

Background

In France, market access for innovative-presumed products, following MA, entails a comprehensive evaluation process overseen by the HAS. This evaluation is a 2-fold process, encompassing assessment by the CT and the CEESP, if eligible.

After assessment by the CT and CEESP, drug manufacturers engage in negotiations with relevant authorities to determine the reimbursement price for the product. The negotiated price is subsequently published in the JO.

Objective

The aim of this analysis was to present the evolution of market access time frames in France for health products (drugs and medical devices) evaluated by the CEESP.

Methods

All published CEESP EOs for a first-time registration were collected until December 2022 and aggregated within an internal Putnam database. From each EO, various details were extracted, such as type of application, date of MA, eligibility decision, date of CTO and CEESP EO validations, and publication of the first price in the JO.

Then, mean and median time frames between these different evaluation steps were calculated.

To assess the evolution of these time frames through the years, 3 non-parametric tests were performed on different year-clusters:

- The **Wilcoxon signed-ranks test** compares the medians of two related samples for significant differences (1). Two time periods were used: 2014 to 2018 and 2019 to 2022
- The **Kruskal-Wallis H test** assesses differences between medians of ≥ 2 groups on a continuous or ordinal variable (2)
- The **Dunn test** is a post hoc analysis that compares groups when the Kruskal-Wallis test finds significant differences (3). Three time periods were assessed with the Kruskal-Wallis and Dunn tests: 2014 to 2016, 2017 to 2019, and 2020 to 2022

The parameters evaluated were the following:

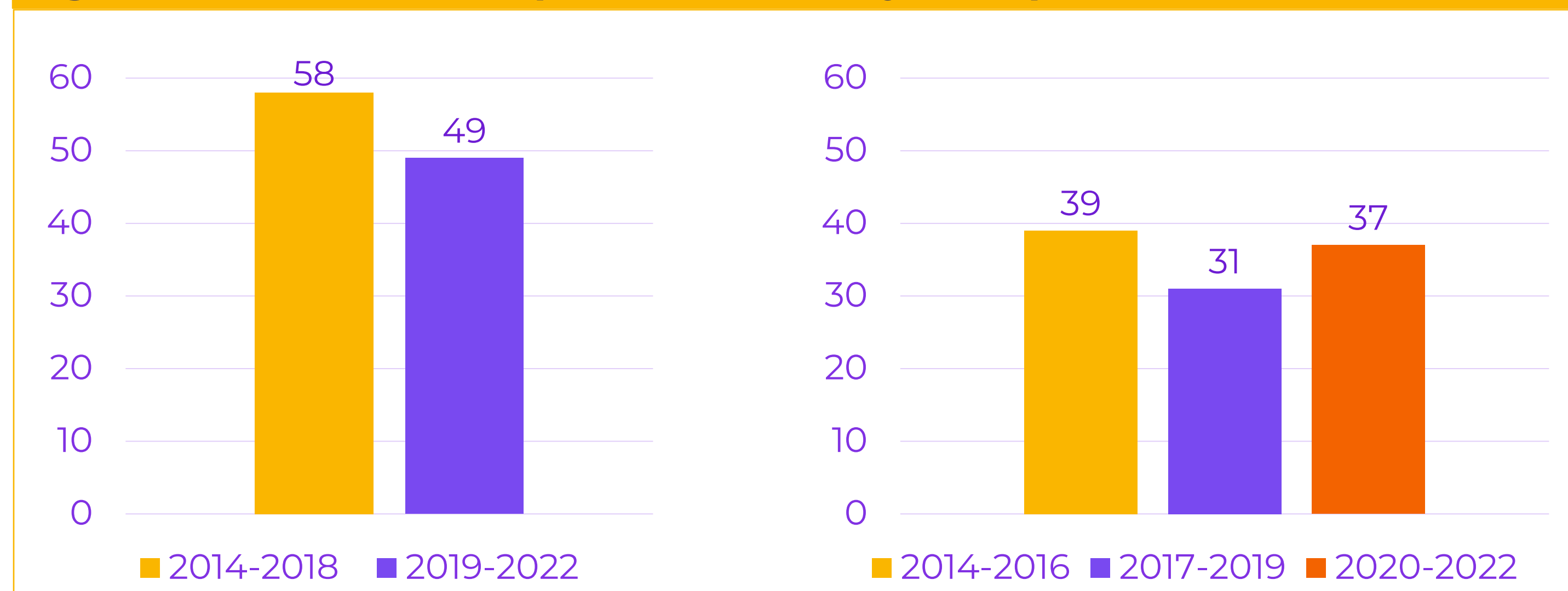
- Time from MA to CTO
- Time from MA to CEESP EO
- Time from MA to first JO
- Time between CTO and CEESP EO
- Time from CEESP EO to first JO

Results

A total of 107 first registrations with an EO have been identified between 2014 and 2022.

Of the 107 EOs, a variety of therapeutic areas was represented, with 27% in oncology, 12% in onco-haematology, and 7% in medical devices. Figure 1 shows the distribution of published EOs by cluster used in the analyses.

Figure 1. Distribution of published EOs by time period



The average and median values for various parameters were computed for raw data and for each time period (Table 1).

Table 1. Overall results for various parameters

Time period	Days from MA to CTO		Days from MA to CEESP EO		Days from MA to first JO		Days from CTO to CEESP EO		Days from CEESP EO to first JO	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
2014-2018	353	210	334	202	956	550	-16	-8	612	337
2019-2022	174	149	208	185	617	565	64	27	412	349
2014-2016	400	209	369	187	1101	550	-29	-15	726	366
2017-2019	217	195	244	238	653	554	86	41	388	344
2020-2022	176	151	204	183	609	549	20	20	428	381
2014-2022	273	177	278	197	837	552	21	13	540	345

Comparing the 2014 to 2018 period with the 2019 to 2022 period with the **Wilcoxon signed-rank test**, 2 statistically significant differences were observed (Table 2):

- Median time from MA to CTO decreased significantly by 61 days ($p < 0.01$)
- Median time between CTO and CEESP EO increased significantly by 35 days ($p < 0.05$)

No other significant difference was observed.

Abbreviations: CEESP, Commission d'Évaluation Économique et de Santé Publique; CT, commission de transparence; CTO, CT opinion; EO, economic opinion; HAS, Haute Autorité de Santé; JO, official journal; MA, marketing authorisation

Table 2. Wilcoxon test results

Time frame	Group 1	Group 2	p
Time from MA to CTO	2014-2018	2019-2022	<0.01
Time from MA to CEESP EO	2014-2018	2019-2022	0.24
Time from MA to first JO	2014-2018	2019-2022	0.41
Time between CTO and CEESP EO	2014-2018	2019-2022	<0.05
Time from CEESP EO to first JO	2014-2018	2019-2022	0.72

On the **Kruskal-Wallis H test**, significant differences in median values were also observed:

- Time from MA to CTO ($p < 0.05$)
- Time from MA to CEESP EO ($p < 0.01$)
- Time between CTO and CEESP EO ($p < 0.01$)

No significant differences were observed in the parameters related to JO.

Dunn tests to identify pairwise distinctions reaffirmed the Kruskal-Wallis test findings (Table 3):

- Time from MA to CTO
 - 2020 to 2022: MA to CTO median time was significantly shorter than the times for 2014 to 2016 ($p = 0.08$) and 2017 to 2019 ($p = 0.08$)
- Time from MA to CEESP EO
 - 2017 to 2019: MA to CEESP EO median time was significantly longer than the times for 2014 to 2016 ($p < 0.05$) and 2020 to 2022 ($p < 0.05$)
- Time between CTO and CEESP EO
 - 2014 to 2016: CTO to CEESP EO median time was significantly shorter than the time from 2017 to 2019 ($p < 0.01$) and 2020 to 2022 ($p = 0.08$)

Table 3. Dunn test results

Time frame	Group 1	Group 2	Statistic	Adjusted p
Time from MA to CTO	2014-2016	2017-2019	0.03	0.98
	2014-2016	2020-2022	-2.24	<0.10
	2017-2019	2020-2022	-2.08	<0.10
Time from MA to CEESP EO	2014-2016	2017-2019	2.66	<0.05
	2014-2016	2020-2022	-0.23	0.82
	2017-2019	2020-2022	-2.80	<0.05
Time between CTO and CEESP EO	2014-2016	2017-2019	3.15	<0.01
	2014-2016	2020-2022	2.05	<0.10
	2017-2019	2020-2022	-1.17	0.24

Discussion

- Although the number of analysed opinions may be limited, it is crucial to highlight that these analyses were based on an exhaustive database. It is also important to note that, at the time of analysis, 29 healthcare products were awaiting their price publication in the JO, resulting to a more limited data set for time frames involving the JO. This may, in part, explain why no significant difference was observed for time frames related to the price published in the JO
- The dates related to the CTO and EO considered are the dates of validation of these opinions. Without knowing the date of CT and CEESP dossier submissions, as well as whether the full dossiers were submitted on the same date, this can misrepresent the real time frame between CT and CEESP evaluations independently
- Statistical tests were conducted to compare medians, rather than means, because of the presence of extreme values (which impact means) and the non-normal distribution of observed time frames. If with naive comparisons on means, certain time frames seem highly decreased, those differences are to be interpreted with very cautious
- Overall, this analysis shows that:
 - Since 2018, MA to CTO time frame significantly decreased by ~60 days in medians.
 - No other significant difference in medians was observed in terms of MA to first JO time frame, which seems steady with a median around ~550 days.
- Globally, a notable and steady median time frame between MA and the price publication to the JO is still observed in France. Nevertheless, the reduced MA to CTO time frame could be explained by early evaluation by HAS within early access process and the overall ongoing objective of respecting the time limit for reimbursement of 180 days stated by the Council of European Communities after the EU-MA (4)

Conclusion

This analysis shows that market access for presumed innovative drugs is still a long process in France. Nevertheless, MA to Transparency Commission opinions and economic opinions time frames seem significantly decreased over time. Further data would enable to sharpen the results. A regression analysis would explain the determinants of these time frames.

References

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