
Innovative medicines assessment action plan

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In recent years, there have been numerous drug innovations in France and worldwide, especially in the field of oncology. Many of these innovations stem from the use of gene and cell therapy. This revolution has been made possible by a better understanding of genes and cells.

Around 2,000 clinical trials, some of which are still ongoing, have been conducted in the field of gene therapy since 1989. The great majority of these have concerned cancers (65%), but there have also been trials in neurological diseases (Duchenne muscular dystrophy), ophthalmological conditions (Leber congenital amaurosis), and blood diseases (haemophilia, beta thalassaemia). In the period of 2020-2021 alone, more than 20 gene therapies are set to arrive on the market.

Since they may actually cure patients rather than merely keep them alive, gene therapies will lead to a radical change in the general clinical attitude towards serious and/or chronic diseases that are currently often fatal.

In addition to the unprecedented hope raised by these therapies, their development is rapid with early marketing authorisations (MAs) granted. They are primarily tested using new, rapid and unconventional study designs, mainly in non-comparative studies on small numbers of patients. These developments are raising new scientific challenges: it is now necessary to monitor efficacy in real-life conditions, identify responder patients, understand and anticipate toxicities, ensure proper use, and support the impact on health care organisation.

These uncertainties also result in a switch-over of evidence to the post-marketing phase. They can only be resolved by successive reviews, something that must now be incorporated into our assessment principles.

These innovative medicines offer much promise, but this promise needs to be fulfilled and verified in the longer term. It is for this reason that data must be collected in real-life conditions, particularly to enable reviews.

Paradoxically, prices asked by pharmaceutical companies are very high and continue to rise in the presence of a number of uncertainties. This alarming trend raises questions about the national health insurance system's capacity to maintain access to innovation and to best treatments for all patients.

This is precisely where HAS may intervene; in other words by promoting patient access to innovations for which costs are covered, in making the necessary distinction between key innovations and mere novelty, and making sure that initial promises are fulfilled.

HAS already initiated measures to promote innovation. It thus wishes to continue its commitment, in accordance with its core values: scientific rigour, transparency, and independence.

HAS therefore launches a innovative medicines action plan consisting of 6 measures designed to anticipate, accelerate, and support the roll-out of useful and safe innovations for the benefit of patients.

1. Issue conditional reviews until uncertainties are lifted

Back in 2015, HAS supported the implementation of a conditional temporary funding scheme for certain medicines not yet offering all the scientific guarantees usually required in assessments performed for reimbursement (see Dominique Polton's report on assessment reform). This temporary funding scheme was restricted to serious diseases only, in which there was an unmet medical need. In these situations, assessments may need to "take certain gambles" that will require short term support to allow for awaited data generation.

This approach more recently led to the publication of [the HAS Transparency Committee \(CT\) Doctrine](#) (December 2018)

In this publication, the CT (Commission de la Transparence, the HTA appraisal committee) acknowledges the need to provide access to certain medicines in serious diseases for which there is an unmet medical need, but only if the following conditions are met: patients and healthcare professionals are fully informed a short-term reassessment is undertaken and a proper follow-up of treated patients is set up.

Given the temporary and reversible nature of these complex situations of assessments, it is crucial that all stakeholders – especially patients – be involved and well-informed with regards to risk-sharing principles.

Today, HAS proposals are to be incorporated into regulation. After which, the CT will be able to grant exceptional funding pending new data.

The timeframe to resolve initial uncertainties and support or refute the initial promise shall short (less than 3 years), and handled by the Committee.

2. Monitor medicines in real-life conditions to make sure that they fulfil initial promises

Observational studies are an essential source of information for all assessments performed by the CT.

The CT also provides real-life data, commissioned from manufacturers and subsequently analysed in the reviews it decides to perform.

In terms of guiding principles for considering these data, it is necessary to be clear about HAS expectations: the requested data should complement clinical trials, making it possible to observe to which extent clinical trials results are confirmed in real life.

Real world data is essential to the promotion of proper use and makes it possible to: better position the medicine in the therapeutic strategy, confirm or refute doubts concerning safety, understand the characteristics of patients actually treated, and reach conclusions with respect to the medicine's impact on healthcare organisation, etc.

The need for real-life studies will increase as more and more of these medicines arrive on the market, carrying high levels of uncertainty concerning efficacy and safety in real use conditions.

The very purpose of conditional assessments is to allow initial promises to be rapidly reviewed and fulfilled. They highlight the need to collect new data, in particular real-life use data, starting with temporary authorisation for use (ATU) data. This very early access (before Marketing authorisation) authorised by the ANSM, for all patients requiring it, should be seen as an

opportunity to collect the first data concerning real-life use of these medicines (usage, safety and efficacy). At present, the way data is collected in the ATU process is not considered efficient and rarely submitted by manufacturers in time for HAS assessments undertaken for reimbursement purposes.

The HAS therefore recommends that continuity of access be reinforced so that each step in the early access process feeds the next step – from granting of ATUs to assessments for reimbursement purposes – and works with the French competent authorities to ensure data is systematically submitted and processed.

3. Reinforce HAS' agility to better support innovation

a. Focus on assessments offering high added value

The HAS is the only HTA organisation in the world to systematically review every product in the pharmacopoeia every 5 years. Hence it issues between 600 and 800 reviews every year, where other European agencies focus on around 50 annual assessments. This level of activity associated with areas of low clinical relevance, hampers HAS' agility.

HAS thus proposes to refocus its work on high added-value assessments only, i.e., the assessment of new medicines and their short-term review. HAS proposes to discontinue its systematic 5-yearly reviews of known medicines that do not raise any issues in terms of efficacy, safety, or role in the therapeutic strategy.

These measures will free up time and improve reactivity, thereby enabling HAS to adapt to new developments requiring short-term reviews.

These recommendations have been acknowledged and regulatory changes are expected.

b. Improve early dialogues process to support clinical developments

Since 2010, HAS has undertaken early dialogues with companies developing medicines to help them design relevant clinical trials. This mission was reinforced following the 2016 French Health Reform.

The objective of early dialogues is to provide requesting companies with scientific advice concerning pivotal study designs and the final development phase for a given medicine. Scientific advice provides companies with a better understanding of the type of data needed to meet HAS assessment requirements.

Scientific advice is issued by HAS departments and reflects current medical knowledge at the time of an early dialogue. Scientific advice does not constitute an assessment and is not an indicator of the final conclusions to be reached by the CT and/or the Economic and Public Health Evaluation Committee (CEESP), another HAS specialist committee.

Early dialogues may be conducted on a national level (HAS only) or on a European level (with HAS and other HTA bodies, as part of the European EUnetHTA network, with or without the European Medicines Agency (EMA)).

In 2018, 41 early dialogues were requested for medicines and 21 were performed by the HAS teams. Six of them concerned advanced therapy medicinal products (ATMP) and nine concerned orphan medicines.

Supported by this experience, HAS is updating its national early dialogue processes in order to make them more relevant. A new guidance document will be published in April 2020; in particular, it will introduce two assessment procedures and will involve patients.

c. Promote accelerated assessment procedures (“fast-tracking”)

HAS offers companies two early assessment options, enabling the CT to start the assessment process for a medicine as soon as possible and ensure early access for patients.

Both procedures substantially reduce time frames. For example, CAR-T gene therapies were assessed within 90 days following MA, which includes the *inter partes* phases. Regrettably, these procedures are under-used to not used at all.

In 2019, the HAS laid out a more flexible, transparent and predictable procedure for pharmaceuticals companies with the aim of attracting more applicants. [All details are published on the website.](#)

d. Improve internal collective efficiency

Since innovation is also a mindset, HAS departments are organised to reinforce their agility and promote innovation, while upholding core values of scientific rigour, transparency, and independence.

HAS launched a number of operational measures to foster innovation:

- increase of the number of annual Transparency Committee meetings, with 25 sessions held in 2019, i.e., almost three 7-hour committee sessions per month;
- reorganisation of Transparency Committee meetings into sessions dedicated specifically to assessments or hearings;
- annual online publication of scheduled Transparency Committee session dates;
- prioritisation of dossiers (e.g. medicines with ATUs);
- implementation of an electronic filing system to simplify and streamline reimbursement applications. It is intended to extend this procedure to all exchanges between companies and HAS, namely with regards to filing real-life study results and early dialogue processes.
- audit of all HAS HTA committees processes to determine possible time savings.

HAS also began carrying out inter-committees sessions, in application of article [R. 161-77, II](#) of the French Social Security Code.

4. Systematically involve patients and consumers

Consideration of patient views in the assessment of health products, including medicines, is a priority for HAS, and an area that has been ramped up in recent years. In terms of assessment of medicines, this is reflected by:

- The presence of two, and subsequently three, voting members representing patients and consumers associations in the CT.
- Since 2016, the possibility for patient and consumers associations to make written contributions to HTA Committees for medicine assessments. In addition, regular public consultation processes are organised.

The CT also highlights the need to consider patient quality-of-life data in assessments undertaken for medicine reimbursement purposes. The Committee considered this type of data

as complementary to efficacy and safety data and that evidence of quality-of-life improvement could lead to recognition of clinical added value.

Today, HAS is particularly reinforcing patients and consumers involvement in the abovementioned uncertainty scenarios and, further upstream in the national early dialogue processes (see above).

5. Improve transparency

a. In terms of timeframes

HAS publishes all the documents it produces, along with the HTA Committees discussion transcripts.

It is committed to ensuring total transparency when it comes to assessment timeframes. A tracking indicator was recently published on its website. This will be improved to become more dynamic and will be regularly updated.

- b. In terms of post-launch studies

In November 2019, HAS published a list of medicines concerned by post-launch study requests, enabling all stakeholders to consult the data required by the CT for a quality assessment. Relevant information is displayed in two tables as follows: a table relating to medicines with an ongoing requested post-launch study, and another table indicating those for which the results of such requested studies are available in the CT review. In each table, HAS specifies product name, therapeutic class, date of the CT review in which the study was requested or in which study findings are mentioned (online link provided to the review), along with study endpoints (prescribing or use condition, efficacy, impact on morbidity and mortality, impact on the healthcare system, etc.).

6. Increase European cooperation to pool knowledge

Cooperating with its European counterparts is a major priority for HAS, enabling to work together to liaise, anticipate, provide support, and assess the most innovative health products.

Pending a European regulation – currently under discussion – concerning European cooperation in the field of HTA, HAS has invested heavily in the European EUnetHTA project, anticipating the future organisation, if this is decided upon.

Hence HAS is Vice Chair of the EUnetHTA Executive Board; HAS set up, leads and coordinates European early dialogues and post-launch evidence generation activities; HAS assesses new medicines in collaboration with other HTA agencies in the European HTA network, particularly in the fields of oncology and infectious diseases.

Finally, again on a European level, HAS is closely involved in activities fostering patients and consumers involvement, in developing procedures to manage conflicts of interest, horizon scanning studies, and methodology reflection processes, particularly concerning the real-life monitoring of medicines.