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EDITORIAL

HAS to be NICE?

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In 2012, two regulatory texts changed the landscape in France quite dramatically with the official introduction of cost-effectiveness analysis (CEA) in the pricing and reimbursement process. The 2012 law for the Financing of Social Security first made a provision requiring HAS to consider cost-effectiveness when assessing new health drugs and medical devices[1]; this was followed by the publication of a decree in October 2012[2] describing the modalities of implementation. In October 2011, the official methodological guideline for CEA had already been published by HAS,[3] the High Health Authority and French HTA body, and its Committee for Economic and Public Health Evaluation (CEESP). So is HAS turning NICE?

The French P&R process at a glance

A brief reminder of the French P&R process is required before proceeding to an analysis of the new regulations. The HAS is mandated to assess all new health care technologies and to provide the Ministry of Health and Social Affairs (MOH) as well as the National Union of Sickness Fund (UNCAM) with recommendations in terms of access to reimbursement on one hand and an assessment of their relative value versus existing interventions on the other. Much like NICE, HAS is a scientific advisory body, but does not make final decisions in terms of reimbursement, coverage level and prices. Setting prices for drugs and medical devices is the responsibility of an inter-ministerial committee, the Economic Committee for Health Products (the CEPS). The pricing principles are themselves subject to a pluriannual agreement (the so-called "accords-cadre") between the French government, represented by the CEPS, and trade unions (the LEEM for drugs and the SNITEM for medical devices). Tariffs for new medical procedures are under the responsibility of the UNCAM and will require some negotiations with physicians' unions. Finally, after advice from the HAS on the level of coverage for reimbursement (i.e., the level of copayments for patients), the UNCAM has the final word.

Principles for assessing and pricing drugs and medical devices have been progressively harmonized in the past years, so for the purpose of simplicity, only the full P&R process for drugs will be discussed here in relation to CEA; references to medical devices will be made only when significant differences are observed. The main body involved in the assessment of drugs is one the eight commissions of the HAS, the Transparency Commission (CT). The assessment is relative to a combination of a product and indication, which means a different advice is given for the same product for different indications. The published advice includes the following elements:

- A recommendation on reimbursement, based mainly but not only on the benefit/risk ratio of new technologies: the SMR (Service Médical Rendu or medical service provided), a five-point ordinal scale, synthesizes the assessment, with a lower level (insufficient

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[1] Loi du 21 décembre 2011 de Financement de la Sécurité Sociale pour 2012. Loi n° 2011–1906, Art.47 (http://www.legifrance.gouv.fr).

[2] Décret no. 2012–1116 du 2 octobre 2012 relatif aux missions médico-économiques de la Haute Autorité de Santé (http://www.legifrance.gouv.fr).

[3] Choix méthodologiques pour l'évaluation économique à la HAS. Guide Méthodologique, 82 p. HAS, October 2011. (http://www.has.sante.fr).

SMR) leading to rejection of reimbursement. For each level, there is a corresponding coverage level, from 100 to 15 %, which will then be confirmed by the UNCAM.
- Guidance on how to best use the new technology considering existing alternatives, thus defining a target population and a preferred indication;
- The estimated size of the target population that can benefit from the product;
- An assessment of the comparative efficacy of the product versus existing technologies for each of its indications: the ASMR (Amélioration du Service Médical Rendu, or medical value added) is also an ordinal five-level scale, from level 1, "major," to level 5, "none."
- Eventually, the CT will recommend that the company should obtain complementary evidence on the usage, efficacy and safety of new products, based on observational studies. There are a few examples of requirements including a CEA or some sort of performance-based pricing agreements, but this will not be dealt with here.

The rules may change in the coming years: the HAS actually redefines the SMR and ASMR to transform it into a unique scale or index, the ITR, for the "Index Thérapeutique Relatif" or relative therapeutic index. The ITR is a five-scale index. It is based on the choice of a comparator by the HAS, each new drug being compared on the following criteria: relative efficacy, safety and mode of administration. For each criterion a score is defined, and the sum of scores leads to the attribution of the final index, from 1 to 5. If a drug proves inferior to the comparator on this scoring system, it will not be reimbursed. To illustrate the scoring method, drugs that reach superiority on hard end points (morbi-mortality) will score better than drugs improving intermediary endpoints. Moreover, the project is to reassess the ITR very rapidly, every 2 or 3 years or more if there are major changes in the therapeutic class. For the moment, this ongoing work is disconnected from the implementation of CEA.

Up to now, agreements between the government and the industry directly link prices to the level of the ASMR. For products granted an ASMR from 1 to 3 (possibly 4 if cost-neutrality or net cost-savings can be established), the company can claim a European price, the level of which must not be higher than prices observed in the UK, Germany, Italy and Spain. Products with an ASMR 4 may be granted a premium price compared to comparative treatments, but there is no specific rule on how high the premium price should be, which leads to potentially lengthy negotiations with the CEPS. Products granted an ASMR 5 should in principle be priced lower by at least 5 % than the average daily cost of treatment of comparators.

In most ASMR 4 and 5 cases, the price setting will be completed by price–volume agreements, which are clearly commercial discounts. Such agreements also allow companies to obtain a European facial price, whereas the final net price for the sickness fund will be lower because of discounts. For companies, this duality is important since it allows them to maintain a price corridor in Europe, thus restraining the margin for other payers who practice international reference pricing.

How will CEA fit in the P&R process?

The main features of the October 2012 decree are the following. First, CEA will be mandatory at the launch and at the reassessment time for drugs with a claim from the company for an ASMR 1–3 and with a significant budget impact. The date of implementation is 1 year after the publication of the decree, i.e., 2 October 2013. Companies will submit their CEA to the CEESP, which shall assess its methodological quality and relevance in parallel to the assessment done by the CT. It is explicitly specified that the CEA will not be used to decide about reimbursement, but should only be used as complementary information for the CEPS. According to the decree, the dossiers should cover the following dimensions:

> Efficacy, quality, safety, organization and costs of prevention and care, as well as their public health benefits, the quality of life of the patient, the contribution to equal access to prevention and care, and the compliance to ethical principles.

Thus, it is expected that the studies should go beyond CEA *stricto sensu*, although the guidelines for the documentation of dimensions beyond economics, like the contribution to public health, access and ethics, are not yet fully defined by the HAS (work in progress).

If judged necessary, the CEESP may require additional explanations or data from the company and potentially reject the dossier on the basis of its methodological quality. The Commission may organize a hearing with the company before presenting its conclusions. Once these have been written, they are communicated to the company, which must present its observations within 8 days, and it may ask for a hearing. The final advice is sent to the company, to the CEPS, and is published online, as is the advice of the CT.

It is noticeable and important that the CT and the CEESP should work in parallel and deliver their advice in the same timeframe. The average publication time for the CT was 80 days in 2011 for the first inscriptions.[4] The CT

[4] HAS. Rapport d'activité 2011. Commission de la Transparence (http://www.has.sante.fr).

does not have access to the economic dossier submitted by the company and as such has no information on the price requested for the products, whereas the CEESP can have access to the clinical report prepared by the HAS staff for the CT. This raises some questions about to what extent communication lines should nevertheless be set between both commissions during the assessment process. For example, it may be that the CT will choose to assess the benefit of a given intervention on specific subgroups on an ad hoc basis, for which the company may not have provided an economic subanalysis ex ante. Similarly, there should be some coordination between the two commissions on the relevant comparators.

Guidelines for CEA

Most probably, although the decree aims at a broad scope of assessment, the first submissions will need to comply with published guidelines for CEA. I will comment on a selection of the 20 recommendations published by HAS.

The first recommendation states that cost-utility and cost-effectiveness studies should be the reference. By cost utility, the guide refers explicitly to calculations of cost per QALY ratios; cost-effectiveness refers here to cost per life years saved. Cost utility is the reference method when the impact of a new intervention on health-related quality of life is a key outcome; if not, then the impact on longevity should be considered. The guide also recommends two generic instruments to measure HRQOL: EQ-5D and HUI 3, for which a published French value set exists.

Studies should adopt a broad societal perspective, inclusive of all actors involved in the intervention either because they contribute to or are impacted by it, or because they fund it. The target population is defined as all patients who directly benefit from the intervention or other individuals whose health may be affected by the intervention. This notion of indirect benefit (or harm) refers explicitly to positive or negative externalities of health interventions, such as vaccination programs, or as the development of germ resistance with antibiotics. The results of the study should include an analysis of the consequences of the intervention from the perspective of the main stakeholders: different payers including patients and health care providers. All relevant comparators should be considered in the CEA, and if not, reasons for exclusion must be documented.

Costs to be considered should be production costs, either medical or non-medical, borne by the stakeholders identified in the perspective, as opposed to transfer costs, like sick leave compensations, or indirect costs, like the burden of the disease for informal caregivers and productivity losses. All relevant service providers should be included whether or not their services are covered by the National Sickness Fund. Direct production costs may include time spent by patients when receiving care (hospital stay, time to visit doctors, transportation,) and by caregivers, formal or informal.

Indirect costs can be included in a complementary analysis and cover potential consequences of an intervention on the usual activity of patients and informal caregivers, be it professional, domestic or leisure, but excluding the time spent by the patient when receiving care. The main resource identified is time, which can be valued according to either the human capital or the friction cost approach for productivity loss. No method is recommended for domestic work or leisure. Indirect costs are not included in the calculation of the baseline incremental cost-effectiveness ratio.

Costs and benefits should be discounted at a rate of 4 %, which is the recommended rate for public investments for all sectors. Beyond 30 years, this rate can be gradually reduced, up to 2 %, to avoid a bias against preventative interventions.

The impact of CEA on the pricing process

There are still many open issues that have not been dealt with by the decree, some related to the process itself and its implementation, some more fundamental, related to the impact of CEA results on the pricing process. There is work in progress on both, little of which is made public, so what follows is reasonable speculation. There are also questions about some choices that were made.

For example, why has the scope of assessment been limited to products with a high ASMR claim? Why include a budget impact threshold and what should this be? In both cases, it seems that these restrictions were made to limit, in a first step, the number of dossiers that the HAS will have to assess. In the present process, assessment is first prepared by the permanent staff of HAS and then discussed within the CT and the CEESP. This pragmatic argument seems to make sense knowing what the flow of dossiers is that the HAS has to manage. In 2011,[5] and only for drugs, 1,274 dossiers were submitted to the Transparency Commission, of which 231 were for a first inscription, 27 for an extension of the indication and 434 for the 5-year revision. The CT actually reviews 1,078 dossiers altogether. In the same year, the Commission for Medical Devices was presented 199 dossiers and reviewed 151.[6] The CT does not

[5] HAS. Rapport d'activité 2011. Commission de la Transparence (http://www.has.sante.fr).

[6] HAS; Rapport d'activité 2011. Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé (http://www.has.sante.fr).

publish the requested SMR and ASMR claims by the companies, either at the first launch or at the revision. The only available data are on granted SMRs and ASMRs. In 2010 and 2011, 8 new launches were granted an ASM 1–3; 18 were granted an ASMR 4, an unknown percentage of which were probably ASMR 3 claims. For medical devices and the same period, 19 products were granted a score from 1 to 3 and 40 a score of 4. Such figures suggest that the annual flow of CEA submitted to the CEESP should be of approximately 40 all together, with drugs and medical devices included. The question here is the capacity of the permanent staff of HAS to cope with this flow within reasonable timelines. As to the budget impact threshold, its level is still under discussion.

Nevertheless, this restriction has opened a debate about whether ASMR 4 should be included in the mandatory requirement for CEA. Indeed, considering the actual pricing scheme, in which requested prices are almost automatically granted for high scores, the utility of CEA is less as in the case of ASMR 4 drugs, where a CEA could bring precious information on the level of the premium price requested by the product's sponsor.

More fundamental is the discussion about the impact of CEA on the pricing process. First, the new "accord cadre" signed in December 2012 between the CEPS and the industry maintains the rules for a European price for drugs with a good ASMR, and surprisingly enough no mention of the role of CEA is made in the present text.[7] So how could a CEA, which may result in a very high incremental cost-effectiveness ratio for drugs with an ASMR 1–3, impact the price negotiation? It is plausible that the CEPS may use the advice from the CEESP to negotiate a net confidential price lower than the facial price for such drugs, based on conclusions from the economic assessment. Interestingly though, the advice from the CEESP and its recommendations will be made public: both companies and the CEPS will have to learn how to communicate about discrepancies between a high facial price and the potentially negative conclusions of the CEESP, stating that at the given price the ICER is too high. It would then be more difficult to keep the net price confidential!

Second, how should one use CEA without a threshold or at least some scale to benchmark the results of the submitted CEA? The industry and the government are each on their own working on this issue, but not much has yet been publicly discussed. There are two underlying issues. The first one is pragmatic: only a small number of CEAs have been published in the French context, since this was not mandatory up to this year for P&R. Studies are scarce and some quite old. So there is little cumulative evidence to set some sort of league table. At first, references to studies in other countries may be required, with the well-known transposition difficulties.

The second is more conceptual. If one does not retain a threshold, will a value emerge implicitly with cumulative experience of the CEPS? How does one maintain some kind of consistency with the ASMR scoring? A rather simple way to reconcile both approaches is to consider the ASMR scoring system as an index not of the incremental quantity of health provided, such as the QALY, but as a synthetic index of the desirability of a new treatment for the community. This index comprises not only the quantity of the effect, but also other dimensions that may not be directly captured by QALYs, such as the severity of the disease and the absence of alternative treatments, or end of life issues. NICE has recently dealt with the end of life treatment issue by accepting a higher ICER threshold. In the French system, one could support the idea that, on average, higher ICERS could be accepted for ASMR 1 drugs versus ASMR 2 s and ASMR 3 s. Thus, if this principle was violated when analyzing the CT and the CEESP advice together, it could guide pricing decisions in cases of major discrepancies. Now this may lead to adaptive strategies from companies, but this also occurs in the UK context. But it must be reminded once more that this would lead to negotiations on the net price, not the facial price, with the critical issue of the confidentiality of pricing agreements.

Thus, in France, the year 2013 is full of uncertainties, but also of exciting challenges in terms of research on decision analysis including cost-effectiveness. Although cost-effectiveness should not affect coverage decisions, it should have an impact on price setting, thus continuing the French tradition and expertise on price controls. It is too early to conclude that HAS is turning into NICE. It could even be argued that the industry will view the new French system to be less nice than in the past in terms of good prices for innovative products. On the other hand, because CEA sets some sort of objective measure of efficiency, however fragmented, this may help companies in some cases to support their price claim and resist the pressure of the Sickness Fund for which lower prices are always better.

[7] Accord cadre du 5 décembre 2012 entre le Comité Economique des Produits de Santé et les entreprises du médicament. www.sante.gouv.fr/comite-economique-des-produits-de-sante-ceps.