

Background and objective

- In France, since 2013, pharmaceutical and medical devices companies are required to submit an economic analysis to HAS, the French National Authority for Health, for presumed innovative products according to submission criteria updated in 2022 (1). The CEESP reviews the dossiers and issues economic opinions with varying degrees of reservations. Depending on the importance of the deviation of submitted dossiers from the CEESP guidelines and their expected effect on uncertainty, reservations are graded as minor, important, or major
- In 2011, the HAS published its first guidelines for economic evaluations to define a French reference framework. In 2020, the HAS decided to update its guidelines, drawing on the CEESP's experience over the past 10 years. The 2020 guidelines (2) meet a threefold need: to improve the interpretation of results and uncertainty, to clarify technical points to improve the quality of assessments, and to update methods in line with scientific knowledge. The impact of the 2020 guidelines on the quality of the submitted dossier is not yet explored
- The aim of this study is to assess the impact of these new guidelines on the number of reservations and their grading in the published opinions**

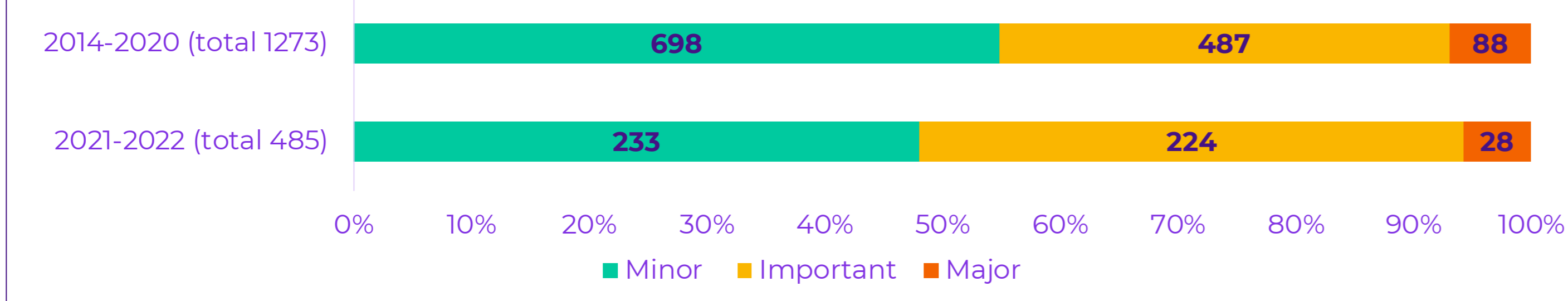
Methods

- The HAS website was screened, and all the economic opinions published by the CEESP until end of December 2022 were extracted and aggregated within an internal Putnam database
- To study the impact of the update of the guidelines, the analysis focused on the reservations issued in the economic opinions. Evaluations were divided before and after the 2020 guidelines according to their eligibility decision dates for economic evaluation. The eligibility decision date was used as a proxy for the date of the submission to the CEESP. A 6-month period after the 2020 guidelines publication was considered, during which the new guidelines had not yet been implemented in dossiers. The 2 periods of analysis were, therefore, defined as 2014-2020 and 2021-2022. The reservations were reviewed by 2 independent reviewers and categorized among 1 of 19 dimensions (shown in the first column of Table 1). The classification was done blindly, and when a discrepancy arose, a third reviewer selected the most appropriate dimension. The average number of reservations per dossier according to the grading (minor/important/major/total) was computed. Naïve comparisons and statistical comparisons were carried out using a *t*-test with a 5% alpha-risk threshold (bilateral test)

Results

- Overall, 197 submissions (including a cost-effectiveness study) were analysed—143 during the period 2014-2020, and 54 during 2021-2022
- Figure 1 displays the grading of the reservations according to each period of analysis. The average breakdown of reservations before and after the 2020 guidelines for an economic opinion was as follows:
 - Before 2014-2020: 4.9 minor, 3.4 important, and 0.7 major reservations per opinion
 - After 2021-2022: 4.3 minor, 4.2 important, and 0.5 major reservations per opinion

Figure 1. Repartition of reservations according to grade and analysis period



- Table 1 shows the list of dimensions with the absolute number of associated reservations and the average number of reservations per period of analysis, regardless of the reservation grade. The last column presents the ranking of the dimensions for each period of analysis, taking all grades together
- The main dimensions with the highest number of reservations (all grades combined, all periods of analysis combined) were as follows: *quality of life*, *modelling and assumption*, *costs*, *exploring uncertainty*, *clinical data (general)*, and *external and internal validation*
- Some dimensions, such as *discount rate* and *perspective*, had a low number of reservations

Table 1. Dimensions of reservations according to the time frame

	Absolute number		Average reservations per opinion		Rank	
	2014-2020	2021-2022	2014-2020	2021-2022	2014-2020	2021-2022
Quality of life	158	65	1.10	1.20	1	2
Modelling and assumption	149	64	1.04	1.19	2	3
Costs	149	41	1.04	0.76	2	5
Exploring uncertainty	141	42	0.99	0.78	4	4
Clinical data (general)	131	36	0.92	0.67	5	6
External and internal validation	97	76	0.68	1.41	6	1
Comparators	74	24	0.52	0.44	7	9
Clinical data (extrapolation and treatment effect)	70	34	0.49	0.63	8	7
Population and subpopulation	59	20	0.41	0.37	9	10
Results presentation and interpretation	50	5	0.35	0.09	10	14
Safety	45	28	0.31	0.52	11	8
Methods of comparison	35	17	0.24	0.31	12	11
Evaluation objective	26	3	0.18	0.06	13	16
Time on treatment	22	14	0.15	0.26	14	12
Clinical expert involvement	22	8	0.15	0.15	14	13
Time horizon	17	4	0.12	0.07	16	15
Evaluation and outcome result method	13	2	0.09	0.04	17	17
Perspective	11	2	0.08	0.04	18	17
Discount rate	4	0	0.03	0.00	19	19

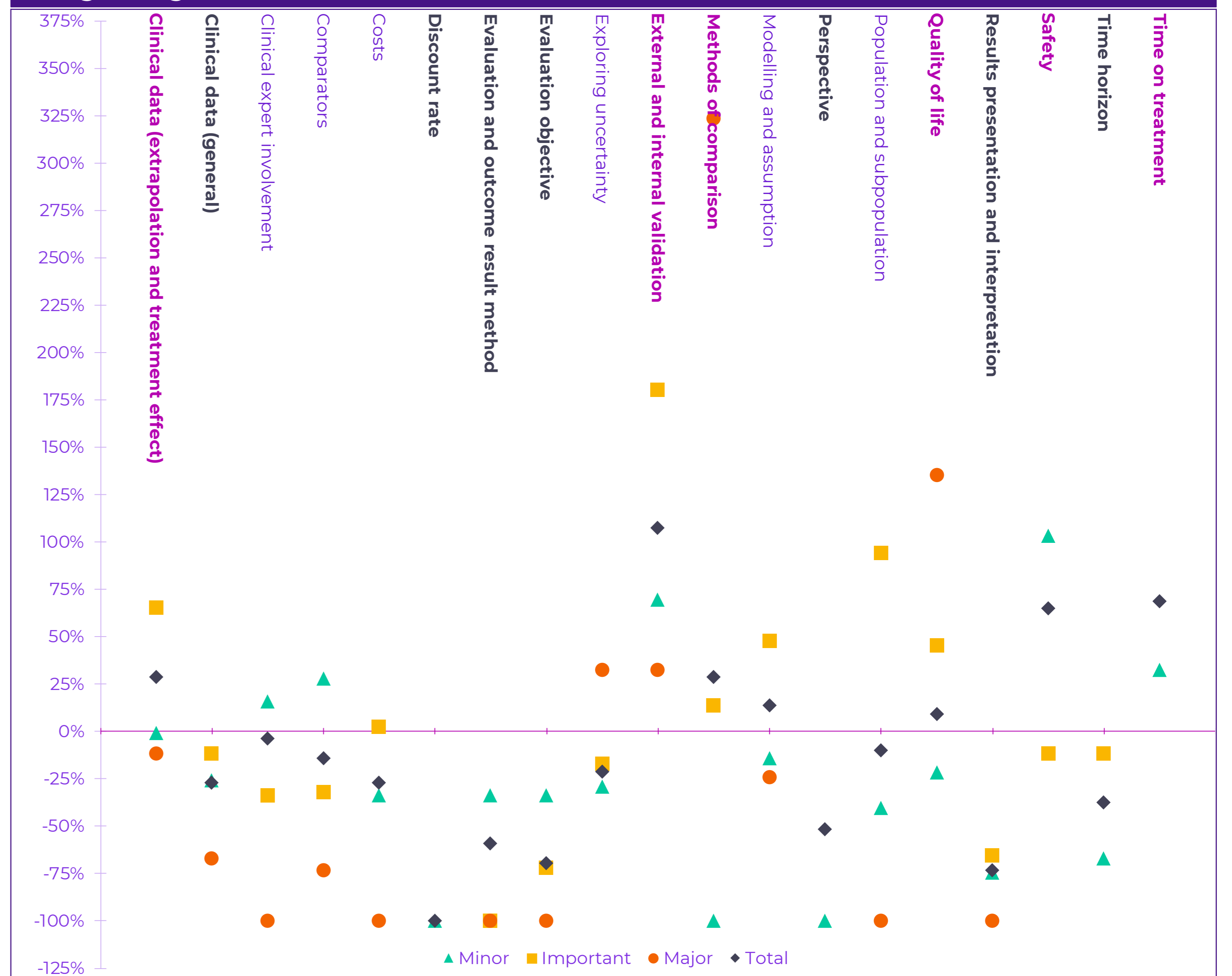
Discussion and conclusion

- The major limitation of this analysis is the classification of reservations, which could be subjective and, therefore, reviewer dependent. This was, however, resolved with the help of review by 2 independent reviewers and a third reviewer, if needed. It is also worth noting that the database used was exhaustive. Despite this and the total number of reservations (n=1758), certain dimensions might have a few reservations making statistical significance difficult to achieve
- The variations in 4 dimensions show a significant difference, which may be explained as follows:
 - By an increase in the level of HAS requirements following the precisions and specific requests added to the guidelines for the increase in validation and safety reservations
 - By more precise recommendations, based on experience acquired, to reduce the reservations on *costs* and *result presentation and interpretation*
- This study identified the following dimensions for which the level of requirements seems to have increased: *clinical data (extrapolation and treatment effect)*, *validity*, *methods of comparison*, *quality of life*, *safety*, and *time on treatment*

Abbreviations: CEESP, Economic Evaluation and Public Health Committee; HAS, Haute Autorité de Santé

- Figure 2 displays the relative evolution of the average number of reservations between 2014-2020 and 2021-2022. The visual analysis shows overall trends—increasing reservations for 6 dimensions (identified in **bold pink**) and decreasing reservations for 7 dimensions (identified in **bold black**)
- The **methods of comparison** dimension corresponds to the highest increase in major reservations (+324%), followed by the **quality of life** (+135%), **external and internal validation** (+32%), and **exploring uncertainty** (+32%). **The 2020 guidelines have emphasised the importance of documenting and justifying these dimensions with better-defined expectations, so these results may be linked to a higher level of HAS requirement. However, the increased use of indirect comparisons in recent years, which has come up against new issues, could also be a factor**

Figure 2. Evolution of the average number of reservations according to dimension and grading between 2014-2020 and 2021-2022



- The statistical *t*-test confirmed significant variations in total average reservations per opinion for 4 dimensions as follows:
 - The **external and internal validation** dimension represents the most important increase (0.68-1.41; *p*<0.001). This was consistent for all the gradings, especially marked for the important reservations (+180%). **The updated guidelines highlighted the need for external and internal validation in dossiers**
 - The **costs** dimension reduced reserves from 1.03 to 0.76 (*p*=0.008). Major reservations are the main reason of the decrease; after the methodological update, no further major reservation on costs was issued. **The 2020 guidelines included new details on costing, which had to improve the quality in the dossiers on this dimension**
 - The **safety** dimension was a concern after the guidelines update (0.31-0.52; *p*=0.03) mostly because of an increase in the minor reservations. **This is certainly linked to an increase in the level of HAS requirements**
 - The **results presentation and interpretation** dimension represents the main decrease (0.35-0.09; *p*=0.04). **It can be assumed that this dimension has been mainly improved by the experience acquired by pharmaceutical and medical devices companies**

References

- Décision n°2022.0212/DC/SED/SEM du 23 juin 2022 du collège de la Haute Autorité de santé relative à l'impact significatif sur les dépenses de l'assurance maladie déclenchant l'évaluation médico-économique des produits de santé revendiquant une ASMR ou une ASA de niveaux I, II ou III. Paris: HAS; 2022.
- Choices in methods for economic evaluation. Paris: HAS; 2020.

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