

Background and objective

- In France, since 2013, pharmaceutical and medical devices companies are required to submit an economic analysis to HAS for presumed innovative products according to submission criteria updated in 2022 (1)
- The CEESP evaluates the efficiency dossiers and publishes EOs (2)
- This study aimed to synthesise outcomes of these evaluations and track these outcomes over time

Results

- Overall, 199 EOs for pharmaceutical products were collected. Of these, 54% (n=106) EOs were for products seeking first registration, 35% (n=69) sought an extension of indication, 7% (n=14) were for a reassessment, 2% (n=4) sought a renewal, <1% (n=1) was for an indication modification, and <1% (n=1) was withdrawn
- The EOs identified covered 23 therapeutic areas. Oncology represented the largest proportion of the EOs (43%), followed by onco-haematology [20 EOs (10%)] and medical devices [19 EOs (10%)]. The rest of the therapeutic areas, each covering 1% to 6% of the total EOs identified, included rare diseases, cardiology, haematology, and virology
- For half of the products assessed in the EOs (48%), early access was granted

Clinical benefit (SMR)

- Between 2014 and 2022, 180 EOs were published assessing drugs. Of these, 89% (n=159) of the EOs focused on drugs with an *important* SMR rating, including 14% (n=22) EOs for drugs that were rated *insufficient* for part of their indication. Only 7% (n=12) of the EOs involved drugs rated *moderate*, 3% (n=7) involved drugs rated *insufficient*, and 1% (n=2) focused on drugs rated *poor*

Clinical added value (ASMR)

- A comparison of the ASMRs claimed and obtained was carried out for each EO
- In the EOs identified, 72.8% (n=131) of the ASMRs obtained were different from the ASMRs claimed; only 23.3% (n=42) were similar
- Of the 180 EOs analysed, 7 EOs focused on drugs with an *insufficient* SMR rating, including 1 case in which the submission was withdrawn. In these cases, no ASMR was communicated

Methods

- The HAS website was screened and all the EOs released by the CEESP until end of December 2022 were extracted and aggregated in an internal Putnam database
- For each EO, information including type of submission, therapeutic area, SMR, ASMR, ICER, MRs, and CEESP conclusion, among other variables, was extracted
- Different year-clusters were used to analyse the evolution of EO outcomes
- For simplification purposes, EOs on medical devices were excluded from SMR and ASMR analyses. ICERs validated by the CEESP were analysed (excluding dominating and dominated cases in order to capture only numeric data). If multiple ICERs were presented in the CEESP EO conclusion, the lowest ICER was considered
- The MRs in each extracted EO were reviewed by 2 assessors and categorised as 1 of 19 dimensions. The classification was done blindly, and when a discrepancy arose, a third reviewer selected the most appropriate dimension

- In the entire database, ICERs published varied from €662/QALY (infectiology) to €2,661,514/QALY (rare disease). Overall, the mean and the median ICERs in the entire database during the period between 2014 and 2022 were €246,895/QALY and €123,674/QALY, respectively
- Mean ICER increased from €206,823/QALY in 2014-2016 to €267,626/QALY in 2017-2019 (a 29% increase), before reaching €269,634/QALY in 2020-2022 (a 1% increase compared with 2017-2019). Median ICER grew from €53,300/QALY in 2014-2016 to €130,000/QALY in 2017-2019 (a 45% increase) and reached €168,076/QALY in 2020-2022 (a 29% increase)
- Overall, mean ICER increased by 30% between the 2014-2016 and 2020-2022 periods in France, whereas median ICER more than tripled (+217%) in the same time frame
- A comparison of mean ICER results by therapeutic area in the whole database shows that rare diseases was the therapeutic area in which mean ICER was, by far, the highest (n=7; €1,492,810/QALY), followed by haematology (n=7; €534,478/QALY) and pneumology (n=2; €528,862/QALY), whereas gynaecology (n=1), virology (n=4), and virology/hepatology (n=4) were the 3 therapeutic areas in which mean ICERs were the lowest (€1961/QALY, €13,375/QALY, and €16,526/QALY, respectively). The same comparison assessing median ICERs shows the same trends

Cost-effectiveness analysis MRs

- The CEESP issued 1758 MRs, of which 53% (n=931) were *minor*, 40% (n=711) were *important*, and 7% (n=116) were *major*
- Special interest was given to *major* MRs because of their impact on the CEESP conclusions
- Figure 2 shows the dimensions each accounting for more than 5% of *major* MRs; these 8 dimensions represent 86% of MR classifications. The 3 most important dimensions are clinical data (23%), quality of life (15%), and comparison methods (11%)

Table 1. Comparison of clinical added value claimed with clinical added value obtained

ASMR decision	n	Percentage, %
Different	131	72.8
Similar	42	23.3
NA	7	3.9
Total	180	100.0

Incremental cost-effectiveness ratio

- Figure 1 shows the distribution, in a boxplot representing 50% of the values (between quartiles 1 and 3), of validated ICERs in each cluster. It shows the evolution of the minimum, median, mean, and maximum ICERs for the 2014-2016 (n=36), 2017-2019 (n=29), and 2020-2022 (n=37) clusters.
- Four EOs were excluded from this analysis because they resulted in findings of dominance

Figure 1. Evolution of validated ICERs for 2014-2016, 2017-2019, and 2020-2022

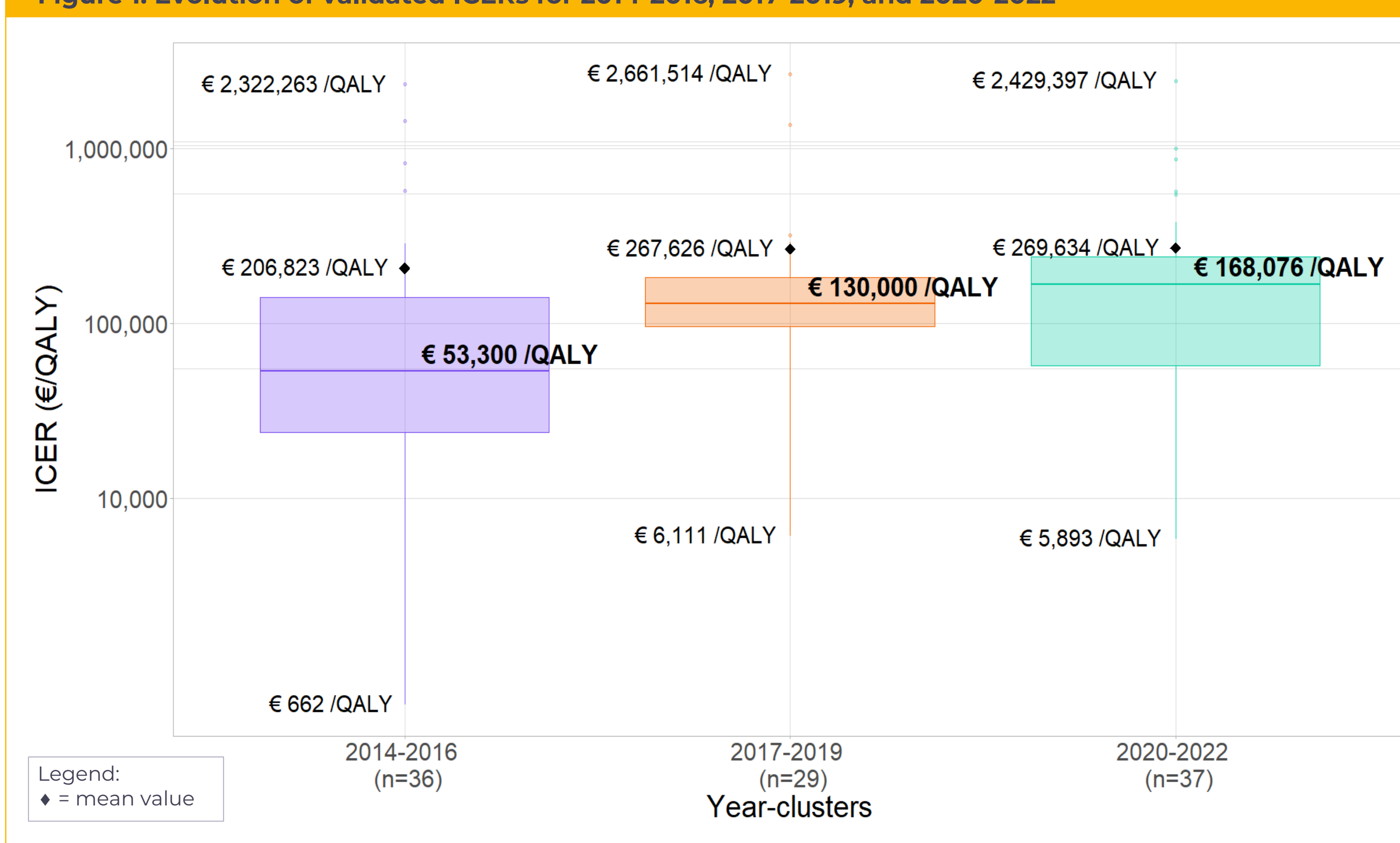
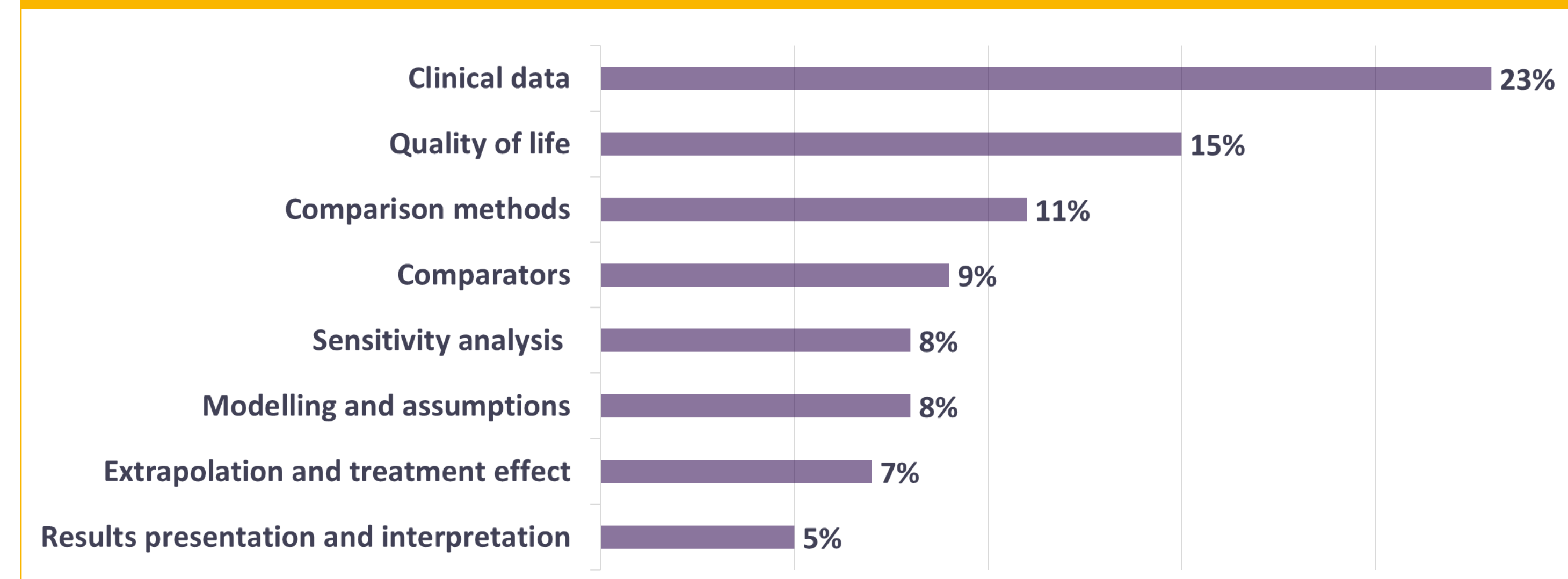


Figure 2. Dimensions covering more than 5% of major MRs



- Other dimensions include costing methods, evaluation objective, population and subpopulation, and validation, covering between 2% and 3% of *major* MRs
- We observed no *major* MRs caused by discount, economic analysis and results criteria choice, treatment duration, time horizon, perspective, or tolerance during the whole period analysed
- Across all EOs, 38% (n=76) reported at least one *major* reservation (of which 39% were for oncology treatments, 13% were for onco-haematology, and 12% were for medical devices)

CEESP conclusions on economic evaluation

- Overall, 44% of the analysed evaluations were considered invalid (n=88). This was most frequently the case for EOs in onco-haematology (65%)
- Between 2014 and 2016, the EO invalidation rate was 37%, increasing between 2017 and 2019 to reach 49% and slightly dropping to 46% between 2020 and 2022

Conclusion

- The **mean ICER validated by the CEESP** over its almost **10-year history** of medico-economic evaluations is **€247,000/QALY (median €124,000/QALY)**. Since 2016, mean validated ICERs increased by ~30%, whereas the median ICER tripled from €53,000/QALY to €168,000/QALY in 2020-2022. The rate of invalidated EOs rose from 37% in 2016 to 46% in 2020-2022. Moreover, **early access was granted for nearly half of the drugs** evaluated, and **only a quarter obtained the ASMR claimed**. The most frequently raised **major reservations** concerned **clinical data, quality of life, and comparison methods**
- **This analysis shows that validated ICERs tend to increase over time. Similarly, the rate of CEESP opinions invalidating economic evaluations rose, probably indicating that the CEESP evaluation is becoming increasingly challenging**
- **Beyond major MRs, more attention needs to be dedicated to the medico-economic evaluation analysis. The CEESP can now invalidate the methodology without raising any major MRs based on a major level of uncertainty or if the assessment scope is extremely limited compared with the indication for which reimbursement is requested (3)**

References

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2. Haute Autorité de Santé. Avis économiques rendus par la Commission d'évaluation économique et de santé publique (CEESP) [Economic opinions issued by the CEESP]. Available at: https://www.has-sante.fr/jcms/p_3149875/fr/avis-economiques-rendus-par-la-commission-d-evaluation-economique-et-de-sante-publique-cesep
3. Accord-cadre du 05/03/2021 entre le Comité économique des produits de santé et les entreprises du médicament (Leem) [French framework agreement between the LEEM and the CEPS]. Paris: Ministère de la Santé et la Prévention; 2021.

Abbreviations: ASMR, amélioration du service médical rendu; CEESP, Commission D'Évaluation Économique et de Santé Publique; EO, economic opinion; HAS, Haute Autorité de Santé; ICER, incremental cost-effectiveness ratio; MR, methodological reservation; NA, not applicable; QALY, quality-adjusted life year; SMR, service médical rendu

Contact

Marine Sivignon
marine.sivignon@putassoc.com

Find out more at putassoc.com

