Biotech partnering: time for a new model

Court rulings alter SPC landscape

The implications of France’s health reforms

Germany tighten regulations on innovative products
Innovation in pharmaceuticals in France has long been subject to price control and cost containment measures. France initiated evaluation of medical benefit by cost containment bodies and mandatory price negotiations in 2004, even as Germany was abandoning the concept of price negotiation. The French system for pricing and reimbursement for innovation has influenced the new German system of Early Benefit Assessment. But while Germany copied part of the French price negotiation, it has not enacted any direct restriction on the volume of sales in its AMNOG reforms (see page 22).

Pharmaceuticals represented around 19% of the budget of health insurance funds in 2009. Total health expenditure in France as a share of GDP was 11.2% in 2008.

Markets are divided between hospital and pharmacy markets and special rules apply to innovative pharmaceuticals in both sectors. In this regard, the 1.3% growth in spending on pharmaceuticals expressed in manufacturer’s price in 2010 was mainly driven by hospital medicines purchases (+6%). At the same time, the manufacturer’s price of reimbursable pharmaceuticals sold in pharmacies increased by 0.5% compared with 2009.

Aims of the reforms
Cost containment measures implemented by the government over the past few years have led to drastic price cuts. New paradigms and healthcare models are emerging and health technology assessments are increasingly taken into consideration. The Debré-Even report following the Mediator controversy – in which the French authorities failed to restrict the use of the anti-diabetic drug and slimming pill, despite its known lethal side-effects – and the consultation process on medicinal products (so-called Assises du Médicament) were the basis for extensive reforms aimed at fostering safety reporting on medicinal products and medical devices. The reforms consist of three key aspects:

- The prevention of conflicts of interests and the transparency of decisions.
- The regulation of off-label use.
- The promotion of better trained and informed health professionals.

The key stakeholders
Before examining the effects of healthcare reform, it is instructive to run through the structure of the main stakeholders.

Among the changes brought by the reforms, which came into force in December 2011, the French Health Products Safety Agency, one of the main institutional stakeholders, responsible for marketing authorisations and vigilance of authorised pharmaceuticals and inspections, has had its name changed to the National Agency for Medicines Safety (ANSM).

In addition to the Healthcare Products Pricing Committee (CEPS), which is in charge of pricing pharmaceuticals and negotiating a Framework Agreement with the pharmaceutical industry in line with ministerial policy, two new institutions were...
created by the healthcare insurance reforms of 2004.

The French National Authority for Health (HAS) is an independent public body, with responsibilities ranging from providing regulatory authorities with the scientific expertise on which to base price setting, to encouraging good practice and the proper use of pharmaceuticals. In this regard, HAS cooperates on a regular basis with its counterparts, the IQWIG in Germany and NICE in the UK.

Within HAS, the Transparency Commission assesses the medical benefit of pharmaceuticals (SMR) and the innovation level by quantifying the improvement of the medical benefit (ASMR) compared to alternative products.

The National Union of Health Insurers (UNCAM), the other institution created in the 2004 reforms, unites the main health insurance funds. UNCAM is also in charge of reimbursement policy and determines the products to be reimbursed and their reimbursement rates.

The 2009 Hospital, Health, Patients and Territories healthcare reform of the Health Regional Agencies (ARS) sought to steer and implement national policies at regional level.

Pharmaceutical companies, which are represented by the pharmaceutical companies’ trade association in France (LEEM), as well as physicians and pharmacists grouped in professional organisations, are also important in the legislative process. For example, LEEM and CEPS together set out the general framework for sales growth pricing and promotion of medicinal products.

**Pricing procedure**

The law stipulates that pharmaceuticals without an ASMR rating or implying no savings on medical treatment costs are not reimbursed by health insurance funds. Their price can be set freely but reimbursement by health insurance funds is prohibited.

The pricing process begins with pharmaceutical companies submitting their applications simultaneously to CEPS and the Transparency Commission. The ex-factory price set by the CEPS is based on the ASMR rating granted by the commission, the expected sales of the product and the prices of pharmaceuticals in other EU member states (informal external reference pricing), as well as the price of possible alternative therapies in France. ASMR ratings are grouped in five main classes:

- **ASMR I** for medicinal products bringing a major therapeutic value.
- **ASMR II** for medicinal products representing a significant improvement in terms of efficacy and/or reduction of adverse effects compared to existing alternatives.
- **ASMR III** for a modest improvement.
- **ASMR IV** for a minimum improvement.
- **ASMR V** for medicinal products without any therapeutic value but still being recommended to be registered on the positive list for reimbursement with a price criterion that does not lead to any non-justified expenses.

The law says new products that cannot show an improvement in medical benefit to patients are not reimbursed by health funds.
After the CEPS has made a decision on price, it formulates a proposal which is then negotiated with the pharmaceutical company. Special timelines exist for products granted an ASMR rating of at least level IV. The ex-factory price is set by a four-year contract between the CEPS and the company.

For innovative pharmaceuticals with an ASMR IV and I to III rating, Article 4 of the CEPS Framework Agreement guarantees that the price will not be lower than in Germany, Italy, Spain and the UK for five years. Medicines granted an extension of indication with an ASMR rating from I to III and paediatric medicines subject to studies based on a paediatric investigation plan benefit from an extension of one year.

**Fast tracking innovation**
A special fast track procedure of notification for innovative pharmaceuticals has been enshrined in law since 2003 to facilitate pricing and reimbursement. Under the Framework Agreement, products with an ASMR I to III and IV rating are considered innovative, with strict conditions. Under this procedure, immediately after the granting of the ASMR, the manufacturer proposes a price that is accepted if the CEPS does not object within two working weeks. Otherwise, the normal application procedure applies.

This price should be in line with the existing price in Italy, Germany, Spain and the UK. However, this procedure applies to a narrow definition of innovative pharmaceuticals. In 2010, two orphan drugs applied for the price notification and both were refused.

The registration of pharmaceuticals on the positive list of reimbursable products is decided by UNCAM, based on the SMR rating. The registration is valid for five years.

Four reimbursement rates – 100%, 65%, 30% and 15% – correspond to SMR ratings. Full reimbursement is granted for pharmaceuticals identified as irreplaceable and for patients having a medical treatment for a disease that is fully reimbursed.

While the final price of products sold in pharmacies includes the fixed margin of the wholesalers and of the pharmacists, as well as a reduced VAT rate of 2.1%, the price set by CEPS also varies due to clawbacks, price review clauses and contractual agreements.

**Clawbacks**
The Framework Agreement provides annual adjustments if sales of pharmaceuticals exceed National Objectives on Healthcare Spending (ONDAM) defined each year in the Social Security Financing Law (LFSS), the so-called ‘safeguard clause’.

Quantitative clawbacks consist of payments per pharmacotherapeutic class grouping and payments based on the turnover of the firm. Specific provisions are provided for innovative pharmaceuticals. Products granted an ASMR I and II rating are exempted from clawback for 36 and 24 months respectively. ASMR III and IV rating have 50% and 25% exemptions, respectively, for 24 months.

Two main price review clause categories exist. The first, ‘daily treatment clauses’, covers situations where time and usage do not confirm the assumptions made when setting the price. The second, ‘volume..."
clauses’, ensures that the volumes of the pharmaceutical sold stay in line with assumptions relating to the established target patient group.

The Contract for the Improvement of Individual Practices (CAPI), introduced in the LFSS 2008 and developed by the UNCAM, is a voluntary incentive scheme that forms part of the framework to monitor physicians’ prescription behaviour.

Hospital pricing

The regulation of hospitals is mainly set out in the LFSS law of 2004 and the framework of the Plan Hôpital 2007. Modalities for the price setting for innovative medicines and hospital outpatient pharmaceuticals were defined in the hospital medicines Framework Agreement, which merged with the general Framework Agreement in September 2008.

The price of hospital medicines is set freely between the hospital and pharmaceutical company. Funding for hospitals and reimbursement for hospital pharmaceuticals is an activity-based payment (T2A) by means of diagnosis related inpatient groups (GHS).

Three main categories of hospital pharmaceuticals exist with a special price and reimbursement framework:

- **Hospital outpatient medicinal products** – Before being delivered to outpatients, hospital pharmaceuticals must be registered on the retrocession list. Pharmaceutical firms must submit the ex-factory price to the CEPS, which may object to this submitted price. Reimbursement of hospital outpatient pharmaceuticals is based on the public final price.
- **Innovative medicines reimbursable on top of the T2A** – With certain innovative pharmaceuticals, especially orphan and paediatric drugs, pharmaceutical firms must declare the price to the CEPS. Full reimbursement is granted on the basis of the public price, provided the hospital legal representative signed a Contract of Fair Usage’ (CBU) with the Health Regional Agencies.
- **Medicines with an authorisation of temporary usage** – Authorisation of Temporary Usage (ATU) is an exceptional and temporary measure granted by the National Agency for Medical Safety for the treatment of serious or rare diseases in the absence of a suitable therapeutic alternative with a marketing authorisation available in France when a positive benefit/risk ratio is assumed. An ATU can be intended for a single, named patient or it can concern a group of patients, treated and monitored according to a protocol for therapeutic use and information collection (cohort ATU).

In both cases, the maximum price of pharmaceuticals with an ATU must be submitted by the pharmaceutical company to the CEPS, which makes these declarations public. For medicines with an ATU that are intended for hospital use only, hospitals receive compensation through special endowments. Products with an ATU that are sold to outpatients are fully reimbursed on the basis of their final price.

**Benefit assessment**

The SMR rating is used to determine reimbursement level. This takes into account the efficacy of the product, its side-effects,
EU member states must not adopt a fragmented approach on the relative effectiveness of pharmaceuticals but ensure that innovation is properly and consistently taken into account.

References
1 Under § 35a SGB V and for the new mandatory price negotiation for all innovative pharmaceuticals under paragraph 130b of the Sozialgesetzbuch V (SGB V)
2 CNAMTS (Caisse Nationale d’Assurance Maladie des Travailleurs Salarie), Data 2009
3 OECD (2010), Health at a Glance: Europe 2010
4 Comité Economique des Produits de Santé Annual Report 2010, July 2011
5 Rapport de la mission sur la refonte du système français de contrôle de l’efficacité et de la sécurité des médicaments
6 Article 7c) of the Framework Agreement, providing that pharmaceuticals with an ASMR IV rating are eligible for this fast-track procedure under two additional conditions: that a comparative pharmaceutical exists and that the price notified is lower than or equal to the price of the comparative product; and that the pharmaceutical does not replace a generic product or a product that is going to be made generic.
7 See decision of UNCAM regarding the creation of a standard contract aiming to improve the practices of contracted physicians, 9 March, 2009
8 In December 2010, around 15,000 physicians signed a CAPI. Modifications of the scheme were brought by the Article 39 in the LFSS 2010.
9 See LFSS 2004.
10 Patients are classified by a Groupe Homogène de Malades (GHM). Each GHM is associated with a Groupe Homogène de Séjour (GHS) which is the basis of the reimbursement for hospitals. Further information on the Health Ministry website.
11 See Decree 2004-546 of 15 June 2004, Article L5126-4 of the Social Security Code regarding the inscription on the retrocession list, and Articles R5126-102 to R5126-110 of the Public Health Code regarding the provisions applying to hospital ambulatory medicines
13 The RTU shall contain information concerning the efficacy, the actual conditions of use and the adverse effects under conditions to be specified by a future decree.
14 Medicinal products with restricted medical prescription are mentioned in Article R.5121-77 of the Public Health Code.
17 See § 35a SGB V and for the new mandatory price negotiation for all innovative pharmaceuticals under paragraph 130b of the Sozialgesetzbuch V (SGB V).
the publication of the Debré-Even report, the starting point for extensive safety-based reforms, has had an impact on the price and reimbursement framework of innovative medicines in France.

**Impact on the ATU system**

With regard to the ATU system, the healthcare reforms now stipulate that an ATU application be accompanied by a simultaneous demand for a marketing authorisation, or by an application for a cohort ATU, or by clinical studies with the medicine for the same indication in France. ATUs are granted for a limited period but can be renewed.

Exemptions from these requirements are possible, particularly in cases where, under the current state of the therapeutic options available, serious consequences for the patients are highly likely, or where the medicinal product is no longer marketed for a specific indication and there is a strong presumption that the product is efficient and safe for a different indication.

The healthcare reforms also introduce mandatory systematic monitoring of patients with regard to tolerance and efficacy of the product.

**Off-label use**

The reforms strengthen regulation of off-label use, which should be subject to the approval of the health authorities. Off-label prescription is authorised in the absence of other alternatives, which means no marketing authorisation or ATU available, under the conditions that either a Recommendation of Temporary Usage (RTU) for a period of no more than three years has been granted by the ANSM for the indications or the conditions of clinical use, or where the prescriber judges it indispensable to improve or stabilise a patient’s condition. Modalities for the RTU will be set later by decree.

The reforms also provide for monitoring patients, a mandatory application for an extension of indications or a modification of the marketing authorisation in a given timeline, and an obligatory statement of off-label use on the prescription.

For reimbursement of off-label medicinal products, when no appropriate alternative is available, products used for the treatment of a chronic or orphan disease subject to a RTU are, by way of exception, reimbursed for a limited time.

**Visits by pharmaceutical reps**

The reforms set limits on visits by pharmaceutical representatives to hospitals. For a trial period of no longer than two years, collective visits by reps to hospitals are allowed only if they are meeting several healthcare professionals. The conditions should be laid down by a convention signed between each healthcare facility and each pharmaceutical firm. Practical modalities for this will be set by a decree from the Health Minister after a favourable opinion from HAS, which should be issued before August 2012.

Exceptions are provided for restricted medical prescription (hospital-only medicines, hospital prescription medicines, medicines with initial hospital prescription or not) and for medical devices.
Financial penalties for non-compliance are expected. The pricing committee can decide to set annual numerical targets for the adoption of those practices, if necessary by drug classification or for certain pharmaceuticals.

Depending on the outcome of an assessment report expected in January 2013 at the latest, the system of limited visits by reps may be extended to the field of outpatient medicines.

**Evaluation of innovation**

It is important that EU member states do not adopt a fragmented approach on the relative effectiveness of pharmaceuticals but ensure that innovation is properly and consistently taken into account when establishing the value of products.

Risk sharing arrangements between the healthcare system and pharmaceutical companies are emerging and can help promote the competitiveness of the companies, while containing costs for national budgets.

The new paradigms redefine the role of the different stakeholders, create new stakeholders and aim to standardise medical practice. However, policy on price and reimbursement should stay consistent and reliable so that pharmaceutical companies can have the confidence to make decisions on strategy in relation to R&D and capital investment.16

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