The First Re-Evaluations in France Based on Real-World Evidence

Another Good Example of Starting with the End in Mind

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Among the many possible uses of real-world evidence (RWE) by pricing and access decision-makers, one is in re-evaluation of initial health technology assessment (HTA) decisions. France, which leverages RWE among other data sources in its HTA reassessments, presents an interesting case to consider RWE's role in such reviews. There were three products reassessed by the French National Authority for Health (HAS) in 2017 for which the Transparency Committee (TC) considered RWE in the reassessment. Table 1 summarizes these three cases.

Given the relative frequency with which Temporary Authorization for Use (ATU) data are considered in reassessments, a key challenge concerns the robustness of ATU data – or lack thereof. For instance, the ATU for Tagrisso suffered from a significant missing data problem. Of the 408 patients in the ATU, treatment evaluation forms were only received for 151. Of these, there was no radiological tumor evaluation for 16 patients, and there were "not assessable" or unspecified results for 8 more patients, leaving only 127 pieces of data to evaluate. The Transparency Commission does not assess the remaining data in percentage terms in its opinion, but rather only cites absolute numbers of the 127 who had partial or complete response, stabilization of disease, or disease progression. It is difficult to see how the HTA body can make good use of such data, which may suffer from a multitude of problems (e.g., selection bias), when considered alongside appropriately powered, well-designed clinical trials, even if the external validity of the ATU data is high by virtue of being "real-world" data.

The case of Kolbam underscores the robustness problem in cases of extremely rare diseases – there may simply be too few patients in the entire country who can benefit from a therapy to build up a robust ATU dataset for consideration by the HTA body.

The case of Myozyme shows that drug registries need to be carefully designed with the HTA body's key question in mind – in this case, whether the drug slows disease progression in late-onset Pompe disease. Failing that, the registry data may not support the reassessment in one direction or the other, as in this case.

Another challenge, exemplified by the Yervoy case, is the potential obsolescence of the RWE in quickly evolving categories. It is rare to see such a wealth of RWE considered in a reassessment, which in this case included:

- post-registrational study set up at the request of CEPS re: survival, safety, and quality of life, using data from MELBASE, a prospective, observational, non-comparative cohort study promoted by Assistance Publique – Hôpitaux de Paris

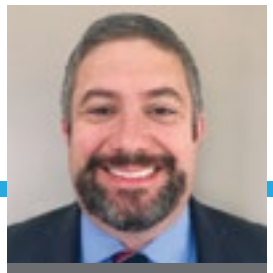

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Table 1. Snapshot of RWE in French HTA Reassessments, 2017

Drug	Indication	Orphan Status	RWE Included in Reassessment	Date of Original Decision to Reimburse & Ratings	Date of Re-Assessment Based on RWE	Impact of Reassessment	Key Issues re: RWE Raised in Opinion
Kolbam (cholic acid)	Lifelong treatment of adults and children who cannot produce enough primary bile acids due to genetic abnormalities that result in lack of sterol 27-hydroxylase, 2-methylacyl-CoA racemase, or cholesterol 7a-hydroxylase	Orphan	ATU (i.e., "temporary authorization for use," aka compassionate use) data	• December 17, 2014[1]: decision on SMR delayed until ATU data are available for analysis	September 13, 2017[2]	SMR insufficient (i.e., no longer reimbursed)	Weak RWE base – in the absence of clinical data, the TC noted it could not make a risk/benefit assessment and therefore determined that the molecule is not to the benefit of health service / patients
Myozyme (alglucosidase alpha)	Long-term enzyme replacement therapy in patients with Pompe disease (acid alpha-glucosidase deficiency)	Orphan	RWE data collected by CSEVR	• September 20, 2006: in juvenile onset disease, SMR major, ASMR II; in late onset disease, SMR insufficient[6] • June 16TH, 2010: in late onset disease, SMR low, ASMR IV[7] • January 13, 2013: no change in late onset disease[8]	October 18, 2017[9]	ASMR downgraded from II to III for juvenile onset disease	Long-term registry data for patients with late-onset disease only confirm that the disease continues to progress in treated patients, not whether the drug slows the rate of progression
Yervoy (ipilimumab)	Advanced (unresectable or metastatic) melanoma	Not orphan	Various, including post-registration study commissioned by CEPS, retrospective studies in U.S. setting, etc.	• December 14, 2011: SMR major, ASMR IV[3] • ASMR maintained in re-evaluation of November 6, 2013[4]	June 7, 2017[5]	• SMR downgraded to insufficient (i.e., no longer reimbursed) in the case of treatment naïve patients regardless of B-RAF status, and 2nd line B-RAF+ patients • ASMR V continues to apply to 2nd line B-RAF- and 3rd line+ regardless of B-RAF status	• RWE in early line patients deemed obsolete because collected before launch of paradigm-changing I-O and other targeted agents • However, Yervoy monotherapy in advanced patients is seen as valuable

ASMR=Improvement of Medical Benefit (Amélioration du Service Médical Rendu)
ATU=Temporary Authorization for Use (Autorisation Temporaire d'Utilisation)
CEPS=Economic Committee of Health Products (Comité Economique des Produits de Santé)
CSEVR=Committee for Studies in Real Life (Comité des Études en Vie Réelle)
I-O=Immuno-Oncology
SMR=Medical Benefit (Service Medical Rendu)

- the observational, prospective, non-comparative IMAGE study conducted at the request of the European Medicines Agency (EMA)
- several retrospective cohort studies from the U.S.
- an electronic medical record study from a U.S. oncology network
- Cytokine Working Group data
- retrospective cohort study using compassionate use data from multiple countries

However, in the end, all of it was essentially discarded as no longer relevant due to market evolution.

Careful consideration of the potential impact of RWE on pricing and reimbursement (P&R) decisions, including reassessments in France, is required to guide investment decisions. It is becoming increasingly important to show products' effectiveness and safety in the real world – regardless of whether in post-launch or in early access such as with an ATU program - beyond efficacy and safety in an internally valid trial. As the case of the Myozyme registry shows, beginning with the end in mind is critical to mitigating P&R decision-makers' uncertainty. ■

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