Supplementary material

Rationale and design of sensitivity analyses

Table S1.1 and S1.2 report the results of the **first sensitivity analysis**. This analysis was based on the rationale that the post-reform system may have required a transition period to fully implement organizational efficiencies, reflecting a learning curve for the new structure. Compared to the base case, the start date for the post-reform group was postponed from 1 March 2024 to 1 April 2024. Consequently, March 2024 was treated entirely as a period of activity under the pre-reform Italian Medicines Agency (AIFA) framework.

Table S2.1 and S2.2 report the results of the **second sensitivity analysis**. This analysis accounted for the fact that P&R applications are not always promptly submitted following a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), as the timing of submission is a strategic decision by the manufacturer. The start dates of each observation was set as the date of the 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 which 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.

Table S3.1 and S3.2 report results of the **third sensitivity analysis**. Following a similar rationale to the previous analysis, observations 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 also observed in the post-reform period. Medicines without a submitted P&R dossier by 19 May 2025 were excluded.

Table S4.1 and S4.2 report results of the **fourth sensitivity analysis**. This analysis addressed the possibility that AIFA might have intentionally delayed or expedited specific P&R procedures in the months surrounding the reform. To control for this potential bias, 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 intervening eight-month period were excluded from the analysis.

Table S1.1. 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 first sensitivity analysis.

	Group of observations prior to the AIFA reform[£]			Group of observations following the AIFA reform[§]		
	Observed	**Reclassified between 26-2-2021 and 31-3-2024 (%)**	**Median time to first reclassification, in days (95% CI)**	**Observed**	**Reclassified between 1-4-2024 and 26-5-2025 (%)**	**Median time to first reclassification, in days (95% CI)**
All included medicinal products	139	75 (54)	483 (413 - 625)	63	35 (56)	357 (304 - *NA*)
Orphan medicinal products	38	24 (63)	413 (365 - 641)	14	8 (57)	357 (199 - *NA*)
Antineoplastic medicinal products	48	28 (58)	413 (392 - 625)	19	15 (79)	304 (175 - 388)
Medicinal products by top twenty corporations[¶]	60	36 (60)	413 (362 - 501)	23	14 (61)	327 (186 - *NA*)
ATC class						
ATC class L medicinal products	60	36 (60)	406 (364 - 492)	23	19 (83)	204 (169 - 304)
ATC class A medicinal products	13	6 (46)	544 (307 - *NA*)	7	5 (71)	327 (110 - *NA*)
ATC class N medicinal products	12	7 (58)	487 (242 - *NA*)	5	2 (40)	*NA* (186 - *NA*)
Medicinal products of other ATC classes	54	26 (48)	643 (477 - 907)	29	9 (31)	*NA* (382 - *NA*)

Legend:

£ 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 31 March 2024.

¶ Medicines whose European Union marketing authorizations belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (13).

Abbreviations: AIFA, Italian Medicines Agency; ATC, Anatomical Therapeutic Chemical; CI, confidence interval.

Table S1.2. Hazard ratios for first reclassification of medicines following the reform of the Italian Medicines Agency (AIFA). Results of the first sensitivity analysis. Results of the first sensitivity analysis.

		HR (95% CI)	p-value for propiortional hazards[$]
Univariate Cox model	**Post-reform**	1.79 (1.16 - 2.77)	0.050
Multivariate Cox model	**Post-reform**	2.01 (1.29 - 3.12)	0.056
	Antineoplastic medicinal products	1.57 (1.06 - 2.31)	0.280
	Medicinal products by top twenty corporations[¶]	1.52 (1.04 - 2.23)	0.224

Legend:
¶ Medicines whose European Union marketing authorizations belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (13).
$ p-value of Schoenfeld's residuals test.
Abbreviations: AIFA, Italian Medicines Agency; CI, confidence interval; HR, hazard ratio.

Table S2.1. 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 second sensitivity 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 26 May 2025 (%)**	**Median time to first reclassification, in days (95% CI)**
All medicinal products	104	72 (69)	289 (258 - 332)	38	32 (84)	101 (83 - 115)
Orphan medicinal products	31	22 (71)	324 (247 - 350)	8	7 (88)	101 (66 - 157)
Antineoplastic medicinal products	40	26 (65)	341 (255- 419)	15	14 (93)	105 (77 - 115)
Medicinal products by top twenty corporations[¶]	47	35 (74)	316 (257 - 415)	15	13 (87)	99 (66 - 106)
ATC class						
ATC class L medicinal products	50	34 (68)	284 (247 - 350)	18	17 (94)	99 (74 - 106)
ATC class A medicinal products	11	6 (55)	327 (301 - *NA*)	6	5 (83)	74 (40 - *NA*)
ATC class N medicinal products	9	7 (78)	232 (64 - 296)	4	2 (50)	126 (116 - *NA*)
Medicinal products of other ATC classes	34	25 (74)	289 (245 - 349)	10	8 (80)	116 (77 - *NA*)

Legend:
£ Observations relate to medicinal products examined by AIFA's Scientific-Technical Committee (CTS; pre-reform office).
§ Observations refer to medicinal products examined by AIFA's Scientific and Economic Committee (CSE; post-reform office).
¶ Medicines whose European Union marketing authorizations belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (13).
Abbreviations: AIFA, Italian Medicines Agency; ATC, Anatomical Therapeutic Chemical; CI, confidence interval.

Table S2.2. Hazard ratios for first reclassification of medicines following the reform of the Italian Medicines Agency (AIFA). Results of the second sensitivity analysis.

		HR (95% CI)	p-value for propiortional hazards[$]
Univariate Cox model	**Post-reform**	11.57 (6.49 - 20.61)	0.670

Legend:
$ p-value of Schoenfeld's residuals test.
Abbreviations: AIFA, Italian Medicines Agency; CI, confidence interval; HR, hazard ratio.

Table S3.1. 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 third sensitivity 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 26 May 2025 (%)**	**Median time to first reclassification, in days (95% CI)**
All medicinal products	108	72 (67)	400 (364 - 432)	37	37 (100)	235 (202 - 330)
Orphan medicinal products	32	22 (69)	410 (351 - 481)	10	10 (100)	230 (14 - 384)
Antineoplastic medicinal products	43	26 (61)	432 (351 - 560)	17	17 (100)	235 (153 - 367)
Medicinal products by top twenty corporations[¶]	48	35 (73)	410 (359 - 514)	14	14 (100)	217 (152 - 294)
ATC class						
ATC class L medicinal products	54	34 (63)	383 (351 - 455)	20	20 (100)	206 (152 - 327)
ATC class A medicinal products	10	6 (60)	431 (83 - *NA*)	5	5 (100)	294 (141 - *NA*)
ATC class N medicinal products	9	7 (78)	347 (131 - 389)	2	2 (100)	217 (217 - *NA*)
Medicinal products of other ATC classes	35	25 (71)	407 (364 - 490)	10	10 (100)	251 (14 - 367)

Legend:
£ Observations relate to medicinal products whose pricing and reimbursement dossier was submitted to AIFA by 29 February 2024.
§ Observations refer to medicinal products whose pricing and reimbursement dossier was submitted to AIFA by 29 February 2024 but were not yet reclassified by the same date and medicinal products whose dossier was submitted after 29 February 2024.
¶ Medicines whose European Union marketing authorizations belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (13).
Abbreviations: AIFA, Italian Medicines Agency; ATC, Anatomical Therapeutic Chemical; CI, confidence interval.

Table S3.2. Hazard ratios for first reclassification of medicines following the reform of the Italian Medicines Agency (AIFA). Results of the third sensitivity analysis.

		HR (95% CI)	p-value for propiortional hazards[$]
Univariate Cox model	**Post-reform**	3.91 (2.53 - 6.04)	0.279

Legend:
$ p-value of Schoenfeld's residuals test.
Abbreviations: AIFA, Italian Medicines Agency; CI, confidence interval; HR, hazard ratio.

Table S4.1. 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 fourth sensitivity analysis.

	Group of observations prior to the AIFA reform[£]			Group of observations following the AIFA reform[§]		
	Observed	**Reclassified by 31 October 2023 (%)**	**Median time to first reclassification, in days (95% CI)**	**Observed**	**Reclassified between 1 July 2024 and 26 May 2025 (%)**	**Median time to first reclassification, in days (95% CI)**
All medicinal products	128	61 (48)	483 (404 - 643)	60	32 (53)	291 (214 - *NA*)
Orphan medicinal products	37	18 (49)	406 (365 - 735)	13	7 (54)	296 (138 - *NA*)
Antineoplastic medicinal products	41	23 (56)	407 (392 - 625)	18	14 (78)	213 (86 - 297)
Medicinal products by top twenty corporations[¶]	55	29 (53)	403 (361 - 501)	22	13 (59)	236 (95 - *NA*)
ATC class						
ATC class L medicinal products	52	32 (62)	404 (364 - 475)	21	17 (81)	172 (80 - 262)
ATC class A medicinal products	13	3 (23)	NA (365 - *NA*)	7	5 (71)	236 (19 - *NA*)
ATC class N medicinal products	12	6 (50)	431 (130 - *NA*)	5	2 (40)	*NA* (95 - *NA*)
Medicinal products of other ATC classes	51	20 (39)	666 (427 - *NA*)	27	8 (30)	*NA* (291 - *NA*)

Legend:

£ Observations relate to medicinal products with their European Union marketing authorization received by 31 October 2023 and reclassified or censored by 19 May 2025.

§ Observations refer to medicinal products reclassified or censored after 30 June 2024.

¶ Medicines whose European Union marketing authorizations belonged to the biggest twenty pharmaceutical corporations by prescription sales in fiscal year 2024 (13).

Abbreviations: AIFA, Italian Medicines Agency; ATC, Anatomical Therapeutic Chemical; CI, confidence interval.

Table S4.2. Hazard ratios for first reclassification of medicines following the reform of the Italian Medicines Agency (AIFA). Results of the fourth sensitivity analysis.

		HR (95% CI)	p-value for propiortional hazards[$]
Univariate Cox model	**Post-reform**	4.96 (2.75 - 8.93)	0.201
Multivariate Cox model	**Post-reform**	5.17 (2.86 - 9.32)	0.230
	Antineoplastic medicinal products	1.65 (1.09 - 2.51)	0.457

Legend:
$ p-value of Schoenfeld's residuals test.
Abbreviations: AIFA, Italian Medicines Agency; CI, confidence interval; HR, hazard ratio.

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