AIFA AGENZIA ITALIANA DEL FARMACO

28 NOVEMBRE | Sala PETRARCA

9:00 - 13:00 | EQUITÀ DI ACCESSO ALLE CURE
IL VALORE E IL BUON USO DEI FARMACI

Variabili di contesto e dati globali: la gestione della complessità nella misurazione del valore

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Settore HTA ed economia del farmaco

Arezzo, 28 novembre 2024

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	☒	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	☒	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	☒	☐	☐	☐ facoltativo
2. Consulenza per una società	☒	☐	☐	☐ facoltativo
3. Consulente strategico per una società	☒	☐	☐	☐ facoltativo
4. Interessi finanziari	☒	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	☒	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	☒	☐	☐	☐ facoltativo
7. Sperimentatore	☒	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	☒	☐	☐	☐ facoltativo
9. Interessi Familiari	☒	☐	☐	☐ facoltativo

*Francesco Trotta, secondo il Regolamento per la disciplina dei conflitti di interesse all'interno dell'Agenzia Italiana del Farmaco approvato dal CdA AIFA con Delibera n. 37 del 13 ottobre 2020.

N.B. Per questo intervento non ricevo alcun compenso

Il contesto Globale & Europeo

I consumi

Europa Occidentale
Outlook Uso: stabile

Globale: 3,8 trilioni di DDD nel 2028 con crescita annuale 2,3%/anno

Europa Occidentale:

- Crescita annuale: 1% all'anno
- Uso Procapite: conferma alta intensità Europa (1000 DDD) vs Nord America (750)
- Maggiore crescita (2018-2023): Immunol. & Endocrinologia (+28%); Oncol. (+21%)
- Le scadenze brevettuali: aumento dell'uso di circa 5% (nell'area di riferimento);

Il contesto Globale & Europeo

La spesa

Europa Occidentale
Outlook Spesa: aumento

Globale:

- 2,3 trilioni di $ nel 2028 con crescita annuale del 6-9%/anno
- 2024-2028: aumento spesa di 630 miliardi $
- Nuovi farmaci (193 miliardi $) compensano quelli che perdono brevetto (192 $)
- Maggiore componente aumento spesa: farmaci lanciati prima del 2021 e ancora on-patent

Europa Occidentale:

- Crescita annuale: 4-7% anno
- 2024-2028: aumento spesa di di 70 miliardi $
- Maggiore componente aumento spesa: nuovi farmaci (50 miliardi $)

Italia:

- spesa SSN 2023 pari a 22,8 miliardi € con crescita al 7% arriverebbe a 33,6 miliardi nel 2028
- Ciò vorrebbe dire che la spesa farmaceutica varrebbe oltre il 20% del FSN.

Il contesto Globale

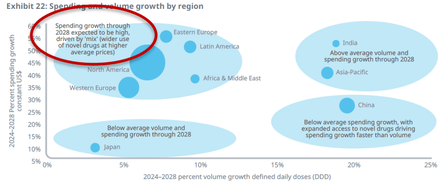
Confronti consumi e spesa tra aree geografiche

Nord America: +6% uso; +45% spesa;
Europa occidentale: +5% uso; +35% spesa
Europa orientale: +7,5 uso; +55% spesa

India: +20% uso; + 55% spesa
Cina: +20% uso; +30% spesa
Giappone: +10% uso; +10% spesa

Spending and volume growth are following diverging trends by region

Exhibit 22: Spending and volume growth by region



Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.

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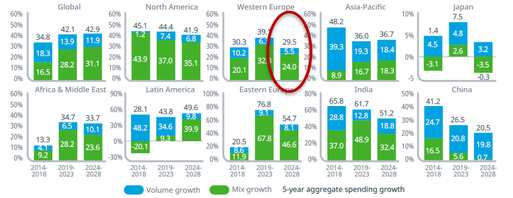
Il contesto Globale

Confronti consumi e spesa tra aree geografiche

- In North America and Western Europe, mix growth accounts for more than 80% of spending growth, while in Asian countries volume growth is a much higher share of the changes in spending.

Spending growth is driven by mix — the change in the average cost of medicines — in many key regions

Exhibit 23: Spending growth globally and in 9 regions, total market excluding COVID-19 vaccines and therapeutics, const US$ 2014–2028



Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.

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Il contesto Globale: l'ampiezza dei «mercati»

SPENDING AND GROWTH BY REGIONS AND KEY COUNTRIES

Faster growing Pharmerging markets are generally improving in their global rankings while developed markets rank lower

Exhibit 34: Global top 20 countries ranking and invoice spending relative to the United States

RANK	2018	% OF U.S. INVOICE SPENDING	RANK	2023	% OF U.S. INVOICE SPENDING	RANK	2028	% OF U.S. INVOICE SPENDING
1	United States	100	1	United States	100	1	United States	100
2	China	27.7	2	China	23.0	2	China	20.0
3	Japan	17.2	3	Japan	10.6	3	Japan	9.3
4	Germany	10.4	4	Germany	9.2	4	Germany	8.9
5	France	7.4	5	France	6.6	5	France	6.5
6 ▲	Italy	6.9	6	Italy	5.9	6	Italy	6.0
7 ▲	United Kingdom	5.6	7	United Kingdom	5.8	7	United Kingdom	5.7
8 ▼	Brazil	5.2	8	Brazil	5.0	8	Brazil	5.3
9 ▲	Spain	5.1	9	Spain	4.7	9	Spain	4.8
10 ▼	Canada	4.5	10	Canada	4.4	10	Canada	4.6
11 ▲	India	4.1	11	India	3.9	11	India	4.0
12 ▲	South Korea	3.2	12 ▲	Russian Federation	2.9	12 ▲	South Korea	2.8
13 ▼	Russian Federation	3.1	13 ▼	South Korea	2.6	13 ▼	Russian Federation	2.6
14 ▼	Australia	2.6	14	Australia	2.3	14 ▲	Argentina	2.5
15 ▲	Indonesia	1.7	15 ▲	Mexico	2.0	15 ▼	Australia	2.0
16	Mexico	1.7	16 ▲	Argentina	1.9	16 ▲	Turkey	1.8
17 ▲	Saudi Arabia	1.7	17 ▲	Poland	1.6	17	Poland	1.8
18 ▼	Argentina	1.7	18 ▼	Saudi Arabia	1.6	18 ▼	Mexico	1.8
19 ▼	Poland	1.6	19 ▲	Turkey	1.4	19 ▼	Saudi Arabia	1.7
20 ▼	Turkey	1.5	20 ▲	Vietnam	1.2	20	Vietnam	1.4

Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Nov 2023.

▼▲ Change in ranking over prior 5 years

Outlook «mercati»:

- Italia: continuerà a essere il 6 mercato al mondo.
- Elevata stabilità nei primi 10 posti

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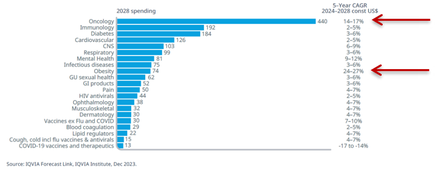
Dove andiamo?

Quali saranno i determinanti della spesa? Quali innovazioni?

Riflessioni programmatiche

Oncology and obesity lead growth while immunology slows due to biosimilars; many other classes are growing in mid-single digits

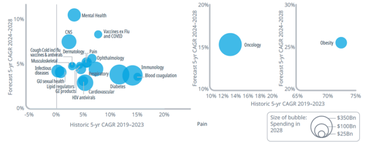
Exhibit 37: Top 20 therapy areas in 2028 in terms of global spending with forecast 5-year CAGRs, const US$Bn



Source: IQVIA Forecast Link, IQVIA Institute, Dec 2023.

Oncology and obesity will lead growth through 2028 while immunology and diabetes growth will slow

Exhibit 38: Global historic and forecast growth for top 20 therapy areas



Source: Source: IQVIA Forecast Link, Dec 2023.

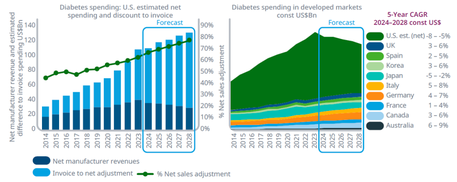
Dove andiamo?

Quali saranno i determinanti della spesa? Quali innovazioni?

Riflessioni programmatiche

Diabetes spending growth is in low single-digits in most developed markets with declines in some, including the U.S., on a net basis

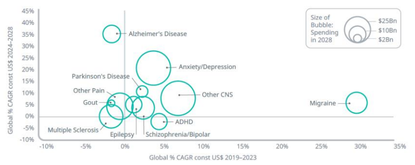
Exhibit 41: Diabetes spending and growth



Source: IQVIA Institute, Dec 2023.

New therapies in Alzheimer's and anxiety/depression are expected to drive spending growth in neurology

Exhibit 43: Leading CNS disorders global market growth dynamics



Source: IQVIA Forecast Link, IQVIA Institute, Dec 2023.

AIFA AGENZIA ITALIANA DEL FARMACO

Dove andiamo?

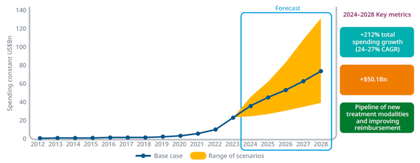
Quali saranno i determinanti della spesa? Quali innovazioni?

Riflessioni programmatiche

Aumenti si rilevanti, ma attenzione all'incertezza

Global obesity spending has accelerated in the past 2 years from novel drugs with a significant upside if more widely reimbursed

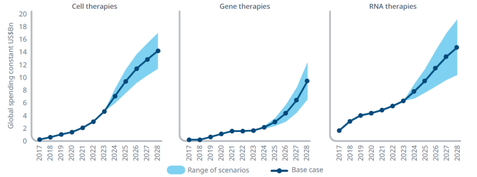
Exhibit 42: Global obesity spending and growth



Source: IQVIA Forecast Link, IQVIA Institute, Dec 2023.

Cell and gene therapies have differing spending outlook and large uncertainties while RNA therapies have the largest potential

Exhibit 45: Cell, gene and RNA therapeutics



Source: Company Financials; IQVIA Institute, Dec 2023.

Come gestite questa complessità ?

Come andare oltre alla richiesta di aumento del finanziamento?

Alcuni esempi, alcune riflessioni, non esaustivi

- Rigore all'ingresso, in particolare quando ci sono alternative
  - Modelli esistenti in altri paesi: QALY, ICER (….e relative deroghe)
  - «pesare bene (meglio) il valore terapeutico aggiunto»
  - Valutare bene i punti di vista (preferenze dei pazienti)
- Concorrenza:
  - secondary patent
  - ritardi di commercializzazione
  - acquisti
- Pazienti attesi & impatto SSN: (ri)contrattazione
- «Nuovi» principi attivi, confronti (in)diretti e comparatori
- L'approvazione P&R non basta: integrazione & silos
- Il valore è dinamico
- Variabilità regionale e (In)Appropriatezze

Rigore all'ingresso, in particolare quando ci sono alternative

- Modelli esistenti in altri paesi: QALY, ICER (….e relative deroghe)
- «pesare bene (meglio) il valore terapeutico aggiunto»
- Valutare bene i punti di vista (preferenze dei pazienti)

Rigore all'ingresso, in particolare quando ci sono alternative

- «pesare bene (meglio) il valore terapeutico aggiunto»


Journal of Cancer Policy 42 (2024) 100509

Contents lists available at ScienceDirect

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jopo

Spending on anticancer drugs among Medicare beneficiaries: Analyzing predictors of drug expenditures

Ashley Nee [a], Alyson Haslam [b], Vinay Prasad [b,*]

[a] Warren Alpert Medical School of Brown University, Providence, RI, United States
[b] University of California, San Francisco, San Francisco, CA, United States

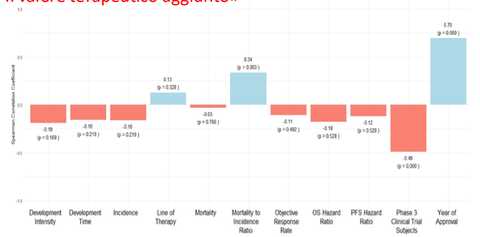


Fig. 3. Spearman Correlation Between Average Spending per Beneficiary (ASPB) Between 2012 and 2021 for Approved Anticancer Drugs. Mortality to incidence ratio, phase 3 clinical trial subjects, and year of approval were statistically significant. P values were adjusted for multiple comparisons using the Benjamini-Hochberg method.

Conclusions: Spending on anticancer drugs by Medicare are predominantly determined by reference pricing and the size of the anticipated treatment population, without an association with therapeutic value. The study advocates for reforms in reimbursement mechanisms for drugs lacking comparator arms and greater transparency for patients treated with these drugs.

Maggiore rigore all'ingresso, in particolare quando ci sono alternative

- Valutare bene i punti di vista (preferenze dei pazienti)

Articles
Lancet Oncol 2024

Preferences for speed of access versus certainty of the survival benefit of new cancer drugs: a discrete choice experiment

Robin Forrest, Mylene Lagarde, Ajay Aggarwal, Huseyin Naci

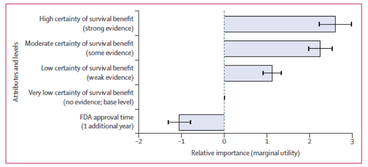


Figure 1: Relative importance of attributes
FDA=Food and Drug Administration. For the certainty attribute levels, marginal utility values illustrate the positive utility associated with increasing certainty, relative to the lowest (reference) level of certainty. For the FDA approval time attribute, marginal utility values present the disutility associated with a 1-year increase in FDA approval time. Error bars represent 95% CIs. Complete marginal utility data are provided in the appendix (p 7). Levels of evidence (strong, some, weak, and none) refer to the evidence linking cancer growth (progression-free survival) to overall survival, which was described to respondents in each choice task. Full definitions of attributes and levels shown to respondents are provided in table 1.

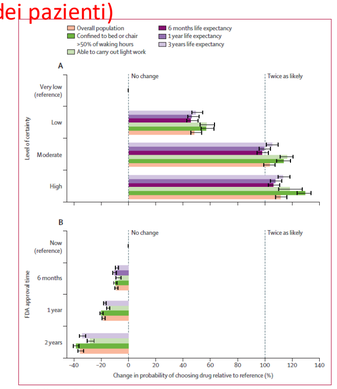


Figure 3: Marginal effect of functional status and life expectancy on drug choice probability—a predicted probability analysis
FDA=Food and Drug Administration. (A) Positive change in probability that a respondent will choose a given drug as certainty of survival benefit increases. (B) Negative change in probability that a respondent will choose a given drug as FDA approval time increases. Scenario analysis within A and B illustrates differences in sensitivities of respondents to certainty and FDA approval time, depending on functional status and life expectancy (see appendix p 2 for additional information). Experimental design was used to restrict scenarios so that wait time (until FDA approval) could not exceed life expectancy.

Maggiore rigore all'ingresso, in particolare quando ci sono alternative

- Valutare bene i punti di vista (preferenze dei pazienti)

Articles

Lancet Oncol 2024
Published Online
November 18, 2024
https://doi.org/10.1016/
S1470-2045(24)00596-5
See Online/Comment
https://doi.org/10.1016/
S1470-2045(24)00654-5

Preferences for speed of access versus certainty of the survival benefit of new cancer drugs: a discrete choice experiment

Robin Forrest, Mylène Lagarde, Ajay Aggarwal, Huseyin Naci

Department of Health Policy, London School of Economics and Political Science, London, UK (R Forrest MSc, M Lagarde PhD, H Naci PhD); Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK (Prof A Aggarwal MD PhD)

Correspondence to:
Mr Robin Forrest, Department of Health Policy, London School of Economics and Political Science, London, WC2A 2AE, UK
r.forrest@lse.ac.uk

Added value of this study

To our knowledge, this is the first empirical study to elicit preferences for certainty of the survival benefit of new cancer drugs versus speed of access, and the first to estimate individuals' willingness to wait for greater certainty of the survival benefit of new cancer drugs.

Implications of all the available evidence

Patients with cancer simultaneously value faster access to new cancer drugs, and high certainty that these drugs will offer survival benefit. The competing nature of these preferences characterises the challenging trade-off faced by the FDA during its drug approval decisions. In its accelerated approval decisions of new cancer drugs, the FDA might be underestimating the willingness of some patients to wait for greater certainty of survival benefit.

Concorrenza

- Secondary patent
- Ritardi di commercializzazione
- acquisti

Concorrenza: secondary patent, ritardi di commercializzazione, acquisti

Secondary patent

SALUTE&BENESSERE / Medicina

Multa Ue da 462 milioni a Teva: 'Abuso su un farmaco per la sclerosi multiplo'

'La società ha abusato del brevetto ostacolando una cura rivale'

BRUXELLES, 31 ottobre 2024, 17:31
Redazione ANSA

Condividi

ANSAcheck

↑ - RIPRODUZIONE RISERVATA

Accordi per ritardare commercializzazione

quotidianosanità.it

Giovedì 06 GIUGNO 2024

Farmaci. Antitrust avvia istruttoria nei confronti di 8 società per intesa restrittiva della concorrenza sul principio attivo ranibizumab

Si ipotizza l'esistenza di un coordinamento delle strategie commerciali tra queste società per ritardare l'ingresso nel mercato italiano di Byooviz (principio attivo ranibizumab), un farmaco biosimilare sviluppato e commercializzato dai gruppi Samsung Bioepis e Biogen. Byooviz è il biosimilare di Lucentis, a sua volta sviluppato da Genentech e commercializzato in Italia dal gruppo Novartis.

Concorrenza: secondary patent, ritardi di commercializzazione, acquisti

- Brevetto scaduto: device market exclusivity e contenzioso


Clinical Review & Education

JAMA | Special Communication

Patents and Regulatory Exclusivities on GLP-1 Receptor Agonists

Rasha Alhiary, PharmD; Aaron S. Kesselheim, MD, JD, MPH; Sarah Gabriele, LLM, MBE; Reed F. Beall, PhD; S. Sean Tu, JD, PhD; William B. Feldman, MD, DPhil, MPH

JAMA August 15, 2023 Volume 330, Number 7

- Strategies include obtaining large numbers of different patents on the same product, obtaining new patents on products even after FDA approval, and settling patent litigation brought by potential generic competitors.
- Lawmakers and regulators should work to develop solutions that facilitate timely entry of generic drug-device combinations forGLP-1 receptor agonists so that manufacturers can earn reasonable returns for limited periods of time, while more patients eventually benefit from lower costs and improved access to these useful drugs.

Concorrenza: secondary patent, ritardi di commercializzazione, acquisti

- Brevetto scaduto: device market exclusivity e contenzioso

Clinical Review & Education

JAMA | Special Communication

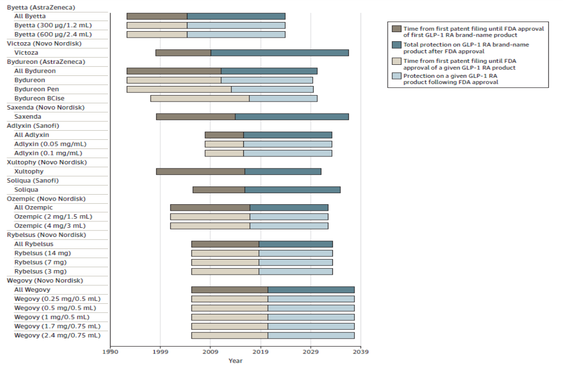
Patents and Regulatory Exclusivities on GLP-1 Receptor Agonists

Rasha Alhary, PharmD; Aaron S. Kesselheim, MD, JD, MPH; Sarah Gabrielle, LLM, MBE; Reed F. Beall, PhD; S. Sean Tu, JD, PhD; William B. Feldman, MD, DPhil, MPH

JAMA August 15, 2023 Volume 330, Number 7

- The median total duration of protectior from FDA approval, when accounting for both preapproval and postapproval patents and regulatory exclusivities, was 18.3 years (IQR, 16.0-19.4)

Figure 2. Protection From Patents and Regulatory Exclusivities on Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists (RAs), 1993-2038



This figure shows the expected duration of protection from generic competition on each GLP-1 RA from the time of first patent filing until the expiration of the last patent or regulatory exclusivity. The dark blue bars (uppermost for each product) represent protection for the product as a whole, while the light blue bars represent protection for each of the product's individual strengths and/or formulations. Products are listed in ascending order based on the initial Food and Drug Administration (FDA) approval date for a given product.

Manufacturers may add new patents in subsequent years, which could expire later than patents depicted in the figure. The median total duration of protection from FDA approval among GLP-1 RAs is 18.3 years (IQR, 16.0-19.4). The median time elapsed from the earliest patent filing date within a given product to the expiration date of the last-to-expire patent or exclusivity on that product is 31.9 years (IQR, 29.9-36.6).

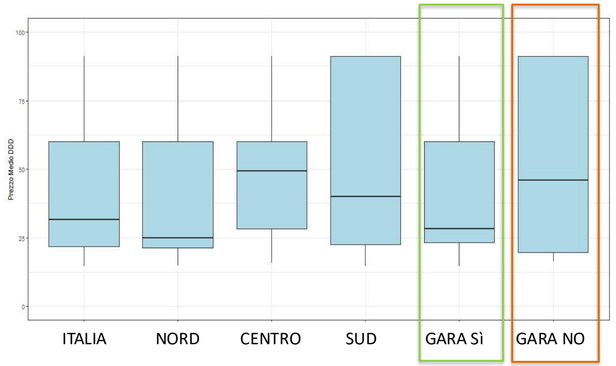
Concorrenza: secondary patent, ritardi di commercializzazione, acquisti

Ok alla protezione, ma quando scade il brevetto?
Se non scade mai come sostengo innovazione?

Concorrenza: secondary patent, ritardi di commercializzazione, acquisti

Capacità di acquisto (centralizzato): fabbisogni & gare in concorrenza

Prezzo medio DDD originator + equivalente **a 12 mesi dalla scadenza** (principio attivo Bortezomib)



• Pazienti attesi & impatto SSN: (ri)contrattazione

- Aumentano i pazienti (rispetto all'atteso)
- Nuove estensioni di indicazione
- Aumenta la spesa
- Aumentano i consumi
- Diminuiscono i costi medi DDD

- Rinegoziazioni
- Diminuiscono i costi medi DDD

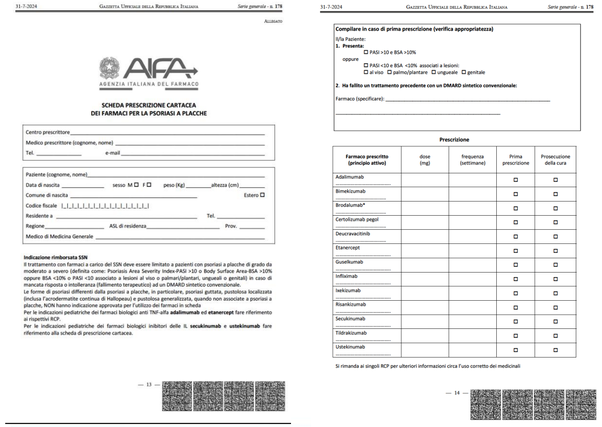
L'uso dei farmaci in Italia
Rapporto Nazionale. Anno 2023

Tabella 3.17 Effetto consumi, prezzi e mix sulla variazione della spesa per i farmaci erogati dalle strutture sanitarie pubbliche: confronto 2023-2022
(per ogni categoria ATC sono stati inclusi i sottogruppi terapeutici in ordine decrescente di spesa pro capite, fino al valore di 0,10 euro)

ATC I livello / ATC IV livello	Spesa lorda *pro capite*	DDD/1000 *ab die*	Δ % 23-22 Spesa	DDD	Prezzi	Mix	Δ % Costo medio DDD
Italia	275,16	194,9	8,2	4,9	-3,7	7,1	3,1
L - Farmaci antineoplastici e immunomodulatori	120,47	13,5	6,3	9,6	-4,8	1,9	-3,0
Inibitori di PD-1/PD-L1 (prot. morte cellulare prog.1/lig1)	14,96	0,5	12,7	26,0	-6,0	-4,9	-10,6
Inibitori dell'interleuchina	11,57	1,3	17,1	19,5	-1,6	-0,4	-2,0
Inibitori di CD38 (cluster di differenziazione 38)	8,21	0,3	18,7	32,8	-6,2	-4,7	-10,6
A - Apparato gastrointestinale e metabolismo	25,66	43,7	13,4	12,7	-6,3	7,4	0,6
Analoghi del recettore GLP-1 (*glucagon-like peptide-1*)	6,55	7,4	32,7	34,8	-5,5	4,2	-1,6
Enzimi	5,78	0,0	2,7	14,4	-6,1	-4,4	-10,2

«Nuovi» principi attivi, confronti (in)diretti e comparatori

Psoriasi, area clinica affollata, 13 p.a



31-7-2024 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA Serie generale - n. 178

ALLEGATO

AIFA AGENZIA ITALIANA DEL FARMACO

SCHEDA PRESCRIZIONE CARTACEA DEI FARMACI PER LA PSORIASI A PLACCHE

Centro prescrittore _____
Medico prescrittore (cognome, nome) _____
Tel. _____ e-mail _____

Paziente (cognome, nome) _____
Data di nascita _____ sesso M ☐ F ☐ peso (Kg) _____ altezza (cm) _____
Comune di nascita _____ Estero ☐
Codice fiscale |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
Residente a _____ Tel. _____
Regione _____ ASL di residenza _____ Prov. _____
Medico di Medicina Generale _____

Indicazione rimborsata SSN
Il trattamento con farmaci a carico del SSN deve essere limitato a pazienti con psoriasi a placche di grado da moderato a severo (definito come: Psoriasis Area Severity Index-PASI >10 o Body Surface Area-BSA >10% oppure BSA <10% o PASI <10 associato a lesioni al viso o palmari/plantari, ungueali o genitali) in caso di mancata risposta o intolleranza (fallimento terapeutico) ad un DMARD sintetico convenzionale.
Le forme di psoriasi differenti dalla psoriasi a placche, in particolare, psoriasi guttata, pustolosa localizzata (incluso l'acrodermatite continua di Hallopeau) e pustolosa generalizzata, quando non associate a psoriasi a placche, NON hanno indicazione approvata per l'utilizzo dei farmaci in scheda
Per le indicazioni pediatriche dei farmaci biologici anti TNF-α/**adalimumab** ed **etanercept** fare riferimento ai rispettivi RCP;
Per le indicazioni pediatriche dei farmaci biologici inibitori delle IL **secukinumab** e **ustekinumab** fare riferimento alla scheda di prescrizione cartacea.

— 13 —

31-7-2024 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA Serie generale - n. 178

Compilare in caso di prima prescrizione (verifica appropriatezza)
Il/la Paziente:
1. Presenta:
☐ PASI >10 e BSA >10%
oppure
☐ PASI <10 e BSA <10% associati a lesioni:
☐ al viso ☐ palmo/plantari ☐ ungueale ☐ genitale
2. Ha fallito un trattamento precedente con un DMARD sintetico convenzionale:
Farmaco (specificare): _____

Prescrizione

Farmaco prescritto (principio attivo)	dose (mg)	frequenza (settimane)	Prima prescrizione	Prosecuzione della cura
Adalimumab			☐	☐
Bimekizumab			☐	☐
Brodalumab*			☐	☐
Certolizumab pegol			☐	☐
Deucravacitinib			☐	☐
Etanercept			☐	☐
Guselkumab			☐	☐
Infliximab			☐	☐
Ixekizumab			☐	☐
Risankizumab			☐	☐
Secukinumab			☐	☐
Tildrakizumab			☐	☐
Ustekinumab			☐	☐

Si rimanda ai singoli RCP per ulteriori informazioni circa l'uso corretto dei medicinali

— 14 —

A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period and a Long-Term Extension Period to Evaluate the Efficacy and Safety of XXXXmab in Patients with Moderate-to-Severe Plaque Psoriasis

- L'approvazione P&R non basta: integrazione & silos

BioDrugs (2024) 38:831–844
https://doi.org/10.1007/s40259-024-00683-0

ORIGINAL RESEARCH ARTICLE

Advanced Therapy Medicinal Products: Availability, Access and Expenditure in Italy

Pia Rivetti di Val Cervo[1] · Eva Alessi[1] · Marilena Lastella[1] · Antonio La Greca[1] · Francesco Trotta[1]

Accepted: 16 September 2024 / Published online: 15 October 2024

- Non basta l'AIC e la rimborsabilità SSN
- Infrastruttura necessaria
- Integrare i silos

Table 4 Distribution of authorized and active facilities in relationship with regional population and number of ATMP treatments in 2023 (*n* = 6 ATMPs)

Region	Authorized facilities	*N* of authorized facilities per Mln inhabitants	Active facilities	Inactive facilities	*N* of active facilities per Mln inhabitants	*N* of treatments in 2023	*N* of treatments per active facility	*N* of treatments per Mln inhabitants
Italy	**107**	**1.8**	**60**	**47**	**1.0**	**360**	**6.0**	**6.1**
Northern Italy	**46**	**1.7**	**34**	**12**	**1.2**	**221**	**6.5**	**8.1**
Piemonte	4	0.9	4	0	0.9	27	6.8	6.4
Valle D'Aosta	1	8.1	0	1	–	0	–	–
Lombardia	24	2.4	18	6	1.8	102	5.7	10.2
Trentino Alto Adige	3	2.8	1	2	0.9	0	0.0	–
Veneto	6	1.2	5	1	1.0	33	6.6	6.8
Friuli Venezia Giulia	2	1.7	2	0	1.7	5	2.5	4.2
Liguria	2	1.3	2	0	1.3	15	7.5	9.9
Emilia Romagna	4	0.9	2	2	0.5	39	19.5	8.8
Central Italy	**16**	**1.4**	**11**	**5**	**0.9**	**63**	**5.7**	**5.4**
Toscana	3	0.8	3	0	0.8	30	10.0	8.2
Umbria	1	1.2	1	0	1.2	7	7.0	8.2
Marche	4	2.7	3	1	2.0	3	1.0	2.0
Lazio	8	1.4	4	4	0.7	23	5.8	4.0
Southern Italy	**45**	**2.3**	**15**	**30**	**0.8**	**76**	**5.1**	**3.8**
Abruzzo	4	3.1	1	3	0.8	9	9.0	7.1
Molise	3	10.3	0	3	–	2	–	6.9
Campania	8	1.4	4	4	0.7	20	5.0	3.6
Puglia	9	2.3	5	4	1.3	15	3.0	3.8
Basilicata	3	5.6	0	3	–	0	–	–
Calabria	2	1.1	2	0	1.1	11	5.5	6.0
Sicilia	5	1.0	3	2	0.6	18	6.0	3.7
Sardegna	11	7.0	0	11	–	1	–	0.6

mln, million

- Il valore è dinamico

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Home > News > EMA recommends revoking conditional marketing authorisation for Ocaliva

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EMA recommends revoking conditional marketing authorisation for Ocaliva

28 June 2024

Benefits of Ocaliva no longer considered to outweigh its risks

News · Human · Referrals

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EMA's human medicines committee (CHMP) has concluded its review of the medicine Ocaliva (obeticholic acid) and has recommended that the medicine's marketing authorisation be revoked, because its benefits are no longer considered to outweigh its risks. Ocaliva is used to treat adults with primary biliary cholangitis (PBC), an autoimmune condition that causes gradual destruction of the bile ducts in the liver, which can lead to liver failure and increase the risk of liver cancer.

At the time of its conditional marketing authorisation in 2016, Ocaliva was shown to reduce the blood levels of alkaline phosphatase (ALP) and bilirubin (markers of liver damage) in patients with PBC, and this was considered indicative of an improvement in the condition of the liver. However, the clinical benefits of Ocaliva needed to be demonstrated in further studies, which were requested by EMA as part of the conditions to the marketing authorisation of the medicine. In particular, study 747-302 was a randomised clinical trial aimed at confirming the clinical benefits and safety of Ocaliva in patients for whom ursodeoxycholic acid (UDCA, another medicine for PBC) does not work well enough, or who cannot take UDCA.

The CHMP has now reviewed the findings from this study, alongside other available data including real-world data and data from supportive studies submitted by the company that markets Ocaliva, and information submitted by healthcare professional and patient associations. In addition, the CHMP took into account the feedback from a group of experts in liver disease, which provided their views on specific questions posed by the CHMP, and views from

- Variabilità regionale e (In)Appropriatezze

Il caso degli antibiotici access

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlae110

JAC-Antimicrobial Resistance

Patterns of community antibiotic use with reference to the AWa classification of the World Health Organization

Carlo Gagliotti[1]*†, Agnese Cangini[2]†, Roberto Da Cas[3], Ilaria Ippoliti[3], Francesco Trotta[2] and Filomena Fortinguerra[2]

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†These authors have contributed equally to this work and share first authorship.

Received 29 January 2024; accepted 29 June 2024

- Maggiori cosumi Ab, Maggiore rischio AMR
- Maggiori consume Ab, minore ricorso a categoria access

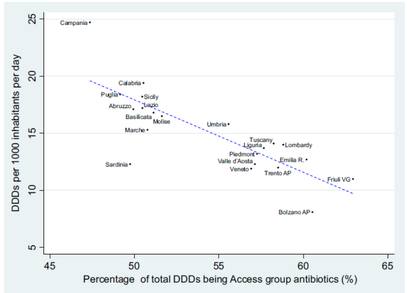

Figure 1. Correlation[a] between overall community consumption of antibiotics for systemic use (J01) by region and percentage of antibiotic consumption belonging to the Access group according to WHO AWaRe classification system (Italy, 2021).[a]Correlation coefficient = −0.8; $R^2 = 0.64$; $P < 0.001$.

Conclusioni

- Previsioni ci sono quindi programmazione possibile
- Spesa in aumento e aree identificate
- Alcuni strumenti disponibili
- Ogni attore può partecipare
- Cooperazione necessaria

Francesco Trotta
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Quali sono i determinanti del prezzo?

Determinants of price negotiations for new drugs. The experience of the Italian Medicines Agency

Federico Villa [a,b,*], Michaela Tutone [a,c,1], Gianluca Altamura [a], Sara Antignani [a], Agnese Casgini [a], Ida Fortino [a,1], Mario Melazzini [a,1], Francesco Trotta [a], Giovanni Tafuri [a,1], Claudio Jommi [d,1]

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Table 3
Overview of the impact that the negotiation of all agreements had on the price of novel drugs in 2013–2017 in Italy.

	New Drugs 2013-2017*	average **ΔP** (average of the difference between the final price negotiated with AIFA and the price proposed by the company)
All Reimbursed Drugs	**133**	**−27.4%**
Reimbursed	44	**−25.1%**
Orphan Drugs		
Reimbursed	89	**−28.6%**
New Molecular Entities		
Reimbursed	23	**−32.2%**
Innovative Drugs		

* all new drugs whose P&R process in Italy was concluded in the last 5 years (2013–2017) with a positive decision on reimbursement.

- The average deltaP for all new reimbursed drugs in Italy is 27.4%.
- The price reduction is higher for innovative drugs(-32.2%).
- The possible **determinants** that influence more the delta P are: the use of a **Registry**, the use of a **MEA**, the target

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JAMA Health Forum

Original Investigation

Financial Outcomes of Managed Entry Agreements for Pharmaceuticals in Italy

Francesco Trotta, PhD;

Table. Number of Medicinal Products, Overall Expenditure, Payback Amount, and Proportion of Payback to Expenditures by Category of Agreement and Subtype[a]

	2019-2021			
Category of agreement/ subtype	Medicinal products, No. (%)[b]	Overall expenditure, €	Payback, € (%)	Median payback on expenditure, %
Financial-based MEAs	24 (38.7)	5 181 664 024	158 145 261 (48.3)	3.7
Capping	4 (6.5)	1 324 160 430	13 373 625 (4.1)	1.9
Capping/cost sharing	1 (1.6)	105 068 629	11 449 359 (3.5)	10.9
Cost sharing	19 (30.6)	3 752 434 965	133 322 277 (40.7)	3.7
Health outcome-based MEAs	30 (48.4)	2 498 959 121	74 494 328 (22.7)	3.3
Payment by result	28 (45.2)	2 293 803 153	72 352 104 (22.1)	4.4
Payment by result/risk sharing	2 (3.2)	205 155 968	2 142 223 (0,7)	1.0
Mixed MEAs	8 (12.9)	1 189 667 550	94 871 381 (29.0)	6.7
Capping/cost sharing/ payment by result	1 (1.6)	351 573 528	51 897 706 (15.8)	14.8
Cost sharing/paymene by result	7 (11.3)	838 094 022	42 973 675 (13.1)	6.6
Total	62	8 870 290 695	327 510 970	3.8

Key Points

Question Are managed entry agreements (MEAs) important for the sustainability of pharmaceutical spending, and what are the financial outcomes of MEAs?

Findings In this observational study of the financial outcomes of medicines with MEAs from 2019 to 2021 in Italy, the median proportion of payback to expenditure was 3.8%.

Meaning These findings suggest that MEAs have limited importance for managing pharmaceutical expenditures; thus, prioritizing MEA use, identifying potential design changes, and improving implementation are valuable considerations.

MEA per gestire innovazione: si, però

La spesa farmaceutica cresce: perché?

Prezzi alti?

Disponibilità di nuovi farmaci?

Aumento aspettativa di vita, demografia?

Variabilità regionale?

(In)Appropriatezza?

Ridotto numero di scadenze brevettuali ultimi anni?

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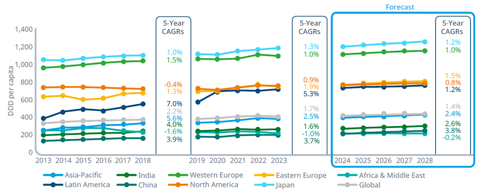
eventuale argomento sezione/slide

Titolo (21 pt)

Outlook Uso: stabile

Per capita medicine use varies by region with Japan and Western Europe having more than double the use of most other regions

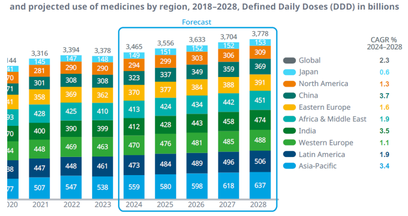
Exhibit 4: Historical and projected per capita use of medicine by region, 2013–2028



Source: IQVIA Institute, Dec 2023; The World Bank, Jul 2023.

nedicines remained flat in 2023 but is expected to grow annually over the next 5 years

and projected use of medicines by region, 2018–2028, Defined Daily Doses (DDD) in billions



Source: 2023.

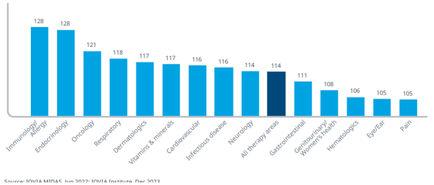
Patient use of medicines grew by 14% over the past five years, driven by increased access to medicines in regions around the world and is expected to grow by a further 12% — or 400 billion defined daily doses — through 2028.

Titolo (21 pt)

Testo compreso tra i 12 e i 18

Medicine use has been growing across therapy areas since 2019, with highest growth in immunology, endocrinology, and oncology

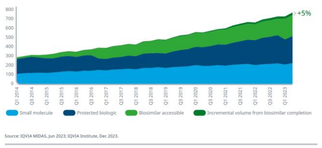
Exhibit 6: Defined daily doses (DDD) in 2023 across select therapy areas indexed to 2018 values (2018 value = 100)



Immunology, endocrinology, and oncology have exceeded the global 14% average growth in defined daily doses in the past five years, driven primarily by substantial numbers of novel products and wider access to them across geographies.

Nearly half of immunology biologic volume is facing biosimilar competition, which has led to increased use

Exhibit 8: Immunology volume in 10 developed countries by molecule type and protection



- It is also possible to see a 5% incremental use of the medicines, which are subject to biosimilar competition, confirming there is additional demand that is able to be met at lower costs.

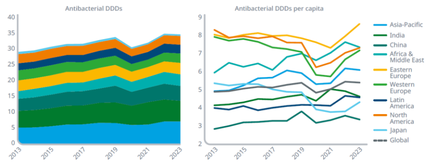
Titolo (21 pt)

Outlook Uso: stabile

Testo compreso tra i 12 e i 18

Use of antibacterials was significantly disrupted by the COVID-19 pandemic but returned to historic levels in 2022 and 2023

Exhibit 11: Antibacterial volume in DDDs and DDD per capita by region

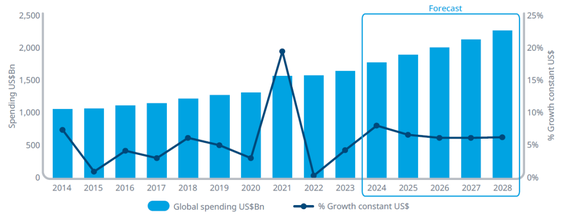


Source: IQVIA MIDAS, Jun 2023; IQVIA Institute, Dec 2023.

Tes

The global medicine market — using invoice price levels — is expected to grow at 5–8% CAGR through 2028 to about $2.3Tn

Exhibit 14: Global medicine market size and growth 2014–2028 including estimated COVID-19 vaccine and therapeutic spending



Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.

- The global medicine market — using list price levels — is expected to grow at 5-8% CAGR through 2028, reaching about $2.3Tn in total market size.

Outlook Spesa: aumento

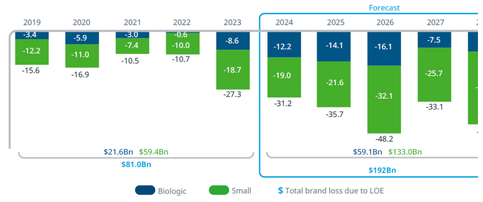
eventuale argomento sezione/slide

Titolo (21 pt)

Outlook Uso: stabile

The impact of exclusivity losses will reach $192Bn over the next 5 years, with around 30% due to the availability of biosimilars

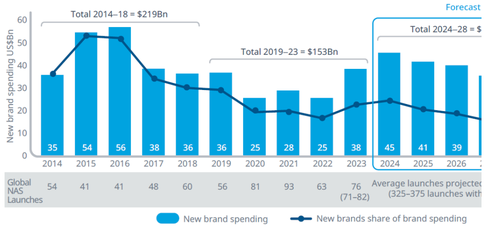
Exhibit 19: 10 developed countries impact of brand losses of exclusivity 2019–2028, US$Bn



Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Nov 2023.

New brand spending in the 10 developed countries is pr be higher than in the last 5 years but a smaller share of

Exhibit 20: 10 Developed new brand spending, excluding COVID-19 vaccines and therapeutics



Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.

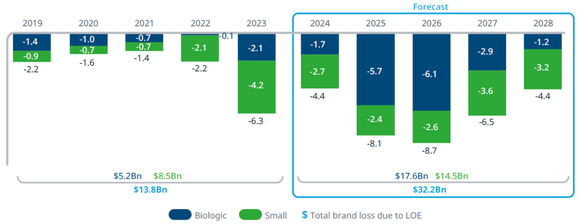
eventuale argomento sezione/slide

Titolo (21 pt)

Outlook Uso: stabile

The impact of exclusivity losses will reach $32Bn over 5 years, with more than half due to the availability of biosimilars

Exhibit 29: EU4+UK impact of brand losses of exclusivity 2019–2028, US$Bn



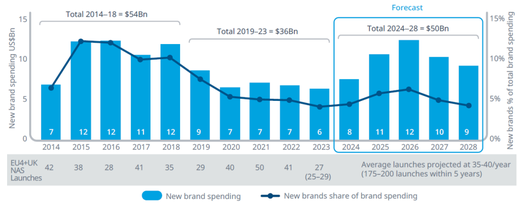
Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Nov 2023.

Titolo (21 pt)

Outlook Uso: stabile

New brand spending in EU4+UK is projected to be higher than the last 5 years but a smaller share of spending

Exhibit 30: EU4+UK new brand spending, excluding COVID-19 vaccines and therapeutics



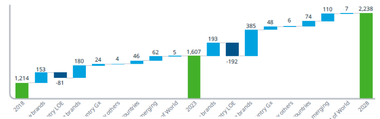
Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.

- New brands in the 10 leading developed markets are expected to contribute $193Bn in growth, up $40Bn from the past five years.

- The largest driver of growth, which is also expected to double, is that from existing protected brands. This is a group of products in the forecast period which were launched prior to 2021 and whose growth contribution has been the most significant driver of the higher growth outlook to 2028.

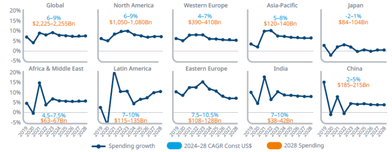
Global growth will continue to mostly be driven by new and existing brands in leading developed countries

Exhibit 18: Global spending and growth, US$Bn 2018–2028, excluding COVID-19 vaccines and therapeutics



Higher global spending growth occurred in key regions after the pandemic, particularly in 2023 in North America

Exhibit 21: Spending growth globally and in 9 regions, total market excluding COVID-19 vaccines and therapeutics, const US$ 2019–2028



Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.

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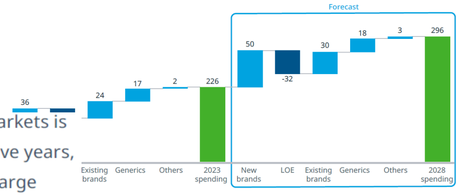
Tit

Testo com

- Medicine spending in the top five European markets is expected to increase by $70Bn over the next five years, up from $65Bn in the past five years but with large shifts in the drivers of growth.

Spending in Europe is expected to increase by $70Bn through 2028, driven by new brands

Exhibit 28: Spending and growth drivers in France, Germany, Italy, Spain, and UK 2018–2028 const US$Bn



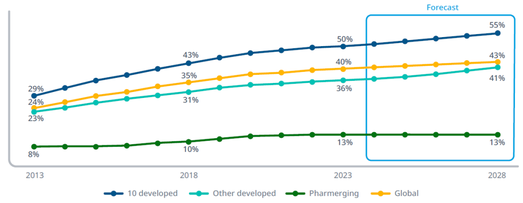
2023; IQVIA Institute, Nov 2023.

eventuale argomento sezione/slide

Specialty medicines will represent about 43% of global spending in 2028 and 55% of total spending in leading developed markets

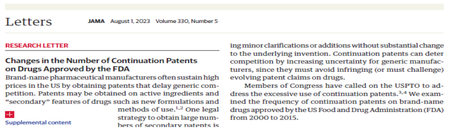
utlook Uso: stabile

Exhibit 36: Specialty medicines share of spending



Source: IQVIA Institute, Dec 2023.

○ Brevetto scaduto: secondary patenting



Letters JAMA August 1, 2023 Volume 330, Number 5

RESEARCH LETTER

Changes in the Number of Continuation Patents on Drugs Approved by the FDA

Brand-name pharmaceutical manufacturers often sustain high prices in the US by obtaining patents that delay generic competition. Patents may be obtained on active ingredients and "secondary" features of drugs such as new formulations and methods of use.[1,2] One legal strategy to obtain large numbers of secondary patents is

Supplemental content

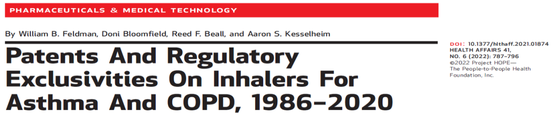
ing minor clarifications or additions without substantial change to the underlying invention. Continuation patents can deter competition by increasing uncertainty for generic manufacturers, since they must avoid infringing (or must challenge) evolving patent claims on drugs.

Members of Congress have called on the USPTO to address the excessive use of continuation patents.[3,4] We examined the frequency of continuation patents on brand-name drugs approved by the US Food and Drug Administration (FDA) from 2000 to 2015.

- One legal strategy to obtain large numbers of secondary patents, called a *continuation*, in which a patent holder adds new applications to a prior submission by offering minor clarifications or additions without substantial change to the underlying invention.
- Continuation patents can deter competition by increasing uncertainty for generic manufacturers, since they must avoid infringing (or must challenge) evolving patent claims on drugs.
- categorized each patent as original or continuation using the Google Patents Public Data Sets on Google BigQuery.

- While the ratio of the number of original patents per approval increased by 15% from 1.3 for drugs approved in 2000 to 1.5 for drugs approved in 2015, **the ratio of continuation patents increased 200%** from 0.6 for drug approved in 2000 to 1.8 for drugs approved in 2015
- While the ratio of the number of litigated original patents per approval increased by 63% from 0.38 for drugs approved in 2000 to 0.62 for drugs approvedin2015, **the ratio of litigated continuation patents increased 213%** from 0.22 for drugs approved in 2000 to 0.69 for drugs approved in 2015.
- Lawsuits brought by brand-name firms on patents listed with the FDA can earn 30-month stays on generic drug approval even if these lawsuits eventually fail.
- These findings suggest that continuation patents are becoming increasingly common in drug patent thickets, likely delaying or deterring generic competition,2,5 and thus potentially contributing to delays in patient access to generic medications and increases in health care spending.

○ Brevetto scaduto: device market exclusivity COPD


PHARMACEUTICALS & MEDICAL TECHNOLOGY

By William B. Feldman, Doni Bloomfield, Reed F. Beall, and Aaron S. Kesselheim

Patents And Regulatory Exclusivities On Inhalers For Asthma And COPD, 1986–2020

DOI: 10.1377/hlthaff.2021.01874
HEALTH AFFAIRS 41,
NO. 6 (2022): 787–796

- Patent protection, and its linkage to the regulatory system, creates circumstances enabling brand-name inhaler manufacturers to limit generic competition through certain “lifecycle management” strategies.
- For example, manufacturers can prolong patent protection by obtaining later-expiring patents on the inhaler devices themselves, not just the medications contained
- within these devices.
- They may also receive nonpatent statutory regulatory exclusivities granted by the FDA alongside patents, add new patents and regulatory exclusivities to inhalers after approval, combine old ingredients into new products, and shift active ingredients from one inhaler device to another.
- analyzed how brand-name manufacturers used these patents in combination with other exclusivities to limit generic competition.
- Overall, manufacturers received a median of 16.2 years (IQR: 11.8–19.6) of protection from regulatory exclusivities and patents.

- **Brevetto scaduto: device market exclusivity COPD**

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NO. 6 (2022): 787–796
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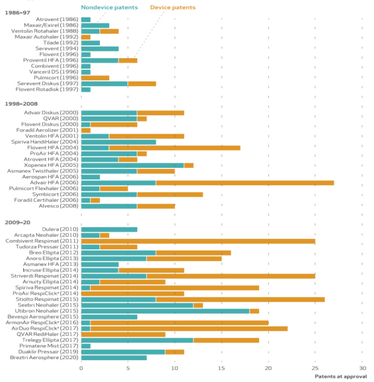
The People-to-People Health
Foundation, Inc.

- Overall, manufacturers received a median of 16.2 years (IQR: 11.8–19.6) of protection from regulatory exclusivities and patents.
- "device hopping." This strategy entails placing the same active ingredient into a new device with new patents and exclusivities that ensure longer protection.
- For example, our analysis shows that GSK received thirty-five years of protection from competition after FDA approval on its fluticasone inhalers through the successive release of new inhaler devices containing fluticasone: Flovent (approved in 1996), Flovent Rotadisk (1997), Flovent Diskus (2000), Flovent HFA (2004), and most recently Arnuity Ellipta (2014).
- The median time that elapsed from the first patent filing for a given product to expiration of the last-to expire patent or

EXHIBIT 2

Patents per inhaler for asthma and chronic obstructive pulmonary disease at the time of Food and Drug Administration (FDA) approval, 1986–2020



SOURCES Authors' analysis of data from the FDA Orange Book and Drugs@FDA, 1986–2020. **NOTES** This figure includes patents granted to inhalers that were filed in the US before FDA approval. The median number of preapproval patents grew from 2 per inhaler (interquartile range: 1–4) in 1986–97 to 8 per inhaler (IQR: 6–11) in 1998–2008 and 11 per inhaler (IQR: 6.5–19) in 2009–20. *These include the corresponding Digihaler lines, which were part of the same new drug applications as the RespiClick inhalers.

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○ Brevetto scaduto: device market exclusivity COPD

PHARMACEUTICALS & MEDICAL TECHNOLOGY

By William B. Feldman, Doni Bloomfield, Reed F. Beall, and Aaron S. Kesselheim

Patents And Regulatory Exclusivities On Inhalers For Asthma And COPD, 1986–2020

DOI: 10.1377/hlthaff.2021.018
HEALTH AFFAIRS 41,
NO. 6 (2022): 787–796

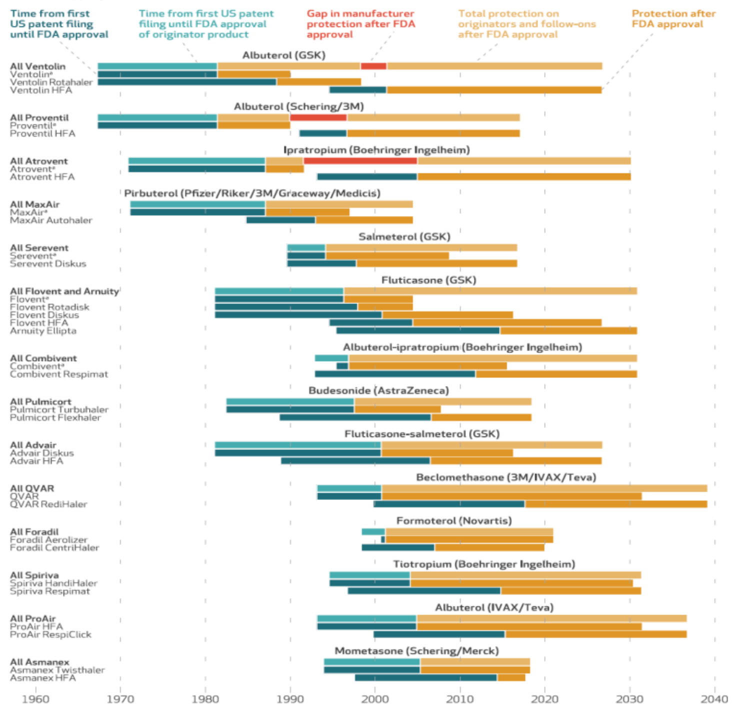
- In the fourteen cases of device hopping analyzed above, the median time from first patent filing in the inhaler product line to expiration of the last-to-expire patent in the originator or a follow-on was 40.7 years (IQR: 33.9–48.7)
- Manufacturers reuse the same patents on multiple inhalers from different classes and shift old ingredients to new devices.
- The FDA is seeking ways to streamline the approval process of drug-d… products … for interc…

Conclusion

Drug manufacturers have employed a variety of strategies during the past thirty-five years to obtain regulatory exclusivities and patents on brand-name inhalers to limit generic competition. Regulatory and patent reforms are critical to ensuring that the rewards bestowed on brand-name manufacturers better reflect the added clinical benefit of new products. ■

EXHIBIT 3

Extensions of patent protection for brand-name inhalers for asthma and chronic obstructive pulmonary disease through "device hopping"



Criteri e valutazione dell'innovatività

frontiers in Medicine
ORIGINAL RESEARCH
published: 08 December 2021
doi: 10.3389/fmed.2021.793640

The Assessment of the Innovativeness of a New Medicine in Italy

Filomena Fortinguerra[*†], *Serena Perna*[†], *Roberto Marini, Alessandra Dell'Utri, Maurizio Trapanese, Francesco Trotta and Scientific & Technical Committee (Commissione Tecnico-Scientifica, CTS) of Italian Medicines Agency-AIFA*[‡]

Italian Medicines Agency, Rome, Italy

I tre criteri sono associati tra di loro?

Nessuna associazione tra i criteri di valutazione

I tre **criteri di valutazione** possono essere considerati **indipendenti**, ovvero misurano aspetti diversi dell'innovatività

TABLE 2 | Relationship between criteria utilized in the multidimensional approach in defining innovativeness of a new medicine.

		Added therapeutic value				
	n	**Maximum**	**Important**	**Moderate**	**Poor**	**Absent**
Therapeutic need	Maximum	1	5	4	3	0
	Important	0	12	14	6	2
	Moderate	0	15	20	16	1
	Poor	0	0	1	4	0
	Absent	0	0	0	0	0
		Therapeutic need				
	n	**Maximum**	**Important**	**Moderate**	**Poor**	**Absent**
Quality of clinical evidence	High	1	8	9	0	0
	Moderate	4	15	38	4	0
	Low	6	11	5	0	0
	Very low	2	2	3	1	0
		Added therapeutic value				
	n	**Maximum**	**Important**	**Moderate**	**Poor**	**Absent**
Quality of clinical evidence	High	0	6	7	3	2
	Moderate	1	17	19	20	1
	Low	0	8	8	5	0
	Very low	0	1	5	1	0

Cramer V = 0.24; p = 0.224. Cramer V = 0.25; p = 0.008. Cramer V = 0.20; p = 0.517. Data were summarized as numbers (n). Chi-squared test was used to compute the p-value for Cramer's V.

V di Cramer: misura del grado di associazione tra due variabili categoriche (0: indipendenza; 1: totale dipendenza)

Fortinguerra F, et al. Front Med. 2021;8:793640.

C’è consistenza tra le valutazioni?

Profili con la stessa valutazione hanno portato allo stesso giudizio finale

Coerenza delle decisioni prese

TABLE 3 | Criteria combination patterns in relation to drug innovativeness definition.

Therapeutic need	Added therapeutic value	Quality of clinical evidence	*n*	Fully innovative (%)	Conditionally innovative (%)	Non-innovative (%)
Moderate	Moderate	Moderate	15	0	100	0
Moderate	Poor	Moderate	10	0	0	100
Moderate	Important	Moderate	10	100	0	0
Important	Important	Moderate	6	100	0	0
Important	Moderate	High	5	80	20	0
Poor	Poor	Moderate	4	0	0	100
Moderate	Important	High	4	100	0	0
Important	Poor	Moderate	4	0	0	100
Important	Moderate	Low	4	0	50	50
Important	Moderate	Moderate	4	25	75	0
Important	Important	Low	4	100	0	0
Moderate	Poor	High	3	0	0	100
Moderate	NA	Moderate	3	0	0	100
Maximum	Important	Low	3	67	0	33
Moderate	Poor	Low	2	0	0	100
Moderate	Moderate	Very low	2	0	0	100
Moderate	Moderate	Low	2	0	100	0
Important	Poor	Low	2	0	0	100
Important	Important	High	2	100	0	0
Maximum	Poor	Moderate	2	0	0	100
Maximum	Moderate	Low	2	0	100	0
Poor	Moderate	Very low	1	0	0	100
Moderate	Absent	High	1	0	0	100
Moderate	Poor	Very low	1	0	0	100
Moderate	Moderate	High	1	0	100	0
Moderate	Important	Low	1	100	0	0
Important	Absent	Moderate	1	0	0	100
Important	Absent	High	1	0	0	100
Important	Moderate	Very low	1	0	100	0
Important	NA	Very low	1	0	0	100
Important	NA	Low	1	0	0	100
Maximum	Poor	Low	1	0	0	100
Maximum	Moderate	Very low	1	0	100	0
Maximum	Moderate	High	1	0	100	0
Maximum	Important	Very low	1	100	0	0
Maximum	Important	Moderate	1	100	0	0
Maximum	Maximum	Moderate	1	100	0	0
			109			

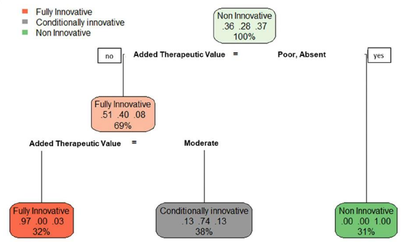
Combination patterns are ordered by decreasing frequency (n).

Fortinguerra F, et al. Front Med. 2021;8:793640.

Peso dei criteri su giudizio finale

Il **valore terapeutico aggiunto** è il **criterio più importante** ai fini della valutazione dell'innovatività di un medicinale

A



B

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%

Fortinguerra F, et al. Front Med. 2021;8:793640.

Il Regolamento europeo di HTA: il punto di vista AIFA/SSN

Joint Clinical Assessment
which issues to be addressed?


The European Journal of Health Economics (2022) 23:913–915
https://doi.org/10.1007/s10198-022-01458-6

EDITORIAL

European union regulation of health technology assessment: what is required for it to succeed?

Michael Drummond[1] · Rosanna Tarricone[2,3] · Aleksandra Torbica[2,3]

- The JCA will have to accommodate the variation in Standard of Care.
- Broader the range of possible alternatives to the new technology of interest, the lower the likelihood of there being head-to-head clinical studies.
- Therefore, it seems inevitable that the JCA will have to include a network meta-analysis (NMA), as well as a conventional meta-analysis of head-to-head clinical trials.
- The use of indirect and mixed treatment comparisons currently divides opinion among the Member States.
- Therefore, an attempt to determine the conditions under which to develop a NMA would

Comparatore & metodo di confronto

Generici: esiste competizione sul prezzo?

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 29 November 2022
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Dynamics of price competition in Italian pharmaceutical off-patent market

Serena Perna[1], Agnese Cangini[1]*, Roberto Marini[1], Maria Alessandra Guerrizio[1], Roberto Da Cas[2], Giuseppe Traversa[1] and Francesco Trotta[1]

[1]Agenzia Italiana del Farmaco, Rome, Italy, [2]Istituto Superiore di Sanità, Rome, Italy

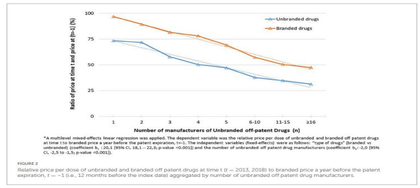

FIGURE 2
Relative price per dose of unbranded and branded off patent drugs at time t (t = 2013, 2018) to branded price a year before the patent expiration, r = −1 (i.e., 12 months before the index date) aggregated by number of unbranded off patent drug manufacturers.

Conclusion

The study detected inverse relation between the number of generic entrants and the price of generics and originators. Non-generics prices fell down more rapidly than generics. This study demonstrated that the patent expiry determines a price decline both for generics and originators, following the same decreasing trend and leaving almost constant the difference among the two groups. The price decline and manufacturer entry were concentrated in the first year of patent expiry.

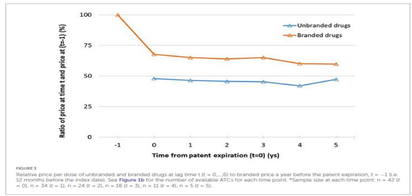

FIGURE 3
Relative price per dose of unbranded and branded drugs at lag time t (t = 0,...,5) to branded price a year before the patent expiration, r = −1 (i.e. 12 months before the index date). See **Figure 1b** for the number of available ATCs for each time point. *Sample size at each time point: n = 42 (t = 0), n = 34 (t = 1), n = 24 (t = 2), n = 18 (t = 3), n = 11 (t = 4), n = 5 (t = 5).

Emofilia A: quale spesa, quale programmazione?

Recenti Prog Med 2023; 114: 268-276

Terapia dell'emofilia A: spesa e consumo per l'anno 2022 e scenari di spesa futura

GIUSEPPE MARANO[1], ROBERTO DA CAS[1], SIMONA ZITO[2], ILARIA IPPOLITI[1], FILOMENA FORTINGUERRA[2], ANDREA PIERANTOZZI[2], FRANCESCA MENNITI-IPPOLITO[1], FRANCESCO TROTTA[2], AGNESE CANGINI[2]

[1]Centro nazionale per la ricerca e la valutazione preclinica e clinica dei farmaci, Istituto superiore di sanità, Roma; [2]Agenzia italiana del farmaco, Roma.

Pervenuto il 19 marzo 2023. Accettato il 27 marzo 2023.

Spesa tot 2022: >400 mln euro

Tabella 2. Fattori della coagulazione per il trattamento dell'emofilia A, spesa *pro capite* e costo medio per tipologia di farmaco: confronto 2020-2021 e 2014-2021.

Tipologia di farmaco	Spesa *pro capite*	Δ % 21-20	Cagr % 14-21	Costo medio Ddd	Δ % 21-20
Emofilia A (short acting-ricombinanti)	2,89	-24,9	-6,6	341,82	0,7
Emofilia A (long acting-ricombinanti)	2,33	47,2	-	327,58	-4,3
Emofilia A (plasmaderivati)	0,36	-2,9	-6,8	254,23	-1,1
Emicizumab	1,27	68,1	-	753,71	-4,0

Legenda: Cagr= compound annual growth rate; Ddd: dose definita *die*.

Take home messages.

- L'emofilia A rappresenta la malattia emorragica congenita con i consumi e la spesa più elevata.
- Nel 2021, i fattori ricombinanti short-acting hanno fatto registrare una riduzione dei consumi; al contrario, i fattori ricombinanti long-acting hanno visto un aumento dei consumi. Ad aumentare sono stati, altresì, i consumi dell'emicizumab, che hanno fatto registrare un costante incremento nell'ultimo triennio.
- Sulla base dei dati OsMed relativi ai primi nove mesi del 2022 e della variazione rispetto allo stesso periodo dell'anno 2021, si è stimato un consumo di 281 milioni di UI per i fattori ricombinanti (short- e long-acting) e in 1,56 milioni di mg nel caso dell'emicizumab.
- Nello Scenario 1 (riduzione degli short-acting del 25% con ridistribuzione tra i long-acting) la spesa relativa ai fattori ricombinanti aumenterebbe del 3,3% (circa 10 milioni di euro). Aggiungendo la spesa dei plasmaderivati e dell'emicizumab si arriverebbe a un totale di 423 milioni di euro (+2,4% rispetto al 2022).
- Nello Scenario 2 (differenti percentuali di switch dai fattori ricombinanti verso l'emicizumab) è stato ipotizzato un incremento di spesa che va dal +8% nel caso di uno switch del 20% dei pazienti, al +28,1% nel caso di uno switch del 70% dei pazienti.
- È stato stimato un aumento medio di spesa di circa 18,4 milioni di euro a ogni variazione del 10% di pazienti trattati con fattori ricombinanti (short- oppure long-acting) che passino all'emicizumab.

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frontiers in Medicine

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The Assessment of the Innovativeness of a New Medicine in Italy

Filomena Fortinguerra*†, Serena Perna†, Roberto Marini, Alessandra Dell'Utri, Maurizio Trapanese, Francesco Trotta and Scientific & Technical Committee (Commissione Tecnico-Scientifica, CTS) of Italian Medicines Agency-AIFA‡

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Non basta l'AIC,
Infrastruttura (integrare i silos)

Jommi et al. Orphanet J Rare Dis (2021) 16:439
https://doi.org/10.1186/s13023-021-02022-w

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Variables affecting pricing of orphan drugs: the Italian case

Claudio Jommi[1*], Elisabetta Listorti[1], Federico Villa[2,4], Simone Ghislandi[1,3], Armando Genazzani[4], Agnese Cangini[2] and Francesco Trotta[2]

Abstract

Background and aim: Evidence on determinants of prices for orphan medicines is scarce and not available for Italy. The aim of this paper is to provide an evidence on variables affecting the annual treatment cost of orphan drugs in Italy, testing the hypothesis of a negative correlation with the dimension of the target population and a positive correlation with the added therapeutic value of the drug and the quality of the evidence of pivotal studies.

Methods: Drugs with a European orphan designation reimbursed in Italy in the last 6 years (2014–2019) were considered. Univariate, cluster analysis and multiple regression models were used to investigate the correlation between the annual treatment cost and, as explanatory variables, the dimension of the target population, the existence of Randomized Clinical Trials as a proxy of the quality of the pivotal studies, the added therapeutic value.

Results: In the univariate analysis prevalence and added therapeutic value, as expected, have a negative and positive correlation with cost respectively. The correlation with RCT is not significant. In the multivariate model, coefficients for prevalence and added value are confirmed but for the latter are not significant anymore. We also found, through an interaction analysis, that the existence of an RCT has a positive impact on annual treatment cost when the target population is very small.

Conclusions: Our results suggest that value arguments and sustainability (dimension of the target population and its impact on budget impact) issues are considered for orphan drugs pricing: the role played by sustainability is systematically supported by our results. A more transparent and reproducible price negotiation process for orphan drugs is needed in Italy. This paper has contributed to highlight the implicit drivers of this process.

Keywords: Orphan drugs, Rare diseases, Health technology assessment, Pricing, Italy

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Anticancer drug prices and clinical outcomes: a cross-sectional study in Italy

Francesco Trotta,[1] Flavia Mayer,[2] Francesco Barone-Adesi,[3] Immacolata Esposito,[4] Ranadhir Punreddy,[3] Roberto Da Cas,[5] Giuseppe Traversa,[5] Francesco Perrone,[6] Nello Martini,[4] Bishal Gyawali,[7] Antonio Addis [1]

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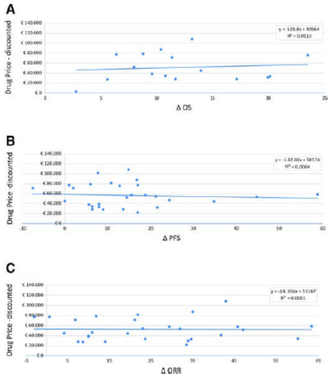

Figure 2 Correlation between anticancer drug prices (discounted) and health benefits. (A) Discounted price with additional compulsory rebates versus difference in median OS (16 drugs related to a single indication are included in the analysis). (B) Discounted price with additional compulsory rebates versus difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and 3 with two indications). (C) Discounted price with additional

Oncologici: esiste correlazione tra evidenza e prezzo?

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Anticancer drug prices and clinical outcomes: a cross-sectional study in Italy

Francesco Trotta,[1] Flavia Mayer,[2] Francesco Barone-Adesi,[3] Immacolata Esposito,[4] Ranadhir Punreddy,[3] Roberto Da Cas,[5] Giuseppe Traversa,[5] Francesco Perrone,[6] Nello Martini,[4] Bishal Gyawali,[7] Antonio Addis [1]

- Price negotiations for approval decisions alone may not bring balance between prices and benefits of anticancer drugs
- Based on the limited outcome data available at the time of reimbursement decisions (OS, PFS and ORR), prices of anticancer drugs do not reflect their therapeutic benefit
- Other strategies, such as value-based price negotiations, price negotiations strictly based on strength of evidence and price

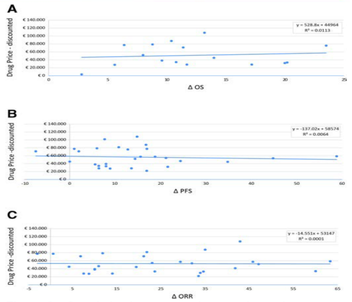

Figure 2 Correlation between anticancer drug prices (discounted) and health benefits. (A) Discounted price with additional compulsory rebates versus difference in median OS (16 drugs related to a single indication are included in the analysis). (B) Discounted price with additional compulsory rebates versus difference in median PFS (25 drugs are included in the analysis: 22 with a single indication and 3 with two indications). (C) Discounted price with additional compulsory rebates versus proportion of ORR (24 drugs are included in the analysis: 20 with a single indication and 4 with two indications). OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

Orfani: esiste relazione tra prezzo e epidemiologia?

frontiers in Medicine
ORIGINAL RESEARCH

Orphan Drug Prices and Epidemiology of Rare Diseases: A Cross-Sectional Study in Italy in the Years 2014–2019

Federico Villa[1,2], Aurora Di Filippo[1], Andrea Pierantozzi[2], Armando Genazzani[1], Antonio Addis[3], Gianluca Trifirò[3], Agnese Cangini[4], Giovanni Tafuri[2,5], Daniela Settesoldi[6] and Francesco Trotta[7]*

[1]Università del Piemonte Orientale, Dipartimento di Scienze del Farmaco, Novara, Italy, [2]Agenzia Italiana del Farmaco (AIFA), Rome, Italy, [3]Dipartimento Epidemiologia Servizio Sanitario Regione Lazio, Rome, Italy, [4]Department of Diagnostics and Public Health, University of Verona, Verona, Italy, [5]Zorginstituut Nederland, Diemen, Netherlands

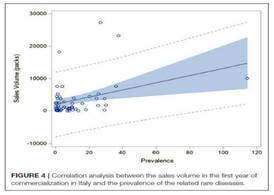

FIGURE 4 | Correlation analysis between the sales volume in the first year of commercialization in Italy and the prevalence of the related rare diseases.

CONCLUSIONS

Pricing is a complex process based on the assessment of multiple criteria. This study documented the absence of correlation between orphan drug cost as well as sales volume in the first year of marketing and the related rare disease prevalence/incidence in Italy.

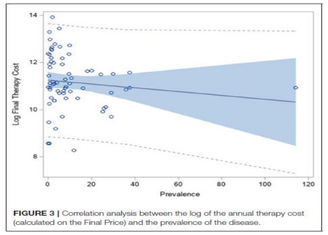

FIGURE 3 | Correlation analysis between the log of the annual therapy cost (calculated on the Final Price) and the prevalence of the disease.

Orfani: quali sono i determinanti del prezzo?

Jommi et al. Orphanet J Rare Dis (2021) 16:439
https://doi.org/10.1186/s13023-021-02022-w

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Variables affecting pricing of orphan drugs: the Italian case

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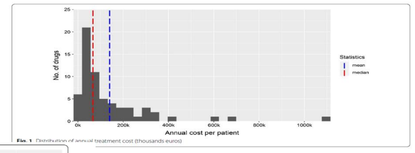
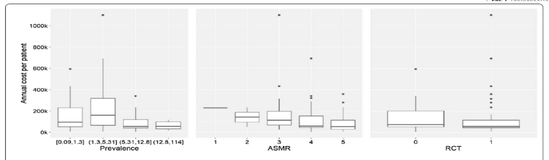


Fig. 1 Distribution of annual treatment cost (thousands euros)



Boolean independent variables, Welch Two Sample t-test with the log cost				
Variable	Mean log cost in group with variable value = 0	Mean log cost in group with variable value = 1	p-value	
Prevalence (boolean variable)	11.55	10.97	**0.04**	
RCT	11.43	11.25	0.56	
Continuous independent variables, Correlation test with the log cost				
Variable	Pearson's Correlation		Spearman's Correlation	
	Estimate	p-value	Estimate	p-value
ASMR	-0.27	**0.05**	-0.25	**0.07**

Fig. 2 Correlation between the independent variables and the annual treatment cost (thousand euros). In bold, correlations significant at 10%. *ASMR* Amelioration du Service Médical Rendu, *RCT* Randomized Clinical Trial

- Prevalence and added therapeutic value, as expected, have a negative and positive correlation with cost respectively.
- The correlation with RCT is not significant.

○ Esistono dei predittori di valore terapeutico (aggiunto)?

Research Paper
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Prediction of therapeutic value of new drugs approved by health Canada from 2011–2020: A cross-sectional study

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- The distribution of therapeutic value (major, moderate, little to no) was determined for drugs with **all three characteristics (expedited review, first-in-class status, clinical outcome in premarket trials)**, two of the three, one and no characteristics.

Table 2. Therapeutic value as a function of the number of drug characteristics* for all drugs.

Number of characteristics	Number of drugs	Number of drugs with therapeutic value†		
		Major	Moderate	Little to no
Three	20	10	4	6
Two	77	14	25	38
One	109	10	25	74
None	37	2	7	28

*Expedited review, clinical trial outcome, first-in-class.
†Distribution of therapeutic value statistically significantly different, Chi-square, $p < 0.0001$.

Rigore all'ingresso, in particolare quando ci sono alternative

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Determinants of price negotiations for new drugs. The experience of the Italian Medicines Agency

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- The average deltaP for all new reimbursed drugs in Italy is 27.4%.
- The price reduction is higher for innovative drugs(-32.2%).
- The possible **determinants** that influence more the delta P are: the use of a **Registry**, the use of a **MEA**, the target **population >20,000** and an expected **expenditure >200 Mln**

Table 4
Overview of the one-way ANOVA analyses for delta-price.

Variable	N Obs	Mean	Std Dev	F	p-value
Orphan Drug Status				0.96	0.3290
no	89	−28.2	18.44		
yes	44	−24.9	16.42		
Size of Pharmaceutical Company				0.13	0.7216
Big Pharma	126	−27.0	17.88		
SME	7	−29.4	17.34		
EMA Authorization				0.06	0.9372
conditional	9	−26.7	16.10		
under exceptional circumstances	4	−24.0	24.39		
full	120	−27.2	17.85		
AIFA assessment process				0.66	0.4178
accelerated	82	−28.1	18.63		
ordinary	51	−25.5	16.43		
Innovativeness Status				0.80	0.4535
none	110	−26.4	16.88		
potential	8	−27.0	7.15		
full	15	−32.5	26.58		
Inclusion on list for Law 648/96*				4.06	0.0458
no	124	−27.9	18.03		
yes	9	−15.7	8.44		
Registry*				6.5	0.0117
no	70	−23.4	15.05		
yes	63	−31.2	19.76		
MEA**				5.9	0.0051
no	101	−24.9	16.46		
yes-FB	20	−38.9	20.63		
yes-OB	12	−25.5	17.50		
Compassionate Use				2.49	0.1167
no	108	−25.9	17.27		
yes	25	−32.1	19.50		
Target population*				3.0	0.0322
0 -| 500	35	−24.2	17.03		
500 -| 3,000	31	−24.8	16.25		
3,000 -| 20,000	33	−24.4	13.88		
> 20,000	34	−34.8	21.40		
Expected Expenditure**				5.2	0.0022
0 -| 15 Mln€	33	−26.2	17.06		
15 Mln€ -| 50 Mln€	35	−25.6	16.95		
50 Mln€ -| 200 Mln€	40	−23.9	14.65		
> 200 Mln€	14	−44.1	24.04		

** Variable significant at 0.01 confidence level.
* Variable significant at 0.05 confidence level.
Legend:
SME: small medium enterprise.
FB: financial-based.
OB: outcome-based.