PHP356: COMPARATIVE ANALYSIS BETWEEN OLD AND NEW ITALIAN INNOVATION RATING SYSTEM

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Introduction

Pharmaceutical innovation has long been a topic of focus in the pharmaceutical industry: although the term "innovative" implies some superior properties, there is little consensus among differing stakeholders as to what constitutes a true pharmaceutical innovation. On July 10, 2007 the AIFA–CTS released the document (resulted from a joint AIFA-industries association Working Group) ''*Criteria for ranking therapeutic innovation of new drugs and elements for supplementing the dossier for admission to the reimbursement system*''. By this algorithm (OldAlg) drugs were divided in three classes: A) therapeutic agents for serious diseases; B) risk factors for serious diseases; C) non-serious diseases. For each therapeutic agent of classes A, B and C, the degree of therapeutic innovation was assessed by evaluating (1) the availability of previous treatments, and (2) the extent of the therapeutic effect. For both (1) and (2), A, B or C scores (in decreasing order of importance) were assigned. As final results, overall scores for therapeutic innovation were 'A', important; 'B', moderate or 'C', modest. Even if the OldAlg was characterized by its simplicity, it has been widely criticized for being too rigid and lacking in transparency. This is why on On 5 April, 2017, the Italian Medicine Agency, AIFA, released a new algorithm (NewAlg, updated by the Determina 1535/2017), aimed to assess the innovation status of a new drug. The new algorithm has improved on previous version by minimising the technical, algorithmic requirements and allowing medical discretion for the assessment. By this new algorithm, the level of innovation will be judged according to three criteria: 1) Unmet Therapeutic Need evaluation determines the availability of other therapies and the extent to which that a new therapy is needed for the patient population. It can be graded according to five levels, from maximum (no therapeutic options) to absent; 2) Therapeutic Added Value is the magnitude of clinical benefit provided by the new drug compared to available alternatives, if any exist. The outcomes must be clinically relevant and validated for the indication. The added therapeutic value is measured on a scale from maximum (demonstrates greater efficacy than alternatives) to absent (no greater clinical benefit than alternatives). And 3) Quality of Evidence: AIFA uses the GRADE method (Grading of Recommendations Assessment, Development and Evaluation) to determine evidence quality, that range from very low to high. For orphan drugs, the quality of evidence will play a smaller role, given the difficulty of conducting trials for rare diseases. In cases where an orphan drug meets the other two criteria, a drug can still be considered innovative, even if the quality of evidence is low. The integrated analysis of the three criteria can lead to a clear innovativeness (green boxes), a clear non-innovativeness (red boxes) or to a situation that has to be assessed on a case by-case basis (yellow boxes).

Therapeutic Need: Maximum	QoE: Very Low	QoE: Very Low	Very Low	Very Low	Very Low
	QoE: Low	QoE: Low	Low	QoE: Low	QoE: Low
	QoE: Moderate	QoE: Moderate	QoE: Moderate	QoE: Moderate	Moderate
	QoE: High	QoE: High	High	High	High
Therapeutic Need: Important	QoE: Very Low	QoE: Very Low	QoE: Very Low	Very Low	Very Low
	QoE: Low	QoE: Low	QoE: Low	QoE: Low	QoE: Low
	QoE: Moderate	QoE: Moderate	Moderate	QoE: Moderate	Moderate
	QoE: High	QoE: High	High	High	High
Therapeutic Need: Moderate	QoE: Very Low	QoE: Very Low	QoE: Very Low	Very Low	Very Low
	QoE: Low	QoE: Low	QoE: Low	QoE: Low	QoE: Low
	QoE: Moderate	QoE: Moderate	Moderate	Moderate	Moderate
	QoE: High	QoE: High	High	High	High
Therapeutic Need: Scarce	QoE: Very Low	QoE: Very Low	QoE: Very Low	QoE: Very Low	QoE: Very Low
	QoE: Low	QoE: Low	QoE: Low	QoE: Low	QoE: Low
	QoE: Moderate	QoE: Moderate	QoE: Moderate	QoE: Moderate	QoE: Moderate
	QoE: High	QoE: High	QoE: High	QoE: High	QoE: High
Therapeutic Need: Absent	QoE: Very Low	QoE: Very Low	QoE: Very Low	QoE: Very Low	QoE: Very Low
	QoE: Low	QoE: Low	QoE: Low	QoE: Low	QoE: Low
	QoE: Moderate	QoE: Moderate	QoE: Moderate	QoE: Moderate	QoE: Moderate
	QoE: High	QoE: High	QoE: High	QoE: High	QoE: High
	Therapeutic Added Value: Absent	**Therapeutic Added Value: Scarce**	**Therapeutic Added Value: Moderate**	**Therapeutic Added Value: Important**	**Therapeutic Added Value: Maximum**

Figure 1: New algorithm used to assign the overall score for innovation (2017); modified from Recchia's reported scheme (sources: Di Marzio S. E l'AIFA tracciò la strada dell'innovatività. AboutPharma 2017 n.148:28-30.; Pinto C., Pappagallo G., Normanno N., Danesi R., Jommi C. e Ravasio G., Schema per la preparazione del dossier di richiesta di innovatività dei farmaci, Economia & Politica del Farmaco e delle Tecnologie sanitarie; Giugno 2018)

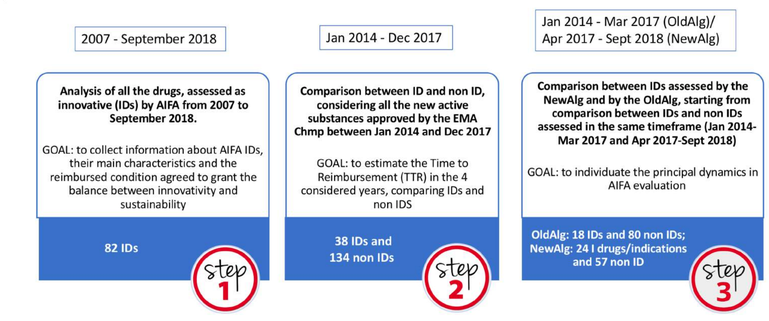
Following this evaluation, if a medicinal product is granted the status of "full innovativeness" for a specific therapeutic indication, its manufacturer can access to 2 dedicated yearly funds (one for oncology and one for non-oncology drugs) amounting to 500 million Euros each, depending on the type of medicine. Alternatively, the product can be granted the status of "conditional innovativeness" which allows immediate access to all Regional formularies, with no additional re-assessment at local level. The third possible outcome is that no innovativeness is recognized. The new algorithm grants different benefits to "real" and "potential" innovation, by differentiating them. Benefits for the "potential innovative" drugs are now shortened, from 36 to 18 months, and the requirement allows only the direct inclusion in regional formularies.

Objectives

The aim of our research is to compare the drugs assessed as innovative by the old algorithm (OldAlg) and by the new AIFA innovation algorithm (NewAlg), analyzing time to reimbursement (TTR), negotiation outcomes (discounts, managed entry agreements,…) and, for those, whose evaluation is publicly available on the AIFA website, quality of evaluation. In order to activate a direct comparison, we also analyzed the main difference between innovative assessed and non-innovative drugs, considering all the new active substances approved by the EMA CHMP between January 2014 and December 2017. The final goal is to check if, even though the innovative status does not officially grant any advantage in time to reimbursement, in real life there is an impact on time to reimbursement and on negotiation conditions.

Methods

The first step was to consider all 82 drugs assessed as innovative by AIFA (IDs) from 2007 on (for which data are publicly available in September 2018), both by the OldAlg and by the NewAlg. For all these drugs, second level ATC and negotiating conditions (i.e. MEAs) have been evaluated. As a second step, in order to compare time to reimbursement, defined as days from the EMA CHMP Positive Opinion to the price publication on the Italian Official Journal (OJ), we selected a restricted timeline, by considering all the new active substances approved by the CHMP between January 2014 and December 2017. As a third step we compared drugs as assessed as innovative through the OldAlg from Jan 2014 to the coming into force of the NewAlg (April 2017) and drugs assessed via the NewAlg (until September 2018). This choice allowed us not only to make a comparison between evaluations made with the OldAlg and with the NewAlg, but also to contextualize the analysis, assessing also the difference between innovative and non-innovative drugs, evaluated in the same timeframe.



Results

Step 1
From 2007 to September 2018, AIFA defined 82 drugs or indications (as allowed by the NewAlg) as "innovative" (58 assessed with the OldAlg and 24 with the NewAlg). Out of the 82 innovative drugs/indications, 80 have been registered via centralized procedure and 2 via mutual recognition procedure, 32 obtaining a full and 50 a potential/conditional innovativeness. In the period covering almost 12 years (2007-September 2018), AIFA, on average, assigned the innovative status to 7 drugs/year (ranging from 0 in 2012 to 19 in the first 9 months of 2018).

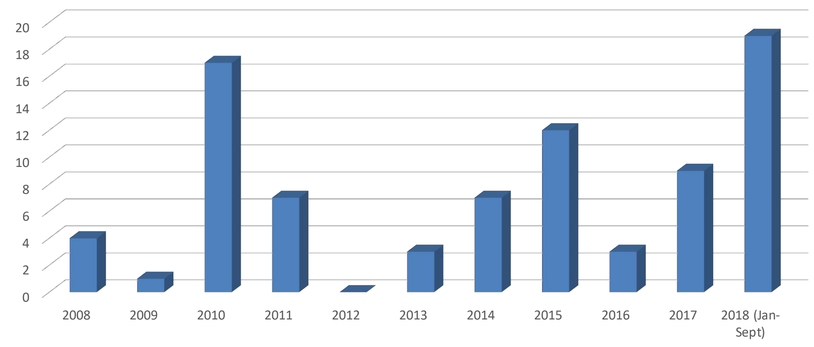


Figure 2: Number of drugs/indications assessed as innovative by AIFA per year, from 2007 to Sept 2018. The first publication into the OJ related to an innovative drug has been made in Jan 2008

By analyzing the innovative drugs/indications, considering the second level ATC, antineoplastic agents (L01) is the category with the highest number of innovative status recognition, followed by drugs used in diabetes (A10), and antivirals for systemic use (J05). Ophthalmological drugs (S01), immunosuppressants (L04), other drugs for disorders of the musculo-skeletal system (M09) and antithrombotic agents (B01) follows, with more than one drug/indication assessed as innovative. All but 9/82 AIFA innovative drugs/indications have been negotiated with special conditions, such as: hidden discounts (HDs) alone (30/82; 37%) or associated with a MEA (11/82; 13%) or associated with more than one negotiable conditions (4/82; 5%). For 18 innovative drugs/indications (22%), AIFA and the Companies agreed for a budget cap (BC) alone (16) or for a budget cap + a CS (1) or a budget cap + a PbR (1). MEAs have been agreed for additional 9 drugs (4 PV, 2 PbR, 2 cost sharing, 1 MEA not otherwise specified). The missing drug has been priced through a HD in addition to an escape clause.

Step 2
By analysing a more restricted timeline, and considering all the 172 new active substances approved by the EMA between January 2014 and December 2017, it has been possible to compare the percentage of innovative drugs vs the total number of the new drugs approved by the EMA, year after year.

	2014	2015	2016	2017
New Active substance CHMP Positive Opinion	58	43	32	39
Innovative Drugs*	8	4	9	17
% of ID	14%	9%	28%	44%

***Table 1:* Number of active substances approved by the EMA's CHMP 2014-2017, number of AIFA Innovative Drug (IDs)s; % or AIFA ID on the total**

In the considered timeframe (2014-2017), the mean time to reimbursement (TTR) for new active substances approved by the CHMP was 320 days (median 297; range 67-742) for innovative drugs versus 525 days (median 464; range 169-1.258) for non-innovative drugs. This means that, in the period of time considered, the TTR for ID was 44% lower (calculated on medians) than the TTR for non-innovative drugs. Similar data can be observed for all the considered years (medians): 270 days for ID vs 505 for non ID in 2014 (-46%), 378 vs 507 in 2015 (-25%), 249 vs 396 in 2016 (-37%) and 338 vs 484 in 2017 (-30%). It is important to consider that for the last year of our evaluation (2017) all the ID already achieved a reimbursement (17/17; 100%) vs a minimal percentage of the non innovative (3/22; 14%), therefore the real data is much more worst for non innovative drugs. These data clearly show how the Innovative Status granted by AIFA leads to a clear and substantial reduction in time to reimbursement.

Step 3
The NewAlg was introduced very recently (it came into force with its publication into the Italian OJ, in April 2017) . A longer time of observation would be needed to perform a solid comparison between the two algorithms, but some initial considerations can still be done. According to AIFA's data, in the timeframe April 2017-September 2018 AIFA received 50 request of innovativeness, on which 48 already evaluated and 2 still under evaluation. 13/50 drugs/indications received a "full innovativeness" status recognition, 17/50 a conditional innovativeness and 18 have been evaluated as non-innovative. At the time of our analysis, data are publicly available only for 29/50 evaluated drugs/indications. By considering all the drugs evaluated by AIFA in the period after the adoption of the NewAlg (until September 2018), for which is available the pricing and reimbursement publication on the OJ (57 in total), the TTR for IDs (mean 312 and median 256 days) is more than halved than the TTR for non-innovative drugs (mean 617 and median 582 days). This data seems to be less marked by considering all the drugs (authorized by the EMA's CHMP from Jan 2014 on) evaluated with the OldAlg, for which is available the pricing and reimbursement publication on the OJ (80 in total); for these drugs the median TTR for IDs was 359 days (mean 321) and for non IDs 490 days (mean 448).

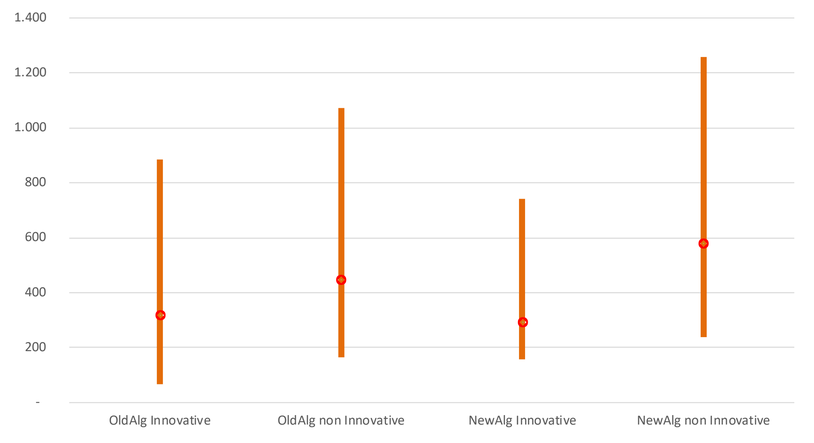


Figure 3: Median (and ranges) TTR (in days) for IDs and non IDs, as defined with the OldAlg and the NewAlg

List of abbreviations: AIFA Agenzia Italiana del Farmaco – Italian Medicine Acgency; ATC Anatomical Therapeutic Chemical Classification System; BC Budget cap; CHMP Comitee for Medicinal Products for Human Use; CS Cost-sharing; CTS Technical-Scientific Commitee; EMA European Medicina Agency; GRADE Grading of Reccomendation Assessment, Developement and Evaluation; HD Hidden discount; ID Innovative Drugs; MEA Managed Entry Agreement; NewAlg New Innovation AIFA's Algorithm; OJ Official Journal; OldAlg Old Innovation AIFA's Algorithm; PbR Payment by results; PV Price-volume; TTR Time to Reimbursement

By our data the Orphan Drug designation doesn't have any impact on the TTR. Both with the OldAlg and with the NewAlg TTR doesn't change by comparing orphan and non-orphan drugs, neither for innovative nor for non-innovative drugs.

			Mean	Median
OldAlg	Orphan Drugs	I	247	247
		NI	484	456
	NON Orphan Drugs	I	295	285
		NI	493	446
OldAlg	Orphan Drugs	I	342	320
		NI	614	745
	NON Orphan Drugs	I	284	289
		NI	581	618

***Table 2:* TTR for innovative and non-innovative, orphan and non-orphan drugs observed both with the OldAlg and the NewAlg;** I = innovative drugs; NI = non-innovative drugs

All the 42 drugs/indications assessed as innovative both with the OldAlg and with the NewAlg considered our the drug's panel (step 3), have been negotiated through specific agreements between Companies and AIFA. 21/24 (88%) IDs/indications evaluated through the NewAlg have a hidden discount, alone (16/24; 67%) or associated with a MEA (3/24; 13%), with an escape clause (1/24; 4%) or with a MEA and a BC. Out of the three missing drugs, one has confidential negotiated condition and the other 2/24 (4%) a MEA. 13/18 (72%) ID assessed with the OldAlg have an HD, alone (6; 33%) or associated with a MEA (6; 33%) or with a MEA and a BC (1; 5%). 5/18 (28%) have been negotiated "only" with a MEA and 1/18 with a budget cap.

Under transparency considerations, starting from January 2018, a full report explaining the rationale for the Agency Committee's decision is made publicly available on the AIFA's website. On the 29 evaluate drugs, 18 have been defined as innovative (11 "full" and 7 "conditional"). At the time of our analysis, the last document's update has been published in September 2018.

Drug	Active substance	Indication	Innovativeness	Therapeutic need	Therapeutic added value	Quality of Evidences
Darzalex	daratumumab	R/R Multiple Myeloma (specific subpoulation)	N	Important	NE	Low
Maviret	glecapevir/pibrentasvir	HCV Infection	Y	Important	Important	Moderate
Ocaliva	obeticholic acid	Primary Biliary Cholangitis	N	Maximum	Scarce	Low
Olumiant	baricitinib	Rheumatoid arthritis (specific subpopulation)	N	Moderate	Scarce	High
Spinraza	nusinersen	5q Spinal muscular atrophy (SMA)	Y	Maximum	Important	Low
Ibrance	palbociclib	Breast cancer (subpopulation)	N	Important	Scarce	Moderate
Ibrance	palbociclib	Breast cancer (subpopulation)	C	Moderate	Moderate	Moderate
Oxervate	cenegermin	Moderate neutrophic keratitis	Y	Important	Important	Low
Zavicefta	ceftazidime/avibactam	Specific severe infections	N	Important	Scarce	Moderate
Opdivo	nivolumab	Urothelial carcinoma (subpopulation)	N	Maximum	NE	Low
Zalmoxis	Gene modifed T lymphocitis	Adjuvant treatment for HSCT in HR hematoilogic malignancies	N	Moderate	Moderate	Very Low
Darzalex	daratumumab	R/R Multiple Myeloma (specific subpoulation)	Y	Moderate	Important	Moderate
Vosevi	sofosbuvir/velpatasvir/voxil aprevir	HCV Infection	Y	Important	Important	Moderate
Humira	adalimumab	Noninfectious uveitis and panuveitis	C	Important	Moderate	Moderate
Revlimid	lenalidomide	Multiple Myeloma mainteinance (subpopulation)	C	Moderate	Moderate	Moderate
Besponsa	inotuzumab ozogamicin	Acute Lymphoblastic Leukeima (ALL; subpopulation)	C	Moderate	Moderate	Moderate
Tecentriq	atezolizumab	Non small cell lung cancer (subpopulation)	Y	Important	Moderate	High
Zinplava	bezlotoxumab	Prophylaxis for relapsed Clostridium difficile (CDI) infection	N	Important	Moderate	Low
Qarziba	dinutuximab beta	HR Neuroblastoma after chemo and SCT	Y	Maximum	Important	Moderate
Qarziba	dinutuximab beta	R/R neuroblastoma	N	Maximum	Important	Very Low
Alecensa	alectinib	ALK + NSCLC already treated with crizotinib	C	Moderate	Moderate	Moderate
Alecensa	alectinib	ALK + NSCLC first line, monotherapy	Y	Moderate	Important	Moderate
Opdivo	nivolumab	Squamous head/neck cancer after platinum	C	Maximum	Moderate	Moderate
Rydapt	midostaurin	AML (subpopulation)	Y	Moderate	Important	Moderate
Rydapt	midostaurin	Aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm, SM-AHN or mast cell leukaemia, MCL	N	Important	Scarce	Low
Imbruvica	ibrutinib	First line CLL	C	Moderate	Moderate	Moderate
Dupixent	dupilumab	Atopic dermathitis (subpopulation)	Y	Important	Moderate	High
Ocrevus	ocrelizumab	Primary progressive multiple sclerosis (PPMS)	N	Maximum	Scarce	Moderate
Prevymis	letermovir	Cytomegalovirus prophylaxis in HIV+ patients	Y	Moderate	Important	High

***Table 3: Evaluation reports (NewALg) publicly available by AIFA (updated September 2018*); Y = innovative; N = non-innovative; C = conditional innovativeness; NE = not evaluable**

The analysis of these reports is very interesting; this helps to understand some dynamics under the evaluation process. All the assessed drugs showed at least a moderate therapeutic need. This clearly shows how this element is recognized even by the applicant as a fundamental characteristic to define drug's innovativeness. As shown by the analysis of the currently published innovativeness report, the therapeutic added value seems to be the most difficult criteria to be evaluated, being in some cases discretionary. The quality of evidences is estimate using the GRADE method, as adopted at international level to grant objectiveness and scientific rigor. By looking at the published evaluations, only 4 drugs/indications demonstrated "high" level of quality of evidences, with data showing a significant remission or a substantial reduction of the disease (baricitinib) or with positive results coming from solid phase III trials, without downgrading criteria (atezolizumab, dupilumab and letermovir). As provided for the law, in case of rare disease, a drug can be defined as innovative even if the quality of evidences is low: this is the case of nusinersen or cenegermin, where there is a maximum/important therapeutic need and an important added value, in the context of a very rare disease.

Conclusions

Our analysis shows that the innovative status recognition is always accompanied with special agreements between AIFA and the Companies, aimed to strike a balance between innovation and sustainability. Hidden discounts are the most frequent negotiation agreements, MEAs alone were used in the past and now combined tools (such as hidden discounts + budget cap or + managed entry agreements) are more widely used. Our data indicates an increasing trend in drugs/indications assessed as innovative by AIFA, but this may depends on the novelty introduced by the NewAlg, which allows even single specific indication to be designed as innovative. The TTR is significantly lower for innovative than for non-innovative drugs (-43% in the considered timeframe), while the orphan drug status doesn't have any impact on the TTR. Even if the OldAlg was characterized by its simplicity, it has been widely criticized for being too rigid and lacking in transparency. On the contrary, the NewAlg allows a multidimensional approach, assuring a balance between objective evaluation and a more comprehensive assessment provided by the CTS, in a transparent process. Whilst the therapeutic need seems to be recognized (both by AIFA and by the applicants) as an essential criteria, the therapeutic added value seems more difficult to be assessed. Thanks to the introduction of the GRADE method, the definition of the quality of evidences is rigorous, even if doesn't take into account, as provided by the law, drugs treating very rare diseases.

References:
http://www.agenziafarmaco.it; http://www.gazzettaufficiale.it; http://www.gradeworkinggroup.org; http://www.ema.europa.eu; Data presented by Annamaria Marata during the 17th Convegno Nazionale "*Economia e Politica del Farmaco e delle Tecnologie Sanitarie*" held in Novara on the 25th of September 2018; Di Marzio S., *E l'AIFA tracciò la strada dell'innovatività*. AboutPharma 2017 n.148:28-30.; Pinto C., Pappagallo G., Normanno N., Danesi R., Jommi C. e Ravasio G., *Schema per la preparazione del dossier di richiesta di innovatività dei farmaci*, Economia & Politica del Farmaco e delle Tecnologie sanitarie; Giugno 2018; Patient Access Monitor

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