Access to innovative drugs in Italy

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	☐	☐	☐	X optional (sub-investigator)
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Patrizia Marconi, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (Resolution n. 37 dated 13/10/2020).

N.B. I am not receiving any compensation

AIFA's definition of innovativeness

- The assessment of the innovativeness of a new medicine and the transparent disclosure of the information on the decision-making process are a challenge for many regulatory agencies and health organizations worldwide.
- In 2017, after more then 5 years of discussion with all relevant stakeholders, new criteria to define the innovativeness of a medicine were approved by AIFA.
- The new decision process used to define the innovativeness of a drug takes into account three criteria:
  - therapeutic need
  - added therapeutic value
  - quality of clinical evidence, which is assessed based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology.
- The assessment process is performed by a Committee of AIFA, which adopts the final provision when deciding on reimbursement and pricing of a new medicine (or new therapeutic indication).
- For each assessment, a full report explaining the rationale for the final decision is made publicly available on the Agency's website

1. Therapeutic need

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 a satisfactory safety profile

2. Added clinical value

ADDED CLINICAL 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: the drug i) can reduce the risk of seriously debilitating or life-threatening complications, ii) better risk/benefit ratio compared to the alternative therapeutic options, iii) can avoid the use of high risk clinical procedures, iv) can significantly change the natural history of the disease in a subpopulation of patients, v) can provide a clinically relevant added value e.g., in terms of quality of life and disease-free interval
Moderate	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. 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	A greater efficacy only for non-clinically relevant outcomes or based on a poor magnitude of effect. The drug offers minor benefits (e.g., favorable routes of administration) compared to the available therapeutic options.
Absent	No added therapeutic benefit compared to the alternative available therapeutic options

3. Quality of evidence

QUALITY OF 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

GRADE

https://gdt.gradepro.org/app/handbook/handbook.html#:~:text=The%20GRADE%20evidence%20profile%20contains,each%20of%20the%20included%20outcomes.

Outcome and benefits associated with the innovative status

THERAPEUTIC NEED	ADDED CLINICAL VALUE	QUALITY OF EVIDENCE
Maximum	**Maximum**	**High**
Important	**Important**	**Moderate**
Moderate	**Moderate**	**Low**
Poor	**Poor**	**Very low**
Absent	**Absent**	

- The overall assessment process results in a new medicinal product being awarded one of the following three innovativeness statuses by a specific therapeutic indication: "fully innovative," "conditionally innovative," or "not innovative."
- Those therapies earning an '**INNOVATIVENESS'** status benefit from gaining access to a special innovative drugs fund, immediate inclusion in regional formularies, as well as becoming exempt from pay-back requirements common in Italy.
- Meanwhile, those therapies given a '**CONDITIONALLY INNOVATIVE**' designation only benefit from immediate regional formulary inclusion.
- Finally, therapies evaluated as '**NOT INNOVATIVE**' will not benefit from any of the above-mentioned allowances.

THERAPEUTIC NEED	ADDED CLINICAL VALUE	QUALITY OF EVIDENCE
Maximum	Maximum	High
Important	Important	Moderate
Moderate	Moderate	Low
Poor	Poor	Very low
Absent	Absent	

Innovative status **Fully Innovative**

Benefits

- Access to special funds: “innovative drug fund”
- Exemption from “payback” mechanism
- Immediate inclusion into regional drug formularies
- Benefit duration period up to 36 months

THERAPEUTIC NEED	ADDED CLINICAL VALUE	QUALITY OF EVIDENCE
Maximum	Maximum	High
Important	Important	Moderate
Moderate	Moderate	Low *
Poor	Poor	Very low *
Absent	Absent	

Innovative status **Absent (Not Innovative)**

Benefits
- No benefit

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

THERAPEUTIC NEED	ADDED CLINICAL VALUE	QUALITY OF EVIDENCE
Maximum	**Maximum**	**High**
Important	**Important**	**Moderate**
Moderate	**Moderate**	**Low**
Poor	**Poor**	**Very low**
Absent	**Absent**	

Case-by-case evaluation. In some cases, depending on therapeutic need and added clinical value, it may be a conditional innovativeness

Innovative status	**Conditionally Innovative**
Benefits	• Immediate inclusion into regional drug formularies

Is the AIFA model consistent?

frontiers in Medicine

ORIGINAL RESEARCH
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The Assessment of the Innovativeness of a New Medicine in Italy

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OPEN ACCESS

Methods: A retrospective analysis was performed on the final reports evaluating the drug innovativeness assessment published on the AIFA's website between April 2017 and January 2021. Profiles of the decision process and their relationship with innovativeness response were described. To evaluate the weight of each criterion in predicting the innovativeness status, a Classification Tree (CT) algorithm was applied.

Results: Overall, of the 109 published drugs reports, 37 (33.9%) were recognized as fully innovative, 29 (26.6%) were considered conditionally innovative, while for 43 (39.4%) reports innovativeness was not recognized.

Fortinguerra F et al. Frontiers in Med 2021

Is the AIFA model consistent?

TABLE 1 | Characteristics of drugs criteria considering the drug's degree of innovation.

	Fully innovative		Conditionally innovative		Non-innovative†		*p*-value*
	n = 37		*n* = 29		*n* = 43		
Oncological drug	24	64.9	20	69.0	23	53.5	0.363
Orphan drug	16	43.2	11	37.9	14	32.6	0.616
Oncological and orphan drug	10	27.0	6	20.7	8	18.6	0.645
Non-oncological and non-orphan drug	7	18.9	4	13.8	14	32.6	0.155
Therapeutic need							
Maximum	5	13.5	4	13.8	4	9.3	0.081
Important	17	45.9	7	24.1	12	27.9	
Moderate	15	40.5	18	62.1	22	51.2	
Poor	0	0.0	0	0.0	5	11.6	
Absent	0	0.0	0	0.0	0	0.0	
Added therapeutic value							
Maximum	1	2.7	0	0.0	0	0.0	<0.001
Important	31	83.8	0	0.0	1	2.6	
Moderate	5	13.5	29	100.0	5	13.2	
Poor	0	0.0	0	0.0	29	76.3	
Absent	0	0.0	0	0.0	3	7.9	
Quality of clinical evidence							
High	10	27.0	3	10.3	5	11.6	0.451
Moderate	19	51.4	18	62.1	24	55.8	
Low	7	18.9	6	20.7	9	20.9	
Very low	1	2.7	2	6.9	5	11.6	

*Data were summarized as numbers (n) and frequencies (%). *Chi-square test, when the conditions were respected, or Fisher's exact test was applied to evaluate the association between categorical variables. †For five observations the added therapeutic value was "Untestable" and therefore classified as NA.*

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Is the AIFA model consistent?

Predicted class \ Observed class	Fully Innovative	Conditionally Innovative	Non Innovative
Fully Innovative	32	0	1
Conditionally Innovative	5	29	5
Non Innovative	0	0	32

Correct Classification Rate=89.4%

The added therapeutic value was the most important variable in predicting the innovativeness status according to the classification tree (CT) model applied, achieving an accuracy of 89.4%.

Overall, similar decision profiles bring the same evaluation of innovativeness status, indicating a good consistency and reproducibility between decisions

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Conclusions

- AIFA's structured decision model ensures that the Committee considers all the important factors for making a decision, enabling discussions on available evidence.

- The systematic, rigorous, and transparent assessment process, incorporating explicit decision-making criteria, as in the AIFA's model, aims to address the most common limitations of the decision-making process in healthcare, such as lack of consistency and transparency.

- Seven years after this new process entered into force, literature shows a strong correlation between added therapeutic value as a criterion and innovative outcome granted, demonstrating the emphasis on clinical value and consistency and standardization of the revised AIFA framework.

- For seeking reimbursement in Italy for new therapeutic products, marketing authorisation holders had to switch their focus from the traditional budget impact evaluations / economic considerations to clinical evidence approach.