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ORIGINAL RESEARCH

The regulatory and Health Technology processes in Europe and drug market access. The case of cystic fibrosis

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ABSTRACT

In order to reach the European market, a new drug needs to receive a positive evaluation regarding its quality, safety and efficacy by regulatory health authorities and also obtain a positive HTA appraisal regarding its cost-effectiveness by HTA bodies. Regulators and HTA bodies are collaborating in several projects at European level in order to harmonize the scientific requirements of both evaluations to the maximum extent possible. The comparison of the regulatory evaluation performed by EMA for Kalydeco and the HTA appraisals issued by several EU bodies exemplifies the dilemma between scientific evidence and local economic considerations and the difficulties in the achievement of harmonization and therefore equity in the access to drugs.

Keywords

Cystic Fibrosis; Agencies/organization & administration; Health Technology Assessment

INTRODUCTION

Health authorities assess the quality, safety and efficacy of a medicinal product[1] based on its own merits whereas Health Technology Assessment (HTA) bodies evaluate the safety and efficacy of a drug comparatively to other available treatments on the market, as well as its cost-effectiveness. As a consequence, industry faces the challenge that the data set required to undertake the two evaluations could not be necessarily the same. In such a context, it is of extreme importance to design correctly from the start the expensive clinical programs with the aim of fulfilling the obligations for the two areas of assessment efficiently and in parallel.

European health authorities, including regulatory and HTA bodies, recognizing all these challenges and the existing room for harmonization have initiated the path towards knowledge sharing and collaboration in order to reach and establish common approaches.

The approval of medicinal products is a highly regulated field. The birth of the unified European legislation of medicines took place in 1965 with the adoption of Directive 65/65/CEE [1]. The sponsor of any new medicinal product should demonstrate the quality, the safety and the efficacy of a drug prior to being granted the permission by the relevant health authorities to put the product on the market at the disposal of patients. The European Medicines Agency (EMA), the scientific body responsible for performing the evaluation, provides a scientific opinion to the European Commission (EC), which will then serve as the basis for the marketing authorization, which will have automatic validity in all European Union (EU) member states.

HTA is taking more and more relevance every day, for authorities, for payers and for industry. Proven quality, safety and efficacy, the three basic guarantees are no longer enough to allow patients access to a new medicine. Now, a medicinal product also has to demonstrate its relative cost-effectiveness, when compared to other available treatments, the so-called fourth guarantee in order to receive

[1] The terms medicinal product, medicine and drug are used as synonyms.

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a positive appraisal by HTA bodies and successful reimbursement negotiations.

An important milestone has been reached in Europe in this context with the establishment of the European Union Network of HTA (EUnetHTA) [2]. In 2004, the EC and the Council of the EU recognized the Health Technology Assessment as a high priority and urged for establishing a sustainable European network on HTA. In 2005, a group of 35 organizations throughout Europe began the activities of the EUnetHTA Project. One of the most important milestones achieved by EUnetHTA is the creation of a Core harmonized Model for HTA appraisals, where the key elements to be evaluated by HTA bodies are represented [3].

As a response to the recommendations from the Pharmaceutical Forum in 2008, the EMA and EUnetHTA initiated a collaboration to improve the contribution that European Public Assessment Reports (EPARs) prepared by EMA could make to the assessment of relative effectiveness of medicinal products [4].

The EU Directive 2011/24/EU [5] on the application of patients' rights in cross-border healthcare set a milestone in the recognition of equity in rights across European Union Members States and also introduced important provisions for the EU collaboration in the area of rare diseases and HTA.

Kalydeco (ivacaftor), is recognized as being the first in a new class of medicines: Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) potentiators. It targets the cystic fibrosis CFTR and so treats the underlying cause of the disease. It increases the time that activated CFTR channels remain open at the cell surface. Kalydeco is one the drugs that has received orphan designation for cystic fibrosis [6] and one of the seven drugs [7] for which the European Medicines Agency has adopted a positive opinion for cystic fibrosis. Kalydeco is at the moment one of the most expensive drugs in Europe. The annual price of the drug per patient makes it difficult to for some national budgets to absorb the cost [8].

The objective of this study was on the one hand to identify the elements that regulators and HTA bodies took into account when performing their respective evaluations of Kalydeco. And, on the other hand, to ascertain the origin of the divergent opinions identified among HTA bodies when confronted with the same clinical evidence.

METHODOLOGY

The EPAR for Kalydeco issued by the EMA in 2012 was taken as the reference document for the regulators evaluation [9].

The publicly available HTA appraisals in English, Spanish and German from European HTA bodies were taken as reference for this analysis. The selected reports correspond to the following HTA bodies[2]:

- Scottish Medicines Consortium (SMC) – UK Scotland [10];
- NHS England statement (NHS) – UK England [11];
- Therapeutic Positioning Report for Spanish Government (IPT) – Spain [12];
- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) – Germany [13];
- National Center for Pharmacoeconomics (NCPE) – Ireland [14];
- Haute Autorité de Santé (HAS) – France [15].

A comparative analysis of the information contained in the EPAR and the HTA reports was undertaken following the 3 steps scheme described below:

1. Analysis following the HTA Core Model developed by EUnetHTA to determine the domains common to the regulatory and HTA fields;
2. Analysis of the study design elements which are frequently source of discrepancies between regulators and HTA bodies (i.e. comparators, study population and endpoints);
3. Analysis of the clinical evidence elements available pre-approval. The items considered were the benefit/risk balance, post-approval studies, degree of uncertainty and clinical added value. Study of the similarities and differences in the opinions among HTA bodies in view of the same clinical evidence which is taken from the EPAR published by the EMA[3].

RESULTS

Each table contains a summary of the information present in the EPAR and HTA reports studied. The EUnetHTA Core Model (Table I) defines the domains that HTA bodies should study for their appraisals. Not all these domains are relevant for the regulatory assessment. In addition, the analysis showed that not all HTA reports considered all domains and also the depth and detail in which the same domains were addressed was different too.

[2] All these HTA bodies have an advisory role but are not the ultimate decision maker in their respective countries.

[3] The clinical studies considered as sources of information were the same both in the EPAR and in the HTA reports (i.e. STRIVE, ENVISION and PERSIST). HTA bodies had more data (i.e. longer periods) from PERSIST study available at the time of appraisal than EMA.

The analyses showed that the clinical study design was considered appropriate in all HTA reports (Table II). No divergent opinions in this area were pointed out between regulators and HTA bodies. The elements analysed under this area showed differences in opinions among HTA bodies, indicating variations in the acceptance of the degree of uncertainty regarding the long-term safety and efficacy. From the six HTA reports studied, four countries acknowledged the uncertainty present but accepted it. Two bodies, the NCPE of Ireland and the SMC of Scotland did not.

The appraisal of the clinical added value (i.e. relative cost effectiveness) also varies among HTA bodies (Table III). No discussion at all is present in the French and Spanish reports. In the German report only global budget considerations are present. The English, Scottish and Irish reports address the pharmacoeconomic studies provided by the Sponsor together with Incremental Cost Effectiveness Ratio (ICER) and Quality Adjusted Life Year (QALY) threshold elements in addition to global budget considerations.

Elements	EPAR Information: *What is sought to grant a Marketing Authorization*?	HTA Reports Information: *What is sought for pricing and reimbursement*?
Health problem and current use	D. Main elements of the disease described.	**NHS**: D. Estimation of number of patients eligible provided (≈270). **SMC**: D. Estimation of number of patients eligible provided (≈70). **IPT**: D. Estimation of number of patients eligible provided (≈16). **NCPE**: D. Estimation of number of patients eligible provided (≈120). **HAS**: D. Estimation of number of patients eligible provided (≈74). **IQWIG**: D. Estimation of number of patients eligible provided (≈180).
Description and technical characteristics	D. Main elements: Marketing authorization (MA) date Indication Posology	**NHS**: D **SMC**: D **IPT**: D **NCPE**: D **HAS**: D **IQWIG**: D
Safety	D. The most frequent adverse reactions were not severe and well tolerated.	**NHS**: ND **SMC**: D. Based on EPAR. **IPT**: D. Based on EPAR. The two post-authorisation measures imposed on the MA mentioned as source of further information. **NCPE**: ND **HAS**: D. Based on EPAR. **IQWIG**: ND.
Clinical effectiveness	D. Observational studies imposed as a condition on the marketing authorization. Details discussed in Tables II and III.	**NHS**: D. Details discussed in Tables II and III. **SMC**: D. Details discussed in Tables II and III. **IPT**: D. Details discussed in Tables II and III. **NCPE**: D. Details discussed in Tables II and III. **HAS**: D. Details discussed in Tables II and III. **IQWIG**: ND.
Costs and economic evaluation	NA.	**NHS**: D. Details discussed in Tables II and III. **SMC**: D. Details discussed in Tables II and III. **IPT**: ND. **NCPE**: D. Details discussed in Tables II and III. **HAS**: ND. **IQWIG**: D. Details discussed in Tables II and III.
Ethical analysis	NA.	**NHS**: D. First drug in class. Severity of the disease. Improvement of health, reduction of hospitalizations. Indicated for children when the damage in tissues could be still slowed down. Mention to the fact that similar ultra-orphan drugs previously financed with similar ICER ranges. **SMC**: D. First drug in class. Incurable disease. **IPT**: D. First drug in class. **NCPE**: D. First drug in class. **HAS**: D. First drug in class. **IQWIG**: ND.
Organizational aspects	D. The medicine was authorized subject to restricted medical prescription (i.e. by specialists) and subject to genetic diagnosis of the mutation. Monitoring system by registries.	**NHS**: D. Genetic diagnosis required and sweat chloride levels controls. Prescribed by specialists. Health outcomes to be monitored by cystic fibrosis registries. **SMC**: D. Based on EPAR indication. **IPT**: D. Based on EPAR indication. **NCPE**: ND. **HAS**: D. Based on EPAR indication. Hospital use. **IQWIG**: ND.

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Social aspects	NA.	**NHS**: ND. **SMC**: ND. **IPT**: ND. **NCPE**: ND. **HAS**: ND. **IQWIG**: ND.
Legal aspects	NA.	**NHS**: ND. **SMC**: ND. **IPT**: ND. **NCPE**: ND. **HAS**: ND. **IQWIG**: ND.

Table I. *EUnetHTA Core Model*

D = element discussed in the report (i.e EPAR/HTA; HAS = Haute Autorité de Santé; IPT = Therapeutic Positioning Report for Spanish Government; IQWIG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NA = not applicable to the evaluation; ND = element not discussed in the report (i.e. EPAR/HTA); NCPE= National Center for Pharmacoeconomics; NHS = NHS England statement; SMC = Scottish Medicines Consortium

Elements	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for pricing and reimbursement?*
Comparators Placebo vs. Active	D. Kalydeco was compared to placebo in two Phase III pivotal trials (double-blind, randomized, multicentre): STRIVE on adults (VX08-770-102) and ENVISION on children (VX08-770-103) The Standard of Care (SOC) (i.e. pre-study medication) was continued in the patients with the exception of the inhaled hypertonic saline, which was not allowed.	**NHS**: D. Statement that 2 well conducted research studies (one in adults/one in children) placebo-controlled trials were undertaken. Only palliative treatments are currently available. **SMC**: D. Superiority over placebo showed. There are no comparators for the disease. **IPT**: D. Currently only symptomatic treatments are available. **NCPE**: ND. **HAS**: D. Currently only symptomatic treatments are available. **IQWIG**: ND.
Study population Homogeneous vs. Heterogeneous	D. Two main studies involving 219 patients with cystic fibrosis who had the G551D mutation in at least one allele of the CFTR gene: one of the studies was in patients >12 years old (n.=167) (STRIVE), the other study involved patients between 6 and 12 years (n.=52) (ENVISION). In addition, patients included had a $FEV_1 \geq 40\%$ and a minimum body weight of 15 kg[1].	**NHS**: ND. **SMC**: D. The small size is acknowledged as appropriate considering the low number of patients affected by the mutation. **IPT**: D. The small size is acknowledged as appropriate considering the low number of patients affected by the mutation. **NCPE**: ND. **HAS**: D. Based on EPAR. **IQWIG**: ND.
Endpoints (Patient Reported Outcomes – PROs, Quality of Life –QoL, Duration of Life, etc.).	D. The studies mentioned above had 48 weeks of duration. The main measure of efficacy was the ability to improve the pulmonary function (measured as the absolute change from baseline in percent predicted FEV_1 after 24 weeks of treatment). This variable was also measured at week 48. Secondary variables: other beneficial aspects as decrease rate of pulmonary exacerbations, sweat chloride concentration and increase in body weight. In addition, the change in respiratory symptoms at week 24 and 48 evaluated through the validated CFQ-R questionnaire[2]. PERSIST study (VX08-770-105) is an extension, non-controlled open-label study of studies VX08-770-102 and 103, the two pivotal trials presented for the marketing authorization application. The open-label study is up to 96 weeks (i.e. 144 weeks of treatment for those already on the drug and 96 for those initially allocated to placebo).	**NHS**: D. Improved lung function, weight gain and decrease in worsening of breathing requiring other treatments. Note is made to the absence of long-term efficacy data but it is recognized that the main indicator of cystic fibrosis, the amount of salt in sweat returns to normal values with ivacaftor treatment). Indication of the extension, non-controlled open-label study up to 96 weeks. **SMC**: D. Acknowledgement of FEV_1 as a surrogate which is the recommended primary clinical endpoint for efficacy studies. CFQ-R mentioned. PERSIST study (up to 96 weeks) also mentioned. **IPT**: D. Based on EPAR. Indication of the extension, non-controlled open-label study up to 96 weeks (PERSIST). **NCPE**: D. Brief reference to FEV_1 as primary endpoint for Phase III clinical trials. **HAS**: D. Based on EPAR. Indication of the extension, non-controlled open-label study up to 96 weeks (PERSIST). **IQWIG**: ND.

Table II Clinical Study Design

[1] FVE1 is the maximum amount of air that a person can breathe out in one second

[2] CFQ-R Questionnaire. In the CFQ-R, patients report respiratory symptoms. It is an indicator of the symptoms on the quality of life.

D = element discussed in the report (i.e EPAR/HTA; HAS = Haute Autorité de Santé; IPT = Therapeutic Positioning Report for Spanish Government; IQWIG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NA = not applicable to the evaluation; ND = element not discussed in the report (i.e. EPAR/HTA); NCPE= National Center for Pharmacoeconomics; NHS = NHS England statement; SMC = Scottish Medicines Consortium

Elements	EPAR Information: *What is sought to grant a Marketing Authorization?*	HTA Reports Information: *What is sought for pricing and reimbursement?*
Positive benefit/risk balance (Quality, Safety and Efficacy: The 3 basic guarantees)	D. Quality: positive Safety: positive. Minor side effects. Efficacy: positive. After 24 weeks of treatment, patients aged 12 years and older who took Kalydeco had an average improvement in FEV_1 of 10.4%, compared with a reduction of 0.2% in those who took placebo. Similar results were seen in patients aged between 6 and 11 years, where Kalydeco treatment led to an improvement in FEV_1 of 12.6% compared with an improvement of 0.1% with placebo. These efficacy values were maintained at week 48.	**NHS**: D. Based on EPAR. **SMC**: D. Based on EPAR. **IPT**: D. Based on EPAR. Efficacy explicitly acknowledged. **NCPE**: ND. **HAS**: D. Based on EPAR. **IQWIG**: ND.
Post-approval studies (Generation of additional evidence: PASS, PAES, Registries).	D. PASS and PAES imposed as a condition of the Marketing Authorisation. Real world data collection as part of these studies required.	**NHS**: D. Mention to PERSIST study. Mention that health outcomes in patients taking ivacaftor will be monitored using data from the cystic fibrosis registry. **SMC**: D. Long-term studies are acknowledged. **IPT**: D. The studies imposed on the MA are acknowledged and recognized as useful to clarify pending long-term safety and efficacy evidence generation. **NCPE**: ND. **HAS**: Discussed. Based on EPAR. **IQWIG**: ND.
Degree of uncertainty accepted	D. EPAR indicates limited data on longer-term effects. Conditions were imposed on the MA to provide further data in this respect: From an ongoing long-term study and to conduct a five-year observational study.	**NHS**: D. Good evidence that ivacaftor is clinically effective although long-term safety and effectiveness data beyond 96 weeks are lacking. Monitoring of sweat chloride test required as indicators of treatment effectiveness and used as a stopping criteria for the treatment to be discontinued. **SMC**: D. The PERSIST study is acknowledged. But long-term efficacy and safety data are considered necessary for chronic conditions and data beyond 48 weeks are limited. **IPT**: D. Absence of long-term efficacy data to prove maintenance of positive effects accepted. Monitor the efficacy in patients receiving treatment. **NCPE**: D. Absence of long-term efficacy and safety data not accepted. 96 weeks in adults and 72 in children considered limited. **HAS**: D. Absence of long-term efficacy data to prove maintenance of positive effects accepted. **IQWIG**: ND.
Clinical added value (Relative Cost-Effectiveness: The 4th guarantee).	NA.	**NHS**: D. ICER and QALY. No global budget discussion. Ivacaftor reduces need for other expensive treatments for progressive clinical deterioration and need of hospital care, including organ transplantation, which accounts for £100m annual expenditure (excluding transplantation). **SMC**: D. ICER, QALY and global budget figures provided. **IPT**: ND. **NCPE**: D. ICER, QALY and general budget considerations. Out of the accepted 45000 Euro/QALY threshold. **HAS**: ND. **IQWIG**: Global budget discussion.

Table III. *Clinical evidence pre-approval*

D = element discussed in the report (i.e EPAR/HTA; HAS = Haute Autorité de Santé; IPT = Therapeutic Positioning Report for Spanish Government; IQWIG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NA = not applicable to the evaluation; ND = element not discussed in the report (i.e. EPAR/HTA); NCPE= National Center for Pharmacoeconomics; NHS = NHS England statement; PAES: Post-Authorisation Efficacy Study; PASS: Post-Authorisation Safety Study; SMC = Scottish Medicines Consortium

Country	Safety & Efficacy	Uncertainty accepted	Price and budget considerations	Recommendation	Final government decision
Spain	+	Yes	No	Positive	Positive
France	+	Yes	No	Positive	Positive
Germany	+	Yes	Yes	Positive	Positive
England	+	Yes	Yes	Positive	Positive
Scotland	+	No	Yes	Negative	Positive
Ireland	+	No	Yes	Negative	Positive

Table IV. *Summary of key decision elements*

DISCUSSION

From the point of view of the scientific evidence, all the HTA reports analysed obtained the main clinical elements regarding safety and efficacy from the published EPAR (Table IV). None of the HTA reports challenged the design of the studies or the clinical evidence generated.

However, there was a clear difference in the way the existing degree of uncertainty was evaluated, being this aspect the key point in the justification of the negative opinions reached by the Irish and Scottish HTA bodies.

All HTA reports alluded to the presence of uncertainty regarding long term effects. In fact, this aspect is well reflected in the EPAR. The EMA opinion noted the limited data on longer-term effects and as a result imposed conditions on the marketing authorization in this respect (provision of on-going long-term study and the conduct of a five-year observational study).

However, while for NHS England, Spain, France and Germany this degree of uncertainty was considered acceptable and did not preclude a positive financing decision, for the Scottish and Irish HTA bodies this represented the scientific clinical evidence factor highlighted and emphasized in order to support the negative opinion.

From a cost-effectiveness point of view, the Irish and Scottish HTA bodies were clear regarding that Kalydeco is not cost-effective. NHS England and Germany highlighted the high cost of the drug but still considered it financeable due to the characteristics of the drug and the illness. The Spanish and French HTA reports provided estimations to the number of patients eligible for the treatment in their respective countries but do not reported further on cost-effectiveness elements.

The HTA reports of NHS England, SCM and Ireland indicated the fact that the public administration engaged in price negotiations with the holder Vertex Pharmaceuticals or would be willing to do it in order to agree discounts that would facilitate the financing of this expensive treatment in their public health systems.

Nevertheless, despite the negative recommendations issued by the Scottish Medicines Consortium and the National Center for Pharmacoeconomics of Ireland, the governments of these two countries finally decided to make the drug available, being the decision ultimately raised to the political level.

It is also to be mentioned that outside the EU, similar conclusions were reached. The Canadian Drug Expert Committee (CDEC) recommended in March 2013 ivacaftor under the condition of a substantial reduction in price to meet cost-effectiveness criteria [16]. The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia reflected in March 2014 that without a substantial price reduction or a pay for performance arrangement, ivacaftor would not be considered cost-effective [17].

CONCLUSION

The case of Kalydeco exemplifies the dilemma between the scientific clinical evidence and the national budget considerations that HTA bodies face. Kalydeco was undoubtedly and unanimously recognized at EU level by regulators on the three first basic guarantees. However, the granting of an EU marketing authorization is not to be taken for granted as synonym of equal access to European patients. Some national HTA bodies can conclude that financing and reimbursement requirements are not met and therefore block entrance into their respective markets.

In such a situation, will the disharmony among European countries be solved if a common core HTA method and efficient sharing of data were established among HTA bodies? The example of Kalydeco evidences that the solution might not be so simple, as it is clear that the clinical evidence can be overruled by price and budget considerations.

In the last two decades, regulatory agencies have enormously increased the level of harmonization, communication and transpa-

rency in relation to their assessment processes. HTA bodies in Europe are now working to achieve the same degree of harmonization and collaboration for HTA process and find a common path where both evaluation meet and align. However, the local focus that the financing perspective has cannot be obviated and as a result, different national conclusions can arise from the same clinical evidence. Some of them could be due to the selection of different factors for the analysis or the outcome of the importance and interpretation given based on local specificities and values or on national cost-effectiveness thresholds and budget's restrictions.

Regulators and HTA bodies are aware of the need to provide industry with clear guidelines for the development of new medicines and are willing to engage in a transparent and productive dialogue with industry in order to ensure predictability and facilitate as much as possible patient's early access to new medicines. A disharmony in this area would also raise controversy across patient' organizations as it will become difficult to justify that in the framework of the European Union not all patients enjoy the same degree of health protection. However, in this subject of access and equity, not only regulators should be seen as the only responsible party. Industry also has a responsible role to play. Regulators and HTA bodies are taking important steps and efforts to harmonize criteria and are willing to embark in a transparent dialogue with industry to facilitate the development of new drugs. But at the same time, sponsors of the new medicines also need to be aware of the European governments' obligation to assure the long term sustainability of their health systems.

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