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Manuscript title:

Was it worth introducing health economic evaluation of innovative drugs in the French regulatory setting?
The case of new Hepatitis C drugs.

Running title:

Health economic evaluation of innovative drugs in the French regulatory setting [see full title above]

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Precis:

The Cost-Effectiveness Opinions recently issued by the French National Health Authority improve the information available to support the pricing decisions.

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1 Abstract

2

3 Objective

4 This paper constitutes the first attempt to draw lessons from the recent uptake of health economic
5 evaluation of innovative drugs in the French regulatory framework.

6 Study Design

7 Taking the example of new direct-acting antivirals against Hepatitis C virus the paper asks
8 whether and how the Cost-Effectiveness (CE) Opinions issued by the French National Health
9 Authority improve the information available to support the pricing decisions.

10 Methods

11 The analysis compares the assessment of these drugs based on three different sources: CE
12 Opinions, Clinical Opinions and the published Cost-Utility Analyses (CUA) available in the
13 literature and identified through a systematic review.

14 Results

15 The results show that CE Opinions bring to the fore 3 issues prone to impact the Incremental
16 Cost Utility Ratio and those were not available to the decision-maker through Clinical Opinions
17 or published CUA: the stage of treatment initiation, the modelling of the disease progression and
18 the uncertainty around the efficacy rates.

19 Conclusion

20 France has introduced the criterion of the cost per QALY gained in the pricing and regulation of
21 innovative pharmaceuticals since 2013. Our analysis shows that the use of CUA does enhance the
22 information available to the decision-makers on the value of the treatments.

23

1 Highlights:

- 2 • The paper constitutes the first attempt to draw lessons from the recent uptake of health
3 economic evaluation of innovative drugs in the French regulatory framework.
- 4 • Taking the example of new direct-acting antivirals against Hepatitis C virus the paper
5 asks whether and how the Cost-Effectiveness Opinions issued by the French National
6 Health Authority improve the information available to support the pricing decisions.
- 7 • The results show that CE Opinions bring to the fore 3 issues prone to impact the
8 Incremental Cost Utility Ratio and that were not available to the decision-maker through
9 Clinical Opinions or published CUA: the stage of treatment initiation, the modeling of the
10 disease progression and the uncertainty around the efficacy rates.

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1 **1. Introduction**

2 Compared to other OECD countries, France only recently includes health economic evaluation
3 (HEE) as an official criterion in innovative drugs regulation. Since October 2013, pharmaceutical
4 manufacturers have been required to submit an economic dossier to the French Health Authority
5 (HAS) for market access [1]. The dossier presents evidence ranging from the determination of the
6 efficiency frontier to the management of uncertainty. The CEESP (*Commission d'Evaluation*
7 *Economique et de Santé Publique*) is in charge of the review and issues a cost-effectiveness (CE)
8 Opinion. CE opinion assesses the reliability and the methodological consistency of the dossier in
9 reference to the HAS guidelines [2] and provides comments that aim at highlighting the salient
10 features of the drugs' value for money. The CE Opinion concludes this critical assessment by
11 rating the limits of the dossier (namely 'réserve') in a four levels scale including none, mild,
12 important or major.

13 HEE is thus added to the clinical evaluation of the drugs which was already carried out within the
14 HAS. The clinical evaluation is performed independently, in the same timeframe, by the CT
15 (*Commission de la Transparence*). The clinical dossier details available clinical evidence on
16 efficacy and adverse events. The Clinical Opinion concludes the review by rating the drug both in
17 terms of its actual clinical benefit in a four-level scale from insufficient to substantial (SMR
18 *Service medical rendu*) and in terms of its clinical added value respective to alternative strategies
19 (ASMR *Amélioration du service medical rendu*) that can be can major (I), substantial (II),
20 moderate (III), minor (IV) or absent (V).

21 Among the very first drugs subject to this new regulatory framework were the newest direct-
22 acting antivirals (DAAs) against Hepatitis C virus (HCV). The arrival of DAAs is considered as a
23 paradigm shift in the HCV treatment because of highly improved efficacy rates - 90% in some

1 settings- with shorter treatment duration and fewer side effects than the existing strategies.
2 However, the newest DAAs are dramatically more expensive than former ones and the issue of
3 making their cost sustainable for national health budgets has come to the forefront of regulation
4 policies and public debates [3–7].

5 In this setting that associates high unit prices and large target population, both the importance and
6 usefulness of HEE have been questioned. For example, Franken *et al.* [8] studying four European
7 countries showed its limited impact in the actual decisions of funding drugs yet deemed not cost-
8 effective, and Van de Vooren *et al.* [9] called for prioritizing budgetary impact over CE
9 considerations to meet high-cost drugs challenge. As the actual usefulness of HEE in the
10 regulation of innovative drugs is debated, it is worth examining the recent French experience.
11 Taking the example of new DAAs against HCV, the objective is to study whether and how CE
12 Opinions have contributed to improving the information provided to support pricing decisions.
13 More precisely, the analysis aims at studying what specific information -if any- has been
14 provided on the drugs' value thanks to the CE Opinions that were available neither in the existing
15 Clinical Opinions nor in the published cost-utility analyses (CUA); the latter were identified
16 through a systematic review.

17 The article continues as follows: the next section presents the drugs under review and their
18 ratings by Clinical and CE Opinions and reports the criteria list for the systematic review
19 conducted. The results presented in the third section show the specific contribution of the CE
20 Opinions in documenting the value of the new DAAs. In the light of these results, the last section
21 underlines key features of the French doctrine regarding the use of the CE Opinion and discusses
22 the issues raised by the implementation of HEE in the French regulatory setting.

23

24 **2. Materials and Method**

1

2 The present analysis deals with all the new DAAs on which the French health Authority issued
3 Opinions, namely sofosbuvir (Sovaldi[®]), simeprevir (Olysio[®]), daclatasvir (Daklinza[®]),
4 ledipasvir-sofosbuvir (Harvoni[®]), ombitasvir-combo (Viekirax[®]) and dasabuvir (Exviera[®]).

5 The purpose is to compare the information on these drugs' value provided by three different
6 sources: CE Opinions, Clinical Opinions and the published CUA available in the academic
7 literature and identified through a systematic review.

8 In the CE Opinions, Sofosbuvir Incremental cost-utility ratio (ICUR) varies from €5,866 to
9 €75,518 per quality-adjusted life year (QALY) gain depending on genotypes and interferon-
10 eligibility [10], simeprevir ICUR from dominated to €18,127 in genotype 1 depending on stages
11 of treatment [11], daclatasvir ICUR from €14,660 to dominated depending on genotypes and
12 interferon-eligibility[12], ombitasvir-combo ICUR from €10,975 to €91,954 per QALY
13 depending on fibrosis stage [13,14]. Ledipasvir+sofosbuvir ICUR was not reported as the CE
14 Opinion assigned a major 'réserve' i.e. the method was not accepted [15].

15 The corresponding Clinical Opinions [16–20] reported ASMR II-III for sofosbuvir and ASMR IV
16 for all other DAAs. The Pricing decisions were taken in November 2014 (sofosbuvir), May 2015
17 (simeprevir and daclatasvir), June 2015 (ledipasvir+sofosbuvir) and August 2015 (ombitasvir-
18 combo and dasabuvir).

19 The systematic review searched the Medline database from January 2010 to August 2015. The 5-
20 year timeframe was aligned with the regulatory timetable in the French setting. For this reason,
21 the literature search period was purposely stopped at the time the pricing decisions were made in
22 order to ensure that the information was available for the pricing negotiation. Indeed the focus of
23 the present study is on the ability of different materials to supply new and timely information to
24 key policy and decision makers and not to provide a review of CUA for new DAAs *per se*. The

1 search covered peer-reviewed CUA of at least one new DAA in French and English; conference
2 abstracts and reviews were discarded. Population, country setting, perspective, comparators, time
3 horizon, measurement of efficacy, cost of treatment, currency and year, type of model, ICUR,
4 uncertainty analysis were extracted using the CHEERS checklist [21] (see appendices for detailed
5 methods and main results).

6 Twenty-one studies were eventually selected among which 16 included sofosbuvir, seven
7 simeprevir, five ledipasvir, one daclatasvir, one ombitasvir and two a new DAA as a hypothetical
8 treatment. Eleven out of 21 were US studies [22–32] and the remaining 10 were performed in
9 Europe; of which four in Italy [33–36], two in the UK [37,38], two in France [39,40] one in Spain
10 [41] and in Switzerland [42].

11 CE Opinions on new DAAs were then screened to identify what variables in the economic
12 modelling were prone to significantly impact CE and consequently the pricing of the treatment.
13 The analysis then searches whether these issues were covered either by the Clinical Opinions or
14 by the published CUA.

15

16 **3. Results**

17 Based on CE Opinions, new DAAs cost-effectiveness appears strongly sensitive to the stage of
18 treatment initiation; the assumptions on the disease progression; and the uncertainty around the
19 efficacy rates.

20 ***3.1. The uncertainty around the efficacy rates***

1 CE Opinions systematically investigated how variation in the efficacy rate of new DAAs impacts
2 the ICUR, while only a few published studies quantify the risk to observe less favourable efficacy
3 results in current practice.

4 The efficacy of treatments against HCV is measured by the Sustained Virological Response
5 (SVR), a surrogate endpoint which corresponds to an undetectable viral load after the end of the
6 treatment.

7 CE Opinions on new DAAs highlighted that SVR rates were mainly based on phase II clinical
8 trials including a limited number of patients and that even within limited range variation, ICUR
9 was highly sensitive to the SVR rate. For example in genotype 1 treatment-naïve patients, a 2%
10 reduction of daclatasvir SVR rate led to an increase of ICUR from 13% to 43% depending on
11 fibrosis stage [12]; the variation of simeprevir SVR rate within the 95% confidence interval
12 modifies the ICUR from €11,336 to €29,731 (vs €14,682 in base-case) [11]; SVR rate was of the
13 main driver of ICUR variability for ombitasvir-combo [13].

14 Clinical Opinions also emphasized the limited data on efficacy rate. Sofosbuvir Opinion
15 acknowledged limited data for cirrhotic patients; simeprevir and daclatasvir Opinions stated that
16 new DAAs against HCV should be limited to patients that need urgent treatment, as they were
17 only evaluated in phase II trials; ledipasvir+sofosbuvir and ombitasvir-combo Opinions
18 acknowledged a better level of evidence but limited the treatment to patients with advanced
19 disease, waiting for more treatments opportunities to be approved.

20 The published CUA also rested on limited clinical evidence and data sources for the SVR rates
21 used in the modelling were quite heterogeneous between studies. Regarding sofosbuvir, in only
22 seven out of 16 studies all SVR rates were extracted from complete peer-reviewed publications
23 [25,26,32,34–36,40]. In the remaining studies, at least one conference abstract or a press release
24 from the pharmaceutical manufacturer was used as a source of SVR rate. Regarding simeprevir,

1 daclatasvir and ledipasvir, one study referred to an original meta-analysis [38]; all others obtained
2 at least one SVR rate from a conference abstract or a press release. Sensitivity analysis on the
3 SVR rates was carried out in 15 out of the 21 CUA published. Results showed that with a
4 variation of the SVR rate ranging from 1% to 30% from the base case, the cost-effective
5 treatment is not cost-effective anymore in 8 studies [23,24,26–28,30,34,40].

6 ***32. Assumptions on disease progression***

7 CE Opinions raised awareness on the gap between SVR achievement and health outcomes and
8 insisted on the importance of modelling the disease progression beyond SVR to give a more
9 realistic picture of patients' lifetime health care costs and utilities.

10 The HCV infection is marked by slowly progressive hepatic fibrosis with severity of disease
11 defined by the Metavir stage ranging from F0 (no fibrosis) to F4 (cirrhosis) and progressing
12 through stages F1 (mild stage), F2 (moderate), F3 (severe). Once cirrhosis has developed, long-
13 term complications include hepatocellular carcinoma (liver cancer) and the need for liver
14 transplantation.

15 The need to take into account the fibrosis stage for modelling liver disease progression after SVR
16 was stressed in the CE Opinions. One dossier (sofosbuvir) did not model any disease progression
17 after reaching SVR, two others (simeprevir and daclatasvir) simulated a slower progression from
18 cirrhosis to hepatocellular carcinoma after SVR and the remaining three simulated a progression
19 from any stage (ledipasvir+sofosbuvir, ombitasvir-combo).

20 Focusing on short-term biological data, i.e. SVR at 12 weeks, Clinical Opinions reported that the
21 expected benefit of the new DAAs in terms of clinical outcomes was weakly documented
22 (simeprevir) or could not be quantified (all other DAAs).

1 Regarding the disease progression modeling choices, the review identified three types of models:
2 i) patients reaching SVR do not progress anymore in the liver disease [27,29,32,33,37,39,42]; ii)
3 patients reaching SVR continue to progress although at a slower pace from F3 [23,24,30,31] or
4 from cirrhosis [22,28,34,38,40,41]; iii) patients reaching SVR do not progress anymore in the
5 liver disease but are applied a lower liver-related mortality rate compared to infected patients to
6 capture the benefit of the SVR [25,26].

7 When the published studies actually investigated how modeling disease progression after SVR
8 impact the ICUR, this parameter was found to be the most influential in the deterministic
9 sensitivity analysis [22]; it modified substantially the ICUR from 137,500 to 324,700 €/QALY
10 gained for genotype 1 treatment-naïve patients at F3 stage and from 30,200 to 42,100 €/QALY
11 gained for patients with cirrhosis [40] or has a significant but lower impact [28,38].

12 ***33. The stage of treatment initiation***

13 CE Opinions stressed that the stage of treatment initiation was the main driver of new DAAs'
14 value for money given the salient features of the epidemiology of the HCV for which the most
15 cost-effective strategy could be postponing the treatment until disease progression has been
16 confirmed. Modelling options used in the dossier should have been adapted to investigate the
17 critical question

18 CE Opinions have discarded the analyses conducted in the DAA dossiers as they were based on
19 an average ICUR that merged F0 to F3 fibrosis stages, failing to account for the ICUR
20 heterogeneity between the stages [43–45]. According to the assumptions retained in the dossiers,
21 F0-F3 patients were all cured in the same proportions and did not develop liver disease after SVR
22 achievement; however, because only a fraction of F0 patients eventually developed a liver
23 disease, the universal strategy that consists in treating all the patients at F0 was found potentially

1 less cost-effective compared to a strategy where only patients \geq F2 were treated. Nevertheless,
2 this trade-off could not be documented in the dossiers submitted due to the fact that fibrosis
3 stages were merged, except for ledipasvir-sofosbuvir [15].

4 A contrasting result appeared in the early stages of the disease between a higher efficacy
5 documented through Clinical Opinions and a lower cost-effectiveness documented through CE
6 Opinions. Nevertheless, Clinical Opinions have recommended putting off the treatment for
7 patients in F0-F1 arguing that the progression rate to late stages was very slow and that these
8 patients' therapeutic options could still be modified with the arrival of new treatments. As far as
9 the published literature is concerned the timing of treatment initiation was barely addressed
10 through a finely grained analysis. Only 10 studies among 21 specifically compare cost-
11 effectiveness for different initiation stages, as main analysis [30,40] or in a sensitivity analysis
12 [24–28,31,39,41]. Four studies did not differentiate at all between the fibrosis stages
13 [23,33,37,38] and the remaining studies were based on the rather crude distinction between
14 cirrhotic and non-cirrhotic patients which means merging F0 to F3 fibrosis stages
15 [22,25,29,31,32,34,42].

16 Among the studies that modelled treatment initiation at different stages, ICUR was always found
17 higher in earlier stages; for instance, it raises from \$14,159/QALY gained at cirrhosis to \$51,344
18 in F0 [26]. The universal strategy was shown to be more costly and to provide more QALYs than
19 treating in later stages, however, the ICUR vary widely among studies ranging from cost-
20 effective with \$15,709/QALYs gained [30] to \$103,500/QALY and \$321,300/QALY [40].

21 **4. Discussion**

1 In the light of these results, three underlying issues about the uptake of HEE and its implications
2 for pricing and coverage decisions in France are worth discussing.

3 First, the analysis allows underlining key features of the French doctrine regarding the use of the
4 CE opinions. CE Opinions are used as an official criterion only in the pricing negotiations
5 between the pharmaceutical manufacturer and the Pricing Committee [46] and are not taken into
6 account in the reimbursement and listing decisions. Moreover, no cost-effectiveness threshold
7 (CET) is used in the French setting. A necessary condition for the pharmaceutical manufacturers
8 to benefit from the European reference prices is that efficiency could be established on the basis
9 of the economic dossier when ASMR I, II or III is obtained. CE Opinion could indicate that it is
10 not the case by ranking the dossier with a ‘major’ reserve grade that points out that the method or
11 the model is flawed or that the level of uncertainty removes all relevance from the quantitative
12 results; as illustrated by ledipasvir+sofosbuvir. Hence, from a purely regulatory perspective, the
13 methodology and its consistency appear more important than the ICUR level. CE opinions pay
14 particular attention to the factors and variables impacting the uncertainty so as to provide a basis
15 to negotiate prices and use; that could be subgroups of patients with different cost-effectiveness
16 or the time to initiate the treatment as exemplified by the results on new DAAs. The question
17 raised is then whether moving toward the uptake of CE opinions in the decisions of what to fund
18 and the definition of a CET would improve the usefulness of HEE to tackle with high-cost
19 treatments in the French setting. Studying countries where these conditions are met, Franken *et*
20 *al.* shows that ways have generally been found to avoid refusing to fund high-cost drugs on CE
21 grounds. The paper concludes that HEE had limited impact on the listing decisions but eventually
22 helped in the price negotiations in particular by determining subgroups of patients who benefit
23 most; which fully corresponds with the role devoted to the CE opinions in the French setting.

1 Hence, the comparison with the results of Franken et al. could lead to arguing that French-
2 specific features regarding the implementation of HEE do not seem to impact its usefulness.
3 More comparative case-studies are needed.

4 The second issue concerns the compatibility between the Clinical and the CE opinions. A
5 distinctive feature of the French innovative drugs pricing regulation system is that it is based on
6 two approaches for assessing the value added by the drugs, namely the cost per QALY gained
7 and the ASMR ranking. This twofold evaluation is debated and the need to converge toward a
8 single Opinion has been underlined by recent public reports [47,48]. The present study shows that
9 the criteria could actually complement each other: the Clinical Opinions' recommendation to
10 postpone treatment initiation to F2 fibrosis stage was indeed reflected in higher ICUR for earlier
11 stages. Drummond *et al.* came to a similar conclusion in the case of anticancer drugs showing
12 that a superior ASMR score was associated with higher QALYs gained [49]. Nevertheless, from
13 the perspective of priority settings, the existence of twofold assessment criteria means that the
14 cost per QALY gained is to be weighted by the level of ASMR reached. The latter is prone to
15 introduce considerations related to the severity of the disease or to the line of treatment, and more
16 generally to the repartition between the quality of life and life expectancy within QALYs gained
17 in a break with the standard principle of cost-utility analysis [50,51]. Indeed the ASMR criterion
18 discriminates quality of life improvement (more often associated with ASMR III or IV) and
19 survival benefit (more often associated with ASMR I or II) whereas the QALY does not. In this
20 perspective, the coexistence of two distinct criteria for assessing the value of the drug might turn
21 to be highly questionable to the extent that it could impede the transparency of the process for
22 prioritisation.

23

1 The last issue questions the usefulness of CE Opinions against the threat to the sustainability of
2 the healthcare budget due to high-cost treatments. As illustrated by HCV drugs, affordability has
3 become a major concern in health care[6,7]. The emphasis on the budgetary impact had taken two
4 different forms in the French regulatory setting. First, regarding new DAAs, the French Ministry
5 of Health has taken the unusual decision of capping the overall yearly social security expenses for
6 funding hepatitis C drugs and taxing the industry on the revenue exceeding the cap [52]. Second,
7 the latest Agreement between the Pricing committee and the pharmaceuticals industry made the
8 Budget Impact Analysis (BIA) compulsory in the market access [53,54]. In this context, the
9 question of which should come first between CUA and BIA may arise as supported by Van de
10 Vooren *et al.* calling for a block contract between the industry and the regulator where the main
11 decision from the latter would be to define what subgroup to treat; the global budget is then
12 estimated from the cost savings provided by the new drugs [9]. As relevant as it is, this proposal
13 sounds like a step backwards in the French setting where CE considerations were discarded from
14 the pricing regulation process until recently. Moreover, the present analysis shows that the ICUR
15 provides precisely pivotal information on the trade-off between who should be treated and the
16 expected health care costs avoided, indicating that CE Opinions remain the necessary first step to
17 implement pricing regulation.

18 Several limitations of the study should be acknowledged. First, the analysis focuses on a single
19 therapeutic class and therefore could not be considered as representative of the dossiers submitted
20 to the CEESP especially since HCV drugs challenge is related to pay for curing a large
21 population of a slowly progressive disease and methodological issues might differ from
22 treatments of chronic diseases, anticancer drugs or orphan drugs. Nevertheless, major regulatory
23 issues were at stakes with new DAAs which makes this case-study paradigmatic so as to analyse
24 the implications of the uptake of CE Opinions in the French setting.

1 Next, the DAAs' dossiers were submitted at the outset of the CEESP review process when all the
2 stakeholders were in the learning curve. CE Opinions probably evolved with the level of
3 expertise of the CEESP and of the laboratories that slightly increased since this time. The present
4 analysis provides an example of this ongoing process: the assumptions on disease progression
5 have indeed evolved between sovaldi dossier and the subsequent sovaldi+ledispavir dossier.
6 Moreover, CE Opinions may still undergo changes to address new issues like reassessment with
7 real-life data or the development of treatment staging for example. There is no doubt that updated
8 health policy analysis will be needed over time.

9 Finally, it should be emphasized that the present analysis is not intended to quantify the impact of
10 CE Opinions on the price actually paid by the health system for the drug partly because the
11 public price does not match up to its contractual price as price-volume agreements or rebates
12 arrangements are not disclosed, and partly because pricing agreements include others
13 considerations than cost-effectiveness like reference pricing or industrial considerations which
14 analyze may require a quantitative approach based on a longer CE Opinions experience.

15

16 **5. Conclusion**

17 France has introduced the criterion of the cost per QALY gained in the pricing and regulation of
18 innovative pharmaceuticals since 2013. Taking the example of the new DAAs against HCV, the
19 analysis shows that the use of CUA does enhance the information available to the decision-
20 makers on the value of the treatments.

21

22

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