. 537 and ss.mm.ii.). The medicinal products reimbursed by the NHS include essential medicines, intended for the treatment of chronic diseases, reimbursed for each authorized therapeutic indication, except for cases where there is an AIFA Note or Therapeutic Plan or Registry that limits the national reimbursement only to some of them, in order to ensure the appropriateness of the use of drugs, in some cases orienting therapeutic choices in favor of more effective and evaluated molecules.

[xi] Regarding the modalities: the company must support its documentation with:

- the demonstration of the therapeutic added value and clinical significance superiority
- The economic analysis impact on NHS and potential avoid costs
- The evaluation elements on therapeutic alternatives used in national clinical practice. In comparing the costs of therapeutic alternatives, it must be made explicit the posology schemes & treatment duration.
- Company self-certified information elements on the product about consumption and reimbursement in other MSs: conditions of price and reimbursement, included payment model (risk-sharing approach)
- The annual market shares expected to be acquired in the subsequent 36 months in the specific market segment
- Company self-certification with which the adequate and continuous supply of the drug to the NHS is guaranteed, according to the needs of the population.
- The forecast and the changes in expenditure for the NHS deriving from the proposed drug prices, in the different components.
- Self-certified quantification of any public contributions aimed at drug research and development programs
- The economic impact (NHS reimbursement) regarding early access: 648/96 Law and 326/2003 Law
- The economic impact on Cnn (C class Non-Negotiate)
- *If the drug has not demonstrated - through evidence of adequate quality - any significant clinical superiority with respect to the alternatives, or that it is effective and safe to the extent equal to other products already available, further elements of interest must also be provided, in terms of economic advantage for the SSN, as constituent elements of the negotiating agreement.*

Regarding the procedure:

- 180 days with only one clock-stop (max 90 days) in case of AIFA request on further docs in order to integrate the dossier. The company can request the PR suspension procedure only once.
- CTS opinion express the drug clinical value (I presumed place in therapy) & added therapeutic value + comparators' analysis including those in early access 648/96 e expired patent drugs
- CTS can limit the label indication for the reimbursement scope: in this case and if such limitations lead to a significant modification of the expected treatable population, compared to what is proposed in the PR dossier, the company transmits to AIFA the update of the doc (I presumed the pharmacoeconomic paragraph) based on the limitations introduced.
- If A12, the negotiation procedure is considered to be concluded negatively, after informing the company, in the event that the outcome of the evaluation shows a substantial overlapping of the drug with the comparator/s identified by the CTS and, the company does not reformulate a proposal that constitutes a lower therapy cost compared to that of the comparator/s.
- If no comparator, the company presents C/E evaluations (for the moment this is too generic: doesn't mean real CEA) motivating the price proposal based on the costs of research & development and production incurred.
- CPR will also take into account the prices applied to the NHS facilities and to the number of treatments expected, possibly updated to the initial PR dossier, following any CTS limitation (B3) related to the SSN reimbursement.
- If A8, simplified dossier will be a simplified one

Regarding the negotiated agreement**,** some of the more details:

1. The procedure take account on sales volumes, product availability for NHS, discounts for supplies to hospitals and public facilities and contribution of a public nature to drug RD programs.
2. Mandatory to monitor sales and turnover annually, as well as to report any discrepancies with respect to what was previously defined. Also, the possibility of proceeding with a price increase for exceptional cases of low-cost drugs, for

which there are objective difficulties in finding raw materials, or in this case the impossibility of remaining on the market under the conditions set for cost manufacturing increases (based on objective evidence).

3. Yes, on innovative payment-models to add to the existing agreements as P/V, payback, expense (or capping) ceiling. No mention on PBRSA or outcome-based and no mention on registry. No mention or correlation on recognition of innovativeness.

The **Contract** will be valid for 24 months.

[xii] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries

[xiii] https://eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/ and https://eunethta.eu/request-tool-and-its-vision-paper/