

PRO70: Italian Law 326/2003 application in the last 6 years: approvals, rejections and economic impact of this early access scheme

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Introduction

In Italy, access to treatment for patients suffering from a rare disease is guaranteed through various legislative instruments. The centralized procedure represents the standard access route; whenever an orphan drug has no marketing authorization, patient access is ensured through different early access schemes. One of these early access tools is the Law 326/2003, Article 48 (also known as 5% AIFA Fund).

The Law 326/2003, Article 48, requires all pharmaceutical companies operating in Italy to pay 5% of their promotional expenses to an independent research fund (in Italian “Fondo AIFA 5%”). The 50% of this fund is dedicated to the purchase of orphan drugs for the treatment of rare diseases and of medicinal products representing a chance for the treatment of serious conditions, which are not commercialized yet. The remaining 50% is used to carry out scientific researches (independent research) on the use of pharmaceutical products (i.e. comparative trials on medicines aimed at demonstrating their additional therapeutic value, or studies aimed at demonstrating the appropriateness of use of medicines, or focusing on scientific information). This fund is fed by the 5% of pharmaceutical companies’ annual expenditure coming from promotional activities intended for physicians (seminars, workshops, etc.) (Article 48, paragraph 19a, Decree-Law no. 269 of September 30, 2003, converted into Law. no. 326 of November 24, 2003).

The request for access to Fondo AIFA 5% is patient-specific and is submitted to the Italian Medicines Agency (AIFA) by a Reference Centre. The following documents are required in order to access the fund: a formal request, supported by scientific literature (if any) and a brief clinical report, including a description of the therapeutic plan for each patient. The application shall be supported by specific information, such as: dose per treatment cycles, number of cycles and the price of the medicine. The application is assessed by AIFA, which issues its opinion after the verification and validation of the requirements set out in the law. On the basis of the supporting documents submitted as a proof of costs incurred for the patient's treatment, AIFA reimburses the invoices submitted.

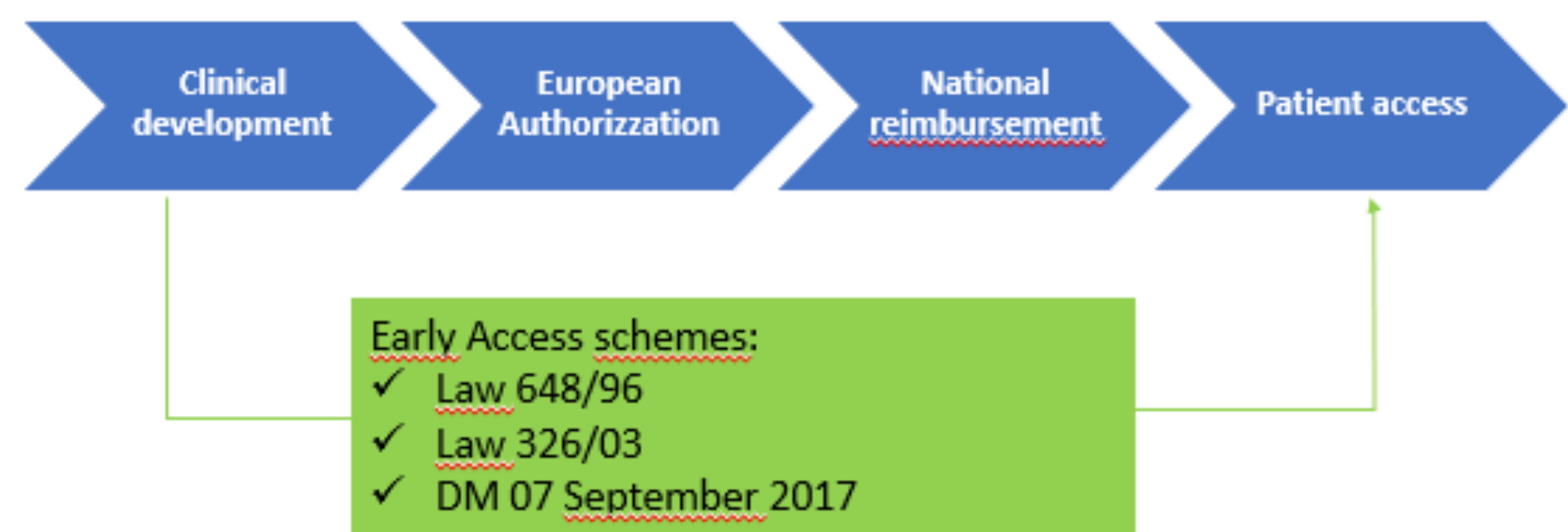


Figure 1 – Drug’s Patient access flow with and without early access schemes

Each year, the AIFA’s Italian National Observatory on Drugs Utilization (OsMed) provides an annual report, aimed to make available data on drug use in Italy, in terms of expenditure, volumes and type. The analyses contained in these reports also give some tips for correlating the prevalence of diseases in the territory with the corresponding use of drugs, and propose the interpretation of main factors that influence the variability in prescription.

In a specific section of these reports the orphan drugs expenditure data are reported. For this reason, OsMed reports provide information on the orphan drugs/rare disease early access tools, and consequently about the Law 326/2003, in the art. 48 (Fondo AIFA 5%).

Objective

This study aims to assess AIFA’s approach on requests related to inclusion in Fondo AIFA 5%, evaluating the number and the characteristic of applications submitted to AIFA and their evaluation by the Agency. Moreover, the economic impact of medicinal products included in Fondo AIFA 5% during the years was evaluated.

Methods

The drugs’ panel was built by systematically reviewing the Reports of the AIFA CTS’ meetings (“Area Pre-Autorizzazione”) published from January 2013 to September 2019, checking the number and characteristics of each drug under evaluation and analysing each single decision taken by the CTS.

EMA withdrawals, applications withdrawn by the applicant and duplicates (evaluations postponed to the next CTS) were excluded from the research.

We have also checked the last available OsMed reports of 2013-2018, to check the economic impact of 326 Law on Fondo AIFA 5% during the years.

CTS positive opinion	Drug	No patient in the request	CTS negative opinion	Drug	No patient in the request	
Feb-13	Abiraterone (Zytiga)	na	Jan-15	Cholic acid (Oprhacol)	1	
Mar-13		na	Mar-15		1	
Mar-13		na	Feb-17	Alipogene tiparovec (Glybera)	1	
Nov-15	Blinatumomas (Blinicyto)	1	Dec-13	Ataluren (Transalarna)	2	
Jan-15	Carfilzomib (Kyprolis)	1	Mar-15	Blinatumomas (Blinicyto)	1	
Jun-15		1	Mar-13	Brentuximab vedotin (Adcetris)	na	
Dec-15		1	Mar-13		na	
Dec-15		2	Apr-13		1	
Oct-14		Delamanid (Delytba)	1		Apr-13	2
	Jul-13				na	
Oct-13	Ivacaftor (Kalydeco)	1	Nov-15	Eculizumab (Soliris)	1	
Oct-14		1	May-14	Ibrutinib (Imbruvica)	1	
Nov-14		1	May-14		1	
Dec-14		1	Jan-15		1	
Jan-15		2	Feb-15		15	
Jan-15		10	Feb-15		8	
dec-15		Pirfenidone (Esbriet)	1	Feb-15	Ivacaftor (Kalydeco)	1
				Feb-15		1
Nov-13	Pomalidomide (Imnovid)	1	Feb-15		1	
Apr-14		1	Mar-15		8	
Apr-14		1	Mar-15		1	
Jul-14		1	Jan-16	Ledipasvir/sofosbuvir (Harvoni)	1	
Jul-14	Sofosbuvir (Sovaldi)	1	Oct-13	Lomitapide (Lojuxta)	na	
Dec-15	Susoctocog alfa (Obizur)	1	Octt-15	Lumacaftor/ivacaftor (Orkambi)	1	
			Nov-15		2	
Apr-15	Teduglutide (Revestive)	2	Oct-13		4	
Dec-15		2	Mar-14	Mannitolo(Bronchitol)	3	
Dec-15		1	May-14		3	
Feb-16		1	Oct-15	Nivolumab (Opdivo) e ipililbumab (Yervoy)	1	
Jan-17		1	Feb-16	Parathyroid hormone (Natpar)	1	
Jan-17		1	Feb-16		1	
Jul-15	Temocillina sodica (Negaban)	1	Mar-16		1	
			Nov-14	Pomalidomide (Imnovid)	1	
			Nov-14		1	
			Jan-15		1	
			Jan-15		1	
			Apr-14	Teduglutide (Revestive)	2	
			Feb-17	Tolvaptan (Jinar)	1	
			May-14	Trastuzumab + emtasine (Kadcyla)	1	
			Jun-14		1	

Table 1 and 2 – CTS evaluation (positive and negative) from 2013 to 2017 (no CTS

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Results

From 2013 to 2017, the CTS evaluated 69 applications. AIFA CTS approved 29/69 (42%) requests for access to Fondo AIFA 5%, regarding 11 drugs. 8/11 drugs approved (73%) had an Orphan Designation.

Between these 29 requests the outcomes were as follows:

- 14 were "positive" (48%),
- 2 were positive but subordinate to the possible AIC (7%),
- 1 was positive only for one of two patients (3%),
- 8 were positive for limited period of time (28%);
- 2 were positive but only if patients are not eligible for the approved indication, not included in the compassionate use programme, and satisfy certain clinical characteristics (7%),
- 2 were positive with subsequent CTS re-evaluation (7%).

The Anatomical Therapeutic Chemical (ATC) code mainly represented is the L (antineoplastic and immunomodulants agents) (50%) followed by the J (antifinfectives for systemic use) (20%). The R (respiratory system), B (blood and blood forming organs) and A (alimentary tract and metabolism) represent 10% for each.

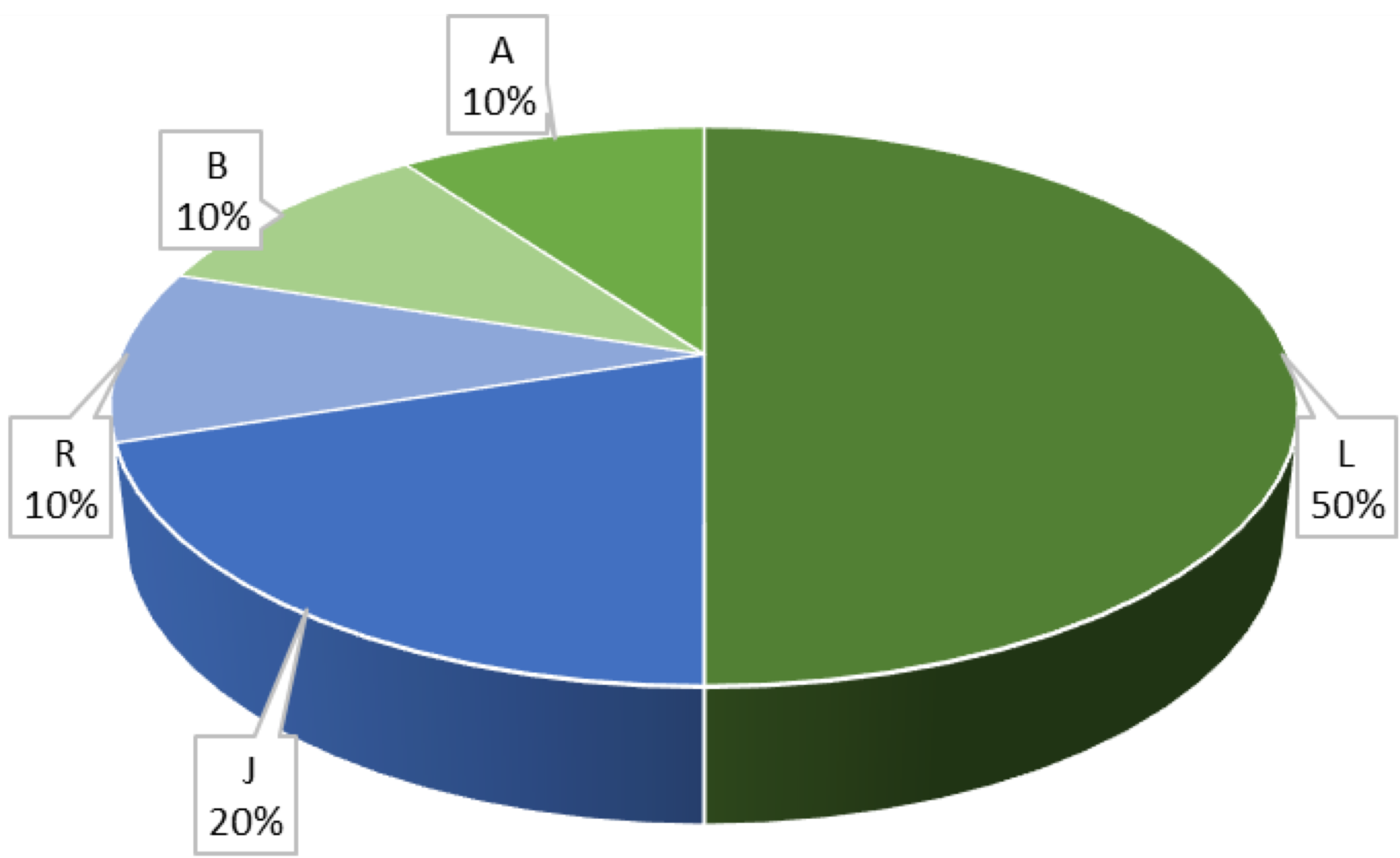


Figure 2 – Positive evaluation by ATC code

40/69 (58%) requests were not approved by the CTS and had the following outcomes:

- 12 were "negative" (30%),
- 16 were suggested the access to the Decree of May 8, 2003 (i.e. old decree for compassionate use) (40%),
- 1 was negative because the drug was in the 648 list (2,5%),

- 1 was applicable for the importation (2,5%),
- 2 were negative because the drug was authorized and available (5%),
- 2 were acknowledging (5%),
- 3 required further evaluation (7,5%),
- 2 had a pending EMA's decision (5%),
- 1 were under evaluation of patient's clinical data (2,5%).

There are no data available concerning requests made in the years 2018-2019, since the last available (i.e. published) CTS’s decision refers to 2017.

We have also evaluated the changes in Fondo AIFA 5% both in terms of amount of this fund and in terms of expenditure related to medicinal products subject to the Law 326/2003. The OsMed reports of 2013 - 2018 provided economic information on Fondo AIFA 5% and the economic impact of drugs included in Fondo AIFA 5%. Between 2013 and 2018 the fund was slowly growing, with the exception to 2015 when it declined.

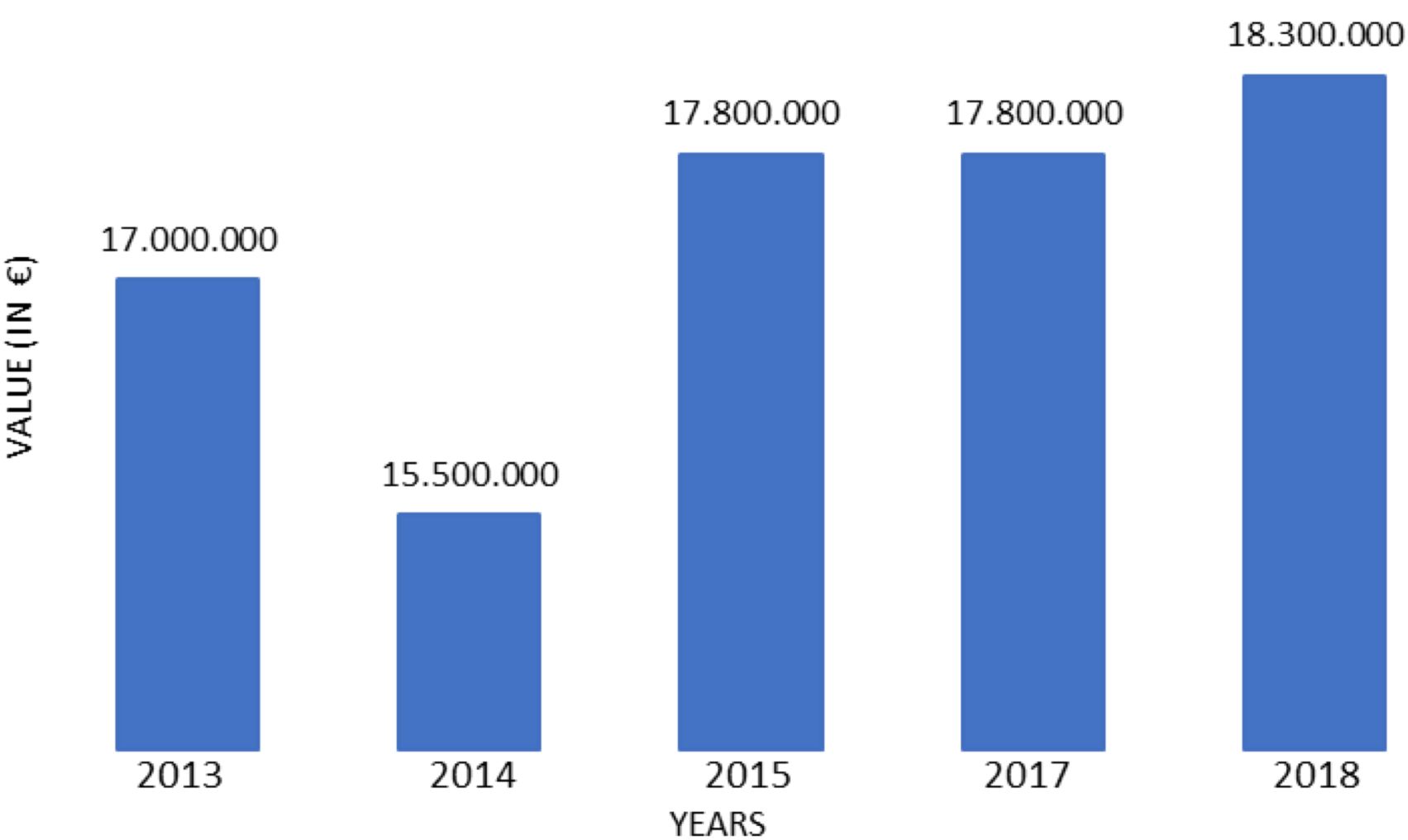


Figure 3 – Fondo AIFA 5% (in C) between 2013 and 2018 (no data available for 2016)

The economic impact (expenditure) of drugs included in Fondo AIFA 5% has increased considerably during the years: 183.382,00 € in 2013 (1%), 239.895,00 € in 2014 (2%), 1.108.530,00 € in 2015 (6%) and 13.465.742,00 € in 2017 (76%). No data for 2016 and 2018 were present in the OsMed Report.

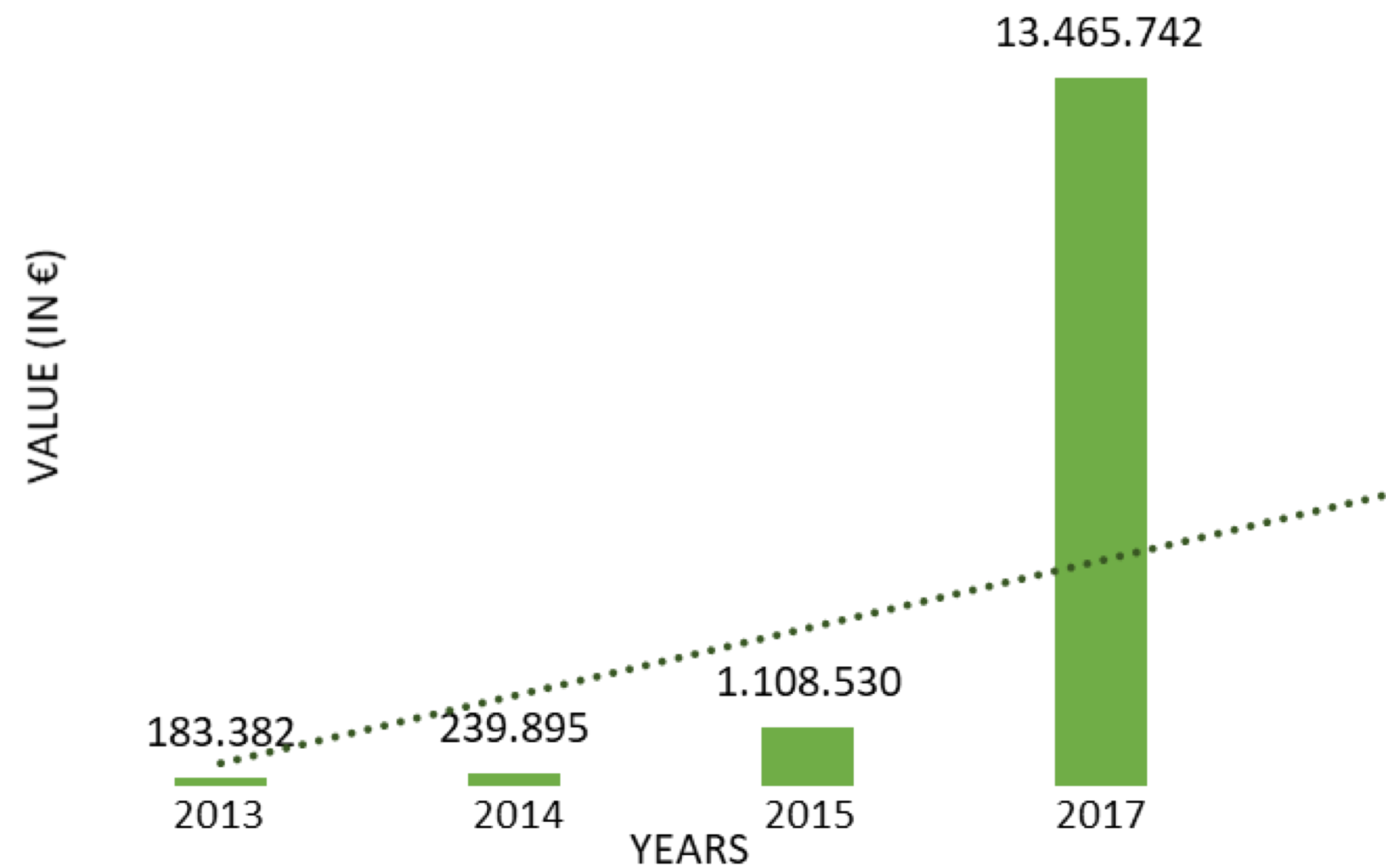


Figure 5 – Economic impact (expenditure) of drugs included in Fondo AIFA 5% between 2013 and 2017 (no data available for 2016 and 2018)

The number of the drugs included into Fondo AIFA 5% has grown during the years. From 3 in 2013 and 2 in 2014 to 5 in 2015 and 13 in 2017. In the same way, also the number of patients who used these drugs has grown: from 5 and 4 in 2013 and 2014 respectively, to 8 and 60 in 2015 and 2017 respectively.

Conclusions

Fondo AIFA 5% is one of the early access schemes in Italy. The 50% of the fund is dedicated to the purchase of orphan drugs for the treatment of rare diseases or medicinal products for the treatment of serious conditions, which are not commercialized yet.

During 2013-2017 the AIFA CTS had evaluated 69 requests of access to Fondo AIFA 5%, approving 48% of them (no data about CTS evaluation was published after 2017). The approved drugs were mainly antineoplastic and immunomodulants agents (ATC-1 L) (50%) followed by the antifinfectives for systemic use (ATC-1 J) (20%).

Moreover, the OsMed Reports provided the economical data about the amount of the fund and its expenditure. The numbers show that the fund has been growing slowly during the years. Similarly, the number of drugs included in the fund (and therefore also the number of patients who have had access to these drugs) has increased, as well as the expenditure of the fund dedicated to these drugs.

Our data showed that Law 326/2003, Article 48, paragraph 19a, is a powerful early access tool and its use has significantly increased during the last years, showing AIFA's commitment to Italian patients.

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