ANALYSIS OF INTRA-REGIONAL VARIABILITY OF DRUGS' TIME TO ACCESS IN ITALY

HPR162

Fattore C.[1], Canali B.[1], Candelora L.[1], Fiorentino F.[1], La Malfa P.[1], Mazza G., Urbinati D.[1]

[1]IQVIA, Milan, Italy

Introduction

The Italian National Health Service (NHS) is decentralized and organized on three different levels (national, regional, local). The Italian Medicine Agency (AIFA) is responsible for drug evaluation and pricing and reimbursement (P&R) decisions, while the 19 regions and 2 autonomous provinces (APs) have autonomy and direct responsibilities for planning healthcare services and allocating financial resources and can autonomously regulate the market access process within their territories.

After national marketing authorization and definition of conditions of reimbursement by AIFA, drugs need to undergo further regional and local steps to be acquired by hospitals and/or local health units in order to be available to patients. These steps may differ across regions and, in some cases, even across districts within the same region. In this context, drugs' time to regional access (TTRA), defined as the time from AIFA Pricing and Reimbursement (P&R) resolution publication in the Italian Official Journal (Gazzetta Ufficiale) to first regional sales[1], is highly variable among different regions (inter-regional variability).

Inter-regional TTRA has already been evaluated[2-4], but limited evidence exists on intra-regional variability and its determinants.

The aim of this study was to investigate intra-regional variability among drugs in terms of time to access.

Methods

The research conducted was based on data retrieved from an IQVIA proprietary database on Italian negotiation dynamics in which products' clinical features, information on regulatory processes and negotiation outcomes for all new active substances that received a positive opinion from the European Committee for Medicinal Products for Human use (CHMP) starting from January 2015 are systematically collected and updated.

For this study, drugs that received CHMP positive opinion from January 2015 to June 2022 were extracted with the following criteria: only active substances, excluding vaccines, that completed the Italian negotiation pathway for their first indication, were assigned to reimbursement class H or A-PHT and were acquired by hospitals in at least one region[1]. Extensions of therapeutic indications, new pack sizes, renegotiation of reimbursement conditions and drugs marketed through early access programs were excluded from the analysis.

First, intra-regional variability was assessed by calculating the Interquartile Range (IQR) for drugs' TTRA in each region. The top 10 regions with the highest intra-regional time to access variability were selected for the analysis.

Six possible explanatory variables expected to have an impact on drugs' time to access were evaluated: innovative status, orphan drug designation, therapeutic area (oncology vs non-oncology), monotherapy use, presence of AIFA monitoring registry, and negotiation of Managed Entry Agreements (MEAs).

To estimate the impact of covariates on regional time to access, a Poisson Generalized Linear Model with a logarithmic link function and robust standard errors was used to compensate for the fact that the dependent variable (TTRA) is over-dispersed (standard deviation is higher than mean value). The level of significance was set at 5%.

Results

By applying the selection criteria (i.e., CHMP positive opinion received from January 2015 to June 2022 for first indication, Italian negotiation pathway completed for first indication, classification in class H or A-PHT and at least one hospital sale) to the products included in the IQVIA proprietary database on negotiation dynamics, 157 new active substances were selected.

The analysis of the TTRA of these drugs shows that intra-regional TTRA is highly variable in Italy. The regions with the higher variability are Abruzzo, Basilicata, Calabria, Friuli-Venezia Giulia, Marche, Molise, P.A. Trento, P.A. Bolzano, Sardegna, and Umbria *(Tab. 1)*.

Among these regions, orphan designation is the only variable that consistently increases TTRA in a statistically significant way in 7 regions (Abruzzo, Basilicata, P.A. Bolzano, Calabria, Friuli-Venezia Giulia, Marche, Sardegna), ranging from 48% ($p < 0.05$) increase in the P.A. Bolzano to 86% ($p < 0.01$) increase in Abruzzo (holding other covariates constant) *(Tab. 2 and Fig. 1)*. In contrast, TTRA is always reduced for drugs used in monotherapy, and the reduction is statistically significant in 7 regions (Abruzzo, P.A. Bolzano, Calabria, Marche, Umbria, Molise, P.A. Trento), with a minimum access time reduction of 44% ($p < 0.05$) in P.A. Trento, up to a 72% ($p < 0.01$) reduction in Marche, compared to combination drugs *(Tab. 2 and Fig. 2)*. Innovative drugs and drugs with AIFA monitoring registries show shorter TTRA compared to non-innovative drugs and drugs with no registries in Sardegna (-36%, $p < 0.05$) and Friuli Venezia Giulia (-51%, $p < 0.05$) for the first, and in Sardegna (-49%, $p < 0.05$) for the second. The presence of MEAs decreases TTRA by 44% ($p < 0.05$) in Calabria. Finally, the therapeutic area (oncology drugs vs non-oncology drugs), shows no statistically significant impact on TTRA in the selected regions *(Tab. 2)*.

Conclusions

In Italy, inter-regional variability in TTRA is accompanied by high intra-regional variability associated with specific drugs' characteristics in some regions, while still mostly unexplained in other regions. Variability may be explained by different elements related to distinctive characteristics of the region, such as administrative procedures, different approaches of regional decision makers, hospitals' organization and size or presence of healthcare regional debt repayment plans.

Table 1. ***Time to Regional Access***

Top ten regions by TTRA IQR (days)

Region	p25	p75	IQR
TRENTO (PA)	192	1115	923
MOLISE	197	1004	808
BOLZANO (PA)	233	1015	782
BASILICATA	135	707	573
UMBRIA	133	624	491
ABRUZZO	117	598	481
SARDEGNA	206	684	478
CALABRIA	144	592	448
FRIULI V.G.	66	476	410
MARCHE	80	453	374

Table 2. ***Time to Regional Access on covariates in selected regions***

Poisson generalized linear model of time to regional access on covariates

	ABR	BAS	BOL	CAL	FRI	MAR	MOL	SAR	TRE	UMB
Innovativeness	-0.187	-0.453	0.0481	0.155	**-0.723****	0.0984	0.0567	**-0.440****	0.0268	0.294
	(0.322)	(0.398)	(0.245)	(0.265)	**(0.355)**	(0.356)	(0.259)	**(0.203)**	(0.312)	(0.376)
Registry	-0.0362	-0.126	-0.411	-0.340	-0.470	-0.590	-0.133	**-0.683****	-0.472	-0.436
	(0.294)	(0.466)	(0.285)	(0.271)	(0.323)	(0.338)	(0.421)	**(0.277)**	(0.331)	(0.318)
MEAs	-0.488	-0.485	0.0473	**-0.573****	0.566	0.303	0.319	-0.482	0.0612	0.100
	(0.348)	(0.398)	(0.267)	**(0.253)**	(0.343)	(0.466)	(0.310)	(0.258)	(0.297)	(0.482)
Oncological drug	0.338	-0.269	0.227	0.0511	0.0282	0.546	0.447	0.00970	0.0680	0.0215
	(0.287)	(0.433)	(0.295)	(0.259)	(0.335)	(0.424)	(0.405)	(0.272)	(0.372)	(0.425)
Orphan drug	**0.623*****	**0.610****	**0.392****	**0.522*****	**0.577****	**0.574****	0.378	**0.556*****	0.245	0.0763
	(0.236)	**(0.286)**	**(0.175)**	**(0.200)**	**(0.237)**	**(0.276)**	(0.318)	**(0.171)**	(0.267)	(0.289)
Monotherapy	**-0.910*****	-0.261	**-0.811****	**-0.699*****	-0.571	**-1.276*****	**-1.088*****	-0.228	**-0.579****	**-0.903*****
	(0.337)	(0.230)	**(0.324)**	**(0.262)**	(0.340)	**(0.289)**	**(0.354)**	(0.177)	**(0.246)**	**(0.335)**
Constant	5.995***	6.476***	6.653***	6.289***	5.941***	5.927***	6.437***	6.569***	6.716***	6.329***
	(0.147)	(0.149)	(0.124)	(0.144)	(0.189)	(0.201)	(0.142)	(0.123)	(0.111)	(0.152)
Observations	90	76	77	94	75	89	60	81	82	85

Robust standard errors in parentheses.
**** p<0.01, ** p<0.05*

Figure 1. ***Kaplan-Meier of Tme to Regional Access for orphan vs. non-orphan drugs in the selected regions***

Time to Regional Access for orphan vs non-orphan drugs (days)

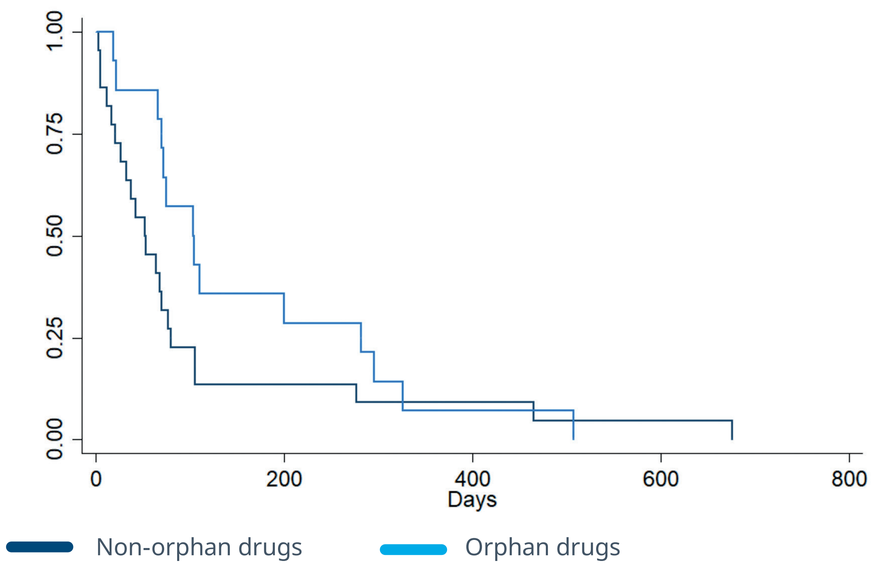
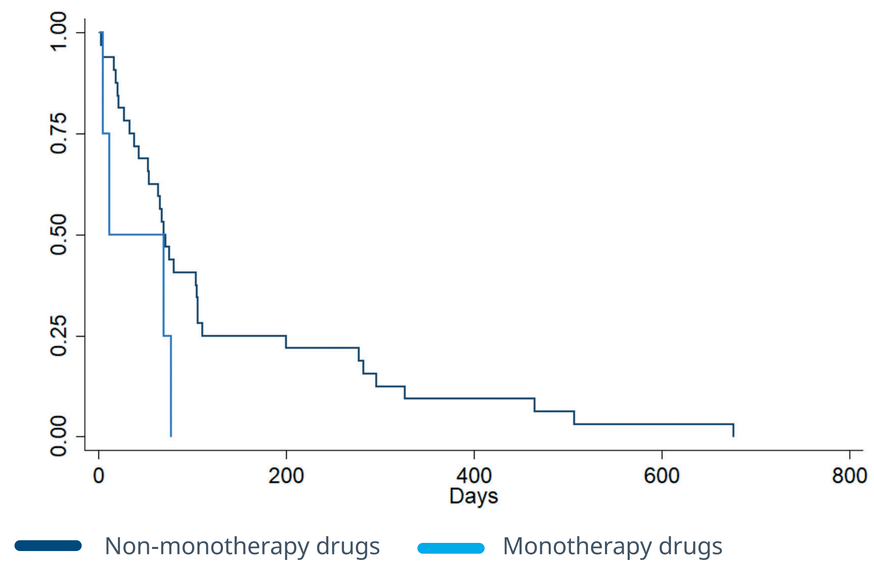


Figure 2. ***Kaplan-Meier of Time to Regional Access for monotherapy vs. non-monotherapy drugs in the selected regions***

Time to Regional Access for monotherapy vs non-monotherapy drugs (days)



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FOR FURTHER INFORMATION: Please contact Duccio Urbinati – duccio.urbinati@iqvia.com IQVIA, VIA FABIO FILZI 29, 20124 MILAN, ITALY

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