FRAMEWORK AGREEMENT OF 25 SEPTEMBER 2008 BETWEEN THE COMITE ECONOMIQUE DES PRODUITS DE SANTE AND THE PHARMACEUTICAL COMPANIES (as amended by the riders of 26 October 2009 and 7 October 2010)

Having regard to European Union Law, the Social Security Code (*Code de la sécurité sociale*) and national ministerial policy;

Whereas Article L. 162-17-4 of the Social Security Code provides that an agreement may be drawn up setting forth the contractual framework for relations between the Comité économique des produits de santé **(**CEPS – the Healthcare products pricing committee) and each of the companies producing the medicines described in Article L. 162-16-4 of the code;

Whereas, subject to the provisions of the Public Procurement Code, Article L. 162-16-5 of the Social Security Code provides that, with regard to pharmaceutical products which have been granted marketing authorisation and are registered on the list provided in Article L. 5126-4 of the Public Health Code, an agreement should be made setting forth the procedure and conditions governing manufacturers' price submissions, the criteria for opposition by the committee, the conditions under which the declared selling prices may be reviewed and the undertakings to be made by the company;

Whereas Article L. 162-16-6 of the Social Security Code provides that, with regard to the pharmaceutical products mentioned in Article L. 162-22-7 of the same code, an agreement should be made setting forth the procedure and conditions governing manufacturers' price submissions, the criteria for opposition by the committee, the conditions under which the declared selling prices may be revised and the undertakings to be made by the company;

Whereas it is fitting that medicines should be given their rightful place in prevention and healthcare and that this requires both rapid access to innovative medicines, improved efficiency and rationalisation of expenditure on medicines and sustained efforts to avoid excessive consumption and promote responsible usage;

Whereas medicines can be both a source of improvement in quality of care and a source of economies for the public purse when used solely for proven medical purposes, within a competitive market in which generic medicines and self-medication are free to play their part;

Whereas advances in treatments, the demographic situation, epidemiological data and the government's public health plans must be taken into account when appraising growth in the consumption of medicines;

Having regard to the benefits of maintaining and developing a strong, competitive pharmaceutical industry and of protecting intellectual property, trademarks and registration data within European Union territory, as reaffirmed in the work done by the G10;

Whereas the majority of spending on medicines is financed out of the public purse, whose resources are finite by nature, and whereas it is therefore fitting that there should be regulation in place which is proportionate to the contribution made by medicines, in accordance with the law and ministerial policy and under fair, transparent conditions;

Whereas the most desirable means of achieving the goals set forth hereabove is through strengthened cooperation between the public bodies and the pharmaceutical companies;

The Healthcare products pricing committee (CEPS) and the pharmaceutical companies now agree to take their relationship forward within the contractual framework set forth herebelow.

CHAPTER I: EXCHANGING INFORMATION AND MONITORING SPENDING COVERED BY NATIONAL HEALTH INSURANCE

Article 1: Exchanging information

For the sake of transparency, the parties agree on the necessity to improve and share the information they each hold regarding consumption and prescription of reimbursable medicines and the actual reimbursements paid out for medicines.

The representatives of LEEM[1] will facilitate access by members of CEPS, via electronic means in particular, to the commercial information which the companies have available.

They will continue to send the committee, both in hard copy and electronic format, commercial data, of which the companies shall retain ownership, including but not restricted to the statistics produced by the industry's statistics gathering association GERS[2] regarding sales to both community pharmacies and healthcare establishments. Furthermore, to enable CEPS to make the necessary forecasts, at the end of each quarter the committee shall be sent information on the quarterly declarations of sales by quantity (number of common dispensing units) and by value (turnover ex VAT per common dispensing unit) to healthcare establishments which the companies governed by this agreement undertake to make to GERS, in accordance with the agreement signed between GERS and CEPS. The quarterly sales declarations shall be made with regard to both medicines covered by pre-market approvals and medicines that already have marketing authorisation, including orphan medicines, and shall cover all companies whether or not they are members of GERS.

The companies undertake to send to CEPS upon request the information available to them regarding real-life use of the products for the various indications stated in their marketing authorisations. For medicines that have been granted pre-market approval (whether in the context of a cohort programme or a named patient programme, before the file is examined the companies shall send a summary and analysis of the data from the study and information gathering protocol to both the Transparency Commission and CEPS, to provide them with a body of information, in particular on how the product should be used and the nature of the population receiving the treatment.

The companies also undertake to allow the committee access to information regarding current prices in force in other EU countries and the reimbursement situation and sales volumes in these countries.

CEPS and national health insurance (*l'assurance maladie*) shall make available to LEEM detailed information regarding the reimbursements paid out by national health insurance and reports of studies conducted into the prescription and consumption of medicines, under the same conditions in which they are made available to the professional healthcare associations, in particular studies regarding statistics derived from the coding of medicines claimed back from national health insurance by the healthcare establishments, as soon as these statistics are available.

CEPS shall inform LEEM every year of its forecasts regarding growth in sales of reimbursable medicines and its forecasts regarding implementation of the end-of-year adjustments under the terms of Articles 17 and 18 herebelow.

CEPS and LEEM agree to set up a joint monitoring group which will be responsible for overseeing the implementation of this framework agreement.

A Generics Monitoring Group shall also be formed, which shall be made up of members of CEPS and representatives of companies operating in the generics market: pharmaceutical companies, wholesaler-

[1] LEEM = Les Entreprises du Médicament: the pharmaceutical companies' trade association in France.
[2] GERS = Groupement pour l'Élaboration et la Réalisation de Statistiques - an economic interest group of pharmaceutical companies which produces market statistics.

distributors and community pharmacists. LEEM shall ensure that companies selling generic drugs are specifically represented among the pharmaceutical industry representatives. The group shall meet to discuss the matters set out in Article 13 herebelow among others.

Article 2: Monitoring spending covered by national health insurance

The parties agree to monitor spending on medicines every three months in consultation with each other, in particular regarding the information mentioned in Article L.162-17-3, paragraph II of the Social Security Code (*Code de la sécurité sociale*). This consultation shall be organised within the framework of the above-mentioned joint monitoring group set up under Article 1 hereabove. The parties shall consult on all medicines covered by compulsory national health insurance, both those distributed to community pharmacies and those included on the lists set out under Articles L. 162-16-5 and L. 162-16-6 of the Social Security Code.

Article 3: Intellectual property

Companies selling pharmaceutical products to which they hold one or more patent or supplementary protection certificate (SCP) may declare these to the committee along with the respective expiry dates. The committee shall make such declarations accessible to any pharmaceutical company that requests access to them.

Details of the registration of any generic pharmaceutical product on the national health insurance reimbursable medicines lists and where applicable the public hospital approved medicines list shall not be published more than six months before the declared expiry date of the intellectual property rights concerned, where the committee has been notified of such date.

However, any pharmaceutical company which believes that it is able to sell the generic products in question without infringing the declared rights may apply for their product to be registered on the appropriate lists. In this event, the pharmaceutical company must inform the committee, which in turn shall promptly inform the company selling the original medicine as mentioned in the first paragraph hereabove and shall then begin the registration procedure.

Article 3a: Early transfer of rights

The owner of the intellectual property rights to a reference proprietary product may, subject to the provisions of the Intellectual Property Code (*Code de la propriété intellectuelle*), assign the following rights before they have expired to a duly authorised pharmaceutical establishment acting in the capacity of sub-contractor under the terms of Chapter 7 of the Good Manufacturing Practices stipulated in Article L.5121-5 of the Public Health Code (*Code de la santé publique*):

- The right to purchase sufficient quantities of raw materials and generally speaking to carry out any activities that are necessary and essential for the manufacturing process described in the following paragraph:
- To manufacture a generic version, as defined in Article L.5121-1, paragraph 5 of the Public Health Code, of the proprietary product in question, on behalf of a pharmaceutical establishment authorised to use the marketing authorisation for the corresponding generic drug;
- To release batches of the generic product thus manufactured 48 hours before the expiry of the intellectual property rights, for the sole purpose of preparing stocks of the product and to the exclusion of any other act, carried out alone or jointly with the pharmaceutical establishment marketing the generic product, which might lead to the sale or delivery of the generic drug. These batches released at this time may not be delivered until after the expiry of the intellectual property rights pertaining to the original proprietary product. The sub-contractor shall guarantee to the owner of the intellectual property rights to the original proprietary product that the pharmaceutical establishment marketing the generic product will refrain from any actions pertaining to sale or delivery as stipulated above.

The authorisations granted by the intellectual property right owners pursuant to this article shall give rise to clawback credits, the sum of which shall be set, depending on the scope of the authorisations, by mutual agreement between the company and CEPS.

CHAPTER II: MEDICINES SOLD TO COMMUNITY PHARMACIES - AGREEMENTS BETWEEN CEPS AND PHARMACEUTICAL COMPANIES

Article 4: The contractual framework

Any company which sells medicines covered by mandatory national health insurance, provided the company is certified pursuant to Article L.162-17-4 of the Social Security Code, shall be offered the opportunity to enter into a multiannual agreement with the Healthcare products pricing committee (CEPS).

The agreements shall be drawn up with a view to ensuring that this framework agreement is implemented, whilst taking into account each company's individual situation and future development prospects and working within the rules set forth in the Social Security Code and the policy guidelines passed on to the committee each year by the relevant ministers.

Within this framework and save for any exceptions warranted by any specific aspect of the French market, for medicines given an ASMR rating of I to III, these agreements shall guarantee that the price set will be no lower than the lowest price in force in the 4 main comparable EU markets mentioned in Article 7 herebelow, for a period of five years starting from the date the medicines become available to patients by virtue of their registration on the community or hospital reimbursable medicines list. This guarantee also applies to medicines which have been given an ASMR price rating of IV in relation to medicines recently rated at ASMR levels I to III, where the Transparency Commission's opinion indicates that this rating is more beneficial to them than a rating which would have placed them at the same ASMR level as these reference products. An extra year shall be added to this guarantee for the paediatric medicines listed in Article 10 herebelow for which studies have been conducted in implementation of the paediatric investigation plan arranged with the AFSSAPS council. In the event that the Pound should fall strongly against the Euro within a short space of time, this shall not be allowed to have any short- or medium-term impact on the French equivalent of the new sale price in Euros of medicines sold in the United Kingdom, in respect of medicines whose prices were set prior to this depreciation

The companies shall inform CEPS should any significant price changes occur in these EU markets.

For medicines which have been under provisional authorisation (ATU), the companies undertake to take the necessary steps to adhere to the deadlines set by AFSSAPS for bringing the medicines into line with the terms of their marketing authorisations and to submit their applications for registration under their new marketing authorisations on the public hospital approved medicines list and/or the national health insurance reimbursable medicines list, no later than 30 days after receiving notification of the MA decision or specific national conditions. Failure to do so shall lead to the period of their European level price guarantee being reduced by a period equivalent to the length of the delay.

When a product covered by a European level price guarantee is approved for extended indications which are rated at ASMR IV or V and concern a significantly larger patient group than the group covered by the ASMR rating which initially warranted the guarantee, the initial period of the European level price guarantee may be shortened.

When a product covered by a European price level guarantee is approved for extended indications rated at ASMR I to III, the initial period of the guarantee may be extended for up to one year, provided that the new indication(s) concern a sufficiently large patient group in relation to the group covered by the existing indications.

When a “quantity clause” is inserted at the time the sale price, official rate or outpatient prescription fee is set, relating to the medicine’s target population or to the indication for which the medicine was given an ASMR rating, including medicines mentioned in Article 10 a), the clause may be revised in the light of new information emerging from the post-marketing studies required by the health regulatory bodies, including

relevant epidemiological data and other data that could lead to revising the target population, after the Transparency Commission has been consulted on the matter and a dossier including a summary of the updated pharmacovigilance data has been studied.

Article 5: Format and content of the multiannual agreements.

The agreements must adhere to the pro-forma agreement attached in Appendix 2. They are made up of three parts:

Part one summarises the prices of medicines which the company sells and which are registered on the national health insurance reimbursable medicines list and the special conditions attached to them where applicable, in the form of a price table and a schedule of conditions. It also includes for information purposes a list of the company's proprietary products that are registered on one or other of the lists provided in Articles L. 162-16-5 and L. 162-16-6 of the Social Security Code (*Code de la sécurité sociale*), together with their published outpatient prescription prices or official rates and decisions made by CEPS under Article L. 162-22-7-1of the Social Security Code where applicable or any undertakings made, especially those made under Article 8 c) herebelow.

Part two contains, pursuant to Article L. 162-17-4 of the Social Security Code, the company's undertakings with regard to controlling its marketing policy and ensuring responsible use of the medicine, and any conditions setting forth the company's contribution to achieving the objectives described in Chapter IV herebelow and implementing government policy.

Part three establishes the company's acceptance of the provisions of this framework agreement, in particular those stipulated in Articles 17 and 18 herebelow where applicable, under the conditions provided in said Articles.

Companies which decide not to take advantage of the financial regulation mechanism described in Articles 17 and 18 herebelow, or for whom the mechanism is cancelled either the company itself or by the committee, may nonetheless enter into or maintain an agreement with the committee under the terms of Article L. 162-17-4, however the agreement will not exempt the company from the contributions provided in Article L. 138-10.

The agreements may be supplemented by contract riders. Parts one and two shall be renewed each year during the first six months of the calendar year. Part three shall be renewed before 31 December each year.

Article 6: General measures to promote new medicines

a) Pre-application procedure for medicines with centralised marketing authorisations

Subject to any subsequent decision by the European Commission, any pharmaceutical company whose product marketing authorisation dossier has received a favourable opinion from the human medicines committee of the European Medicines Agency may immediately submit a pre-application dossier to CEPS, the Transparency Commission and the ministers responsible for registration, to allow them to examine in advance the issues involved in registering the new product as a reimbursable medicine and to shorten the registration process. This procedure does not exempt the company from the official procedure governing the submission of applications for registration of a product on the reimbursable medicines list and price setting, in accordance with the procedures outlined in Article R. 163-8 of the Social Security Code. Once the official application has been submitted, the committee shall appoint a rapporteur to begin processing any elements of the application which do not require the Transparency Commission's opinion.

b) Special processing times for medicines which have been given an ASMR rating

The parties agree upon the benefit of shortening the usual statutory 180-day listing procedure in the case of medicines which represent an advance in treatment.

For all medicines with an ASMR rating of at least IV but which nonetheless would not fall within the scope of Article 7 herebelow, the committee undertakes to write to the company within 75 days after the date on which the Transparency Commission delivers its final opinion, proposing a draft agreement, or failing this to set out the reasons why it has not yet been able to formulate a proposal.

This same procedure shall be implemented for paediatric medicines which address the list of paediatric needs sent to LEEM by the committee.

c) Statutory processing times

For all proprietary products, CEPS shall ensure that the statutory processing time of 180 days is adhered to, among other ways by keeping track of the intervals before publication of the undertakings which the committee signs.

d) Evaluation

The procedure and the undertaking stated in the above paragraphs shall be subject to a joint annual evaluation by LEEM and CEPS.

Article 7: Fast-track registration for innovative medicines: price submission

The fast-track registration procedure provided in Article L.162-17-6 of the Social Security Code for certain medicines which have been recognised as making an innovative contribution shall be applied under the following terms and conditions:

a) Description of the procedure

No earlier than the day after and no later than one month after it has received the Transparency Commission's final opinion, a company which meets the conditions mentioned in paragraph b) herebelow may apply for a fast-track price-listing procedure for proprietary products which meet the conditions mentioned in paragraph c) herebelow. This application must adhere to the pro-forma sample attached in Appendix 1 and must contain the undertakings stipulated in paragraph d) herebelow. If after two clear weeks following the week in which the committee received the company's application the committee has not informed the company of its opposition to the application under the terms set forth in paragraph e) herebelow, the application shall be deemed to have been accepted. The agreement shall then be signed within 48 hours and the price decree and notice shall be published in the *Journal Officiel* (the official gazette of the French government) at the earliest possible opportunity. No negotiation shall be entered into with the company regarding the application. In the event of opposition by the committee, the price shall be set according to due process.

The first two working weeks of August and the last week of the year shall not be taken into account when calculating processing times. Furthermore, no price submissions may be made during these periods.

b) Companies concerned

This procedure is open to any company which has a multiannual agreement with CEPS, pursuant to the terms of Article L.162-17-4 of the Social Security Code.

c) Medicines concerned

Proprietary products which the Transparency Commission has rated at ASMR level I to III, provided that these ASMR levels are applicable to the main indications specified in the products' marketing authorisations.
Proprietary products which the Transparency Commission has rated at ASMR level IV, subject to the following additional conditions:

1) There must be a reference medicine and the daily treatment cost of the new medicine, based on the submitted price, must be equal to or lower than that of the reference medicine. CEPS reserves the right

however to accept price submissions for products where the daily treatment cost would be higher than that of the reference medicine if the applications can demonstrate that the additional cost is outweighed or exceeded by savings on other items of national health insurance expenditure.

2) The medicine must not be not intended to replace a medicine which has been genericised or is soon to be open to genericisation.

d) Undertakings to be made by the companies

- Regarding prices: the company undertakes to submit a price which is consistent with the approved prices in the following countries: Germany, Spain, Italy, and United Kingdom. In the event that the prices in force in one or more of these countries should alter this price consistency at a later date, the company also undertakes to re-establish consistency by accepting a contractual change to the original price.

- Regarding sales volumes: in the event that its sales volumes exceed the volumes in the mandatory forecast for the first four years as stated in the price submission application, the company undertakes to compensate by means of clawback payments for any additional costs to national health insurance which are not justified by public health decisions made later by public bodies.

- Regarding studies which the company may be requested to carry out in application of Article 11 herebelow.

- The company undertakes, subject to general or specific obligations of information governing pharmaceutical companies, to inform both CEPS and the Transparency Commission of any new scientific information which comes to light and which may affect the cost-benefit ratio as assessed during the Transparency Commission's evaluation. Where the company is aware of any such information prior to the deadline for receipt of the committee's opposition, it shall waive the right to the fast-track procedure.

In addition to the above-stated mandatory undertakings, the company may make other undertakings (regarding posology, daily treatment cost, consultations, etc.) which in the light of the characteristics of the product in question it feels will make its application more favourable to the committee.

The company shall have the opportunity to present its case to the committee prior to entering into the contractual obligations.

e) Conditions governing the committee's right to opposition

The committee must present its opposition in writing, providing valid grounds for the opposition. It may oppose an application on the following grounds:

- Due to explicit public health considerations

- If the level of the proposed price is excessive in relation to the prices in force in the four above-mentioned EU Member States.

- If the sales forecasts are inconsistent with the size of the patient group identified by the Transparency Commission.

- Due to obvious inadequacy of the undertakings made by the company.

- If the company has breached any of its undertakings made during a previous application.

- With regard to ASMR IV-rated medicines, where the special conditions regarding these medicines are not met or simply where the product represents additional costs in relation to the reference product.

CHAPTER III: MEDICINES PURCHASED BY HOSPITALS

Article 8: Implementation of Articles L 162-16-5 and L 162-16-6 of the Social Security Code

a) Common procedure

For the purposes of Articles L. 162-16-5 and L. 162-16-6 of the Social Security Code, outpatient prescription fees for the products included on the list provided in Article L.5126-4 of the Public Health Code and "accountability tariffs" (*tarifs de responsabilité*) for products included on the list provided in Article L. 162-22-7 of the Social Security Code shall be determined on the basis of the common procedure outlined in Articles b) to e) herebelow, subject to any specific conditions detailed in these Articles where applicable.

b) Conducting the procedure

Price submissions formulated according to the terms of paragraph c) herebelow should be handed to the committee in return for proof of receipt or sent by registered post within one week after details of the product's inclusion on one of the lists mentioned in paragraph a) hereabove have been published in the *Journal Officiel*, or in the case of products registered on the list provided in Article L. 5126-4 of the Public Health Code before receiving marketing authorisation, within ten days following receipt of the marketing authorisation decision.

The committee may find the submission inadmissible or may oppose the submitted price under the terms stipulated in Article d) herebelow, within two weeks following receipt of the submission. In the event of inadmissibility or opposition, the company shall be given two weeks starting from the date of receipt of the committee's decision within which to draw up a new submission or to amend its initial submission. The committee shall then have ten days within which to find the submission still inadmissible or to oppose the price submitted. In this instance, the committee's decision regarding inadmissibility or opposition shall be final, pursuant to the above-mentioned Articles of the Social Security Code. If after the committee presents its initial opposition the company does not draw up a new declaration or amend its initial declaration within the above-mentioned two-week time limit, the committee's opposition shall be final.

If the committee does not find the submission inadmissible or oppose the submission within the time limits mentioned in the previous paragraph, the committee shall publish the prescription fee or "accountability tariff" in accordance with the price submitted at the earliest possible opportunity.

In the event that the company does not adhere to the time limit for submission stipulated in the first paragraph hereabove, the committee may announce its opposition to the price at its own convenience, provided that it adheres to the overall seventy-five day statutory time limit for the procedure. If the committee does oppose the price, the time which the company shall have to draw up a new submission or amend its initial submission shall be reduced by a length of time equivalent to the initial delay. If this delay is more than ten days, any opposition by the committee shall be final.

In the event of final opposition, or if the company has not drawn up an admissible submission within thirty days after the start of the time limits stipulated in the first paragraph hereabove, the committee shall set the prescription fee or accountability tariff unilaterally.

c) Content of company price submissions

For each product included in the price submission, the company's submission must contain the following, failing which the submission shall be inadmissible:

- The proposed selling price to healthcare establishments per pack type.

- The current prices in force in the main EU Member States and the product's reimbursement status in these states, plus for products which have been on sale for more than one year, the annual sales volumes recorded in these states.

- Where applicable, up to three years' worth of data on the prices at which the products have been sold to French healthcare establishments.

- The Transparency Commission's opinion or opinions, where such opinions have already been delivered.

- An estimated sales forecast for the next three years.

- An undertaking to inform CEPS each year of the prices in force and volumes sold in the main EU Member States, as well as any alterations to the product's official reimbursement status.

Depending on the particular nature of the products in question, price submissions may also contain undertakings by the company, in particular regarding implementation of Article L. 162-18 of the Social Security Code or the conduct of follow-up studies on the products.

d) Criteria for opposition by the committee

The committee must provide explicit, clear grounds for its opposition.

It may oppose the proposed price on the grounds that it is exceptionally high in relation to the prices in force in the main EU Member States, or in relation to prices in force in the French market where directly comparable products are already being sold on the French market.

It may also oppose the price due to the inadequacy of any undertakings made by the company, in particular, in cases where the proposed price is only justified for some of the indications included in the marketing authorisation, if there is a clear risk that the quantities sold will incur exceptionally high national health insurance spending or if, given the current market, the product's inclusion on one of the lists could lead to sales volumes giving rise to volume discounts on the company's proposed price.

e) Reviewing tariffs and prices

Prices and tariffs may be reviewed either at the company's or the committee's request, in particular when a change occurs to any of the factors on which the existing price or tariff and the parties' undertakings were based; or when new information emerges in France or the European Union, especially regarding the product's evaluation or current prices, or when the product's price is closely linked with variable costs, especially those connected with product safety requirements.

Article 9: Quantity Clauses

When the committee intends to apply the terms of Article L. 162-22-7-1 of the Social Security Code to a drug included on the list provided under Article L 162-16-6 or it is considering inserting a “quantity clause” for a medicine included on the list provided under Article L. 162-16-5, which would include provisions on clawback payments or price reductions, the committee shall inform the company selling the medicine of its intention; however the publication of the official rate or the outpatient prescription price shall not be delayed until this process has been completed.

The committee shall make every effort to reach an understanding with the company and to formally set out this understanding in a rider to its agreement with the company.

If no agreement is reached, once the company has been given the opportunity to present its comments, the committee shall notify the company of its decision under Article L. 162-22-7-1 or if applicable of the conditions under which it will announce that it is requesting a price reduction in the light of the quantities that have been sold.

Article 9a: Implementation of Article L. 162-16-5-1 of the Social Security Code

The declarations regarding the maximum prices chargeable to healthcare establishments, which the companies are obliged to make under the terms of Article L. 162-16-5-1 of the Social Security Code, must be

sent to CEPS within month after the drug has been given provisional authorisation (ATU) by the AFSSAPS Chief Executive.

These prices shall be published on the CEPS website.

If any clawback payment is owing by virtue of the price or tariff published after the drug has obtained marketing authorisation, this payment shall be determined at the time the price or tariff is set. The payment shall take into account the sums actually charged to the healthcare establishments and any quantities which were supplied free of charge.

CHAPTER IV: IMPROVING THE COST-EFFECTIVENESS OF SPENDING ON MEDICINES

Section I: Novel drugs, orphan drugs and paediatric drugs

Article 10: Special advantages for novel drugs, orphan drugs and paediatric drugs

In the context of agreements with CEPS, novel drugs, orphan drugs and paediatric drugs shall benefit from the provisions of Article 18 herebelow, in particular concerning provisional, full or partial exemption from clawback payments per pharmacotherapeutic class grouping.

The parties wish to promote the orphan drugs market in connection with the EU's incentive policy as expressed in regulation (EC) no 141/2000 of the European Parliament and of the Council of 16 December 1999.

The parties also wish to promote steps to bring paediatric drugs onto the market, in line with the EU regulation.

CEPS shall forward to LEEM the list of paediatric needs drawn up by AFSSAPS: new paediatric products or approval of paediatric indications for existing products.

If a drug is included on the list produced by the European Medicines Agency's paediatric committee or appears on the list of paediatric needs drawn up by AFSSAPS, its pre-tax manufacturer price shall be set so as to guarantee a daily treatment cost which is equal to the drug's daily treatment cost for adults. These provisions shall only apply to drugs which are defined as orphan drugs pursuant to regulation (EC) no 141/2000 of the European Parliament and of the Council of 16 December 1999.

Article 10 a: Access to orphan medicines

To ensure that the patients concerned continue to have access generally to orphan medicines under conditions that are acceptable to the pharmaceutical companies and *l'assurance maladie* alike, and subject to the provisions of Article 4 hereabove, the committee may request a company selling an orphan medicine costing more than €50k per patient per year, under the terms of its agreement with the company, to undertake to supply the medicine to all patients eligible for the treatment without restriction in return for setting a price in keeping with standard international prices, up to a set turnover threshold.

Article 11: Real-life monitoring of new drugs in clinical practice

The parties are agreed on the benefits of gathering data on use of new drugs in real-life situations.

This Article relates to studies which are governed by contractual agreements between CEPS and the company concerned. The studies may be initiated at the instigation of either the Transparency Commission or CEPS.

The recommendations of ADELF (Association des épidémiologistes de langue française, the French speaking epidemiologists' association) and good epidemiological practice shall apply to the manner in which the data is gathered and the studies are audited. The relevant public bodies may exercise their right to monitor compliance with these rules.

The aims of these contractual studies, the obligation to set up a scientific committee where applicable and the timescale within which the studies must be conducted and their findings obtained shall be set forth in a rider to the agreement, which may also make provision regarding the consequences of non-compliance with the timescales.

If the company can demonstrate that the findings of the study it has been requested to carry out would fully or partly duplicate the findings which the studies required as part of the marketing authorisation application process and included in the approved risk management plan would produce within the same length of time, the contractual study shall be modified accordingly. In such cases, CEPS and where applicable the Transparency Commission must be given copies of the findings of the studies included in the risk management plan.

Where a scientific committee is formed, information on the committee's composition and its members' declarations of interest must be sent to the Transparency Commission if the Commission instigated the study or to DGS (Direction Générale de la Santé - Health Department of the Ministry of Health) for other contractual studies. The scientific committee shall be responsible for deciding which type of study is best suited to address the issues raised and/or for approving the study protocol; the committee shall also give an independent expert opinion on the team appointed to carry out the study. This opinion must be sent to either the Transparency Commission or the DGS as applicable. The contract rider stipulates that the studies must be published, notwithstanding any intellectual property rights associated with them.

For studies which the Transparency Commission has instigated and for other contractual studies where this is stipulated in the agreement, the study protocol must be submitted to the Transparency Commission, which will give an opinion as to whether the study design is fit to address the issues raised. This procedure involving the Transparency Commission shall not entitle the company to any extension of the agreed schedule for starting the study and producing the findings.

The findings of the contractual studies shall be submitted to CEPS and to the Transparency Commission, where the latter instigated the study. The parties to the agreement shall discuss what action to take on the basis of the findings.

The committee shall oversee regulation of the costs involved in the studies, which must be reasonable in relation to standard industry practice (regarding number of cases, complexity, etc.) and shall ensure that the overall, proven costs to the company of carrying out the study are proportionate to the anticipated pre-tax turnover from sales of the drug. In the event that the costs are disproportionate in this respect or that the scope of the study is extended for public health purposes to include elements other than the use of the product in question, the company may be compensated for the additional costs incurred via a reduction of its clawback payments.

CEPS may request the companies to draw up protocols which could allow the findings to be extended to other drug products with related therapeutic targets.

These provisions do not rule out the possibility that other studies presented at the company's own initiative may be taken into account.

Penalty payments payable in the event of failure to carry out the studies within the agreed timescale, under the terms of Article L. 162-17-4-5, of the Social Security Code, shall be set according to the procedure provided in Article 15 b) herebelow.

Article 12: Essential medicines

If a company plans to halt production or sale of one of its proprietary products which satisfies a particular medical need that would no longer be fulfilled if the product were removed from the market, the company undertakes to enter into discussions with CEPS regarding the financial situation involved in keeping the product on the market, failing which the company's status as an approved supplier may be removed.

If a company requests a price increase for one of its proprietary products that satisfies a medical need not catered for by any other less expensive medicine and the price increase is justified in view of the financial circumstances surrounding the production of the medicine, when evaluating the request account shall be taken of obligations arising from tests on traces of the medicine in water and of the specific cost of the collection and disposal of sharps waste from patients self medicating with the product.

Section II: Sources of savings

Article 13: Development of generics and fixed accountability tariffs (*tarifs forfaitaires de responsabilité* – TFRs)

The parties to this agreement agree that the development of the generics drugs market represents a valuable contribution to the funding of medical advances.

The generics monitoring group shall study the development of the generics market and carry out a critical analysis of how the market is functioning and the prevailing economic conditions for companies affected by the development of this market.

The group shall be consulted about all plans to set or to change a "fixed accountability tariff", as shall the manufacturers of the proprietary products concerned.

The group shall also be consulted about all public plans to lower generics prices and about changes that the committee is considering introducing to its overall price setting procedure for the substitution list: allowance entitlements, price increase rules for original drugs and generics, etc.

The committee shall take into consideration the logistical pressures which the pharmaceutical companies will be put under by any changes to the fixed tariff levels.

Article 13 a: Price consistency

In the event that a significant number of less expensive medicines, in particular generics, emerge within a pharmacotherapeutic group in which this is justified in view of the degree to which the medicines that constitute the group are sufficiently interchangeable from an economic point of view in terms of the nature and degree of the medical benefit they provide, the prices of the more expensive medicines, in particular of those still protected by patens, may be gradually brought into line so that in the long term there will be no significant gap between the prices of these medicines and those of the less costly ones. The desired price reductions may not be introduced until at least one year after these less expensive medicines have come onto the market and shall only apply to medicines that represent little or no medical progress in the majority of their indications.

Article 14: Development of self-medication not covered by national health insurance

The parties agree that responsible self-medication should be allowed to develop in France, as it will contribute to the responsible use of medicines without affecting the levels of payments made by national health insurance.

Section III: Responsible use of medicines

Article 15: Information for prescribers, promotion and advertising

a) Information for prescribers and promotion of medicines

The parties are agreed upon the view that promotion of medicines, whilst playing an essential informative and educational role for prescribers, can to differing degrees depending on the type of medicine, exert a disproportionate influence on prescribing practices.

The parties also agree on the view that in cases where the primary aim of the promotional activities is to obtain a market share by fair competition, with no proven risk that it will lead to excessive prescription volumes or irresponsible use of the medicine, limiting the companies' corresponding marketing budgets shall not constitute a high-priority issue in the agreements between the committee and the companies.

Conversely, the parties agree that in any circumstances where there is a risk that the drugs could be prescribed in unjustifiable quantities or under unjustifiable conditions, promotional materials must be produced which pro-actively and explicitly promote the responsible use of the drugs.

To this end, for drugs which are specifically identified as being among those described in the paragraph above, the committee may require the individual agreements to contain undertakings by the companies concerned to adapt their publicity materials and the training and materials given to their medical sales personnel so that they promote responsible use of the drugs and are directed only at the appropriate patient groups. The companies must be prepared to prove at the committee's request that they are abiding by these undertakings.

The pharmaceutical companies undertake to produce and promote a sales visit quality charter setting out the training requirements for and role of their sales personnel and emphasising the quality required of the promotional materials used by sales personnel.

b) Advertising bans

For the purposes of Article L. 162-17-4 of the Social Security Code, in particular in relation to advertising bans issued by AFSSAPS and the financial penalties which may arise therefrom, the parties agree that CEPS shall follow the procedure below when making its decisions.

For advertising bans which the committee considers may give rise to financial penalties:
the committee shall designate a rapporteur who will examine the case and present it at a committee session;
the committee shall draw up a draft decision giving its grounds for the decision;
the committee shall send the company the draft decision, asking the company to present any comments in writing;
the company may request a hearing by the committee; it may also enlist the help of experts or legal advisers;
the committee shall then hold fresh discussions and shall notify the company of its decision.

Article 16: Cooperative action to promote responsible use of medicines

The pharmaceutical companies undertake to actively pursue action undertaken with regard to the responsible use of medicines, in liaison with the appropriate social security bodies.

When HAS, UNCAM, INCA or AFSSAPS[3] are planning actions of a public or general nature which may affect the economic balance of the drugs sector, LEEM may request CEPS to arrange suitable consultations, after having applied to the ministers concerned if necessary.

CHAPTER V: ANNUAL FINANCIAL ADJUSTMENTS

Article 17: Annual financial adjustments: principles

Any company wishing to be exempted from the contributions required under the terms of Article L. 138-10 of the Social Security Code must undertake in the form of a contractual clause, to pay clawback payments, known as end-of-year quantity clawbacks, to the relevant URSSAFs[4]

[3] HAS = Haute Autorité de Santé: France's independent health advisory body; UNCAM: Union Nationale des Caisses d'Assurance Maladie; INCa: Institut National du Cancer; AFSSAPS = Agence Française pour la Sécurité Sanitaire des Produits de Santé: government medicines and healthcare products regulatory agency.
[4] URSSAF = Union de recouvrement des cotisations de sécurité sociale et d'allocations familiales: main social security body which collects social security insurance contributions and distributes them to ACOSS (agence central des organismes de sécurité sociale), which in turn distributes the money to the various *Caisses*.

However, regardless of whether or not the company has signed an agreement,, no end-of-year quantity clawbacks shall be payable if the cumulative growth of sales of reimbursable medicines to community pharmacies and sales to healthcare establishments of medicines included on the list provided in Article L. 5126-4 of the Public Health Code (and as of 1 January 2010 "or on the list provided in Article L. 162-22-7 of the Social Security Code") for all the companies put together does not exceed the sales-weighted mean value of the 'K' growth rates set each year by the Social security finance law (LFSS) pursuant to Article L. 138-10 of the Social Security Code. Furthermore, the committee undertakes to ensure that the total amount of all the end-of-year quantity clawbacks paid by all the companies put together is less than the sum of the contributions which those companies would have had to pay if none of them had entered into the agreement.

At the end of each year, and by 31 January of the following year at the latest, companies which sell products included on the list provided in Article L. 5126-4 of the Public Health Code (and as of 1 January 2010 "or on the list provided in Article L. 162-22-7 of the Social Security Code") must send a declaration to CEPS, in the format of the pro-forma declaration provided in the attached appendix, giving details, for each product and product format, of the volume and actual turnover of its sales to healthcare establishments over the year and identifying among these figures all sales of products which were on the list (as of 1 January 2010, "on either list") on 31 December in the year for which the payments are owing and had been on the list since at least 1 January of the previous year.

The contractual clawback payments shall be paid to the appropriate URSSAF by 30 April the following year, on the basis of an assessment drawn up by CEPS following discussions during which the company may present arguments for a review of the amount of clawback payments calculated.

The end-of-year quantitative clawbacks are made up of payments per pharmacotherapeutic class grouping and payments based on turnover.

a) Clawback payments per pharmacotherapeutic class grouping

Each year, the committee shall draw up a table dividing the medicines concerned into groups for the whole of the sector concerned. These groups are made up of sets of pharmacotherapeutic classes defined using the EPHMRA codes. The committee shall set a growth rate for each group, in such a way that the weighted mean value of the rates is equal to the weighted mean of the 'K' growth rates established for the year in question by the social security finance law.

LEEM shall be consulted before the table is finalised.

The gross clawback payments owed by the companies, before deducting any exemptions as provided in Article 18 herebelow, shall be calculated as follows:

For each of the drug groups in which the annual growth rate is higher than the rate set by the committee, the total amount owing by all the companies who have agreements with CEPS and sell drugs belonging to that group shall be equal to the difference between the two rates multiplied by a given coefficient, which shall be the same for all groups and shall be set the committee in the light of the forecast sales growth for all the drugs concerned. For drugs sold to healthcare establishments, the sales taken into account shall be those corresponding to products included on the list (as of 1 January 2010, " on one of the lists") as at 31 December in the year for which the payments are owing which had been on the list since at least 1 January of the previous year.

The total clawback payment owing for each group shall be split into two portions, and the relative sizes of these portions, which shall be identical for all groups, shall be determined after consultation with LEEM. The first portion shall be split proportionally between all the companies with agreements who are selling drugs belonging to that group, on the basis of their respective sales figures. The second portion shall be split proportionally between those companies whose annual growth rate is higher than the rate set by the committee, on the basis of their respective excess turnover amounts.

Sales to healthcare establishments shall be calculated by multiplying the number of units sold by their prescription price (as of 1 January 2010, "or their *tarif de responsabilité*").

b) Clawbacks based on capped turnover rates

The companies shall also be liable where applicable for a clawback payment based on the difference between their turnover and a fixed threshold stipulated each year in a contract rider. The rate for this clawback is set, unless otherwise stipulated in the contract, at 10%.

For sales to healthcare establishments, the turnover figure used shall be the actual turnover.

When the sum of the safeguard contributions which the company would have had to pay if it had not signed the agreement is used as a basis for working out the threshold mentioned in the paragraph above, this sum is adjusted to cancel out, where applicable, sales of generics and products on fixed accountability tariffs and sales of drugs which were not claimed back from national health insurance.

Article 18: Annual financial adjustments: special implementation conditions

a) Exemptions from clawback payments per pharmacotherapeutic class grouping

1) Medicines which were given an ASMR rating when they were registered on the reimbursable medicines lists.

- ASMR I and II: full exemption for 36 months and 24 months respectively.
- ASMR III: 50% exemption for 24 months.
- ASMR IV: 25% exemption for 24 months.

For medicines sold to community pharmacies, these exemptions shall be effective as of the date they are sold, and for medicines on the list provided in Article L. 5126-4 of the Public Health Code (as of 1 January 2010, "or on the list described in Article L. 162-22-7 of the Social Security Code"), from the date on which the relevant sales are included in calculations for the clawback payments per pharmacotherapeutic class grouping.

Companies may opt for a fixed, non-extendable exemption period which is longer than the periods provided above, up to a period of five years. In such cases, the exemption rate shall be reduced to ensure that the length of the exemption multiplied by the rate remains constant.

Where the ASMR rating only relates to some of the drug's indications or where different indications have different ASMR ratings, the exemptions shall be worked out in proportion to the sizes of the patient groups concerned.

Where a drug has been covered by a provisional authorisation (ATU) or by a temporary treatment protocol for one of its indications which is not included in the marketing authorisation, the agreement may stipulate clawback exemptions on a case-by-case basis, based on a similar method to the one described above. These exemptions shall be deducted from those arising from any ASMR rating given to the indication in question once marketing authorisation has been obtained.

2) Extension of indications with an ASMR rating

The sum of the clawback payments shall be reduced according to the same rates and for the same periods as stipulated in paragraph 1) above, in proportion to the amount of turnover made by virtue of the new indication, starting from the date of the Transparency Commission's final opinion. Likewise, if a drug which has been exempted on the basis of its ASMR rating has one of its non-ASMR rated indications extended, the exemption shall be proportionally reduced, starting from the date of the Transparency Commission's opinion on the extended indication, according to the size of the patient group concerned. The pro-rata rates shall be established in the individual agreements.

3) Orphan drugs and paediatric drugs

Orphan drugs as defined in the legislation shall be exempted from clawback payments, unless otherwise stipulated in the agreements. For the purposes of the agreements, orphan drugs may be taken to include both legally defined orphan drugs and de facto orphan drugs which were marketed before the relevant legislation came into force.

Paediatric drugs included on the list announced by CEPS shall be exempt from clawback payments, under the same conditions as those stated in paragraph 1) above except that their ASMR ratings shall be set one level higher for these purposes than the level set by the Transparency Commission.

4) Low cost drugs

Generic medicines, medicines on generic prices and medicines on fixed accountability tariffs (TFR) whose price is equal to or lower than that of the tariff, shall be exempt from clawback payments.

5) Medicines for which a significant percentage of sales are not presented for reimbursement

The clawback payments owing shall be reduced proportionally in relation to the value of sales which were not presented for reimbursement, calculated from national health insurance reimbursements data.

6) (until 31 December 2009) Where a drug which is listed on the outpatient medicines list but is primarily issued to inpatients represents a significant proportion of the gross clawback figure payable by a company due to the size of its sales or sales growth, the agreement may contain conditions regarding partial exemption from clawback payments due to this drug.

b) Rules governing double clawbacks per pharmacotherapeutic class grouping and for products under special contractual conditions

Where clawback payments are owing under the terms of an individual agreement relating to a specific drug (e.g. daily treatment cost refunds, volume discounts etc.), any clawback payment per pharmacotherapeutic class grouping which the company owes for this drug shall be recalculated to take the sales of this medicine and any excess turnover made on it as the net sales actually earned by the company (GERS turnover data-specific rebates).

c) Clawback credits

1) Clawback credits for price reductions or reimbursement reclassifications

Price reductions proposed by the companies, with the exception of reductions proposed following the creation of generic groups or in groups on fixed accountability tariffs, shall give rise to a clawback credit equivalent, unless otherwise stipulated in the agreements, to the amount of the reduction of the manufacturer price ex VAT multiplied by the number of units sold during the twelve months preceding the reduction.

Price reductions proposed by CEPS under the terms of Article L. 162-17-4 of the Social Security Code and put into practice through the company's agreement with CEPS may give rise, under the terms stipulated in the agreement, to clawback credits.

The above two paragraphs shall be applicable to reductions in the outpatient prescription prices or the official rates for medicines included on one or other of the lists under Articles L. 162-16-5 and L. 162-16-6 of the Social Security Code (*Code de la sécurité sociale*), provided that these reductions also relate to the sale prices used in practice and on condition that the reductions are not being introduced for the purpose of bringing the prices back into line with current prices in the main European Union Member States.

Refund reclassifications may give rise, under the terms stipulated in the agreements envisaged in Articles 4 and 5 hereabove, to partial compensation in the form of clawback credits.

2) Clawback credits for Braille

Contributions which companies make to funding the production of patient information leaflets in Braille shall be recognised in the form of clawback credits.

3) Carrying over credits

The companies shall be entitled to carry any clawback credits they receive over into subsequent years.

CHAPTER VI: SCOPE OF THE AGREEMENT

Article 19: Scope and term of the framework agreement

This agreement, which replaces the 'community' framework agreement of 13 June 2003 as amended and the "hospital" framework agreement of 23 March 2004 as amended, shall be effective until 31 December 2012.

The agreement constitutes a framework agreement under the terms of Article L. 162-17-4 of the Social Security Code.

Subject to statutory and regulatory provisions relating to the pharmaceutical sector and in particular to the taxes applicable to the sale and marketing of drugs, this agreement sets out the conditions regarding financial regulation of medicines as they apply to companies which enter into an agreement with CEPS pursuant to Article L. 162-17-4 of the Social Security Code.

The agreement may be supplemented by riders.

In the event that one of the parties should withdraw from the agreement before it expires, the terms of the agreement shall be extended for a maximum period of one year until such time as a new agreement is signed or, for the purposes of Article 8 hereabove, until publication of the decrees provided in Articles L. 162-16-5 and L. 162-16-6 of the Social Security Code.

In the event that the overall balance of this agreement should be altered, in particular following amendments to the applicable statutory or regulatory provisions, a major change in government policy or consequences of the enlargement of the European Union, in such a way as to increase the burden of the pharmaceutical companies' obligations, the agreement shall be renegotiated in order to re-establish a balance between the parties. If such negotiations are unsuccessful, the agreement may be terminated by either party.

Done in Paris in two original copies, 25 September 2008

For the pharmaceutical Companies (LEEM)	For the Comité économique des produits de santé
Christian Lajoux	Noël Renaudin