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ORIGINAL ARTICLE

Using GRADE methodology to assess innovation of new medicinal products in Italy

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Aim: In April 2017 the Italian Medicine Agency (AIFA) developed new criteria to grant any new medicinal product with an innovative designation. The aim of this study is to describe this new model and how it works.

Methods: A retrospective descriptive analysis was performed on the results of the assessment process of innovativeness of new medicinal products (or therapeutic indications) based on the AIFA's new innovation criteria (therapeutic need, added therapeutic value and quality of clinical evidence through GRADE methodology) carried out between April 2017 and February 2019 and made publicly available on the AIFA website starting from January 2018.

Results: A total of 37 full reports (22 for oncological indications) explaining the rationale for the AIFA's decision is made publicly available on the agency's website. A total of 12 therapeutic indications (5 oncological) were evaluated as *fully innovative*, 13 indications (11 oncological) were evaluated as *conditionally innovative*, while 12 indications (6 oncological) as *non-innovative*.

Conclusion: The new AIFA innovation criteria resulted in a much more flexible and transparent model to define and assess what constitutes a therapeutic innovation. In particular, the choice of AIFA to use the GRADE methodology to evaluate the quality of clinical evidence within a process of drug innovativeness assessment is essential for the early identification of the discrepancy between the need for patients of a rapid access to innovative therapies and the available clinical data needed to make decisions on drug innovativeness.

KEYWORDS

added therapeutic value, drug therapy, GRADE, innovativeness, therapeutic need

1 | INTRODUCTION

The concept of innovation has been, for a long time now, strategic in the field of pharmaceuticals. Part of the controversy over the state of drug innovation may arise from how innovation is defined. Although the term innovative implies some superior properties, there is still little consensus among different stakeholders (patients, decision- and policy-makers, regulatory authorities and pharmaceutical companies) as to what a true drug innovation represents. In recent years, regulatory authorities have been working hard on the concept of innovativeness and how to define and evaluate a new medicinal product as innovative, as they are pressured to ensure patient access to these new expensive therapies in a timely manner.

There is no single definition of innovation. Not every medicine is innovative or, when innovative, to the same degree.[1] It is necessary to define clearly what is an innovative drug and how to measure the

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degree of the innovativeness. For decades, a new compound class or a new chemical structure, i.e. new chemical entity with fewer adverse reactions or drug–drug interactions, or a new pharmacological approach, defined as such having a new target or novel mechanism of action, justified the claim that a drug represented an innovation. One or more other properties, such as improved pharmacokinetics or a new delivery of a drug or a novel use of an existing compound could potentially also be considered when classifying a medicinal product as innovative.[2] However, the innovative value of a drug is not simply an intrinsic property of a new compound, but also depends on the specific context in which the medication is introduced and the availability of other drugs to treat the same clinical condition, thus today a new drug must exhibit a clinically relevant therapeutic advantage over the existing therapies in order to be considered innovative.[3]

In this context, it is important to develop new approaches able to define the value of innovation comparing health benefits and quality of evidence between different drugs. This clearly represents a great challenge for all regulators (or payers), which have to find a transparent and user-friendly tool to help answer how and if a new drug offers an additional therapeutic benefit compared to what is already on the market in order to define it as really innovative.[4]

The accelerated pathways for drug approval, which have the goal of getting potentially innovative therapies to patients earlier, commit the regulatory agencies to first approve a novel drug on the basis of limited clinical evidence, with the condition for the drug manufacturer to conduct postapproval trials to confirm the drug's efficacy for the original approved indication. Moreover, national regulatory agencies must evaluate the innovativeness level of a drug and whether to pay for it on the basis of uncertain evidence on clinical benefits. These decisions are becoming increasingly complex in light of the rising prices of new drugs. Thus, accelerated approval can lead to situations in which payers are forced to cover the drugs not yet shown to have clinical benefits and to pay high prices for an unproven therapy.[5,6]

During the past few years, several algorithms have been developed by different regulatory agencies in order to assess the level of innovativeness of a new medicine. Unfortunately, most of these attempts has been often criticized for lack of structure, unclear methods of assessment, and dubious transparency.

In Italy, the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA), which has both regulatory and reimbursement functions, has the assignment to define and evaluate the drug innovativeness, which was taken into consideration when deciding on reimbursement and price of a new medicine; the process of assessment and designation is conducted by a Scientific and Technical Committee (*Commissione Tecnico-Scientifica*, CTS) and is largely based on clinical evidence available at the moment of the marketing authorization of the medicinal product.

In 2007 AIFA adopted for the first time an algorithm[7] developed to rank the therapeutic innovation of a new medicine by awarding an innovation score. As this model was very limited and the criteria outdated, other attempts have been made by AIFA in recent years to update the algorithm. Nevertheless, recurrent criticisms characterized the innovation algorithm developed by AIFA, since it was too rigid and hard to apply consistently and in a transparent manner. Ultimately, it became evident that the algorithm was not the most suitable tool for assessing therapeutic innovativeness of a new medicinal product.

This situation led AIFA to look for a solution to overcome the limits of the algorithm model and switch to a new structured system of assessment based on a decision-making process. In April 2017, after several years of discussion and debate, AIFA developed a new system of assessment of drug's innovativeness, which was more user-friendly and clearer than the previous ones.[8] This model resulted in a much more flexible tool to define and assess what constitutes a drug innovation. Our aim is to describe this new model and how it works.

What is already known about this subject

- Several innovative therapies have been introduced on the European market for the treatment of diseases with unmet medical needs and many others are close to marketing.
- Currently, the assessment of innovativeness of a new medicinal product and the transparent disclosure of the information on decision-making process are challenges for many agencies and organizations worldwide, while it is well recognized that all decision-making processes should be explicitly explained to inform healthcare professionals, patients and the public in general.
- In April 2017 the Italian Medicines Agency (AIFA) established new criteria to define innovative medicines, leading to a multidimensional approach, which takes into account 3 variables: the therapeutic need, the added therapeutic value, and the quality of clinical evidence, assessed through the GRADE methodology.

What this study adds

- Starting from January 2018, a full report explaining the rationale for the AIFA's decision on drug innovativeness is made publicly available on the agency's website. So far 37 final reports have been already published, 22 of which regarded oncological indications.
- Following an assessment, a medicinal product can be designated for a specific therapeutic indication as *fully innovative*, *conditionally innovative* or *non-innovative*.
- The choice of AIFA to use the GRADE methodology to evaluate the quality of clinical evidence within a process of drug innovativeness assessment achieves two goals: (i) improvement of the transparency and reproducibility of the decision-making process; (ii) early identification of the discrepancy between the need of rapid access to innovative therapies and the quality of clinical evidence available at the moment of the decision-making.

TABLE 1 The new Italian Medicines Agency criteria for assessing a drug's degree of innovation

Dimensions	Level				
Therapeutic need	**Maximum** No alternative therapeutic options available	**Important** Alternative therapeutic options available, with no impact on clinically relevant outcomes	**Moderate** Alternative therapeutic options available with limited impact on clinically relevant outcomes, and/or uncertain or not satisfactory safety profile	**Poor** Alternative therapeutic options available with high impact on clinically relevant outcomes and a satisfactory safety profile	**Absent** Alternative therapeutic options available, which are able to slow down the progression of the disease and have satisfactory safety profile
Added therapeutic value	**Maximum** Greater efficacy than alternative therapeutic options (if available) in clinically relevant outcomes, ideally curing the disease or altering its natural history	**Important** Greater efficacy based on clinically relevant outcomes, or alternatively one of the following options: (i) the drug can reduce the risk of seriously debilitating or life-threatening complications; (ii) the drug has better risk/benefit ratio compared to the alternative therapeutic options; (iii) the drug can avoid the use of high-risk clinical procedures; (iv) the drug can significantly change the natural history of the disease in a subpopulation of patients; (v) the drug can provide a clinically relevant added value, e.g. in terms of quality of life and disease-free interval compared to the available therapeutic options	**Moderate** A slightly better efficacy profile or improved efficacy in some patient sub-populations or based on surrogate endpoints and has limited impact on the quality of life. For situations when the lack of a study comparator is acceptable, evidence showing relative efficacy compared to the available therapeutic options should be taken into account	**Poor** Greater efficacy only for nonclinically relevant outcomes or based on a poor magnitude of effect. The drug offers minor benefits (e.g. favourable routes of administration) compared to the available therapeutic options	**Absent** No added therapeutic benefit compared to the alternative available therapeutic options
Quality of clinical evidence*	**High** We are very confident that the true effect lies close to that of the estimate of the effect		**Moderate** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	**Low** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	**Very low** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

(Continues)

TABLE 1 (Continued)

Dimensions	Level		
Innovativeness status	Fully innovative	Conditionally innovative	Non-innovative
Commercial implication	• Funded via *innovative drug fund* • No payback mechanism • Immediate inclusion into regional drug formularies • Benefit duration up to 36 months	Immediate inclusion into regional drug formularies	No benefits

*An orphan drug can still be considered innovative, even if the quality of clinical evidence is low or very low, when the other 2 criteria are evaluated as maximum or important.

2 | METHODS

A retrospective descriptive analysis was performed on the results of the assessment process of innovativeness of new medicinal products (or therapeutic indications) based on AIFA's new innovation criteria carried out between April 2017 and February 2019 and made publicly available on the AIFA's website starting from January 2018.

2.1 | AIFA's new innovation criteria

The new model used for the assessment of drug innovativeness is based on a multi-dimensional approach. The innovativeness is judged on the grounds of 3 criteria: therapeutic need, added therapeutic value and quality of the evidence from the clinical trials (Table 1).

The assessment takes place on the request of pharmaceutical company through a form at the time of the price and reimbursement decision-making process for a new medicine or therapeutic indication. It is conducted by the AIFA's CTS and is largely based on the same clinical evidence provided for request of the market authorization.

The overall assessment process resulted in a new medicinal product being awarded with one of the following three innovative status by a specific therapeutic indication: *fully innovative*, *conditionally innovative* or *non-innovative*.

2.2 | Therapeutic need

This evaluation is based on the availability of alternative therapies and the patient's need for a new therapy. The *therapeutic need* indicates how much the introduction of the new drug is needed in order to respond to unsatisfied therapeutic needs. It is classified in five levels as follows:

- **Maximum**: no alternative therapeutic options for the specific indication exist.
- **Important**: alternative therapeutic options for the specific indication are available, with no impact on clinically relevant outcomes for the disease of interest.
- **Moderate**: alternative therapeutic options for the specific indication are available with a limited impact on clinically relevant outcomes, and/or the safety profile of these options is uncertain or not satisfactory.
- **Poor**: alternative therapeutic options for the specific indication are available with a high impact on clinically relevant outcomes and whose safety profile is satisfactory.
- **Absent**: alternative therapeutic options for the specific indication are available, which are able to slow down the progression of the disease and have satisfactory safety profile.

The manufacturer proposes a level of therapeutic need to AIFA describing the rationale for its choice.

TABLE 2 Innovativeness status of medicinal products in Italy

Medicinal product	Pharmacotherapeutic group	Therapeutic indication	Orphan	Status
Alecensa® (*alectinib*) Roche	Antineoplastic agents	As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase-positive advanced nonsmall cell lung cancer (NSCLC) previously treated with crizotinib.	No	Conditionally innovative
		As monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase-positive advanced NSCLC	No	Fully innovative
Bavencio® *(avelumab)* Merck Serono	Antineoplastic agents	As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma.	Yes	Conditionally innovative
Besponsa® (*inotuzumab ozogamicin*) Pfizer	Antineoplastic agents	As monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia. Adult patients with Philadelphia chromosome positive relapsed or refractory B cell precursor acute lymphoblastic leukaemia should have failed treatment with at least 1 tyrosine kinase inhibitor.	Yes	Conditionally innovative
Darzalex® (*daratumumab*) Janssen Cilag	Antineoplastic agents (monoclonal antibodies)	As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who demonstrated disease progression on the last therapy.	Yes	Non-innovative
		In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	Yes	Fully innovative
Dupixent® (*dupilumab*) Sanofi-Aventis	Immunosupressants	Treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy. (*The assessment of innovativeness refers to the following reimbursed indication only: adult patients with severe atopic dermatitis who are eligible for treatment with systemic therapy, for whom treatment with cyclosporin is contraindicated, ineffective or not tolerated.*)	No	Fully innovative

(Continues)

TABLE 2 (Continued)

Medicinal product	Pharmacotherapeutic group	Therapeutic indication	Orphan	Status
Hemlibra® (*emicizumab*) Roche	Antihemorrhagics	Routine prophylaxis of bleeding episodes in patients (all age groups) with haemophilia A with factor VIII inhibitors.	No	Fully innovative
Humira® (*adalimumab*) Abbvie	Immunosupressants	Treatment of paediatric chronic non-infectious anterior uveitis in patients aged >2 years who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.	No	Conditionally innovative
Ibrance® (*palbociclib*) Pfizer	Antineoplastic agents	Treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer: in combination with fulvestrant in women who have received prior endocrine therapy.	No	Non-innovative
		Treatment of HR positive, HER2 negative locally advanced or metastatic breast cancer: in combination with an aromatase inhibitor.	No	Conditionally innovative (follower)
Ilaris® (*canakinumab*) Novartis	Interleukin inhibitors	Periodic fever syndromes in adults, adolescents and children aged 2 years and older: -Tumour necrosis factor receptor associated periodic syndrome (TRAPS) -Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) -Familial Mediterranean fever (FMF), in combination with colchicine, if appropriate (*for this indication the assessment of innovativeness refers to the following reimbursed indication only: patients with FMF for whom treatment with colchicine is ineffective or not tolerated*).	No	Conditionally innovative
Imbruvica® (*ibrutinib*) Janssen-Cilag	Antineoplastic agents (protein kinase inhibitors)	As a single agent for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia.	Yes	Conditionally innovative
Kisquali® (*ribociclib*) Novartis	Antineoplastic agents	Treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy.	No	Conditionally innovative

(Continues)

TABLE 2 (Continued)

Medicinal product	Pharmacotherapeutic group	Therapeutic indication	Orphan	Status
Maviret® (*glecaprevir/pibrentasvir*) Abbvie	Antivirals for systemic use	Treatment of chronic hepatitis C virus infection in adults	No	Fully innovative
Ocaliva® (*obeticholic acid*) Intercept Pharma	Bile and liver therapy	Treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.	Yes	Non-innovative
Ocrevus® (*ocrelizumab*) Roche	Immunosupressants	Treatment of adult patients with early primary progressive multiple sclerosis in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	No	Non-innovative
Olumiant® (*baricitinib*) Eli Lilly	Immunosupressants	Treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs. Olumiant may be used as monotherapy or in combination with methotrexate.	No	Non-innovative
Opdivo® (*nivolumab*) Bristol Myers Squibb	Antineoplastic agents	As monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.	No	Conditionally innovative
		As monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.	No	Conditionally innovative
		As monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.	No	Non-innovative
Oxervate® (*cenegermin*) Dompè Farmaceutici	Ophthalmologicals	Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults.	Yes	Fully innovative
Prevymis® (*letermovir*) Merck Sharp Dohme	Antivirals for systemic use	Prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult cytomegalovirus-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).	Yes	Fully innovative

(Continues)

TABLE 2 (Continued)

Medicinal product	Pharmacotherapeutic group	Therapeutic indication	Orphan	Status
Qarziba® (*dinutuximab beta*) Eusa Pharma	Antineoplastic agents	Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myelo ablative therapy and stem cell transplantation.	Yes	Fully innovative
		In patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilized by other suitable measures.	Yes	Non-innovative
Revlimid® (*lenalidomide*) Celgene	Immunosupressants	As monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.	Yes	Conditionally innovative
Rydapt® (*midostaurin*) Novartis	Antineoplastic agents	In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia who are FLT3 mutation-positive. (*The assessment of innovativeness refers to the following reimbursed indication only: in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy for adult patients with newly diagnosed acute myeloid leukaemia acute myeloid leukaemia who are FLT3 mutation-positive*)	Yes	Fully innovative
		As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis (ASM) with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).	Yes	Non-innovative
Spinraza® (*nusinersen*) Biogen Idec Ltd	Other nervous system drugs	Treatment of 5q spinal muscular atrophy.	Yes	Fully innovative
Stivarga (*regorafenib*) Bayer	Antineoplastic agents	As monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.	No	Conditionally innovative

(Continues)

TABLE 2 (Continued)

Medicinal product	Pharmacotherapeutic group	Therapeutic indication	Orphan	Status
Tecentriq® (*atezolizumab*) Roche	Antineoplastic agents	As monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy.	No	Fully innovative (follower)
Vosevi® (*sofosbuvir/velpatasvir/voxilaprevir*) Gilead	Antivirals for systemic use	Treatment of chronic hepatitis C virus infection in adults	No	Fully innovative
Xermelo® (*telotristat etiprate*) Ipsen	Other alimentary tract and metabolism products	Treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue therapy in adults inadequately controlled by somatostatin analogue therapy	Yes	Non-innovative
Zalmoxis® (*allogeneic T cells genetically modified*) Molmed	Antineoplastic agents	As adjunctive treatment in haploidentical haemato poietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.	Yes	Non-innovative
Zavicefta® (*ceftazidime/avibactam*) Pfizer	Antibacterials for systemic use	Treatment of the following infections in adults: - Complicated intra-abdominal infection (cIAI) -Complicated urinary tract infection (cUTI), including pyelonephritis -Hospital-acquired pneumonia, including ventilator-associated pneumonia (VAP) -Treatment of infections due to aerobic gram-negative organisms in adult patients with limited treatment options.	No	Non-innovative
Zejula® (*niraparib*) Tesaro	Antineoplastic agents	As monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	Yes	Conditionally innovative
Zinplava® (*bezlotoxumab*) Merck Sharp & Dohme	Immune sera and immunoglobulins	Prevention of recurrence of *Clostridium difficile* infection in adults at high risk for recurrence of *C. difficile* infection.	No	Non-innovative

2.3 | Added therapeutic value

The Added therapeutic value is defined on the basis of the magnitude of clinical benefit provided by the new medicine compared to the available therapeutic alternatives, if any exist. The outcomes must be clinically relevant and validated for the therapeutic indication. Demonstrating added therapeutic benefit compared to other available therapies is particularly important in the treatment of diseases that are: potentially fatal, cause repeated hospitalizations, cause disability or significantly impair quality of life. Similar to therapeutic need, added therapeutic benefit is measured on a scale as follows:

- **Maximum**: the drug has demonstrated greater efficacy than alternative therapeutic options (if available) in clinically relevant outcomes, ideally curing the disease or altering its natural history.
- **Important**: the drug has demonstrated greater efficacy than alternative therapeutic options (if available) in clinically relevant outcomes, or alternatively one of the following options: (i) the drug can reduce the risk of seriously debilitating or life-threatening complications; (ii) the drug has better risk/benefit ratio compared to the alternative therapeutic options; (iii) the drug can avoid the use of high risk clinical procedures; (iv) the drug can significantly change the natural history of the disease in a subpopulation of patients; (v) the drug can provide a clinically relevant added value e.g. in terms of quality of life and disease free interval, compared to the available alternative therapeutic options.
- **Moderate**: the drug has demonstrated either to have a slightly better efficacy profile or improved efficacy in some patient subpopulations or based on surrogate endpoints and has limited impact on the quality of life, compared to the available alternative therapeutic options. For situations when the lack of a study comparator is acceptable, evidence showing relative efficacy compared to the available alternative therapeutic options should be taken into account.
- **Poor**: the drug has demonstrated greater efficacy only for nonclinically relevant outcomes or based on a poor magnitude of effect. The drug offers minor benefits (e.g. favourable routes of administration) compared to the available alternative therapeutic options.
- **Absent**: the drug has demonstrated no added therapeutic benefit compared to the available alternative therapeutic options.

The manufacturer is again asked to propose a level and justify it.

2.4 | Quality of clinical evidence

This dimension is based on the evaluation of the robustness of the clinical evidence submitted by manufacturer to support the request for drug innovation. For this purpose, AIFA decided to adopt the approach of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system,[9,10] a methodology already used by many international organizations to provide support in grading the quality (or certainty) of evidence for systematic reviews (i.e. Cochrane Collaboration) and the strength of recommendations for guidelines development.

According to the GRADE methodology, the quality of evidence ranges from a high level (assigned to randomized controlled studies) to a low or a very low level (assigned to observational studies); it is possible to downgrade (usually for randomized controlled studies) or upgrade (usually for observational studies) the level within the range on the evaluation of the followingfive dimensions: risk of bias, inconsistency, indirectness, imprecision, other considerations (i.e. publication bias).

For orphan drugs, the quality of clinical evidence will play less of a role, given the difficulty of conducting clinical trials for rare diseases. In cases where an orphan drug meets the othertwo criteria as maximum or important, a drug can still be considered innovative, even if the quality of clinical evidence is low or very low.

The manufacturer is again asked to propose a level and justify it.

3 | RESULTS

3.1 | Status and level of innovativeness of the evaluated medicinal products

Between April 2017 and February 2019, 84 requests for innovativeness assessment of a specific therapeutic drug indication were submitted to AIFA by pharmaceutical companies; to date 67 (80%) assessments based on new AIFA's innovation criteria were concluded. Out of these medicinal products, 43 (64%) were oncological drugs and 24 (36%) were non-oncological ones.

At the end of each assessment process, AIFA's CTS discloses its own assessment on therapeutic need, added therapeutic value and quality of clinical evidence and the final judgment (*fully innovative*, *conditionally innovative* or *non-innovative*) with the manufacturer through an official form. The manufacturer can comment on the received judgement, enhancing the level of dialogue between the manufacturer and AIFA on the assessment.

At the end of the decision-making process for the definition of price and reimbursement of a new medicine or therapeutic indication, AIFA makes the documentation of the assessment process publicly available. Every month the documents reporting the final innovative status of the medicinal product for the specific indication, with the description of the reasoning behind the assessment of each dimension are published on AIFA's website.[11]

Starting from January 2018, a total of 37 (55%) of the 67 final reports were published (Table 2), 22 of which regarded oncological indications. The final judgments on innovative status were:

- *fully innovative* for 12 indications, of which 5 are oncological (1 follower);
- *conditionally innovative* for 13 indications, of which 11 are oncological (1 follower);
- *non-innovative* for 12 indications, of which 6 are oncological.

In 2 cases the assessment within the same oncological indication was *fully innovative* for a specific sub-population and non-innovative for the other one.

For the remaining 30 indications, the price and reimbursement negotiation were still ongoing.

The status of *fully innovative* is granted for up to 36 months. In the case of a first *conditionally innovative* designation, the status can be reviewed and turned into a *fully innovative* status by AIFA after 18 months, if additional clinical evidence is provided by the manufacturer and if the new data are capable of changing the first judgment.

While the benefits will last 36 months for each *first-in-class* innovative drug, any subsequently launched innovative medicine with the same therapeutic indication (or patient population and mechanism of action), called as a *follower*, will benefit for the time remaining from the initial first-in-class drug assessment. In other words, the second-in-class therapy with an innovative status cannot extend the period of benefits up to 36 months—it can only benefit of the remaining period of the first-in-class drug. Moreover, a drug registry is mandatory for all *fully innovative* medicinal products.

For products designated with a *non-innovative* status, the manufacturer can re-submit its application and request a new assessment by the CTS if and when new evidence becomes available.

3.2 | Benefits and access to the innovative drug fund

In Italy, the manufacturer of an innovative drug has many clear benefits, ranging from a rapid inclusion in regional formularies (with no additional re-assessment at the local level) to access to a special *innovative drug fund*, to boost the availability of the innovative medicines within the Italian market and to ensure a rapid patient access to these therapies. In particular, the therapies designated as *fully innovative* receive a series of special benefits for up a period of 36 months, including access to a special innovative drug fund, immediate inclusion in regional formularies and exemption from pay-back mechanism. The latter consists of an exemption for manufacturers from the system of expenditure ceilings, which enables the Italian National Health Service to curb overspending and reduce budget overruns. Indeed, the manufacturer of an innovative product is exonerated from pay back to AIFA for the therapy costs if national ceilings on expenditure on drugs in community pharmacies (community budget) and hospital settings (hospital budget) are not respected.

The therapies earning a *conditionally innovative* designation can only benefit from immediate regional formulary inclusion, while therapies designated as *non-innovative* will not receive any of the above mentioned benefits.

The innovative drug fund was established by Italian Ministry of Health in parallel with the implementation of the new criteria of drug innovativeness; it was a 1 billion Euros per year fund (€500 million allocated to oncology therapies, €500 million to other indications) that should be used *ad hoc* for the payments of highly innovative medicines.[12]

Furthermore, immediate access to regional formularies translates into a less complicated approach with the regional health authorities, as it forces prompt access to innovative medicines at the subnational level, with no or only minor delays for the patients and diminished access inequalities throughout the pharmaceutical market.

Theoretically, the new assessment method of drug innovativeness and the related benefits should allow a faster market access for all those medicines that demonstrate a clear therapeutic innovation compared to the available alternatives.

4 | DISCUSSION

The new AIFA approach on decision-making process for the assessment of drug innovativeness is based on an overall assessment across three criteria (therapeutic need, added therapeutic value, quality of clinical evidence), which should be informed by the best available evidence, according to which the panel must reach a conclusion about the decision (for or against the drug innovativeness). For each medicinal product, the overall assessment process was intended to give a clear framework when assessing the drug innovativeness, in which each member of the AIFA's CTS makes their own subjective and independent evaluation with respect to each criterion; after that, a discussion is made between all the members to arrive to an agreement on the level to be assigned to each criterion. The final judgment on drug innovation in relation to an individual therapeutic indication will be formulated based on the combination profile deriving from the set of evaluation levels for each criterion. Drugs may be considered *fully innovative* whether both the therapeutic need and the added therapeutic value have been recognized as maximum or important, and the quality of the clinical evidence as high. By contrast, a drug cannot be recognized as innovative if the therapeutic need and/or the added therapeutic value has been judged as *poor* or *absent*, or if the quality of clinical evidence has been judged to be low or very low (with the exception of the orphan drugs, which can achieve the *fully innovative* status even with low or very low quality of clinical evidence). Intermediate situations are evaluated case by case, taking into account the relative weight of the individual elements considered for each criterion and reaching an agreement between all the members of the panel.

Although the certainty of the evidence for some relevant criteria, including the clinical effects of the alternative options being considered (quality of clinical evidence or confidence in effect estimates) is often low or very low, the decision is taken. In any case, the panel provides a justification for their final decision. In this way the AIFA's approach is quite similar to those of the Evidence to Decision (EtD) frameworks, developed by the GRADE Working Group to support the process of moving from evidence to decisions, which help to ensure that all important criteria for making a decision are considered and that the best available evidence informs the decisions. In particular, the GRADE EtD frameworks help to use evidence in a systematic way to inform the decisions in different contexts, such as clinical recommendations, coverage decisions, and health system or public health recommendations and decisions, while making the process transparent and accessible to those whom they will affect.[13,14]

Although the GRADE EtD frameworks are more structured and detailed than the AIFA's model for the assessment of drug

innovativeness, it is true that the strength of the frameworks is their flexibility in terms of the relative importance attached to the included criteria, since this depends on the nature of the decision being made.[15]

As with the EtD frameworks, the AIFA's model is flexible and structured at same time and can help to facilitate panel discussions, make discussions more efficient and clarify the evidence used to inform discussions. The AIFA's approach helps to ensure that the panel members consider all the important factors for making a decision, providing a concise summary of the best available evidence about each criterion to inform their judgements, helping them to structure and document discussion, and identify reasons for disagreements. As the EtD frameworks strengthens the credibility of decisions by documenting the evidence-based decision-making process,[16,17] in the AIFA's approach, decisions flow from judgments about relevant criteria in a structured and transparent manner, while making the users aware of the rationale (justification) for their decisions.

It is well-known that decision-making process often lacks consistency and transparency. A systematic, rigorous and transparent process to identify, appraise and apply the best available evidence, particularly if the process incorporates explicit decision-making criteria, could address the most common limitations of the decision-making process in healthcare.

Several tools have been developed by other European countries to assess the innovation level provided by a new medicinal product, but none of them can be considered similar to AIFA's system, especially for the use of the GRADE methodology, an internationally well-recognized standard for the evaluation of the quality of clinical evidence. Further efforts on harmonizing the decision-making process on drug innovativeness across European countries are needed. In this context, the GRADE EtD frameworks can play a relevant role in sharing a common methodology for the assessment of drug innovativeness, thus helping the decision-makers to enhance research that effectively target the real therapeutic needs and possibly ensuring equity and timely access of patients to innovative medicines throughout Europe.

To our knowledge, AIFA is also the first regulatory agency that publishes both positive and negative outcomes of the assessment process of innovativeness of a new medicinal product. Despite the fact that AIFA does not make any documents related to its decision-making process publicly available, starting from January 2018, a full report explaining the rationale for the Agency CTS's decision on drug innovativeness is published on the AIFA's website.

Currently, the transparent disclosure of information is a challenge for many agencies and organizations in other foreign countries, while it is well recognized that all decision-making processes should be explicitly explained as to inform healthcare professionals, patients and the public in general.[18]

5 | CONCLUSION

The application of the GRADE methodology in evaluating the quality of clinical evidence goes in the direction of improving the transparency and reproducibility of the decision-making process on drug innovativeness; this methodological tool, which is well structured and flexible at same time, provides a systematic approach in the assessment in order to minimize biases and improve consistency of the decisions. As far as the decisions on drug innovativeness can be arbitrary, the GRADE EtD framework makes the decision-making process more documentable and reproducible.

Furthermore, the assessment of innovativeness of a new medicinal product in unsatisfied therapeutic areas at the time of national negotiation for pricing and reimbursement means that on the one hand the added therapeutic value of a new medicinal product should be evaluated in a short time to guarantee the rapid access to innovative therapies, but on the other one, few clinical data were available at the time of the decision-making process. As several innovative therapies were introduced on the European market for the treatment of diseases with unmet medical needs and many others are close to marketing, the choice of AIFA to use the GRADE methodology to evaluate the quality of clinical evidence within a process of drug innovativeness assessment is essential for the early identification of the discrepancy between the need of patients for rapid access to innovative therapies and the available clinical evidence on the basis of which regulatory agencies have to make decisions.

COMPETING INTERESTS

There are no competing interests to declare.

AUTHORS CONTRIBUTIONS

FF carried out the analysis and drafted the manuscript; GT participated in the design of the study and revisedthe manuscript. FT and AA provided methodological advice. All authors read, revised and approved the finalmanuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in *Report di valutazione dell'innovatività per indicazione terapeutica* at https://www.aifa.gov.it/farmaci-innovativi, reference number.[11]

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