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ORIGINAL RESEARCH ARTICLE

Italian Medicines Agency's reform and time until pricing and reimbursement decisions: a time-to-event analysis

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ABSTRACT

Introduction: The duration of pricing and reimbursement (P&R) negotiations is a key performance indicator for medicines agencies in universal health coverage systems. In early 2024, the Italian Medicines Agency (AIFA) underwent a major reform, including the merging of the previous Scientific-Technical Committee and Price and Reimbursement Committee into a single Scientific and Economic Committee. This study evaluates the reform's impact on time to P&R determinations for new medicines in Italy.

Methods: A time-to-event analysis was conducted on 139 new chemical entities authorized by the European Commission (EC) between February 2021 and December 2023. The primary outcome was the time from marketing authorization (MA) to publication of AIFA's P&R determination. Kaplan-Meier curves and Cox proportional hazards models were used to compare reclassification hazards between pre- (before March 2024) and post-reform groups of medicinal products, based on a fixed separation date, adjusting for antineoplastic therapeutic area and pharmaceutical company size. Four sensitivity analyses tested the robustness of the results.

Results: The multivariate Cox model, adjusting for antineoplastics, products from major corporations, and orphan medicines, showed that the reform was associated with an 84% increase in reclassification hazards (HR = 1.84, 95% CI 1.20-2.82, p = 0.005). Sensitivity analyses corroborated these findings, showing even greater improvements when focusing on national evaluation timeframes (HR = 11.57 and HR = 3.91).

Conclusion: The consolidation of separate committees into a unified structure, as a part of the 2024 AIFA reform, was accompanied by accelerated P&R negotiations for new medicines in Italy, demonstrating that structural optimization of health technology assessment processes may enhance system efficiency.

Keywords: AIFA, Health Services Accessibility, Pricing and reimbursement, Pharmaceutical policy, Pharmaceutical preparations, Survival Analysis

Introduction

The time elapsed between marketing authorization (MA) and pricing and reimbursement (P&R) determination is a sensitive health policy issue. In European universal health coverage systems, such as the Italian National Health Service (NHS) (1), these durations contribute to the overall time required for patients to gain access to medicines authorized by the European Commission (EC).

Among its several responsibilities, the Italian Medicines Agency (AIFA) establishes the conditions (e.g., the relevance of disease, the patient characteristics) at which medicines can be reimbursed with national public funds specifically allocated for medicines, and negotiates with companies (when they opt to submit a P&R application) the maximum price of medicines to be offered to the payors within the NHS (2).

Following centralized EC MA, and irrespective of a P&R application submission, every medicine is initially classified by AIFA as not negotiated (Cnn class). This classification

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grants the MA holder the freedom to set the product's price and sell it across the country, although free prices discourage NHS healthcare providers from buying the medicine. In fact, except for some circumstances (3), public providers avoid buying Cnn medicines since the expenses would contribute to the health system deficit.

The national negotiation process formally starts when the dossier submitted by the company is notified as eligible after an "administrative check" (4), and concludes with the medicine's reclassification from the Cnn class to a definitive status. The outcome agreed upon by AIFA and the company may involve either a regulated price for defined clinical indications or the confirmation of an unregulated price (C class) (4).

In early 2024, AIFA underwent a reorganization process, widely referred to as "the AIFA reform", involving its offices responsible for P&R negotiations and their internal procedures (5). A new single entity named the Scientific and Economic Committee replaced two distinct bodies, the Scientific-Technical Committee (CTS) and the Price and Reimbursement Committee (CPR), and became operational in March 2024. The stated general goal of the reorganization was to make the Agency more "modern and agile" (6).

The timelines of P&R negotiations in Italy have been frequently evaluated in the scientific and grey literature, both by AIFA (7-9) and by third parties (10,11), with diverse methodologies, each carrying distinct informative advantages and limitations. Simpler analyses typically calculate the average and median durations of the procedures completed within a given time period, often stratified by variables of interest, and are reported alongside measures of dispersion (9). This approach addresses common descriptive needs, providing summary information on the duration of negotiations and allowing for easy comparison between countries (10). On the other hand, more sophisticated approaches may involve measures of time to regulatory and P&R milestones in time-to-event (or survival) analyses (7,8), allowing for the inclusion of medicines whose negotiation procedures are not yet completed at the end of the study (12). The main advantages of time-to-event analysis are that it incorporates censored data, exploits partial observations, and bypasses the requirement for normally distributed data.

The objective of this study was to investigate possible changes, compared to the pre-reform P&R negotiation system, in the timeframe between the MAs for medicines by the EC and the publication in the Official Gazette of AIFA's P&R determinations.

Methods

To identify differences in performance between the P&R system for medicines in Italy prior to and after AIFA reform, a survival (or *time-to-event*) analysis was performed.

Data extraction and dataset building

Data on all medicines whose centralized MAs were published in the Official Journal of the European Union (EU) between 26 February 2021 and 29 December 2023 were extracted from a database developed by Intexo Società Benefit (Rome, Italy). The extracted data included, for each medicine, the brand name, the date of centralized MA, the date of submission of the P&R application to AIFA (if present), the date of the first examination of the medicine by AIFA's Technical Scientific Committee (if present), the date of the first examination of the medicine by AIFA's Scientific and Economic Committee (if present), the date of the first AIFA reclassification (which corresponds to the "failure" event, if present), the authorized indication, the therapeutic area, the Anatomical Therapeutic Chemical (ATC) class (13), and the orphan medicine status assigned by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). Among the medicines extracted, those with an authorized antineoplastic indication were identified. Furthermore, the medicines whose EU MAs belonged to the biggest twenty pharmaceutical corporations by prescription sales of fiscal year 2024 (14) ("big pharma" hereafter) were identified and marked.

Medicines indicated for the treatment or prevention of COVID-19, vaccines, generics, biosimilars, hybrids, gene therapy medicines, and fixed-dose combination medicines were excluded from the analyses. These exclusions are motivated by the peculiarities of negotiations for these products, which either shorten (e.g., vaccines, generics) or lengthen (e.g., gene therapies) their evaluation times. The exclusions were intended to reduce heterogeneity in time-at-risk and reduce potential confounding bias.

Study design

To assign the medicines to two non-mutually exclusive groups, reflecting their negotiation prior or after the AIFA reform (pre-reform and post-reform group, respectively), 29 February 2024, was identified as the "separation" date for the groups. Thus, observations relating to medicines that underwent reclassification or censoring by 29 February 2024 or after this date belonged to the pre-reform and post-reform group, respectively. Consequently, products not yet reclassified by 29 February 2024 contributed observation time to both the pre-reform and post-reform groups.

Observations of the pre-reform group had their start date set on the date of publication of the centralized MA in the Official Journal of the EU, while the date of the first reclassification in the Italian Official Gazette was used as the event (or failure) date if it took place by 29 February 2024. Instead, all observations of the post-reform group had their start date set on 1 March 2024, while the date of the first reclassification was used as the event (or failure) date if it took place by 19 May 2025. By design, the post-reform group included all medicines that had not yet been reclassified by 29 February 2024.

For each observation, the time between the start date considered and the publication of the first AIFA reclassification or the date of censoring was calculated in days. The censoring of an observation, resulting in the end of "time at risk" of reclassification, happened on the day when the observed medicine: *i*) reached the study end date (29 February 2024 for the pre-reform group; 19 May 2025 for the post-reform group) without having obtained reclassification; *ii*) was suspended from use or had its MA withdrawn by EMA or AIFA; the P&R application submitted to AIFA was withdrawn. The study sample was observed until 19 May 2025; this data lock

date was chosen to cover at least a full year of AIFA's activity within the post-reform negotiation system.

Four separate one-way deterministic sensitivity analyses were envisaged to test the robustness of results. The first sensitivity analysis was based on the rationale that the post-reform negotiation system may have needed more time to completely implement the possible gain in time to reclassification, as to reflect a learning process of the new organization. For this analysis, the start dates of the observations of the post-reform group were postponed from 1 March 2024 until 1 April 2024. The whole of March 2024 was considered a time of activity for pre-reform AIFA.

The second sensitivity analysis considered the fact that P&R applications are not systematically and promptly submitted by the company whose product received or is about to receive a positive opinion from EMA's Committee for Medicinal Products for Human Use, since the choice to submit the P&R application is ultimately up to the company (7). For this second analysis, we chose as the start date of each observation the date of their first examination by AIFA's Technical Scientific Committee (CTS; pre-reform office) and/or Scientific and Economic Committee (CSE; post-reform office), therefore excluding the medicines that were not examined either by CTS or CSE by the data lock date of 19 May 2025. Medicines having been examined by both offices were observed in both groups using separate time frames.

For the third sensitivity analysis, observation started on the date of the first P&R dossier submission. If a medicine with a submitted dossier was not reclassified by 29 February 2024, it was observed in the post-reform period as well. Medicines without a submitted P&R dossier by 19 May 2025 were excluded.

The fourth sensitivity analysis considered that AIFA may have intentionally delayed and/or expedited some P&R procedures in the months surrounding the reform (6). To control for this phenomenon, the end of the pre-reform observation period was moved up to 31 October 2023, while the start of the post-reform period was delayed until 1 July 2024. Data from this eight-month period (both time at risk and "failure" events) were excluded from the analysis.

Statistical analysis

Descriptive statistics relating to the selected covariates and ATC classes were calculated for the two groups of observations. The time unit considered is days.

Survival functions were calculated and graphically represented using the Kaplan-Meier method. To verify whether the differences between the hazards of the groups over time were statistically significant, two-sided log-rank tests were performed. The covariates for which the log-rank test p-values were significant were integrated in the subsequent multivariable Cox model.

To estimate the effect of AIFA's reform on reclassification hazards of medicines, univariate Cox proportional hazard models were first generated. Then, to obtain adjusted hazard ratios of reclassification for each covariate, a main-effects multivariable Cox proportional hazards model was generated. To assess influential observations, DFBETA statistics were calculated for all included covariates using the conservative $2/\sqrt{n}$ threshold (15). Compliance with the proportionality of hazards (PH) assumption of the two models was verified using Schoenfeld's residuals test.

All confidence intervals are reported at 95%, with significance levels of p = 0.05. Stata software, version 18.5 (Stata Corporation LLC, College Station, USA), was used for statistical analysis.

Results

Base case analysis

After applying the exclusion criteria, the final sample comprised 139 medicinal products. According to the study design, all 139 medicines were included in the pre-reform group, while 66 of them were also observed in the post-reform group. In the base case analysis, the median time to reclassification was 483 days before the reform and 388 days post-reform, that is, 95 days shorter. Other descriptive statistics are reported in Table 1.

Significant differences in reclassification hazards over time were observed between the pre-reform and post-reform groups overall, and within the subgroups of antineoplastic and big pharma medicines (respectively, log-rank test: $\chi^2 = 5.65$, p = 0.018; $\chi^2 = 6.06$, p = 0.014; $\chi^2 = 6.08$, p = 0.014). Conversely, reclassification hazards did not differ significantly by orphan status ($\chi^2 = 0.97$, p = 0.324). Figure 1 displays the Kaplan–Meier curves of the base case time-to-event analysis and the sensitivity analyses.

The univariate Cox model indicated approximately 66% higher hazard of reclassification for medicines under the post-reform system compared with the pre-reform period (p = 0.019; HR = 1.66, 95% CI 1.09-2.54). Based on the multivariate Cox model, when controlling for the covariates antineoplastic medicines and big pharma medicines, a statistically significant advantage in time to reclassification post-reform was confirmed (p = 0.005; HR = 1.84, 95% CI 1.20-2.82). The global Schoenfeld residuals test supported the validity of the PH assumption for the overall model ($\chi^2 = 5.50$, p = 0.138). Detailed results are presented in Table 2. There was no evidence of particularly influential observations for both the univariate and multivariate models, since all observations remained below the DFBETA threshold.

Sensitivity analyses

In the first sensitivity analysis (S1), 139 medicines were included in the pre-reform group, and 63 were also observed post-reform. When the start date of post-reform observations was postponed by a month, the difference between the median times to reclassification of the two groups was 126 days in favour of the post-reform system, and the univariate Cox model showed approximately 79% higher hazards of reclassification (p = 0.009; HR = 1.79, 95% CI 1.16-2.77). The PH assumption was satisfied (Schoenfeld's residuals $\chi^2 = 3.83$, p = 0.050). Consistent with the base case analysis, log-rank tests identified statistically significant differences in reclassification hazards over time for all covariates except orphan medicine status ($\chi^2 = 0.98$, p = 0.322). The multivariate Cox model indicated that the post-reform case mix had

TABLE 1 - Characteristics of observations relating to medicinal products in the sample and median time to first reclassification in the Official Gazette of the Italian Republic. Results of the base case analysis

	Group of observations prior to the AIFA reform£			Group of observations following the AIFA reform§		
	Observed	**Reclassified by 29 February 2024 (%)**	**Median time to first reclassification, in days (95% CI)**	**Observed**	**Reclassified between 1 March 2024 and 19 May 2025 (%)**	**Median time to first reclassification, in days (95% CI)**
All included medicinal products	139	72 (52)	483 (413-633)	66	38 (58)	388 (327 - *NA*)
Orphan medicinal products	38	22 (58)	413 (365-735)	16	10 (63)	384 (208 - *NA*)
Antineoplastic medicinal products	48	26 (54)	413 (393-633)	21	17 (81)	330 (202-384)
Medicinal products by the top twenty corporations¶	60	35 (58)	413 (362-501)	24	15 (63)	294 (208 - *NA*)
ATC class						
ATC class L medicinal products	60	34 (57)	406 (374-501)	25	21 (84)	230 (164-335)
ATC class A medicinal products	13	6 (46)	544 (307 - *NA*)	7	5 (71)	358 (141 - *NA*)
ATC class N medicinal products	12	7 (58)	487 (242 - *NA*)	5	2 (40)	*NA* (217 - *NA*)
Medicinal products of other ATC classes	54	25 (46)	666 (443-907)	30	10 (33)	*NA* (377 - *NA*)

£ Observations relate to medicinal products reclassified or censored by 19 May 2025, corresponding to the total number of medicinal products in the sample; § Observations refer to medicinal products reclassified or censored after 29 February 2024; ¶ Medicines whose European Union MAs belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (14).

TABLE 2 - Hazard ratios for first reclassification of medicines following the reform of the Italian Medicines Agency (AIFA). Results of the base case analysis

		HR (95% CI)	**p-value for proportionality of hazards$**
Univariate Cox model	**Post-reform**	1.66 (1.09-2.54)	0.039
Multivariate Cox model	**Post-reform**	1.84 (1.20-2.82)	0.045
	Antineoplastic medicinal products	1.55 (1.05-2.29)	0.345
	Medicinal products by the top twenty corporations¶	1.54 (1.05-2.26)	0.373

$ p-value of Schoenfeld's residuals test; ¶ Medicines whose European Union MAs belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (14).

nearly double the hazard of reclassification compared to the pre-reform group (p = 0.002; HR = 2.01, 95% CI 1.29-3.12), confirming faster progression from EU MA to national P&R determinations.

In the second sensitivity analysis (S2), where the start dates of observations were defined as the dates of AIFA's examination of the medicine, there were 104 observations in the pre-reform group and 38 in the post-reform group. As a feature of this analysis, 12 medicines were uniquely observed in the post-reform group, as they were never examined by AIFA's Scientific-Technical Committee (pre-reform office). The median time to reclassification was 188 days shorter for the post-reform group. The univariate Cox model revealed a markedly higher reclassification hazard

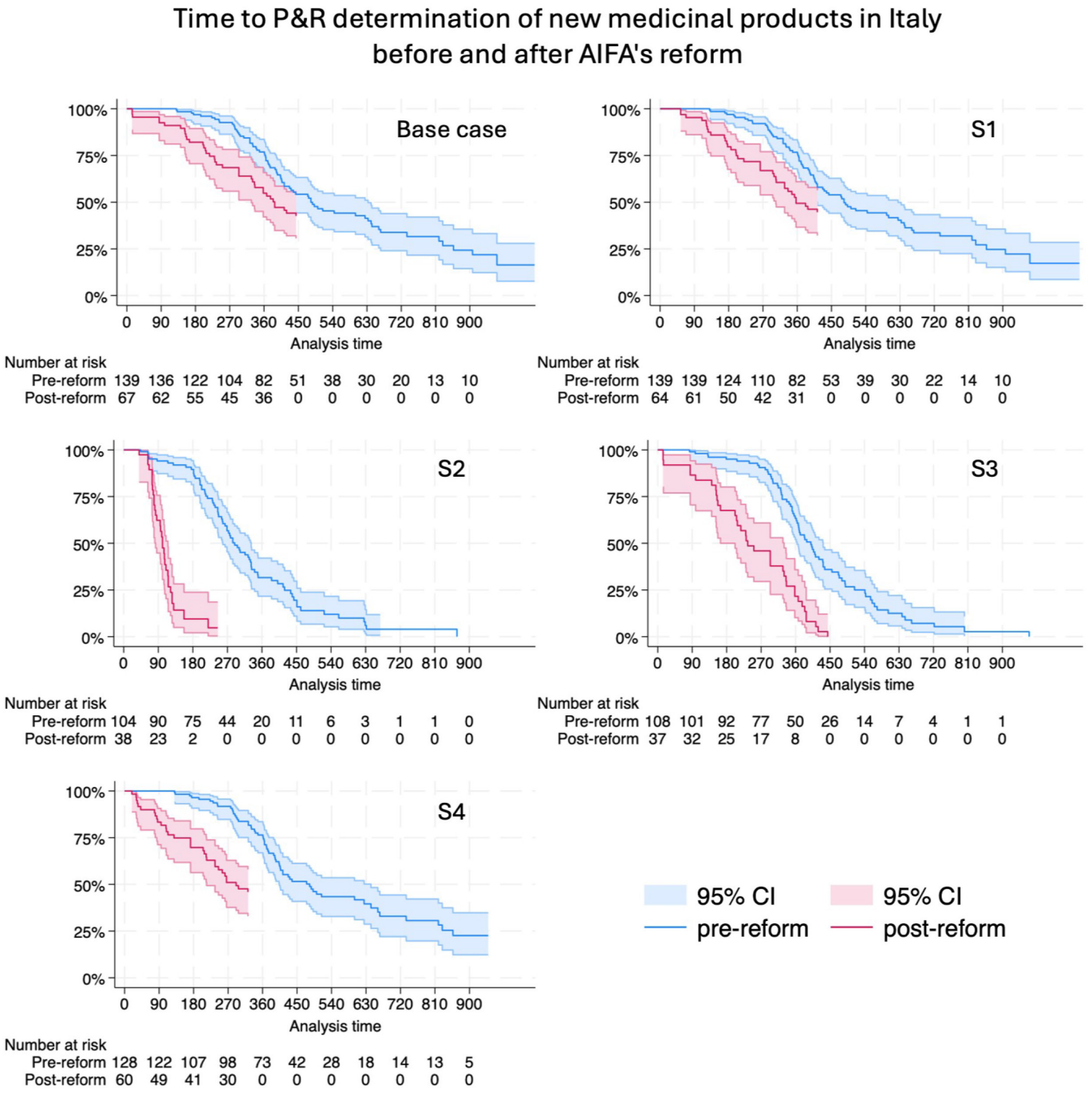

FIGURE 1 - Kaplan–Meier curves for time to P&R determination before and after the 2024 AIFA reform. Base case analysis (base case) and sensitivity analyses (S1-S4). In all analyses, post-reform observations represent a subset of medicines not yet reclassified by the separation date.
(Base case), base case analysis, with observations starting on the date of EMA MA and separation between groups set on 01 March 2024; (S1), first sensitivity analysis, with observations starting on the date of EMA MA and separation between groups set on 01 April 2024; (S2), second sensitivity analysis, with observations starting on the date of AIFA's first examination of the medicine and separation between groups set on 01 March 2024; (S3), third sensitivity analysis, with observations starting on the date of P&R dossier submission by the company and separation between groups set on 01 March 2024; (S4), fourth sensitivity analysis, with the pre-reform group observed from the date of EMA MA until 31 October 2023, and the post-reform group observed from 01 July 2024 onwards.

($p < 0.001$; HR = 11.57, 95% CI 6.49-20.61). Proportional hazards assumptions were met ($\chi^2 = 0.18$, $p = 0.670$). None of the covariates showed statistically significant differences in survival according to the log-rank tests; therefore, a multivariate model was not estimated.

In the third sensitivity analysis (S3), where the dates of P&R dossier submission were considered, there were 108 observations in the pre-reform group and 37 in the post-reform group. Only one medicine was uniquely observed in the post-reform group, since its P&R dossier was submitted after 29 February 2024. A difference of 165 days was observed between the median times to reclassification, favouring the post-reform period. The univariate Cox model demonstrated a substantial increase in reclassification hazard ($p < 0.001$; HR = 3.91, 95% CI 2.53-6.04), with the proportional hazards assumption validated ($\chi^2 = 1.17$, $p = 0.279$). Given that log-rank tests indicated no statistically significant survival differences across covariates, a multivariate model was not developed.

The fourth sensitivity analysis (S4), excluding a symmetrical eight-month window around the reform, included 128 pre-reform and 60 post-reform observations. The median duration from authorization to reclassification was 192 days shorter post-reform. The univariate Cox model revealed a higher reclassification hazard ($p < 0.001$; HR = 4.96, 95% CI 2.75-8.93), with proportional hazards assumptions satisfied ($\chi^2 = 1.64$, $p = 0.201$). Log-rank tests identified statistically significant differences in reclassification hazards over time only for antineoplastic medicine status. The multivariate Cox model indicated that the post-reform case mix had a five-fold hazard of reclassification compared to the pre-reform group ($p < 0.001$; HR = 5.17, 95% CI 2.86-9.32), indicating faster progression from MA to national P&R determinations.

An influential observation was identified via DFBETA in the second sensitivity analysis, nevertheless its exclusion did not substantially alter the significance or direction of the findings. No influential observations were detected in the remaining sensitivity models.

Kaplan–Meier curves for all sensitivity analyses are shown in Figure 1, and detailed results are reported in the supplementary material.

Discussion

This study represents the first comprehensive time-to-event analysis evaluating the impact of the 2024 AIFA reform on P&R timelines in Italy. The present observational study found that the post-reform negotiation system was positively associated with decreased time to reclassification for the case mix of medicines included, which consisted of "new chemical entities," namely, innovator medicines that received MA based on complete dossiers of preclinical and clinical trial data. The multivariate Cox model revealed an 84% increase in reclassification hazards when controlling for antineoplastic status and "big pharma" designation. The direction of this result held true for the case mix of medicines in the four sensitivity analyses performed, and its magnitude increased largely when the time frame of the observation shifted from a European and national perspective to a solely national one.

A critical distinction must be drawn between analyses measuring different aspects of pharmaceutical access. The base case and first sensitivity analyses assess the performance of Italy's entire pharmaceutical governance ecosystem, reflecting both company behaviours (e.g., timing of P&R submissions) and AIFA's evaluation processes. These system-wide perspectives are valuable for understanding overall patient access timelines from European authorization to Italian reimbursement. However, the second and third sensitivity analyses provide more targeted evaluations of AIFA's institutional performance by restricting observations to medicines that actively entered the review process, thereby reducing confounding from non-submitted applications. The substantially higher hazard ratios observed in these focused analyses (HR = 11.57 and HR = 3.91) are compatible with improvements that occurred specifically within AIFA's evaluation procedures, independent of pharmaceutical industry submission patterns. This distinction is crucial for policymakers seeking to identify where system improvements occurred and where further interventions may be needed.

Our results provide empirical evidence suggesting that the AIFA reform achieved its stated objective of expediting the negotiation workflow. The improved timeliness is particularly relevant given that clinically valuable medicines in the Cnn class face practical barriers to NHS procurement, limiting patient access. Institutionalizing time-to-event analysis as a routine monitoring tool for health technology assessment agencies could provide valuable insights into system efficiency and support evidence-based policy adjustments.

Other peer-reviewed studies examined the time to P&R determinations of medicines in Italy and internationally. Tedesco et al. (11) measured the durations of steps of AIFA's P&R evaluation of new chemical entities from 2018 to the last sitting of the CTS (pre-reform office) of January 2024. They compared the durations of single administrative steps between classes of medicines but did not perform comparisons between time periods. Orphan medicines were found to require approximately two-month longer evaluations compared to non-orphans. Our adjusted multivariate analysis recorded shortenings of time to reclassification for orphan medicines, showing an institutional improvement benefiting patients with rare diseases. Two distinct AIFA-led workgroups performed nationally focused time-to-event analyses (7,8). Gallo et al. (7) produced Kaplan-Meier curves representing time until intermediate milestones of the P&R process and until P&R determinations. They compared in-patent with off-patent medicines and, separately, three years of P&R activity from 2018 until 2020 to assess the impact of the COVID-19 pandemic. Procedures for in-patent medicines were longer and more variable compared to off-patent products. Russo et al. (8) performed an investigation across the European to the sub-national level to measure each sequential phase involving the market access of a sample of oncology medicines, from European MA until the first purchase by healthcare providers of every Italian Region. They also ran a Cox model to identify the potential predictors of time from AIFA's P&R determination until regional access, or until a fixed date for the censored cases. Vancoppenolle et al. (16) used a mixed-methods approach to study hospital access for

a small sample of innovative oncology medicines in Italy and in other European countries. Based on the data from surveyed hospital pharmacies, they calculated time to patient access as the difference between EMA approval and time of first delivery of the medicine to a patient. This interval was shorter when Early Access Programs took place. Post et al. (12) compared the access of oncology medicines authorized by EMA from 2016 to 2020 in six European countries, finding that the major factors contributing to earlier P&R determinations were a higher gross domestic product and the ownership of the MA by a best-seller pharmaceutical company, which is in line with our results.

The present study carries a series of strengths and limitations, which influence the validity and interpretation of results. A major limitation of this study is that procedural changes in the AIFA Committees' workflows may have occurred before the reform was implemented. Although the fourth sensitivity analysis (S4) tries to take into account this issue by introducing an eight-month "buffer" period, this bias cannot be fully eliminated. Likewise, unaccounted external factors might have influenced AIFA's workload and efficiency. For instance, shifts in Agency priorities or backlogs following the COVID-19 pandemic could have played a role in negotiation timelines independent of the reform.

Other limitations of this study pertain to the use of time-to-event (or survival) analysis methods. Despite being mostly used in clinical research, time-to-event (or survival) analysis is a consolidated technique in public policy research, being relied upon also in fields other than healthcare (17). Its main advantage, compared to the other techniques applied in the literature, is the possibility of extracting information even from statistical units (medicinal products) whose P&R process was interrupted before the event (in our case, P&R determination) for any reason, thereby allowing to leverage a substantially larger sample than we would if we had to include only medicines with concluded negotiation procedures. A main limitation of this study pertains to the time points at which the observations for each group began and ended. In the base case and first sensitivity analysis (S1), EMA authorization triggered the pre-reform observation, whereas post-reform observation began universally on 1 March (base case) or 1 April 2024 (S1), resulting in unequal time-at-risk structures. In this situation, the use of standard survival analysis methods is not fully appropriate.

Furthermore, the repeated observation of the same product across both groups potentially violates the assumption of independence of observations, because the comparison groups are not fixed and mutually exclusive over time, with some medicines contributing to follow-up both before and after the reform date. This introduces left-truncation for medicines "surviving" the pre-reform period, which may influence variance estimation. Additional limitations include the potential for informative censoring and the absence of a competing risk framework. While administrative censoring was applied based on fixed study end dates, we did not explicitly model competing risks, such as withdrawals of P&R applications or suspensions. These two events caused censoring and, although rare, could prevent reclassification and affect the hazards.

Another limit consists of the relatively short list of covariates or classes of medicines investigated. Innovative status was not investigated; however, it should be considered that innovative status is granted by AIFA towards the end of the P&R procedure, making its relationship with P&R duration less interesting. Another limitation is the exclusion of several classes of medicines, such as generics and biosimilars. These exclusions were necessary to obtain a homogeneous pool of in-patent medicines undergoing standardized procedures. The resulting case mix consists of medicines requiring full dossiers for P&R assessment and not subject to special pricing or distribution processes. For instance, vaccines require timely market arrival to address seasonal demand patterns, which could confound P&R duration analyses. Third, the medicine price was not considered as a covariate. However, recent evidence from our group (18) shows that price appears to have no influence on negotiation times in the Italian context, supporting our decision to exclude this variable. Finally, the sample size for certain subgroup analyses likely limited the detection of significant differences for specific covariates. This was evident for orphan medicines (38 observations pre-reform; 16 post-reform), where reclassification hazards did not reach statistical significance despite observed numerical shortenings in negotiation times.

Future research should address several important areas. Time-to-event analysis might be expanded to include both the regional level, in order to provide a comprehensive picture of patient access from EMA authorization to actual clinical availability, or the European level, to enable benchmarking of performance and identification of best practices. Additionally, longitudinal studies tracking the impact of the AIFA reform over multiple years would clarify whether observed improvements represent a temporary adjustment phase or a stable enhancement in system performance.

Conclusions

This time-to-event analysis demonstrates that the 2024 AIFA reform was associated with shorter P&R negotiation times for new medicines in Italy. According to the base case analysis, adjusting for multiple medicine classes, including antineoplastics, products from major pharmaceutical corporations, and orphan medicines, the consolidation of separate committees into a single Scientific and Economic Committee was associated with an 84% increase in reclassification hazards. Sensitivity analyses corroborated these findings, suggesting even greater improvements when observation periods were adjusted for system maturation (HR = 2.01; HR = 4.96) and when focusing exclusively on national evaluation time frames (HR = 11.57; HR = 3.91).

Disclosures

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Authors' contributor role: GMR: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing – original draft; BF: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project

administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing; MCN: Conceptualization; Software; Supervision; Validation; Visualization; GD: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – review & editing; RC: Data curation; Methodology; Project administration; Resources; Software; Visualization; Writing – review & editing; PT: Data curation; Methodology; Project administration; Resources; Software; Visualization; Writing – review & editing; DP: Data curation; Methodology; Project administration; Resources; Software; Visualization; Writing – review & editing; PN: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Data Availability Statement: The datasets generated and analyzed during the current study, along with the statistical code, are available from the corresponding author upon reasonable request. The data are not publicly available as they are derived from a proprietary commercial database (Intexo Società Benefit).

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