Market Access Newsletter

Editorial

by Prof. Mondher Toumi
EMAUD Chairman

Dear Colleagues & Friends,

For the 5th edition, EMAUD organised the annual Market Access Day on 3 December in Paris under the theme "the place of uncertainty within the public decision". Once again speakers from leading pricing and HTA agencies could present their perspective on the subject and debate with the audience.

Currently, we are observing an increased payers' aversion to uncertainty while regulators are increasingly managing uncertainty. The first point is to well distinguish uncertainty from risk, two concepts often confused. Uncertainty is a situation where the current state of knowledge is such that the outcomes are unpredictable, and no credible probabilities can be assigned to them. The risk is characterized by the identification of more than one possible outcome and a probability can be assigned to each possible outcome.

This increased aversion to uncertainty shifted from fixed point time decisions to decision windows depending on the levels of uncertainty (e.g. G-BA (Germany) decision window varying from 1 to 5 years, case of Risperdalconsta L.P® in France with a decision window of 7 years, case of sitagliptin in France with a decision window of more than 5 years, case of sitagliptin in Scotland with a decision window of more than 3 years or case of Duodopa® in Sweden with a decision window of 6 years). The main issue faced by the pharmaceutical companies is the minimization of the uncertainty at drug launch time, to reassure the regulators and payers. Narrowing uncertainty will narrow the decision time window. Pharmaceutical companies are encouraged to anticipate the uncertainty via a mitigation plan to move from uncertainty to controlled risk.

One of the major sources of uncertainty is the transferability of clinical trial results to the real world setting, i.e. moving from efficacy to effectiveness in terms of performance (efficacy, tolerability and safety) and utilisation (dose, treatment duration, population heterogeneity and starting/stopping rules).

From regulator side, the risk assessment and risk management is part of regulator culture and a number of tools are in place to control uncertainty such as conditional approval, marketing authorization under exceptional circumstances, restricted marketing authorization, Risk Management Plan or adaptive licensing.

Payers face uncertainty from different sources, other than the transferability of clinical trials results in real-life:

- Inherent to study design: either directly related (inclusion/exclusion criteria, study duration, comparators, range for non-inferiority studies, premature cross-over to active treatment, premature trial to discontinuation, patient censoring effect, post-hoc analysis) or indirectly related (clinical relevance of the observed benefit, surrogate endpoint, validation of endpoint, relevance of endpoint for payers, composite endpoint)
- Related to prescribers: linked to their behaviour (off-label use, off-reimbursement use or misuse-dose, duration, co-prescription) or not (difficulties in differential diagnosis, patient management within the healthcare system, concomitant medications and diseases)
- Related to patient attitude in terms of adherence, mismanagement and concomitant medications
- Related to the context: identified before the marketing authorization (target size population, guidelines, medical practice, patient management, scientific knowledge) or hard to identify before the marketing authorization (development of resistance, shifting age of infection, new serotype emergence, prescription transfer, new competitive environment -generic, new brand-, scientific knowledge)

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Payers use also a number of tools to control uncertainty such as budget impact analysis, cost-effectiveness analysis, financial agreements, payment for performance, coverage with evidence development, real world data collection or restricted reimbursement.

Five levers can be used by pharma companies to manage the payer's uncertainty:

- Appropriate development plan
- Early dialogue with Health Technology Assessment agencies
- Modelling to extrapolate efficacy to effectiveness and cost-effectiveness
- Coverage with evidence development to follow on the effectiveness
- Financial agreement to minimize budget impact of inappropriate decision

The management of uncertainty by pharma companies is essential to secure optimal market access conditions. A poor management of uncertainty can lead to substantial time delay following marketing authorization, lower reimbursement, reduction of the eligible target population for reimbursement and prescription complexities due to burdensome procedures.

The public decision maker and the aversion to risk

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The risk aversion is a concept pointed by the economists, based on the behaviours of humans, to generally choose a more certain scenario. For example, if a person is given the choice between two scenarios, one certain scenario where the person receives €1,000 and one uncertain scenario where the person receives €2,000 in 50% of cases or nothing, basically, one could say that the person would prefer to receive €1,000. But the reality is much more complex, the higher the level of benefit, the higher risky assets will be chosen by individuals.

However, individuals may have different risk attitudes, with some people liking the risk, while some others not. Psychologists who studied personality traits defined two types of models called model based (investigating the neurobiological foundation for personality) and language based (language used to describe personality).

One well known neurobiological model is the Cloninger Temperament and Character Inventory (TCI), with a newer version called the Temperament and Personality Questionnaire (TPQ). It includes 7 dimensions of personality traits: 4 for temperaments (harm avoidance, novelty seeking, reward dependence and persistence) and 3 for characters (self-directedness, cooperativeness and self-transcendence). It can be shown with this model that risk avoidance is not a basic trait of personality or temperament, even if it is close to novelty seeking and harm avoidance.

One well known language model is the Big Five Model including 5 dimensions of personality: openness to experience, conscientiousness, extraversion, agreeableness and neuroticism. As for the other model, there is no dimension related to the risk aversion but neuroticism (sensitive/nervous versus secure/confident) and openness (inventive/curious versus consistent/cautious) might constitute risk aversion trait of personality.

Societies with high level of risk aversion are generally "comfortable society" as occidental societies where basic needs are covered and upper needs are becoming a source of anxiety as illustrated with the *principe de précaution* (precautionary principle) or the controversy around the vaccine against measles/mumps/rubella and autism (reluctance to use the vaccine even years after the claims were disapproved). Epidemiologists have found that last decades saw an increased prevalence in anxiety symptoms (and not necessarily anxiety disorders). As such, public decision makers are fundamentally risk-averse to miror society attitude and require risk minimization, even at the cost of losing the utility of the risky activity.

Moreover, the high level of risk aversion for decision makers is more linked to safety issues than to efficacy issues. However, in practice this risk aversion does need to be counterbalanced to gain health product approval and this balance is not an easy thing. One of the solutions of the decision makers is the use of utility model to balance the benefits and risks but most often it does not incorporate the question of risk aversion and is

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not really used in most of the countries. The management of risk aversion has thus to come from the debates and transparency related between citizens, politicians, philosophers and physicians.

NICE Review Process and PAS

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The procedural principles of NICE are based on scientific rigour, inclusiveness, transparency, independency, challenge, review, support for implementation and timeliness, all targeting accountability for reasonableness.

A NICE technology appraisal combines clinical and economic evidence for pharmaceutical products and devices with the purpose of giving funding recommendations. There are two different processes used to evaluate a technology:
Multiple Technology Appraisal (MTA) was established in 1999 and involves the evaluation of classes of technologies, or single technologies with multiple indications, and lasts approximately 14 months.
Single Technology Appraisal (STA) was established in 2006 and involves the evaluation of single indications close to marketing authorization and lasts approximately 9 months.
The final decision is made by the independent committee and decision is appealable.

The majority of appraisals are focused on the therapeutic area of cancer followed by cardiovascular and musculoskeletal disease areas. The breakdown of diseases will largely depend on which drugs are going through the regulatory process.

The appraisal committee consists of 34 members (including the Chair) drawn from Primary Care, Secondary Care, Royal Colleges, Patient Groups, Health Economists, NHS Management, Public Health, Healthcare Industries and Biostatisticians. There are four committees who each meet once a month, reviewing two to three appraisals. The Committee works across the whole spectrum of technologies/interventions and conditions. The decision making as mentioned above is independent and members with a conflict of interest for a drug cannot participate in the appraisal of the particular drug.

The appraisal committee decision making depends on clinical and cost effectiveness, how innovative the drug is, NICE's principles on social value judgements, extent of uncertainty around the evidence and other health benefits. NICE also has a legal duty to consider equality and diversity.

The economic evaluation examines the relationship between the costs of a medicine with how well the medicine works compared with established practice in the NHS. This exposes the opportunity costs of new technologies. Since every evaluation follows the same process- either the STA or MTA process, this ensures that there is consistency and fairness across the decisions made by the four committees.
The incremental cost-effectiveness ratio (ICER) is used to show the cost-effectiveness of the product under evaluation compared to another product or any standard of care and is calculated by:

$$\frac{\text{cost}_{\text{new}} - \text{cost}_{\text{current}}}{\text{health gain}_{\text{new}} - \text{health gain}_{\text{current}}}$$

Where health gain is expressed in quality adjusted life years (QALYs).

Above an ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will take account of factors such as the degree of certainty around the ICER, the presence of strong reasons indicating that the assessment of the change in the quality of life has been inadequately captured, the innovative nature of the product and the non-health objectives of NHS. The process was updated in 2009 to provide supplementary advice on appraising life-extending, end-of-life

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treatments using the following criteria:

- Life expectancy was less than 24 months
- Life extension was expected to be higher than 3 months
- The product under evaluation concerned small proportion of total population (<7,000)
- Estimation of extension to life was found to be robust.

This allows the Committee to give greater weight to QALYs achieved in later stages of terminal disease. In addition to the ICER, the Committee considers the application of other special circumstances, like the persuasion of stakeholders, the severity of disease, the targeted population and if the technology is innovative.

Until the 31st of October 2013, 297 appraisals with 530 individual decisions have been published. From these, 80% had received positive recommendation for routine use or under specific circumstances and the remaining 20% were either not approved or recommended 'only in research'. More than one recommendation can be obtained in a published technology appraisal.

NICE does not negotiate or set drug prices, instead the pricing policy in UK is regulated by Pharmaceutical Price Regulation Scheme (PPRS). It is a voluntary agreement between industry and UK Department of Health which caps profits on earnings from the sale of branded drugs to the NHS. In 2009, Patient Access Schemes (PASs) and flexible pricing were introduced in order to improve the cost effectiveness of a drug and enable patients to receive access to cost effective innovative medicines.

When a company proposes a PAS, the Department of Health and the company have the first negotiations and agree in principle. The company includes the proposed scheme in its submission to NICE (in special cases the scheme may be submitted between the two appraisal committee meetings). The scheme should be clinically robust, plausible, appropriate, easy to manage and monitor without adding extra costs and bureaucracy. Full costs of the scheme should be included in the submission to be reviewed by the Committee. The Committee considers the rational and duration of the scheme, the patient population and any criteria to be met. Additionally, the incorporation of the scheme is considered, along with implementation, operational and treatment-related costs.

The types of schemes are listed below:

- Full: Based on certain criteria, with rebate, dose cup or refund. Sometimes administered heavily.
- Two parts: Initial price is agreed with further outcome-based alteration to price.
- Transition: Change from one scheme type to another.
- Simple: Offering simple discount with minimal administrative burden.

In the years 2010/2011, 50% of PASs were simple discounts, 43% were full schemes and only 7% were two part schemes. In the years 2011/2012, 83% of PASs were simple discounts, and transition and full schemes accounted for 9 and 8% respectively. For the years 2012/2013 all PASs were simple discounts.

Since 2009 when PASs were introduced, a total of 179 individual technologies have been appraised and of these 44 included a PAS (about 25%). Thirty eight resulted in positive guidance and the remaining 6 technologies were not recommended. This shows that the inclusion of a PAS does not necessarily lead to a positive recommendation since the Committee will still consider the degree of uncertainty around the ICER and the other factors discussed previously, especially if the ICER is higher than £30,000 per QALY gained.

In summary, approximately 25% of appraisals have included a PAS, but not all of appraisals that include a PAS receive a positive recommendation. The inclusion of a PAS doesn't change the way the Committee appraises cost effectiveness and it will still consider other factors such as uncertainty around the ICER, innovation and end of life criteria.

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Database analysis to monitor the use and misuse of medicine, and the negative impact on drug budget

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Once Health Technology Assessment (HTA) has determined whether an intervention should be implemented in the National Healthcare System (NHS), patients' eligibility, follow-up and outcomes criteria are defined to frame the use of the technology in order to stick to costs and effects forecasted.

Ensuring respect of these criteria requires real-life data on effectiveness, safety, patient population size and characteristics… Such data can be gathered through patients registries and outcomes monitoring and impact the financing of the concerned technology and its surrounding environment within the NHS.

Such information system is at the core of the strategic plan of CatSalut's pharmaceutical services. It is based on patients records database, electronic prescription and benchmarking tools.

Electronic prescription allows a real-time monitoring of 91% of outpatient prescriptions and dispensations in Catalonia representing over 500 000 dispensations and 100 000 prescriptions daily. Results are aggregated in two databases monitoring the pharmaceutical activity (SIRE: Integrated Systems of Electronic Prescription and RAF: Pharmaceutical activity register). Analysis instruments have been developed in order to benchmark real life use of treatments, controlling budget, detect misuse, and assess safety as well as policies impact on the use of medicines.

A Quality index for prescription (QIP) is built for each primary health care team (PHCT) to measure technical-scientific dimension of the quality of prescription and encourage the use of safe and cost-effective drugs, and reduce the variability of primary-care practice. A correlation was found between quality index for prescription and lower cost per patient and respect of allocated budget. PHCT have QIP objectives leading to incentive measures if respected.

Inpatient cares are monitored in order to benchmark the treatments' utilization and outcomes variability among hospitals. Monitored drugs and indications are reported when prescribed, initial, follow up and ending variables of each treatment are informed in the register. Concerned indications include neoplasms, multiple sclerosis, growth deficits, HCV, AIDS, rheumatoid arthritis, etc.

Such real-life data can then be used in order to elaborate hospital budgets as well as follow-up risk sharing agreements between CatSalut and manufacturers. It also allows new more efficient drugs to be quickly recommended and included in good practices scheme, having rapidly demonstrated the clinical innovation they provide in real-life settings.

Managing uncertainty when setting new HTA and pricing policy

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Distorted principal-agent relations between patient, physician, payer and manufacturer have been an important factor leading to mistrust, and HTA & reimbursement policies often appear as payers' counter-reactions to these distortions. Uncertainty and mistrust together may lead to 'instances of paranoia' on the payer side, with different manifestations ranging from concern about overspending, fear of precedent-setting and fear of being overpowered to being seen as incompetent.

There are negative uncertainty reduction strategies on the payer side such as minimising contacts with external stakeholders, being overly critical of any incoming proposals, diluting proposals, cherry-picking elements from proposals and the 'chimney effect' (sending everything to higher decision levels for approval). On the other hand there are positive strategies such as moving from individual to collective decision-making all along the policy-making process,

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relying on formal guarantees (for example claw-back mechanisms, turnaround options and industry-level contracts), and individual strategies such as reinforcing competence and negotiation skills. The latter will also lead to increased self-confidence, which is a driver at individual level of more balanced policy decisions.

How can the industry minimise uncertainty for payers? There are technical tools for example providing easy-to-validate background research, looking for issues that payers really want to solve, presenting several scenarios, and preferably using sick-fund data instead of commercial data. As well as, some practical soft tools, for example initiating early dialogue, offering easy-to-substantiate benefits, entering into open discussions and avoiding unfounded statements which might undermine the collective credibility of industry.

Trust is a fragile notion; hard to build, easy to destroy. As policy decisions are never taken in a sterile rational environment, instead they are always subject to perceptions, biases and attitudes, industry must understand how to take payers out of the mistrust cycle.

G-BA approach to uncertainty management

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The number of consultations of industry with the G-BA (benefit assessment under AMNOG) has increased over time with about 40 consultations in 2011 and over 100 in 2013. The G-BA also participates in joint consultations at the European level, for example within the framework of EUnetHTA and EMA advice pilots.

The benefit assessment results in a classification of the extent of the additional benefit over the appropriate comparator. There are 6 categories: 1) Major additional benefit 2) Considerable additional benefit, 3) Minor additional benefit, 4) No additional benefit, 5) Less benefit than the comparator and 6) Non-quantifiable additional benefit. The last category “non-quantifiable additional benefit” is itself a way to deal with missing data. In addition to the extent, the level of certainty of conclusions (the so-called probability of the additional benefit) is determined too.

Sometimes, the G-BA sometimes handles uncertainty with time-limited resolutions. There are short-term requirements (1-2 years), most often linked with concerns that can be addressed through ongoing studies, and also long-term requirements (3-5 years) which tend to concern uncertainty that cannot be addressed over a short period of time. A few cases have requirements linked with the market authorisation, e.g. conditional approval.

As an example, the assessment of orphan drugs is challenging, especially because of the lack of comparator, the small number of patients and the lack of patient-relevant endpoints. The legislation in Germany states that the additional benefit is proved through the market authorisation until the turnover of the orphan drug with the statutory health insurance in the last twelve calendar months exceed the amount of €50 million. Accordingly, the benefit assessment of orphan drugs had to be adjusted in its implementation to meet the legal requirements.

The G-BA is still in a learning process regarding the AMNOG benefit assessments and mentioned some areas where improvements have already been achieved or where changes could be expected: participation of regulators in early consultations, dealing with surrogate endpoints, dealing with conditional approval, and handling missing evidence for last-line products. Bearing in mind that the overall goal and challenge is to set a fair price for a new drug.

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How can EUnetHTA joint work along the technology life-cycle contribute to minimize payers uncertainty?

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The European network for Health Technology Assessment (HTA) or EUnetHTA was established to create an effective and sustainable network for HTA across Europe following a European Commission call in 2005. EUnetHTA activities were organized through the establishment of the EUnetHTA Collaboration 2009, the EUnetHTA Joint Action 2010-2012, putting tools and approaches into practice, and EUnetHTA Joint Action 2 2012-2015, strengthening practical application of tools and approaches. The next phase of scientific and technical cooperation will cover the period 2016-2020, defining the long term vision of design and management of EUnetHTA.

The Directive 2011/24 EU on patient rights' application in cross-border healthcare implemented a permanent voluntary European network for HTA (by the end of 2013). Article 15 specifies that "*The Union shall support and facilitate cooperation and the exchange of scientific information among Member States within a voluntary network connecting national authorities or bodies responsible for health technology assessment designated by the Member States*".

EUnetHTA consists of 44 partner organisations designated by the EU Member States for the Joint Action 2, including a large number of regional agencies and non-profit organisations that produce or contribute to HTA (for example ISCIII, AETSA, OSTEBA, Avalia-T, AQuAS (Spain); IQWIG, DIMDI (Germany); THL, FIMEA (Finland); NOKC (Norway); INFARMED (Portugal); AAZ (Croatia); HAS (France); NICE, NETSCC (UK); AHTAPOL (Poland); LBI, HVB, GÖG (Austria); KCE (Belgium); CVZ (The Netherlands); AGENAS, AIFA, ASSR Emilia Romagna, Veneto Region (Italy); DHMA (Denmark-Coordinator)). EUnetHTA collaborates also with payers, patients/consumers, industries and providers (the stakeholder forum and the stakeholder advisory group) and with the European Medicines Agency (EMA).

EUnetHTA objectives are to support efficient production and use of resources available for HTA in countries across Europe by harmonising HTA methodologies/processes, sharing knowledge and promoting good practice, as well as increasing collaboration and open dialogue between HTA authorities, industries, patient organisations and payers to promote transparency and fairness of pricing and reimbursement decisions.

Several initiatives were set up by EUnetHTA to harmonise evidence requirements including early scientific advice on technologies between HTA bodies and companies, information sharing between HTA institutions, additional data collection on related health technologies, methodological guidelines on e.g. assessing outcomes, and alignment between HTA and regulatory needs.

EUnetHTA outputs include:

- The HTA Core Model®: A common set of data to be used for HTA reports and built to enable reliable, timely, transparent, transferable HTA information. Nine domains are included in the model (health problem and current use of technology; description and technical characteristics; safety; clinical effectiveness; costs and economic evaluation; ethical analysis; organisational aspects; social aspects; and legal aspects). The Core Model for Full HTA includes these nine domains and the Core Model for Rapid HTA includes 4 main domains (health problem and current use of technology; description and technical characteristics, safety, clinical effectiveness)
- Pilot assessment of pharmaceuticals and other medical technologies' relative effectiveness to test the capacity of national HTA bodies to collaborate and produce structured rapid core HTA information

on relative effectiveness of pharmaceuticals and other medical technologies (such as medical devices, surgical interventions or diagnostics)

- Early dialogue between HTA bodies and companies
- Planned and Ongoing Projects (POP) database that allows HTA agencies to share information with each other on planned and ongoing projects conducted at the individual agency. It aims to reduce duplication and facilitate collaboration among HTA agencies

The EVIDENT Database that allows sharing and storage of information on reimbursement/coverage and assessment status of promising technologies and on additional studies requested or recommended further to a HTA. It aims to reduce redundancy, promote generation of further evidence when necessary and facilitate European collaboration in this domain

Methodological guidelines for the relative effectiveness assessment: 9 guidelines were produced:

1. Clinical endpoints
2. Composite endpoints
3. Surrogate endpoints
4. Safety
5. Health-related quality of life
6. Criteria for the choice of the most appropriate comparator(s)
7. Direct and indirect comparison
8. Internal validity
9. Applicability of evidence in the context of a relative effectiveness assessment

Budget allocated for Joint Action 2 is of €9,428,550 including at least 28 pilot exercises (e.g. joint assessments, early dialogues, training in tools and approaches) and at least 40 national HTA reports using tools and recommendations from the Joint Action 2 on the future of HTA in Europe.

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HTA in Italy: promising or confusing?

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The Italian NHS is a public service funded by general taxation, which provides universal coverage and comprehensive healthcare free at the point of delivery.
Like the Spanish system, the Italian NHS is highly decentralized in 19 Italian regions and 2 autonomous counties. Regions are responsible for planning healthcare services and allocating financial resources. This heterogeneity originates discrepancies in economic strategies and funding of the health care services.
HTA was formally introduced in Italy by the Ministry of Health in the 2006-2008 National Health Plan.

At national level, there are two agencies involved:

- AgeNaS (the National Agency for Regional Healthcare) coordinates and supports HTA in the regions since 2007. It also aims at performing medical devices assessment, although just a few reports are available and the priority setting process is unclear. As an example, AgeNaS has concluded in a HTA report in 2008 that, due to the impossibility to collect and manage real practice data on effectiveness and costs, the concept of "best evidence" is impossible to apply at present in Italy.
- The second agency is AIFA (the Italian National Drug Agency). AIFA has introduced an innovation algorithm to evaluate new drugs. This kind of evaluation could be seen as an HTA assessment; however, no HTA report has been published so far. Consequently, the AIFA decision process is not yet transparent.

At regional level, HTA is not evenly implemented. In fact, two thirds of the regional authorities have issued official documentation to formally introduce HTA under

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the coordination of AgeNaS. However, our survey on the actual implementation and achievements of regional

HTA showed significant discrepancies between them. In 21 regions, 16 have structured workgroups, 6 are funding HTA activities and only 5 publish HTA reports. Regarding the published HTA reports, Veneto and Emilia Romagna regions have published most of the drugs assessments, respectively 266 and 121, which account for 91% of the total reports. This is explained by the fact that Veneto and Emilia Romagna have a tradition of assessing pharmaceuticals for their regional formularies and many reports have been labelled as HTA reports afterwards.

To conclude, HTA landscape in Italy is still unclear. All public "players" need a clear-cut role to contribute to the HTA process, starting from the central authorities. Not all the regions can perform HTA, probably on account of their wide differences in size, tradition and skills in the health care field. The role of industry needs to be clarified, to maintain transparency and avoid conflicts of interest.

How could HTA contribute to inform about uncertainty related risk for payers: from comparative efficacy pre-launch to post-launch observational studies?

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In France, Health technology assessment (HTA) for a drug is performed by the Haute Autorité de Santé (HAS) which then informs three bodies: the Comité Economique des produits de Santé (CEPS, price decision), the Union Nationale des Caisses d'Assurance Maladie (UNCAM, decision on level of co-payment), and the Ministry of Health and of social security who makes the final decision and allows inscription of the drug the positive drug list.

When assessing a drug, a number of uncertainties are encountered. Granting market access is a kind of bet on the risk/benefit ratio of a drug as there is still no evidence on the impact of the drug in real life. Thus, some processes were put in place to reduce uncertainty.

At regulatory level, the Agence Nationale de *Sécurité du Médicament et des Produits de Santé* (ANSM), these processes include Risk Management Plans (PSUR, pharmacovigilance) and observational studies.

At HTA level, the HAS will have recourse to periodic reassessment of drug risk/benefit ratio every 5 years and to post-launch studies. The HAS wants to give more weight to the latter. Therefore, the objective and requirements of these studies are currently being reconsidered in order to ask for specific data to address a specific topic of uncertainty instead of collecting general information as it is currently performed.

More recently, the introduction of the economic evaluation in the HTA process by law, is expected to reduce this uncertainty because of additional health economic assessment. However, the extent to which this will impact the CEPS decision is still unknown.

Another instrument that may reduce uncertainty is the establishment of an early dialogue process which allows manufacturers to develop evidence that will be relevant for regulatory and HTA/payers, such as defining the appropriate comparator, endpoints, inclusion criteria, target population, study duration, study design, , health economic models. Early dialogue can take place at many levels (EMA, EUnetHTA, HAS), through the development process. As such, the drug should fulfill three conditions: it should have a new mode of action, it should cover an unmet or partly unmet need, and the Phase II results should be available as well as Phase III design studies are in preparation.

The HAS is aiming towards more transparency and openness with regard to HTA assessment, following the doctrine of the Transparency Commission (annual reports 2011-2012) by developing guidelines to explain how this commission assesses drugs and on which criteria decision is made.

The various topics considered for pricing and reimbursement decision were listed, such as disease characteristics, quantity of effect, clinical relevance,

target population, etc.; as well as which evidence needed to be assessed like efficacy, tolerance, comparator, therapeutic strategy, target population, interest for public health.

In France, there is a well known process to facilitate HTA to pricing and reimbursement decision-making. First at the Transparency Commission level a number of criteria are quantified such as the level of evidence (design and methodology of trials), quantity of effect, relative effectiveness over the most pertinent comparator, external validity (extrapolation of results to the clinical practice), etc.

In case of demonstration of superiority the importance of the difference is rated in the ASMR. An improvement in actual medical benefit (ASMR) rated I to III allows a faster access to European price (Price notification instead of negotiation); an ASMR IV will allow for price negotiations and ASMR 5 (no improvement in actual medical benefit) will lead to a cost lower than the comparative strategy.

Regarding access to innovation, in France, the drug can follow a fast track procedure where the HTA assessment starts before market authorization has been granted and where opinion can be issued a few weeks after the marketing authorization. This can be done provided the drug fulfills three conditions: it is a new therapeutic modality, it fulfills a medical unmet need, and probably offers a therapeutic progress with regard to existing therapies.

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Sustainable healthcare system budgets and pharmaceutical expenditure at EU level

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In the past few years, some relevant European Union (EU) initiatives related to the pharmaceutical sector have been undertaken to promote:

- The transparency of measures regulating the prices of medicinal products for human use (*Directive 89/105/EEC relating to transparency of measures regulating pricing and reimbursement of medicinal products for human use*)
- The safety and efficacy of medicines with harmonized marketing authorizations in the EU (European Medicines Agency-EMA)
- The cooperation and exchanges between various stakeholders such as HTA agencies, National authorities, health care professionals, EU institutions, etc (Pharmaceutical forum, EUnetHTA, pricing and reimbursement network) for common set of best practices in pharmaceuticals pricing and reimbursement
- The rationale use of medicines to keep public budgets under control through targeted policies ("Joint Report on Health Systems" prepared by the European Commission-Directorate General for Economic and Financial Affairs -DG ECFIN and the Economic Policy Committee (EPC), High Level Pharmaceutical Forum, the Pharmaceutical Sector Inquiry of DG Competition, Report on pricing and reimbursement systems in Europe funded by DG enterprise (Espin 2007), PPRI initiative co-funded by DG SANCO)

Effective ways of investing in health for modern, responsive and sustainable health systems, including the cost-effective use of pharmaceuticals ("Reflection process -Toward modern, responsive and sustainable health systems, including the cost-effective use of pharmaceuticals ("Reflection process -Toward modern, responsive and sustainable health systems" of EU Member States)

Pharmaceutical expenditures are an increasing dilemma for EU Member States and a large number of cost containment measures have been adopted by EU member States to overcome the ever growing pharmaceutical expenditure. Based on OECD Health Statistics 2013, average expenditure on pharmaceuticals (outpatient) per capita, as a share of GDP for 31 OECD countries, reached 1.5% (public drugs spending represented 0.8% of the GDP while private represented 0.6%), varying between 0.6% to more than 2.5% in some countries. These differences in pharmaceutical

budgets across EU Member States are likely to be strongly driven by the variance in GDP per capita between countries. Of note, at the international level there is still a need for data standardization to estimate accurately the pharmaceutical expenditures (e.g. type of products to be considered, i.e. in/off patent drugs, type of data to be considered, i.e. price or volume).

The European Commission has set up a tool for economic policy coordination called the European Semester. It is a programme established each year by the European Commission to provide recommendations to EU Member States in terms of economic and structural reforms, among other to ensure that 2020 targets are achieved by all Member States. EU priorities are defined each year. Member States present their National Reform Programme and Stability and Convergence Programme in April and the European Commission provides country-specific recommendations in June.

At the 2013 European semester, 11 Member States (Austria, Bulgaria, Czech Republic, Germany, Spain, Finland, France, Malta, Poland, Romania, and Slovakia) received country-specific recommendations related to healthcare systems, focusing on the cost-effectiveness and hospital reform. These recommendations concerned pharmaceuticals for two Member States, France and Spain, which were requested to improve the cost-effectiveness of pharmaceutical expenditures.

The European semester illustrates the importance of fiscal coordination, with budgets matching the current trends and avoiding fiscal imbalance between EU Member States. This goes beyond the traditional focus in health systems related to the co-operation between the Member States. As such, fiscal sustainability of the healthcare systems is currently one of the main perspectives at EU level and could be seen as an "indirect" way in which the EU's role for national health systems is growing.

www.emaud.org

EMAUD News

The Annual Market Access Day has experienced an increasing success for the past five years since its launch. The EMAUD team is assessing a possible new format of the event. More to come shortly!

EMAUD Alumni

Students: Connect on Linkedin!

The EMAUD Alumni group is intended as a debating and networking platform for the students and contributors of our educational programme. Be aware of latest news, articles, regulations, job or event opportunities via discussions and connections.

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