Medicinal products assessment

Transparency Committee Doctrine

Principles of medicinal products assessment and appraisal for reimbursement purposes

September 2018
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## Abbreviations and acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ANSM</td>
<td>Agence nationale de sécurité des médicaments et des produits de santé (French national medicinal product and other health product agency)</td>
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<td>ATU</td>
<td>Autorisation temporaire d’utilisation (Compassionate use program, French early access program for medicinal products)</td>
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<tr>
<td>CAV</td>
<td>Clinical added value (Amélioration du service médical rendu)</td>
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<tr>
<td>CB</td>
<td>Clinical benefit (Service medical rendu)</td>
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<tr>
<td>CEPS</td>
<td>Comité économique des produits de santé (French healthcare products pricing committee)</td>
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<tr>
<td>CNEDiMTS</td>
<td>Commission nationale de l’évaluation des dispositifs médicaux et des technologies de santé (National committee for the assessment of medical devices and health technologies)</td>
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<tr>
<td>CT</td>
<td>Commission de la transparence (Transparency committee)</td>
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<tr>
<td>HAS</td>
<td>Haute autorité de santé (French national authority for health)</td>
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<tr>
<td>MA</td>
<td>Marketing authorisation</td>
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<tr>
<td>PRS</td>
<td>Post-registration study</td>
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<tr>
<td>PHI</td>
<td>Public health impact</td>
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<tr>
<td>RTU</td>
<td>Recommandation temporaire d’utilisation (Temporary recommendation for use)</td>
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<tr>
<td>SNDS</td>
<td>Système national des données de santé (National health data system)</td>
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Message of the Transparency committee chairman

The Transparency Committee’s doctrine is designed to provide benchmarks and visibility with respect to the main criteria of medicinal products assessment and appraisal for reimbursement purposes.

Based on medical and scientific criteria, the doctrine needs to consider the number of dossiers presenting a high level of uncertainty, innovations and changes in clinical trial methodology, taking into account patient care pathways.

In this context, highlighted by Dominique Polton’s report in 2015 and by the CSIS (French Strategic Council for the Healthcare Industries) in its July 2018 report, the Transparency Committee wanted to detail its methodology and update its doctrine with a view to improving reproducibility, transparency and fairness.

Following discussion by the Transparency Committee members, it was decided this document should be focused on:

- Clarification of the factors determining the CAV score and extension of eligibility conditions for major CAV;
- Assessment of innovation and the management of uncertainty using surrogate endpoint for example;
- Elements related to the predictability of CB and, in particular, an insufficient CB;
- Definition of a public health benefit and of the criteria used to assess it;
- Clarification on how quality-of-life data and real-life data are taking into account;
- Incorporation of the patient perspective.

These notions have thus been included in the doctrine.

This doctrine should be considered as an evolving document, rather than a static text. What was important to me was to clarify - both internally within the HAS and with respect to industry and the public authorities - the necessary evolutions in the criteria guiding our decisions.

It is only by ensuring precise, fair assessment, taking into account the benefit provided by an innovation as well as the potential risks related to a treatment, that patients can benefit the most new medicinal products and that companies can be encouraged to innovate.

We hope that this new version of the doctrine will facilitate patient access to innovation and meet the expectations of all relevant stakeholders.

Prof. Christian THUILLEZ
Chairman of the Transparency Committee
1. Introduction

In France, scientific and medical appraisal of medicinal products for reimbursement purpose is performed by an independent scientific committee, the Transparency committee (TC) of the French national authority for health (HAS).

This document outlines the main elements and criteria taken into account by the TC in its assessments and appraisals.

1.1 Definitions

General definition

The term “doctrine” can be defined as the basic principles underpinning a strategy, actions and theoretical concepts adopted to guide actions or help to interpret facts.

The doctrine described hereafter does not include any ideological or dogmatic dimension.

Definition of the TC doctrine

The doctrine is a work tool designed to provide reference and visibility with respect to the main criteria used in the assessment and appraisal of medicinal products for reimbursement purposes. The doctrine consequently defines HAS expectations for the Company file submission.

The doctrine outlines the basic principles of the TC’s scientific and methodological rationale with regards to data analyses within a given medical context and used it in its assessments. The doctrine serves as a general framework to be applied to all assessments. It may be updated if deemed necessary by the TC, in particular with regards to methodological and regulatory changes.

1.2 Context

The objective of this document is to contribute to a transparent, reproducible and fair assessment.

The TC’s assessments and appraisals are based on an analysis of all clinical data available at a given time, for a given medicinal product in a given indication. An assessment is, by definition, temporary and subject to change in case of new efficacy and safety data.

Numerous recent national studies – including Dominique Polton’s report in 2015 – showed the importance of improving reproducibility and transparency of health technology assessment. This particularly applies to the clinical added value (CAV), which directly impacts price negotiation.

Furthermore, for the past few years, the TC has faced an increasing number of requests for assessment of new medicinal products presenting a high level of uncertainty (uncertain clinical benefits, poorly demonstrated given immature data) or very rapidly changing care pathways. In response to the multiplication of these situations that do not meet the usual methodological requirements, the TC considered it useful to specify the main principles underpinning its assessments and its expectations.

This approach, designed to provide clarification and transparency, also fits squarely with the international context of comparison of assessment and analysis methods underpinning the decisions taken in different countries.

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1 The regulatory framework for medicinal product assessment and appraisal is laid down in articles R. 163-1 et seq. of the French Social Security Code and in the Transparency Committee’s internal regulations.

2. Clinical added value

2.1 Determinants of CAV

As defined in article R. 163-18 of the French Social Security Code, the TC's opinion includes the appraisal of the CAV. The CAV is an assessment of the therapeutic (or diagnostic) progress provided by a medicinal product – notably in terms of efficacy or safety – compared with existing alternatives. It measures the medical added value of the medicinal product compared with existing therapies. This assessment is a snapshot at a given point in time within an environment that may evolve. It may be rated as major (CAV level I), important (CAV level II), moderate (CAV level III), minor (CAV level IV) or non-existent (CAV level V); the latter level corresponding to no clinical added value. The CAV defines the framework for price negotiations.

Particular attention is paid to the following criteria:

1. **The quality of research evidence**, which includes the comparison and the choice of comparator(s), the design of the study, the appropriateness of the population included for the indication, the relevance of the clinical endpoint and its significance, etc.,

2. **The effect size in terms of clinical efficacy, quality of life and safety** in view of the robustness of the demonstration,

3. **The clinical relevance** of this effect compared to clinically relevant comparators,

In view of the medical need.

The TC’s main expectations with respect to these three criteria are detailed below:

- **Quality of research evidence**

  - **The comparison and the choice of the comparator**

    Since the CAV is a relative approach, the first step in assessment of the quality of research evidence therefore assumes that:
    - 1/ a comparison is available,
    - 2/ a clinically “relevant” comparator has been identified,
    - 3/ and that the available data enable the assessment of the medicinal product contribution compared to the comparator.

    A clinically “relevant” comparator may be a medicine (active substance or placebo, with or without MA), a medical device, a procedure or any other non-medicinal therapy (or diagnostic method). It can be use at the same step of the care pathway as the new medicine and aims the same patients.

    Hence, a medicinal product subject to an early access programme such as a compassionate use program (ATU) or a temporary recommendation for use (RTU), or used off-label in routine practice in the indication assessed may be considered to be a clinically relevant comparator.

    Comparison with the clinically relevant comparator corresponds to an important step in the TC’s rationale for CAV assessment.

    **A direct comparison with a clinically relevant comparator, in a double-blind, randomised trial, is expected wherever possible.**

    Double-blind, randomised trials remain the prerequisite and the essential reference for the assessment of any medicinal product. Only randomisation and double-blind comparison can guarantee the similarity of the groups compared all along the trial and thus make it possible to attribute the differences observed to
the medicinal product studied in a given treatment regimen. Double-blinding reduces biases related to the subjectivity of follow-up, the assessment of outcome measures, etc.

The absence of direct comparison with a clinically relevant comparator must be justified by the company and may be accepted by the TC in certain situations, such as concomitant developments, specific populations for whom extrapolation of efficacy can be performed on the basis of pharmacokinetic data or real-life data, etc.

If direct comparison is impossible, an indirect comparison, conducted on the basis of defined and validated methodological principles, may be taken into account. Indirect comparisons that are not performed in accordance with these methods are not generally considered to be appropriate for claiming a CAV. However, new methods of indirect comparison may be used to specify the position in the treatment strategy, for example.

Data from real-life studies may also be taken into account (see Chapter 5 Real-life studies).

In practice, the rationale adopted by the TC generally follows the approach presented in Figure 1. This rationale is not frozen and can be adapted to the context of each assessment.

The absence of any direct comparison when the TC deems that it would have been possible, may lead to a CAV V. In this context, the CB may be considered to be sufficient if a loss of opportunity can be eliminated (see “Insufficient AB” chapter).

Figure 1. Comparison in the Transparency Committee's assessment

![Diagram of comparison in the Transparency Committee's assessment](image)


The outcome measure

The TC considers that the primary outcome measure of a trial must be a relevant clinical endpoint whenever possible. If a relevant clinical endpoint is not used in the trial, justification by the company explaining this choice is expected.

The use of a surrogate endpoint – in particular a biomarker – is acceptable if the surrogacy for a clinical endpoint (morbidity or mortality) is adequately demonstrated in the specific population, in accordance with the definition of a surrogate endpoint.

The use of an intermediate endpoint (without demonstration that it can reliably substitute for a relevant clinical endpoint) may be taken into account in assessment of the CAV.

For example, in the field of oncology, the TC may take into account progression-free survival in situations whereby overall survival cannot be documented in the short or medium term (long life expectancy, multiple subsequent therapeutic conditions, etc.) or where a link has been demonstrated between these two endpoints.

The study design

The study design must be consistent with the objective and, wherever possible, the statistical analysis plan must schedule appropriate control of the type I error.

Additional effect size and clinical relevance

The effect size measures the magnitude of the medicinal product’s effect compared to a clinically relevant comparator, usually in terms of morbidity and mortality, quality of life and safety. The clinical relevance corresponds to the benefit provided to patients (a statistically significant difference alone may not be clinically relevant).

The additional effect size is assessed on a case-by-case basis by the TC, in terms of the following conditions, in particular:

- when the outcome measure is a dichotomous qualitative variable, by the absolute risk reduction and its confidence interval,
- when the outcome measure is a variable such as time to event, by the difference in time-to-event medians and its confidence interval,
- when the outcome measure is a quantitative variable with normal distribution, by the difference in means and its confidence interval,
- when the outcome measure is a quantitative variable with non-normal distribution, by the difference in medians and its confidence interval.

The clinical relevance of this effect is assessed on a case-by-case basis depending on the medical context. Hence the TC does not wish to redefine clinical relevance thresholds or systematically correlate these with CAV levels.

The effect size and its clinical relevance are also assessed on the basis of the medicinal product’s safety and the medical need in the indication assessed. For example, a low effect size in terms of morbidity and mortality could lead to a CAV level of V when the medical need is already met or to a CAV level higher than V5 when the medical need is not met. Similarly, a low effect size in terms of morbidity and mortality could lead to a CAV level higher than V5 in the event of a clinically relevant improvement in safety and/or quality of life. However, at the time of the first assessment, it is rarely possible to conclude to an improved medium or long time safety profile. In the event of any doubt, the patient’s interests will always take precedence in the TC’s conclusions.

A CAV level of higher than V may correspond to a CAV level of I (major), II (important), III (moderate) or IV (minor).
Quality of life

Quality-of-life data contribute to benefit assessment of the medicinal product.

In addition to efficacy and safety data and depending on the medical context, if an improvement in quality of life is demonstrated, this could lead to a CAV level higher than V\(^5\) in situations in which this finding is based on:

- the use of validated scales appropriate to the objective (preferentially disease specific scale),
- a rigorous methodology: objective and clinical relevance threshold pre-specified in the protocol, double-blind conditions, multiplicity management, appropriate analysis frequency, time and duration, few missing data.

The quality-of-life data collected using different methods may be useful for the assessment but is not generally sufficient to lead to a CAV.

The absence of quality-of-life data may have a negative impact on the CAV if it is expected by the CT, particularly for chronic and/or disabling diseases and end-of-life patients.

Medical need

Assessment of the CAV is performed in view of the medical need in the indication assessed. An unmet need may be considered favourably, without being the only justification for concluding to a CAV higher than V\(^5\).

An answer to a medical need is one of the elements taken into account in the assessment, on three levels:

- as an element for appraisal of the CB and hence access to reimbursement (number of alternatives, public health impact),
- as a criterion informing the clinical data, within the CAV,
- as an element in favour of an accelerated assessment process.

2.2 Details concerning CAV levels

Major clinical added value (CAV I)

The TC may recognise a medicinal product as representing a major clinical added value if it has a new mode of action, has demonstrated, with a high level of evidence, its superiority, combined with a clinically relevant effect in terms of mortality or morbidity, compared to a clinically relevant comparator, in a context of an inadequately met medical need for a serious disease.

This assessment corresponds to therapeutic breakthrough situations (that save or change the lives of patients with a serious disease) for which all the CAV determinants are judged to be satisfactory by the TC.

Important and moderate clinical added value (CAV II and III)

The TC may recognise a medicinal product as representing important or moderate clinical added value if it has a demonstrated superiority combined with clinical efficacy in terms of mortality and morbidity, in a context of an inadequately met medical need. The evaluation of this efficacy may be positively adjusted by a substantial improvement in quality of life and/or safety.

A moderate or substantial CAV will qualify the clinical added value, depending on its intensity, the quality of research evidence and the severity of the disease or symptom. Hence, the value attributed to the progress increases along with the effect size, the evidence quality and the severity of the disease.
Minor clinical added value (CAV IV)

A minor CAV is allocated to progress that is small compared to existing therapies. It reflects a non-optimal demonstration and/or effect size (efficacy, quality of life, safety) in view of the medical context. It may concern a medicinal product having demonstrated relevant efficacy with a slight and acceptable decrease in quality of life or safety. Conversely, it may concern a medicinal product with little or non-optimally demonstrated additional efficacy but which is associated with an improvement in terms of quality of life or safety. It may also concern a major improvement in care conditions, either demonstrated or expected by the TC (see “Specific cases” chapter).

No clinical added value (CAV V)

The TC may conclude that there is no clinical added value, particularly in any of the following situations:

- demonstration based on a non-inferiority trial,
- a medicinal product that is a generic medicinal product, a biosimilar or a line extension.

In the absence of therapeutic alternatives or when the alternatives are limited, a CAV level of V may also reflect an uncertainty related to the choice of comparator, the quality of research evidence, the effect size or its clinical relevance that does not indicate an insufficient CB (see “Insufficient CB” chapter).

2.3 CAV wording

The CAV is worded compared to comparators or with respect to the care pathway.

The wording specifies the population or subpopulation of the indication likely to benefit from the identified progress. It usually summarises the justification of the CAV obtained, particularly in view of the evidence quality, the effect size and the clinical relevance, the safety and/or care conditions or the medical need.

While quantification of the CAV level from I to V indicates the contribution of a medicinal product, the CAV wording explains it. For example, a minor CAV (IV) compared to a medicinal product with an important or moderate CAV (II) differs in terms of its additional contribution, to a minor CAV (IV) compared to a medicinal product with a no CAV (V). In the former case, the medicinal product provides a minor benefit compared to a medicinal product with an important benefit, while in the latter, the contribution is minor compared to no improvement. Therefore the CAV wording and level need to be considered jointly.

Furthermore, the TC highlights that it may consider that two medicinal products have an identical CAV level in the following situations:

- therapeutic class reassessments,
- concomitant developments.

CAV wording following therapeutic class reassessments

In a therapeutic class reassessment, the TC reaches a conclusion concerning the value of having access to the medicinal products in this class as well as their relative value in the care pathway. It may therefore consider that several medicinal products have a similar value and allocate them the same CAV level in the care pathway.

For example, a medicinal product with a CAV level of V compared to its clinically relevant comparator, which has itself obtained a CAV level of higher than V at its initial assessment may obtain the same CAV level in the care pathway following a class reassessment. This same CAV level then means that the two medicinal products make an equivalent contribution to the care pathway without it being possible to rank them in order on the basis of clinical data following the reassessment.
CAV wording in the event of concomitant developments

Identical CAV levels may be allocated to medicinal products concomitantly developed.

For example, the TC considers that two medicinal products are concomitantly developed when their respective pivotal clinical trials were performed totally or partially during the same period or when they were begun before one or other became available.

In practice, these medicinal products can be cited among the clinically relevant comparators at the time of the assessment but a direct comparison will not be expected in the initial assessment.

2.4 Assessment of innovation

The elements characterising a health innovation are, in particular:

- a new mechanism of action in the indication concerned,
- and the existence of an inadequately met medical need,
- and filling the medical need thanks to a demonstrated additional efficacy clinically relevant for the patients. For example, in oncology, the medicine must provide a response in terms of overall survival and quality of life.

A new medicinal product may be considered to be an innovation if it saves or changes the lives of patients with a serious or progressive disease in the context of an inadequately met medical need (no alternative or alternatives not very effective).

The “new” mechanism of a medicinal product cannot, therefore, define innovation. Likewise, addressing a need is not itself systematically an eligibility criterion for innovation.
3. Clinical benefit

3.1 Determinants of the CB

As defined in article R. 163-3 of the French Social Security Code, the clinical benefit (CB) of a medicinal product in a given indication is assessed on the basis of five factors:

- The efficacy and adverse effects of the medicinal product,
- Intended role in the care pathway, in comparison with other therapies available,
- The severity of the condition targeted by the medicinal product,
- The preventive, curative or symptomatic aim of the medicinal product,
- The public health impact of the medicinal product.

3.2 Focus on certain determinants of CB

- Intended role in the care pathway

When it assesses a medicinal product, the TC describes the care pathway for the disease concerned and specifies the place of the medicinal product in this strategy. For example, and depending on the clinical data available, the place of the medicinal product assessed may be ranked or put into perspective with respect to the other therapies available.

This is dependent on the context of the assessment and may therefore evolve. Consequently, it is reconsidered at each new assessment, and particularly during therapeutic class reassessments.

The place in the care pathway can value the medicinal product, particularly in situations where the quality of research evidence and the effect size do not enable to recognize a CAV.

- Public Health Impact

The aim of the public health impact (PHI) is to indicate the benefit provided by the medicinal product to the community in terms of public health, compared to the alternatives.

The TC considers that a medicinal product is liable to have a PHI when it provides a service to the community, either because it helps markedly improve the state of health of the (or a) population, or because it addresses a public health need, or because it reduces the consumption of resources (see Table 1).

The various dimensions that can be used to assess the PHI are, in particular:

- the medical need, the severity of the disease concerned and the prevalence of the target population,
- the potential impact of the medicinal product on the health of the population considered in terms of morbidity and/or mortality, compared to the therapeutic alternatives,
- the impact on health care organisation or improvement of the care pathway and/or life course for the patient or his/her family.

When the need is partially met (existence of clinically relevant comparators), the additional potential impact can be assessed compared to the comparator(s). In this case, when the indication concerns a serious disease with a high prevalence, the situations in favour of recognition of a PHI are, in particular:

- the demonstration of an additional impact on morbidity and mortality and the absence of any deterioration in the care pathway and/or life course,
- a substantial change in the care pathway and/or life course without deterioration in morbidity and mortality.

When the indication concerns a **serious disease with a low prevalence**, the demonstration of an additional impact on morbidity and mortality combined with a substantial improvement in the care pathway and/or life course are, for example, in favour of recognition of a PHI.

**When the need is not met**, the impact can be assessed relative to the best supportive care **independently of the prevalence**. For example, when the indication concerns a serious disease, the situations in favour of recognition of a PHI may be:

- a demonstrated impact on morbidity and mortality without deterioration in the care pathway and/or life course,
- a substantial change in the care pathway and/or life course without deterioration in morbidity and mortality.

### Table 1. Examples of elements for assessment of the PHI depending on the context

<table>
<thead>
<tr>
<th>PHI criteria</th>
<th>Partially met need (existence of clinically relevant comparator)</th>
<th>Unmet need (absence of clinically relevant comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High prevalence (&gt; 1/2,000; &gt; 30,000)</td>
<td>Low prevalence (&lt; 1/2,000; &lt; 30,000)</td>
</tr>
<tr>
<td><strong>High severity</strong></td>
<td>Case 1 – additional impact on morbidity and mortality and absence of deterioration in the care pathway and/or life course</td>
<td>additional impact on morbidity and mortality and substantial improvement in the care pathway and/or life course</td>
</tr>
<tr>
<td></td>
<td>Case 2 – substantial improvement in the care pathway and/or life course without deterioration in morbidity and mortality</td>
<td></td>
</tr>
<tr>
<td><strong>Lower severity</strong></td>
<td>additional impact on morbidity and mortality and substantial improvement in the care pathway and/or life course</td>
<td></td>
</tr>
<tr>
<td><strong>Specific cases</strong></td>
<td>- vaccines and preventive treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- concomitant development of two comparable medicinal products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- other exceptional situations, on a case-by-case basis, depending on the assessment of the CT</td>
<td></td>
</tr>
</tbody>
</table>

Based on the criteria detailed above, the TC assesses whether the medicinal product is liable to have an impact on public health or not, on a case-by-case basis. In certain situations (negative impact on the organisation of care without morbidity and mortality benefit, increased toxicity compared to available treatments), the TC may consider that a negative impact on public health cannot be excluded for the medicinal product.

In general, a medicinal product indicated in a non-serious disease is not eligible for a PHI, irrespective of its target population and efficacy.
3.3 Details concerning CB levels

► Insufficient CB

The factors that may result in an insufficient CB are, in particular:

• A confirmed or potential loss of opportunity in view of the clinically relevant comparators, defined by:
  
  ▶ A low efficacy and/or not clinically relevant and/or inadequately established compared to the comparator (even if the disease is serious and the medical need substantial).
  
  In particular, this may concern:

  - a non-statistically significant comparative study ("negative study") and, even more so, several negative studies,
  - a comparative study versus a non-clinically relevant comparator without acceptable justification of this choice,
  - a demonstration less robust than that performed with the clinically relevant comparators, that cannot eliminate the possibility of a loss of opportunity for the patient,
  - a non-comparative study when a comparative study could have been performed,
  - a demonstration of efficacy in a selected specific population for which the generalisability to clinical practice is not guaranteed,
  - a demonstration of efficacy using an irrelevant outcome to quantify the benefit for patients,
  - the accumulation of several methodological biases leading to a high level of uncertainty,
  - an effect size that is not clinically relevant.

  ▶ And/or unacceptable toxicity, particularly if this is greater in terms of severity or frequency to that of the comparators or in view of a modest efficacy.

• No place in the care pathway or a place judged to be “not established” by the TC, including all situations in which the TC considers that there is a risk of loss of opportunity for patients (see above).

• A medicinal product aimed at a non-serious symptom of a benign, non-progressive disease, for which the demonstration of efficacy presents a low level of evidence and/or for which the safety is poor.

Any one of these factors may lead to allocation of a CB insufficient to justify funding by the national health insurance fund.

However, they are assessed in view of the medical need (i.e. the presence or absence of an alternative and their quality). In fact, the medical need will provide additional information to the efficacy, the adverse effects and the place in the care pathway of the medicinal product assessed. Hence, an effect size will be assessed on the basis of the medical context. For example, a medicinal product having demonstrated weak or uncertain efficacy of moderate quality and/or a low effect size, may have a place in the care pathway in the absence of any alternative whereas it may not have a place in the presence of recommended and/or better studied alternatives, in order to avoid a potential loss of opportunity for the patient.

An insufficient CB does not mean that no patient may benefit from this medicinal product; however, on a collective way and in view of the alternatives, this medicinal product does not present sufficient medical benefit for the national health insurance fund to contribute financially.

► Sufficient CB

The clinical situations not covered by the above mentioned scenarios may lead to allocation of a sufficient CB. In practice, this applies to any medicinal product having demonstrated clinically relevant efficacy and an acceptable safety profile with a sufficient level of evidence in view of the clinical context (i.e. based on an appropriate study design in terms of population, comparator, outcome measure and duration, in particular).
The CB level is modulated, in view of the available alternatives and clinical context, by the quality of research evidence and/or the effect size and adverse effects.

### 3.4 Assessment of the CB in the event of major uncertainties

The assessment of some medicinal products is based on the analysis of early or still limited data, in a context of major uncertainty with respect to their real effect. In addition, the safety profile of these medicinal products is generally associated with high levels of uncertainty, particularly in the medium and long term.

In this case, the TC may consider that additional data will be necessary to reassess the medicinal product. The TC may then specify in its opinion the information and additional studies that must be submitted by the pharmaceutical company for the CB reassessment.

Pending new data, a CB may be allocated if the absence of reimbursement is liable to result in a loss of opportunity for patients in view of the preliminary data:

- **Serious disease**, independently of the prevalence, and
- **Unmet medical need**, and
- **Initial data suggesting a clinical benefit** for the patient, and
- **Development plan enabling short term elimination of uncertainties** on the basis of:
  - clinical studies: in this case, the development plan must be predefined by the company and known at the time of the initial assessment to enable the TC to assess whether it will be able to eliminate the uncertainties,
  - and/or real-life studies capable of eliminating uncertainties.

The reassessment may be performed once the clinical data is available and within a maximum period of 5 years.

The renewal of a sufficient CB level following reassessment may then be envisaged only if the results eliminate the uncertainties identified in the initial assessment.
4. Estimation of target population

One of the TC’s missions is to estimate the target population liable to be treated by the medicinal product. It is calculated for the population corresponding to the sufficient CB, which may sometimes be smaller than the one of the MA indication.

Determination of the target population is based on:

- available epidemiological data and the effects of existing treatments (obtained from observatories, registries, prescription, hospital activity or reimbursement databases, the number of patients with registered chronic conditions, the scientific literature, etc.),
- a rationale leading, in stages, to the population liable to receive the medicinal product.

The choice of the incidence or prevalence for this estimation is made on a case-by-case basis depending on the posology and nature of the disease: the target population of a medicinal product used once over a short period may be based on the incidence whereas in the case of chronic use, the prevalence will be required.

Data concerning the actual population is not generally used, except in certain situations – for example when the care pathway is well established.

Dynamic modelling of the target population may be conducted in exceptional cases and at the request of the CEPS (French healthcare products pricing committee).
5. Real-life studies

Real-life studies correspond to data obtained from observational studies. These data may have different sources (ATU, registries, queries of databases such as SNDS, post-registration studies, etc.).

▶ Requests for post-registration studies by the TC

During the initial assessment of a medicinal product, the available data primarily comes from clinical trials and data obtained in real-life use conditions is rare. The TC may therefore identify uncertainties or questions concerning the clinical benefit of the medicinal product, its place in the care pathway, misuse, as well as the short or long-term consequences of introduction of the medicinal product on public health.

As defined in article R. 163-18 of the French Social Security Code, the TC may then request that additional data be collected, in a post-registration study (PRS) to eliminate uncertainties or answer these questions. These requests may concern any medicinal product and are generally made at the time of the initial assessment or an indication extension but may also be made during a reassessment.

Requests for such data are strongly linked to the essential nature of this data for a subsequent reassessment and its feasibility.

▶ Objectives

These requests made by the TC usually have the objective of documenting:

- the modalities of use: patient characteristics, role in the care pathway, treatment duration, dosage, co-prescription, conditions for stopping or continuing treatment, misuse, etc.
- the effectiveness,
- the safety (although pharmacovigilance is under the remit of the ANSM).

▶ Wording of requests

The TC requests take particular care to:

- limit the number of objectives,
- rationalise the number of real-life studies by encouraging the use of any study already under way liable to provide satisfactory answers (risk-management plan, secondary analysis of cohort data or academic registries, studies on the basis of the SNDS, all pre-identified studies),
- specify the time-frame for results, which are usually expected within a maximum period of 5 years.

▶ Study methodology

The methodology of a PRS depends on the TC request\(^6\). It is usually a descriptive observational study to assess the use and impact of the medicinal product in non-selected populations, over prolonged durations or with different criteria from the clinical studies available. If it deems it necessary and possible, the TC may request the performance of randomised clinical studies or analytical observational studies.

▶ Assessment of studies

The results of these studies are systematically assessed and contribute to reassessment of medicinal products by the TC.

\(^6\) Document models relative to the post-registration studies requested by the Haute Autorité de santé. Available online: https://www.has-sante.fr/portail/jcms/c_1725427/fr/modeles-de-documents-relatifs-aux-etudes-post-inscription-demandees-par-la-haute-autorite-de-sante
The TC therefore pays particular attention to this data, which supports the data obtained in investigational conditions and supplements knowledge concerning the actual conditions of use, potential misuse, potentially modified care pathway, the methods for initiation or discontinuation of treatments, etc. Although it is rarely appropriate in terms of the level of evidence to claim a CAV upgrade, this data can contribute to an increase in or maintenance of the CB or the CAV and generally provides crucial information for the recommendation of good practice conditions for medicinal products.

▶ Other real-life data

Independently of requests for a PRS, real-life data – especially ATU data – contributes to assessments (PHI, target population, care pathway, etc.) and can also be taken into account in the assessment of the CB and the CAV, for example in situations where the TC considers that a comparative clinical study cannot be performed (see “Quality of demonstration” chapter).

The TC recalls the fact that it is not appropriate to confront randomised clinical trials with observational studies. Randomised clinical trials remain the reference design to demonstrate the efficacy of a medicinal product. This means that observational studies cannot be a substitute for clinical studies in situations in which the latter are expected or provide evidence of efficacy that clinical studies have failed to demonstrate.

Observational studies are always analysed in view of all the efficacy data available concerning the treatment and may be one of the elements leading the TC to increase or maintain a CAV.

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7 Randomised clinical trials provide the best level of scientific evidence to causally link the difference in result to the medicine and remain, apart from in exceptional cases, the pre-requisite and the essential reference for initial assessments.
6. Focus

▶ Improvements in care conditions

Potential improvements in care conditions, related, for example, to new administration conditions, dosage forms, follow-up, etc. are taken into account by the TC. These may lead to a CAV when a major modification in care conditions (care pathway improvement, hospitalisations reduction, compliance improvement, etc.) is demonstrated or expected by the CT.

▶ Fixed combinations medicinal products

The TC assessment of fixed combination of active substances already available separately takes into account the rationale of the combination, as well as evidence of the pharmacodynamic equivalence compared to the free combination at the same doses (or of their synergy when the doses are lower).

These combinations may be considered to have an added value if improvement in terms of efficacy, compliance or safety is demonstrated.

▶ Medicinal products combined with a medical device or procedure

In some cases, the use of the medicinal product may be combined with a medical device or a diagnostic or therapeutic procedure (for example, an insulin to be specifically used with a pump, a radiopharmaceutical used in the context of an imaging exam, a test to be performed to identify the patients to be treated, etc.). In this case, if the medical device or diagnostic or therapeutic procedure is not included in the list of products and services reimbursable by the French National Health Insurance system, it is assessed by the National committee for the assessment of medical devices and health technologies (CNEDIMTS) and/or the HAS College in parallel with assessment of the medicinal product.

▶ Targeted therapies

Targeted therapies can be understood in two ways:
- a medicinal product for which the mechanism of action has a specific target,
- a medicinal product aimed at specific patients, identified by a marker, which is usually biological.

In oncology, targeted therapies is a medicinal products designed to stop the growth and/or spread of tumour cells by specifically attacking some of their abnormalities. Modes of action are heterogeneous and based on oncogenesis inhibition with a high level of specificity for cancer cells or their microenvironment\(^8\).

The identification of patients who will benefit from a targeted therapy may be based on an associated diagnostic test (or "companion test"). The medicinal product and the test must then be assessed jointly on the principles outlined in the HAS\(^9\) methodological guidelines. These guidelines present the ideal method for a companion test development. Any differences with respect to this method must be justified.

The TC’s requirements concerning targeted therapies are common to all medicinal products and their assessment is based on the same criteria (see “Assessment criteria” chapter). Hence, as for other medicinal products, the TC considers that a direct comparison with clinically relevant comparators, conducted within the framework of a double-blind, randomised trial, is expected wherever possible.

The fact that a treatment is a targeted therapy does not automatically mean that it will be granted a favourable recommendation for reimbursement.

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