EMAUD
European Market Access University Diploma

Market Access Newsletter

Editorial

by Prof. Mondher Toumi
EMAUD Chairman

Dear Colleagues & Friends,

The 3rd Annual Market Access Day was held last December and allowed to have an overview regarding the latest deep changes in the field of market access. It was a privilege to listen to contributors from European pricing and HTA agencies who are key leaders in market access and who are daily involved in the decision making process and its set up. We could evaluate how much they are constantly torn between obtaining drugs or products at the best conditions for patients, and the regular budget constraints within a worldwide economic crisis. The event was also the occasion to measure how HTA agencies and EMA have expanded their collaboration in a context of European willingness to liaise, coordinate and maintain transparency of assessment.

Our goal is to maintain innovative thinking in our annual meeting, so that it is not "just" another meeting, but one of these occasions where we can share freely perspectives and even sometimes go beyond what has been set up so far.

The special issue of the EMAUD newsletter will give you the key points of what was said during the day.

Market Access: the new rules of the game - Is there a plan and who should have one?

For a long period of time, patients have not been at the centre of market access decisions, except for cases where "emotional" considerations were the focus. The IQWIG in Germany is the first organization to take into account the patients' point of view, through a scientific process; discrete choice experiment .

There is no easy answer to the complex question on how to maximize health production in a society with limited investment in healthcare, and under budgetary constraints. There is an important need in controlling the health expenditures, which continue to increase (with variations between the countries). Each country has a different culture and does not see the value of medicines in the same manner.

The Value Based Pricing (VBP) paradigm is a business with value to the customer's appreciation/perception of the product. A better product should deserve a better price. The question is: how to measure value, how to quantify the willingness to pay for an extra unit of benefit? VBP is the perception of the payer, which can be distorted by various issues therefore payers rely on HTA organization to assess value through evidence based methods. Those who developed Evidence based-pricing (EBP) wanted to use it to save money, but in fact it is the opposite. Indeed, EBP does not consider the cheapest, but rather the best way to treat people, which is usually the most costly. VBP is not exempt of risks and is not a long-term solution. By paying a higher price for a better benefit, it will not prevent prices from increase as more effective drugs will be launched overtime. Should VBP remains in force, sustainability of EU national health insurances will be challenged. French authorities aim at a maximum (ceiling) price thought to be €50,000. The question is: what is the appropriate and reasonable level of health expenditure, and how to prioritize? Incremental cost effectiveness ratio does not seem to be the appropriate way to do it, although it is one element to consider.

Market Access Agreements are temporary wrong solutions, to a real issue: affordability.

The EMA is responsible for delivering regulatory approval. Payers should not interfere and disturb these requirements. It is dangerous to mix payers' expectations and regulatory requirements. There is not an EU vision on how to control health expenditures yet, except the "cut prices"; therefore new products will face challenges when being launched in the future.

Psychological and sociological determinants in the resistance to change of health authorities

Prof. Bruno Falissard
Paris Sud University, Director INSERM U669 - France

Research and mainly Development cost too much. The interest of these activities seems debatable now because they are done in different countries and induce difficulties for interpretation. Furthermore, the payers ask for new data very often. These new data required and the initiation of the RCTs cost a lot.

The system of evaluation of medications is homeostatic, and continues to go forward in "freewheel". There is a lot of resistance to changes: psychological, sociological and technological. The system succeeds in resisting. One explanation of the resistance is that people (the Academy, the Industry, Health Authorities) are happy as it is; they are comfortable with current 'rules', they have all an interest in these rules. It is in the human nature to resist to changes. Also, RCTs seem to be the totem: nobody wants to change it and everybody follows this model whereas observational studies seem more appropriate. There is no scientific evidence to support that RCTs are really better than observational studies.

The pharmaceutical system is a closed circuit, with no external feedback. Students from the Academy go directly to the Industry or Health Authorities, people in the Industry often become few years later members of the Health Authorities and *vice versa*. Joseph Tainter looked at the collapse of the Roman and Greek societies: when organizations refuse to change, and become too complex to be changed, they collapse. The only external feedback comes from economists, epidemiologists, payers (different payers, heterogenic actors in the system) who ask for new pieces of evidence on the drugs.

The academy and authority employees are supposed to improve the system. But it is not done this way, as there is a conflict of interest and a joint venture between the authorities, the firms and the academies. Energy is necessary to initiate and implement the changes. A possible accelerator to changes could come from the dramatic decrease in the level of reimbursement of new products. If there is no more money the fuel maintaining the system of drug evaluation will collapse.

The pharmaceutical scandals arise only from safety problems, never from topics related to efficacy alone (FDA's initial mission was to guarantee the safety of the products, only lately on the efficacy). Indeed, efficacy is expressed in probabilities, unlike safety.

****** Editorial note: all contributions done at the conference on 16 December 2011 shall prevail. ******

Expert Viewpoint

The French reform: what are the impacts in market access?

Prof. Bruno Falissard
Paris Sud University, Director INSERM U669
Prof. Mondher Toumi
EMAUD Chairman

The new drug regulation is a major shift in practice on behalf of national authorities. From about five years, the SMR has been taking more and more into account the effect size of the drug becoming overlapping with ASMR. In recent years, the levels of ASMR attributed have globally decreased. The ASMR is considered more intuitively than scientifically: indeed, the decision-making is complex, with many elements to look at.

Similar products have not been evaluated in the same way in the last years: for instance, Alzheimer products passed from ASMR II to ASMR V, while SMR moved from important to moderate and then low. There is no clear explanation for that, the process may not be as transparent as it should.

One could ask whether both SMR and ASMR indexes should be merged? The problem in France is that the one who pays, does not participate in the HTA process and the health insurance is resistant to such merger. However, it is likely to happen.

The new bill in France was triggered by the Mediator scandal, the reform has been done in a hurry. The former ministries have been involved in maintaining the Mediator reimbursement, despite the warnings from transparency committees. Obviously the issues in that case were related to ministers and not to agencies as they recommended twice to disreimburse Mediator, while ministers refused. Warnings were issued.

The new elements in the reform are: the AFSSAPS will change name to become ANSM. The Board will include parliament members, a few changes on pharmacovigilance topics as well as changes for ATU (Temporary Use Authorization) will occur. Conflicts of interest will be a key topic and the Sunshine Act will be set up. It has already impacted some working groups at the AFSSAPS who failed to recruit the expected number of experts.

The health insurance budget bill establishes a mandatory health economics assessment for innovative products, mandatory head to head trials for reimbursement; however it is anticipated that the Transparency Committee and the health economics committee will work independently and will reconciliate their view once their assessment is finalised. This might generate duplicate work and difficulties in resolving divergent perspectives.

The benefits have to decrease the budget impact, by improving the patient pathway management. QALYs are allowed, but they will not drive and impact the decision-making (there are still tensions between the TC and the CEPS to define the degree of importance of the QALYs). Both agencies prefer to see ICERs through real world data. It is wise for manufacturers to negotiate with the authorities which clinical design should be taken in priority. Eventually, a new HAS guideline on HEOR has recently been published under the title of: "Methodological Choices for Economic Assessment".
www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf

EU cooperation in Europe

Mr. Jérôme Boehm
Policy Officer, Healthcare systems Health and Consumers
Directorate General, European Commission

The systematic development of methodologies to HTA core models has recently been considered as a major topic in the healthcare systems in order to improve the health of European citizens by providing input to decision making. The importance and the difficulties in the European wide Health Technology Assessment (HTA) development and cooperation are noticeable. The version and objectives of the Commission are to reduce the duplication of HTA work, the diminishing of national hurdles to market access after licensing and to promote the early objective scientific dialogue between HTA bodies and sponsors within the 34 government appointed organisations from the EU Member States. Furthermore the European Commission is supporting the cooperation through sharing information with Member States who have less expertise and with little HTA capacity. Pooled expertise and knowledge will lead to high-quality information and methodological frameworks for HTA, promote good practice in methods and processes and improve the links between decision and HTA. On the other hand the possible synergies have always to meet the regulatory requirements. It should be clear that HTA assessment is just a tool for decision makers at national level and core HTAs are intended to serve as a basis for local HTA reports. The harmonization is not in regards to the local decision but rather to the process and production of HTA's.

HTA production is linked to drug and other health technologies pathway. Therefore stakeholders like patients associations, health professionals, companies or payers would like to be involved in the HTA process. It is obvious that the regulations of HTA assessment should be clear and transparent. Currently HTA assessment only includes assessment and reassessment of health technologies based on real-life data and post market access studies on pharmacovigilance especially concerning safety and efficacy. The most interesting thing would be to get additional information regarding study design and the choice of comparators before starting the phase III of clinical studies.

Expert Viewpoint

The European Network for HTA Joint Action (EUnetHTA) started phase II with new objectives for 2012/2014 such as the development of a general strategy and a business model for sustainable European collaboration on HTA, development of methodologies to HTA core model, and the test of HTA methods and tools with an increased budget for patient associations by stakeholders up to €9.4m with 70% EU support.

The objective of the European Commission market access initiative (where Member States for each EFTA country and stakeholders are on board) is to find common non-regulatory approaches and recommendations for timely and equitable access to medicines after market authorization in Europe. The market access initiative addresses, among other things, contractual agreements in managed entry schemes (MES) for innovative medicines, market access for biosimilars, access to orphan medical products and small markets peculiarities.
EU actors also call for post market access requirements like cross border registration of care for pharmaceuticals and medical devices. There is a need for registry in safety and efficacy studies. Pricing and reimbursement decision should be based on evident and available data. For this overall goal all actors will be needed.

12 months post-AMNOG The early benefit evaluation in Germany: first experience

Dr. Thomas Müller
Head of Pharmaceuticals Department of the G-BA
(Federal Joint Committee)

The process started in the beginning of 2011. All pharmaceuticals with new active ingredients and new combinations of active ingredients, that are made available on the German market for the first time after 1 January 2011, have to show additional benefit against an appropriate comparator previously appointed by the G-BA. Moreover, pharmaceuticals in the existing market, especially those important for care or those competing with pharmaceuticals already assessed within the scope of AMNOG, can also be requested by the G-BA for a benefit assessment. A dossier has to be submitted to the G-BA at launch (new pharmaceuticals) or within 3 months after request (pharmaceuticals in the market). A pharmaceutical company can apply for exemption from submitting a dossier once the costs of the statutory health insurance for the pharmaceutical are expected not to EUR 1 million per year.

A variety of important questions have to be clarified before the dossier is submitted. Indeed, an appropriate comparator is the core of the assessment. The appropriate comparator is defined as the currently accepted therapy in

the German healthcare system against which the benefit of a new pharmaceutical is compared. It is important to know the appropriate comparator for the comparison of therapies, for further investigations after market launch and for the price negotiation with health insurances after the assessment. The fact that the comparison targets the German health care market is perceived as a challenge by the pharmaceutical companies. However, if data are not available at early assessment and direct comparison is not possible, indirect comparison can be made. On the basis of a written request, an advice meeting with the G-BA can take place before the submission of a dossier. About 40 advice were requested by pharmaceutical companies during the first year.

The dossier is assessed by the Institute for Quality and Efficiency in Health Care (IQWiG), a commissioned independent institute. However, the final decision is made by the G-BA. Patient representatives participate in the discussions, but have no voting rights. The impact of patient opinion in the decision making process during discussions on additional benefit with scientists and health care professionals has become prominent.

Ticagrelor, in combination with acetylsalicylic acid (ASA), is the first new drug assessed within the scope of AMNOG. Out of four indications, only one (Ticagrelor + ASA in patients with unstable angina pectoris and acute coronary syndrome without ST-segment elevation) was assessed with significant additional benefit in comparison with clopidogrel + ASA. For a second important indication, Ticagrelor + ASA in patients with ST segment elevation myocardial infarction who had undergone percutaneous coronary intervention (PCI), the G-BA identified two subgroups of patients with non-quantifiable additional benefit in comparison with prasugrel + ASA. This decision is the basis for the price negotiations which occur during the consecutive months. If an agreement cannot be reached, an arbitration board will fix the reimbursement price which will be valid from the 13th month after market launch.

In 2012, the G-BA will assess about 30 new drugs. The G-BA has until now made no decision on the assessment of pharmaceuticals in the existing market, but it seems probable that the G-BA will request dossiers for drugs which are in a direct competition with already assessed drugs, e.g. “gliptines” or “xabanes”.

Expert Viewpoint

Risk sharing in Italy: lessons from experience and what directions for the future?

Prof. Monica Otto
Fellow Researcher, University of Bocconi

The concept of risk sharing represents a new trend of contractual agreement between payers and the pharmaceutical industry in order to assess the value of an innovative drug by demonstrating its effectiveness and efficiency in real life.

Conditional price and reimbursement process in Italy

Following the EMA drug assessment, the main decision for pharmaceuticals is made by AIFA. Both the scientific committee and the cancer sub-committee make a first assessment which will be taken as basis for the pricing and reimbursement decision made by the Price-Reimbursement committee. Risk sharing agreements involve, on one hand, the industry, and, on the other hand, the AIFA cancer subcommittee. Conditional reimbursement agreement and price and reimbursement decisions are made at the same time.

Three types of risk sharing agreements could be developed:

- Cost-sharing for the first treatment cycles / months (in practice, discounts)
- Risk-sharing (50% of the price is reimbursed by the industry for non-responders)
- Payment for performance (100% of the price is reimbursed by the industry for non-responders)

Risk sharing agreements: the Italian experience

Since 2005, sixteen risk sharing agreements have been decided but they are not publically available.
Interestingly, the impact of some agreements has been assessed in terms of savings generated. Presented data were from an Italian region, Veneto (4.8 million inhabitants) giving an estimation of the number of patients and savings. As seen in the table below, the estimated savings ranged from 20.5% to 45.9%. These are the only evaluations of the impact of risk sharing agreements in Italy.

Molecule	Years	Indication	Agreement	Patients	% non responders	Savings
Erlotinib	2007 - 2009	Advanced metastatic NSCLC M+	Cost-sharing	52	51.9%	20.5%
Sorafenib	2007 - 2009	Advanced renal cell carcinoma (II line)	Cost-sharing	30	53.3%	34.6%
		Liver cancer	Payment per result	44	72.7%	45.9%
Sunitinib	2007 - 2009	Advanced a/o metastatic renal cancer	Cost-sharing	39	35.9%	22.1%
Bevacizumab	2005 - 2009	Metastatic colon rectal cancer	Cost-sharing / Risk sharing	144	41.7%	21.5%

It is important to mention that some drug monitoring registry exists in Italy such as the Anti-cancer drugs registry (AIFA, 2006) but other expensive drugs are also included. These databases are used to collect data on drugs usage and patients monitoring but also to identify non responding patients, which represents important information especially in case of drugs under risk sharing agreements. In practice, for cancer drugs, it is the responsibility of the oncologist to include all patients in this register and then to evaluate their response to treatment (responders or non responders) and take into consideration the agreement.

Risk-sharing agreements were recently implemented in Italy and therefore there are still some issues that should be addressed in the future such as:

• Difficulties to detect non responders as inclusion and exclusion criteria are not usually well defined from the beginning.
• Lack of transparency as agreements are not published
Difficulties to manage agreements at the local level. It is not the same authority that defines the agreement and follows up implementation. Some regions have their own health network and decisions where it could be complicated to implement the agreements.
• Another difficulty is the way the agreements are chosen and how to define the best agreement.

Direction for the future

The process should be revised in order to manage better the agreements. The personal insight is not to generalize those agreements to all drugs but should only focus on drugs the outcomes of which are uncertain.

In term of the organisational issue, finding the right balance between the national and the regional/local level involvement is of importance.

Patient-centered benefit-risk assessment using multi-criteria decision analysis

Prof. Maarten IJzerman
Chair Dept. Health Technology & Services Research, University of Twente School of Management and Governance - Netherlands

Many new concepts have emerged with the expanded use of HTAs. One of these new fundamental issues is how HTA can better involve patients in the decision making process. This could be done by involving patients directly in the decision making process. However, patient preferences can also be elicited to inform benefit-risk trade-offs. These patient preferences could be used in HTA by combining drug's related benefits and risks into one weighted aggregate measure (for drug approval), but also for incorporating patients' views in the reimbursement and recommendation decisions.

Quantitative approaches to benefit-risk assessment

Decisions makers always seek for decision thresholds aiming to find the right balance between benefits and risks. However, various endpoints could be used to make an assessment but these data are not equally important and it is generally difficult to weight the impact of each outcome on the final decision. Here, quantitative benefit-risk assessment methods could be helpful even though they are not formally used by regulatory agencies today.

Several recent articles have been published around this topic. A review carried out by the ISPOR risk-benefit working group identified 12 different quantitative risk-benefit assessment methods that could be used to support drug assessments and, hence, guide authorities towards more objective and transparent decision-making. Moreover, in August 2010, the European Medicines Agency published a review about the applicability of current tools and processes for regulatory benefit risk assessment. They concluded that decision analysis, bayesian statistics and Multi-Criteria Decision Analysis (MCDA) are among the most comprehensive approaches for quantitative benefit-risk assessment.

According to the EMA, conjoint analysis or stated preference methods could be used for trading off benefits and risks and thus measure patient preferences. Therefore, MCDA techniques are also suitable for eliciting patient preferences to be used in benefit-risk assessment.

Demonstrate the use of MCDA methods to weigh patient-relevant endpoints

MCDA provides a rigorous and flexible framework for quantifying multiple criteria into a single summary measure. It actually mimics all we do in daily life, which is decision making. MCDA methods employ a decision tree structure where patients and expert are asked to weigh relevant endpoints. It could be represented as a decision matrix with various criteria such as: effectiveness, adverse events and quality of life. There are several weighing techniques for the criteria in the matrix, of which the Analytic Hierarchy Process (AHP) is one specific MCDA approach. In an MCDA it is also possible to incorporate the available clinical evidence (e.g. ORs from systematic reviews) and to compare various drugs to determine which drug would prefer taking into account the weights of benefits and risks obtained from patients, physicians or policy makers.

Some uncertainties could exist with MCDA models, especially with the use of assumption in the value structure that needs to be validated and well established. Uncertainty could also be related to preference heterogeneity, i.e. different preferences among the target population, and the questioned representativeness in case one would use a panel of patients. To deal with these uncertainties, MCDA allows deterministic or probabilistic sensitivity analysis. However, it is recommended to keep this MCDA simple and flexible and do not make it unnecessary complicated which may result in the loss of its relevance for decision makers.

Nowadays, given the number of panel sessions at ISPOR, HTAi and other meetings as well as some publications, it seems that the use of MCDA is emerging. In addition to what EMA has already concluded, both MCDA and Conjoint Analysis are appropriate and can be used to measure patient preferences. So, decision makers should look with more attention to these new methods and think about the most appropriate use in benefit-risk assessment.

Expected impact of the new royal decree on market access and market value of pharmaceuticals in Spain

Prof. Antoni Gilabert
Managing Director of Pharmaceutical Care and Complementary Benefits, Catalan Health Service, Catsalut

Spain is one of the many countries that had been struggling over the past years with sharp increases on the pharmaceutical expenditure. The new Royal Decree-Law 9/2011 ('Improvement of quality and cohesion of the National Health Service (NHS), 19th August 2011') was the latest to come in a row of a certain number of measures adopted to tackle this problem since 2010.

Royal Decree-Law 4/2010 ('Measures for rationalizing pharmaceutical expenditure, 26th March 2010') and Royal Decree-Law 8/2010 ('Extraordinary measures for reducing public deficit, 27th May 2010') were the precursors of the 2011 changes. These two legislations achieved a combined reduction in the pharmaceutical expenditure on prescriptions of 13% between 2009–2011. More specifically, the earlier two recent Royal Decree-Laws resulted in, on average, 20% cuts in generics' prices and 30% reduction of prices of brand products that have been on the market for ten or more years. These reductions were achieved through numerous cost-containment measures. These measures ranged from simple rebates on hospital products and orphan drugs to price cuts on primary care drugs. The criteria used for international price referencing system have changed, too, with the selection of the minimum price among all European prices as a basis of negotiations. Reference pricing calculation system was also changed. A new "minor price" system was introduced, taking into account the lowest price of European Union countries (previously calculated according to the three lowest prices).

The new Royal Decree-Law 9/2011 brought further cost-containment measures. The key measure is the budget cap, that is, the requirement for the Spanish NHS to stay within the limits of the current budget no matter how restrictive it might be. Failure to the above could lead to a new more strict regulation. The new Royal Decree-Law is supposed to save around €2.5 billion which is around 20% of the current pharmaceutical budget. However, no more than around 5% saving can be anticipated.

Royal Decree-Law 9/2011 introduced a number of key economic and policy measures. These measures can be summarized as follows:

- Immediate equation of prices in clusters for the branded products (without the gradual voluntary decrease period of 2 years) was implemented.
- Mandatory INN prescription was implemented. Pharmacists are obliged to dispense the cheapest alternative. Branded description is permitted if there is a medical need or if the branded product is the cheapest available option in the reference group .
- Creation of a cost-effectiveness committee that will be responsible for the production of evaluation reports on the medicines. This committee will answer to the General Direction of Pharmacy and Health products of the Ministry of Health. Experts will be appointed by the Inter-Territorial Council of the National Health System, proposals from the regional governments, and by officials of the Mutual and the Ministry. Rules of organization and operation of this Committee will be established by the Inter-Territorial Council of NHS.
- A 15 percent reduction for all branded products that have been for more than ten years in the market with no generic comparators was also implemented.
- Moving drugs from community pharmacy to hospital (based on health reasons and seriousness of illness)

This new and the previous Royal Decree-Laws aim at enhancing (or saving as highlighted by many stakeholders) the financial sustainability of the Spanish NHS. Nevertheless, one critical prerequisite for the sustainability of the Spanish NHS is the ability of all different stakeholders to look at the broader picture. Expenditure is not necessarily bad if it leads to successful investments. In times where gambling was not an option, health outcomes monitoring (via patient registers) was the key to assess investments. Finally, the efficiency on selecting, harmonizing and evaluating treatments and the willingness to share responsibility with risk-sharing agreements between payers and pharmaceutical industry would be equally important.

Policy recommendations for drug reimbursement systems and for market access of high-risk medical devices

Dr. Raf Mertens
Director, Belgian Health Care Knowledge Centre -Belgium

A summary report and highlights on the Belgian perspective can be found at:

https://kce.fgov.be/publication/report/the-pre-market-clinical-evaluation-of-innovative-high-risk-medical-devices

https://kce.fgov.be/publication/report/drug-reimbursement-systems-international-comparison-and-policy-recommendations-0

EMAUD News

Latest Key Publications

• **Addressing Regional Market Access Hurdles in Decentralized European Countries: An Innovative Segmentation Methodology for Optimal Industry Strategy**
ISPOR Connections, January/February 2012, Vol.18, n°1.

• **Access to Orphan Drugs in Europe: Current and Future Issues**
Expert Review Pharmacoeconomics Outcomes Research 2012; 12(1):23-29.

• **Define Access Agreements**
Pharmaceutical Market Europe

• **Market Access Agreements for Pharmaceuticals in Europe: Diversity of Approaches and Underlying Concepts**
BMC Health Services Research 2011, 11:259.

• **Segmentation of Regional Payers**
International Journal of Medical Marketing, 2011; 11(3) 244-253.

• **Design of Patient Access Schemes in UK is Driven by Health Technology Assessment by NICE**
Applied Health Economics and Health Policy, 2011; 9(4):209-215.

Save the date

The **4th Annual Market Access Day** will be held on **10 December 2012** at *Cité Internationale Universitaire de Paris.*

Students Corner

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 etc. via our discussions and connections.

Course Annoucement
Module 4, April 2012 – Special Schedule
Tuesday 10, 11:00 to Friday 14, 15:00.

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