Innovation Value Framework Evidence from EU-4 and UK

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Introduction.

The assessment of health technologies is a key tool used in the decision-making process in health policies. The innovation assessment and clinical benefit is a complex discipline for which different methodologies are adopted at the national level. Although various initiatives have been launched in recent years, [1-5] ratings still differ significantly between European countries [6, 7] in terms of the variability of the approach of the legislative framework that regulates the activities of the national agencies.

In Italy, the authority responsible for the evaluation of medicinal products and the negotiating of pricing and reimbursement is the Italian Medicines Agency (AIFA). The therapeutic innovation evaluation model implemented by the AIFA CTS (*Commissione Tecnico-Scientifica*) consists of a multidimensional approach based on three criteria [8]: unmet therapeutic need, therapeutic added value (TAV), and quality of evidence (GRADE methodology). [8] The fully innovative status has 36 months of duration of the judgement of innovativeness, included the allocation of economic benefit, consent the access to the fund for innovative or cancer innovative drugs and automatic inclusion in the regional therapeutic formularies. Generally, all innovative drugs are monitoring with data collection at national level within AIFA registries. Italy is recognized as the country of managed entry agreements implemented by AIFA in the last 16 years through the AIFA registers (mainly individual-level outcome-based). Since 2017 there has been a drastic change in the use of MEAs with an important preference for financial-based ones such as price/volume, budget caps and confidential discounts. [9]

In UK, the National Institute for Health and Care Excellence (NICE) selects medicines and other health technologies for HTA where national guidance is expected to add value (clinical impact, variation in practice, need for information or resource impact), and aims to appraise all new inpatient and ambulatory medicines and indications. The process and timetable depend on whether the appraisal is single technology or multiple technologies. NICE bases decisions on cost-utility analysis and has an explicit ICER threshold between £20,000 and £30,000 per QALY, with flexibility to recommend medicines for patients at the end of their lives or for very rare diseases at a higher ICER. Following an unfavourable decision by NICE, payers are not obliged to finance the medicine. The manufacturers in some cases enter into negotiations with the Ministry of Health over “patient access schemes” to try to improve its cost-effectiveness. Such a scheme might contemplate a price discount, overall expenditure cap, or risk-sharing agreement. Some medicines rejected by NICE have in the past been publicly financed by other means (e.g. Cancer Fund). [10]

In France, the *Haute Autorité de santé (*HAS) is an independent public body and its duties include providing adequate information to regulatory bodies in order to set prices and encourage good practices and ensuring the correct use of medicinal products (17). The *Commission de la Transparence* (CT) uses two criteria to evaluate medicinal products: the *Service Médical Rendu* (SMR), representing the actual clinical benefit, and the *Amélioration du Service Médical Rendu* (ASMR), representing the improvement of the effective clinical benefit. The combination of the scores of the two criteria is used by the CT to determine the reimbursement level for the medicinal product. The reimbursement rate will be defined according to the SMR: Important (65%), Moderate (30%), Mild (15%), and Insufficient (not included on the positive list). To express the ASMR judgment, the HAS considers the added therapeutic value that the medicinal product brings compared with the therapeutic alternatives for the same therapeutic indication and the improvement it brings. Therefore, the ASMR judgments (represented by a score on a scale of 1 to 5) answers the question of whether the drug improves the clinical benefit for patients compared with the current standard of care. [11]

In Germany, innovative drugs are being assessed within the so-called AMNOG (German Medicines Market Reorganization Act) process with a 12-month free pricing period. AMNOG includes a benefit assessment based on evidence-based medicine criteria. Core focus is on unbiased clinical evidence with patient-relevant endpoints. Final decision by the decision-making body G-BA (*Der Gemeinsame Bundesausschuss*, Federal Joint Committee) is a benefit level which lies between lesser and major added benefit. In case of a positive added benefit companies are allowed to negotiate a premium price on top of comparative therapies. Standard price discounts within negotiations is 20-25%. If no agreement can be reached, an arbitration board is being called. [12]

The *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS) conducts clinical HTA for new medicines. To inform the P&R decision, AEMPS usually produces a clinical HTA report (Therapeutic Positioning Report, IPT) about relative efficacy and safety, the nature of the disease, other therapeutic options, whether any especially vulnerable groups may benefit from the treatment, and other social or medical aspects. The IPT includes little consideration of costs, mainly because is made before setting the price of the medicine. Spain operates a dual pricing system for hospital medicines. The official (list) price is for medicines for sale outside the NHS (parallel exporters and private patients). The Ministry of Health may also negotiate a discounted and confidential “reimbursed price” for the NHS. Once the MoH and manufacturer have negotiated a price, the CIPM make the final decision on P&R. [13]

Objectives.

The aim of this analysis was to compare the value framework from HTA bodies in EU-4 and UK in assessing the same drug/therapeutic indication.

Methods.

DATA EXTRACTION

Drugs with valid Fully Innovativeness' status recognised by AIFA Italy in the period 2019-2020 were identified.

A database was created by extracting the data from the AIFA innovation reports from the AIFA web page (ref). Consequently, national appraisals for each product/therapeutic indication from NICE UK, HAS France, G-BA Germany and AEMPS Spain, were collected.

For the analysis were considered the following variables:

- NICE recommendations,
- HAS Actual benefit (SMR) & Improvement in actual benefit (ASMR),
- G-BA added benefit and,
- AEMPS Therapeutic Positioning Report (TPR).

Other variables such as indication by age group, the type of EMA approval, orphan designation and the application of risk-sharing agreements, are to support the interpretation of data analyzed.

DATA COMPARISON

Considering that for AIFA all the indications in analysis have received the highest level of value recognition, we have identified three Groups to analyze the accordance. (Tab. 1): 1) NICE recommendation yes, HAS ASMR I-III, GB-A considerable and major added benefit, AEMPS TPR reimbursed without restrictions; 2) NICE recommendation yes but with conditions, HAS ASMR IV, GB-A minor added benefit, AEMPS TPR reimbursed with label restriction; 3) NICE recommendation no/ NA, HAS ASMR IV/NA, G-BA no/non-quantifiable or exempted due to insignificance added benefit, AEMPS TPR no-reimbursed.

Table 1. Criteria to compare Italy and EU-4 & UK

GROUP	NICE	HAS	G-BA	AEMPS
(1) Complete agreement/ alignment	Positive recommendation	ASMR I-III	Major and Considerable added benefit	Funded without restrictions
(2) Partial agreement/ alignment	Positive recommendation but with managed access agreement	ASMR IV	Minor added benefit	Funded with restrictions
(3) Disagreement or Lack of alignment	Negative recommendation and NA	ASMR V and NA	Exempted due to insignificance and Non-quantifiable and No added benefit	Non-funded and NA

AEMPS, *Agencia Española de Medicamentos y Productos Sanitarios;* ASMR, Amélioration du Service Médical Rendu; SMR, Service Médical Rendu; HAS, Haute Autorité de Santé; G-BA; German Federal Joint Committee; NICE, National Institute for Health and Care Excellence

The similarities between AIFA and EU-4 & UK evaluations were investigated according to the following pragmatic criteria reported in Tab. 1. The rationale is based primarily on the similar wording expressed by the HTA bodies on the therapeutic added value. Second, and specifically for the French authority given the good agreement (even by subcategories) between AIFA and HAS. [14]

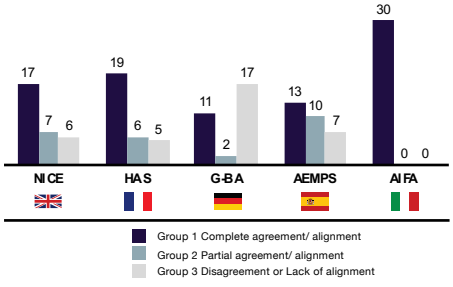
Statistical Analysis.

First, descriptive statistics were conducted. Quantitative data were expressed as frequency and percentage. Contingency tables were then used to analyse the associations between assessments on innovative status taken by the HTA bodies in EU-4 and UK included in our analysis.
Concordance was assessed as raw agreement (%) and the Fleiss' Kappa was estimated. For the Fleiss' Kappa were considered the NICE, HAS, and G-BA, and AEMPS decisions.

Results.

A total of 30 therapeutic indications for 24 medicinal products, were analysed. For AIFA, given the Innovative status, the medicinals subject to analysis are all reimbursed by the NHS and included in the Innovative or Cancer Funds. It is specified that there are 12 cancer indications out of a total of 30 analyzed. Furthermore, for the Italian authority, the recognition of innovativeness' for 10 products has seen a restriction of the label indication.
According to criteria reported in Tab. 1, NICE recommended 17 indications. For HAS are 19 the cases with ASMR I-III. For G-BA are 11 assessed as considerable/major the extent of added benefit. For AEMPS are 13 with TPR and no label restriction and reimbursed. (Fig. 1)
Compared to AIFA, and referring to the Group (1) Complete agreement/ alignment (in blue), NICE recognized 56,7% of cases, HAS 63.3%, G-BA 36.7% and AEMPS 43,3%. In these cases, HTA bodies are aligned in their decisions.
Only in 4 cases (two cancer treatments and two orphan indications) all other agencies agreed with the AIFA assessment of fully innovativeness. If, Germany were to be excluded from the sample given the G-BA opinions less favorable to the recognition of added value, the cases in accordance with AIFA rise to 12 therapeutic indications where the percentages remain the same (50% cancer treatment and 50% orphans).
Comparisons were conducted not only versus AIFA decisions but also among the agencies. From the Fleiss' Kappa statistics emerge a slight alignment (kappa= 0.106, p-value= 0.05).
Our analysis confirmed the result of a previous first study on this argument which compared AIFA and HAS decisions. As reported in xxx (ref nostra) AIFA would seem significantly more “generous.”

Figure 1. The categories on the criteria defined for EU-4 and UK relatively the 30 innovative indications based on AIFA assessment



We are aware on the limitation rating criteria: our approach is based on the figures (Fig. 1) and definitions used by the HTAs. The criticality is particularly for Group (2) Partial agreement/ alignment cases where the distribution is similar for NICE and HAS instead for G-BA and AEMPS so different. Particularly noteworthy is Group (3) Disagreement or Lack of alignment where HAS, NICE and AEMPS almost overlap and G-BA stands out with 17 indications with no-added value.

Conclusion.

These preliminary results underline the importance of implementing transparency procedures in terms of the value definition criteria used by HTA organisations. Further analysis are needed to detail drug assessments by HTA bodies in EU4 & UK.

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