The attractive position of France in International Clinical Research: 2008 survey assessed by Leem (French Pharmaceutical companies)

La France, un pays attractif pour la recherche clinique internationale : enquête 2008 du Leem

France et recherche clinique internationale

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Summary

In order to evaluate the attractiveness of France for conducting international clinical trials, a survey is performed every two years among pharmaceutical companies that are based in France or have affiliates in France. 19 companies (61.9 % of the French market) have participated in the current survey which included 385 international phase II and III clinical studies, 77 countries, 29,708 centres and 312,835 patients (included in 2006/2007). France (400 patients/million inhabitants) ranked among the best European recruiters in second position behind Scandinavia. Since 2006, France has improved administrative processes and reduced deadlines for hospital contracts. Protocols are now to be given the go-ahead by French Authorities (Afssaps and CPP) within 60 days, in accordance with European directive. Its performance in early phases, oncology/hematology and vaccines/anti-infectious contribute to the attractiveness of France in international clinical research.

Key words: international clinical research, pharmaceutical companies, France, competitiveness

1. Introduction

The French pharmaceutical sector is the second biggest in France in terms of R&D, behind the automotive sector and ahead of New Information and Communication Technologies (NICT) and aviation, with a total of 4 billion euros invested in research, 99% of which is funded by pharmaceutical companies[1]. Private sector research is one of France's strengths in the healthcare sector. Nevertheless, France has strong competition from other European countries and emerging countries. These countries are competing among themselves, and some are actively seeking to attract this research, which is essential if there is to be good-quality medicine, skills among experts, training for doctors and rapid access for patients to new treatments. In these terms, French clinical research is overall in a precarious position.

Surveys carried out by Leem (French Association of Pharmaceutical Companies) in 2002, 2004 and 2006, and this new 2008 survey, provide an exceptionally broad range of data, the only one of its kind in Europe, about France's place within international clinical research[2-4]. These surveys provide a precise view of the current state of affairs and reveal trends and potential changes by identifying the specific advantages of France when compared to its main competitors. These visible factors are starting points for consideration, proposals and action plans to improve the situation in France.

In France, restructuring of clinical research based in hospitals (the classic location for clinical trials) in favour of academic research has been ongoing for several years. A culture of clinical research within university hospitals (CHU) has been developed around clinical research delegations (DRC), which are tasked, in particular, with developing research within institutions (for example the Hospital Clinical Research Programmes or PHRC), supported by operational research structures such as clinical investigation centres (CIC). In order to combine resources in order to achieve better international visibility for these structures, inter-regional clinical research delegations (DIRRC) have been established[5].

The strategic importance of pharmaceutical industry sponsored clinical research has only recently been recognised. In 2005 the Healthcare Industries Strategic Council (CSIS), under responsibility of Prime Minister, noted that France was becoming less attractive as a location for clinical research with industrial sponsorship. The most prominent measure taken was the creation, in March 2007, of a Public Interest Group (GIP) to last four years,

supported by the DIRRCs and named the National Centre for Management of Health Products trials (CeNGEPS), the aim of which is to maintain and increase industrial clinical research activity on French soil[6].

This fourth Leem (French Association of Pharmaceutical Companies) survey was carried out during a period of great change, while the CeNGEPS public interest group was being established and at the height of the changes to French biomedical research regulation. The clinical studies included in the survey were subject either to the regulation in force before 27 August 2006 (on which date the Huriet-Sérusclat law was in force), or the new regulations which include measures from the 2001 European clinical trials directive (Public Health Law dated 9 August 2004 and decree of application dated 26 April 2006)[7].

2. Methods

2.1. Participation of pharmaceutical companies

All LEEM members were informed of the survey. LEEM members participated voluntarily, and were subject to a rigorous process of information, training and monitoring.

Within pharmaceutical companies, the managers responsible for management of clinical trials and operations were surveyed [Directorates for Clinical Development and/or International Medical Affairs at the global headquarters, European Departments for Clinical Development and/or Medical Affairs and Medical and/or Clinical Development Directorates within French subsidiaries]. Project leaders were trained in questionnaire use and methodology within the medical directorate of each French subsidiary.

2.2. Scope of surveys

The survey involved international phase II and III studies that are intended for registration (including extensions of indication), sponsored by the global and/or European headquarters of these companies and involving the French subsidiary at any stage of development, provided that the first patient was included between 1 January 2006 and 31 December 2007, including all methodologies and including studies subcontracted to Contract Research Organisations (CROs) and directly monitored by the parent company or the European Region. For the first time, pharmaceutical companies provided data on the number of phase I studies.

2.3. Quantitative performance indicators

Two quantitative performance indicators were identified for phases II and III:

. *Levels of recruitment:* this is divided into 3 variables (number of studies, number of patients per study and number of patients recruited per centre).

. *Speed of recruitment:* this is defined by the number of patients recruited per centre and per month.

2.3.1 Data specific to France

Performance criteria that are specific to the French situation have been included in the French part of the study: Data on the number of protocols submitted to and accepted by Ethics Committees (CPP) and time taken for CPPs and Afssaps to approve protocols (submission date versus approval date) were collected. Analysis of time taken to implement phase II and III studies has enabled determination of median time elapsed between submission of a protocol to a CPP and signature of the first hospital contract. A breakdown of activity by DIRRC is given, with number of studies and patients recruited, number of patients recruited per study and per centre, breakdown of centres initiating studies and studies being initiated as a percentage of the total studies carried out within each DIRRC.

2.3.2 International data for comparison

For phase I studies carried out worldwide or in Europe, only data about French participation, expressed as a number of trials carried out, are reported in this survey. For phase II and III trials, in order to facilitate analysis in comparison to the 2006 survey, some countries have been grouped together geographically as they were in the previous study, without taking into account the fact that there are now more European Union member states[4].

2.4. Qualitative performance indicators

As in the two previous surveys, global and/or European head offices were asked to fill in a qualitative questionnaire to show how is their perception of the performance and attractiveness of each country to international clinical research. They were asked to give a score between 0 (minimum score) and 5 (maximum score) to their perception of the following three qualitative performance indicators:

. *"Productivity of clinical research":* this was assessed as a function of cost of clinical development, the quality of investigators, recruitment speed and consistency with recruitment aims.

. *Attractiveness of market:* this is defined as the size of the market and the importance of registration authorities.

. The *"infrastructure and healthcare system quality":* this indicator includes the importance of opinion leaders, quality of medical care in the country, organisation of Clinical Research in the country and the level of complexity of the administrative authorisation procedure.

2.5. Collection and analysis of quantitative and qualitative study data

Study data were collected by the companies themselves and were sent in electronic form directly to an independent strategic consultancy specialising in the healthcare sector, AEC Partners (Paris), which was responsible for monitoring, consolidation and analysis of all data. Each company was responsible for the quality and consistency of the data it provided.

Data analysis was carried out according to the following principles:

- Respect for integrity of data as sent
- Studies which did not involve France were excluded
- A company was not taken into account for a given indicator if the response rate was less than 50%
- Country data were not taken into account if the number of open centres and patients recruited was zero
- For the criteria "percentage of centres enrolling at least one patient" and "average number of patients recruited per centre" countries with no patients recruited are taken into account but only if open centres and length of study demonstrate active international recruitment
- Country data are not taken into account if they are inconsistent: for example, if there are no recruitment centres but the number of patients recruited is greater than zero, or if the number of recruiting centres is greater than the number of open centres
- If a country does not have a figure for "recruitment centres": patients recruited is equal to zero, with a number of recruitment centres that is greater than zero, these data are not taken in account
- If a country does not use the "recruitment speed" indicator: if the number of patients recruited is zero and the duration of recruitment is greater than zero (but this is taken into account for other indicators), these data are not taken in account.

The main performance indicators were also analysed in sub-groups, divided by country of origin of the pharmaceutical company, recruiting countries, study phase and treatment area.

3. Results

The survey involved nineteen pharmaceutical companies that were members of Leem (French Association of Pharmaceutical Companies), the majority of which (74%, 14 companies) had taken part in the previous survey (table I). These companies represent 61.9% of the French market (GERS 2007 data).

3.1. Data specific to France

The nineteen companies that took part provided data on studies carried out in France. Of the 457 studies initially reported by the 19 companies, only 319 studies were taken into account in the analysis, as for two of the participating companies there was a lack of data in this section of the questionnaire (94 studies), as studies for which a CPP was not named were excluded (26 studies) and as studies with no recorded key date were excluded (18 studies).

3.1.1. Time taken for Afssaps to approve

The median and mean time elapsed before a protocol is approved by Afssaps are 53 days and 58.7 days respectively. Times reported for the various companies began with submission of a dossier to Afssaps, and for dossiers that were submitted after 27 August 2006, do not take into account whether the dossiers were initially accepted or not, as the time taken to bring dossiers up to acceptable standards are included in the decision-making period is included for dossiers that were acceptable from the start.

3.1.2. Time taken by Ethics Committees (CPP)

The 319 studies which were analysed were submitted to 40 ethics committees (Figure I). More than half of these (184 studies, 58%) were dealt with by the 11 busiest CPPs (which each dealt with more than 10 dossiers, the median figure being 6 studies per CPP, compared with 4 in 2006). The median time taken for a CPP to approve a protocol is 49 days (compared with 50 days in 2006), regardless of the number of studies dealt with. Median time is shorter for phase III studies than for phase II studies (48 days compared with 53 days).

3.1.3. Time taken to set up studies in hospitals

The median time taken between submission to CPP and signature of the first hospital contract is 124.5 days (compared with 140 days in 2006). After deduction of the median time between submission and approval of the protocol by the CPP, the median time taken to signature of the first hospital contract is 75.5 days (compared with 90 days in 2006) but with significant variation between studies.

3.1.4. Assessment of DIRRCs

Analysis by DIRRC involved questionnaires from 11 companies, involving 225 studies and almost 6200 patients. Of the 1951 data items provided (one data item = one company, one study and one centre), 71% could be analysed, and data involving individual doctors' clinics, community clinics and centres that cannot be affiliated to DIRRCs could not be used. Table II provides an overall breakdown of studies carried out and numbers of patients recruited for each DIRRC, given that one study may involve several DIRRCs. Analysis taking into account the populations of the various DIRRCs demonstrated significant differences between them in terms of numbers of patients recruited, and the Ile-de-France DIRRC has the best ratio (table II). This DIRRC also has higher ratios of mean numbers of patients recruited per study and by open centre. The ratios for the North East and Rhône-Alpes-Auvergne DIRRCs are lower (table II). In terms of first patient included, here too there is an unequal distribution between regions (table II).

3.1.5 Quantitative analysis

3.1.5.1 Choice of France in international programmes

Of the 1351 phase I studies carried out worldwide and reported in this survey (13 firms, representing 68% of responses), 550 studies were carried out in Europe of which 36% (n=199) were in France, 31% (n=171) in the United Kingdom, 26% (n=143) in other Western European countries, 24% in Germany (n=131), 13% (n=71) in Italy, 13% (n=70) in Eastern Europe, 12% (n=67) in Scandinavia and in Spain (n=66).

Of the 1218 phase II and III studies carried out worldwide with European involvement and reported by 15 companies (70% of responses), 536 studies (44%) were offered to France compared with 70% in 2006 and 407 studies were finally carried out in France, representing one third of all studies. France is therefore less in demand than it was as a venue to carry out clinical studies. The reasons why 129 studies were not finally carried out in France involved a change of mind at the parent company (39 studies) or refusal by the French subsidiary, which had fallen since the last survey (17%, 90/536 studies compared with 24%, 75/309 in 2006). The main reasons for refusal by French subsidiaries (protocol not feasible, lack of human and financial resources and potential non-approval by Afssaps) are the same as those given in 2006. The country of origin of the pharmaceutical company has an effect on the proportion of international studies that are carried out in France: French companies carry out on average 40% of their studies in France (compared with 92% in 2006), while for European (not France) and

American companies the figures were 44 % (compared with 52% in 2006) and 26% (compared with 48% in 2006) respectively.

3.1.5.2 Performance indicators

Analysis of performance criteria for studies carried out in France involved 396 phase II and III studies (87% of studies reported). 12 studies which were still recruiting at the end of 2007 and 49 studies with no open centres or recruited patients were excluded from the analysis. Despite the fact that numbers of companies participating were similar, the scope of the 2008 survey was broader than for the 2006 survey, with 20% more phase II and III studies (396 studies compared with 329), 76% more patients recruited (26,392 patients compared with 14,993) and 20% more centres (3082 centres compared with 2583). Performance criteria improved following the 2006 survey, with a 45% increase in the number of patients recruited per study (67 patients compared with 46), a 40% increase in the mean number of patients recruited per centre (8.6 patients compared with 6.2) and a 64% increase in recruitment speed (2.3 patients/centre/month compared with 1.4). The majority of studies carried out in France, as in the previous survey, were phase III studies, which represented 60% of studies (239 phase III studies compared with 145 phase II studies). Two thousand three hundred and twelve centres (75%) are involved in phase III studies and 685 (22) in phase II studies. Trial phase was not stated for 85 centres (3%).

France's participation in international trials varies depending on the pharmaceutical company's country of origin. 78% of studies carried out in France (309 studies, 14,715 patients, 1989 centres) were carried out by foreign companies, the majority of which were European (56%: 172/309 studies, 9524 patients, 1126 centres). Performance ratios for foreign companies were different from those of French companies, with fewer patients recruited per study (55 for European firms, 38 for American firms and 134 for French firms), fewer patients recruited per centre (8.5 for European firms, 6 for American firms and 10.7 for French firms), fewer open centres per study (6.5 for European firms, 6 for American firms and 13 for French firms) and a recruitment speed that is 3 to 7 times lower (2.4 patients/month/centre for European firms, 0.99 for American firms and 6.8 for French firms). The overall productivity improvements noted with respect to the 2006 survey can be explained by the obviously higher productivity of phase III studies. There has been a 57% increase in the number of patients recruited per study in comparison to the 2006 survey for phase IIIA trials (84 compared with 48) and a 76% rise in phase IIIB studies (104 compared with 59). The mean number of patients recruited per centre has also increased by 42% for

phase IIIA studies (9.8 compared with 6.9) and by 60% for phase IIIB studies (8.3 compared with 5.2). Finally, recruitment speed was 3.5 times higher in phase IIIA trials (4.6 patients/centre/month compared with 1.3 in 2006) and increased by 46% for phase IIIB studies (1.6 patients/centre/month compared with 1.1 in 2006).

The proportion of studies carried out in France within the scope of the survey, in the field of haematology/oncology, broadly increased following the last survey and this field is increasingly predominant (39%, 156/396 studies compared with 25%, 82/329 studies in 2006) over other fields, and includes 19% of all patients (5087/26 392 compared with 2823/14 993 in 2006). Of the other treatment areas, vaccines/infectious disease recruits the most patients (34.5%, n=9071) for 7% of all studies (28 studies), cardiovascular/metabolism/diabetes has almost a quarter of patients (23.5%, n=6163) in 16% of all studies (64 studies), central nervous system/geriatrics/Alzheimer's has 11% of patients (n=2884, 54 studies which is 14% of all studies) and inflammatory diseases/rheumatology has 6% of patients (n=1582, 42 studies which is 11% of all studies). Three treatment areas (haematology/oncology, vaccines/infectious disease and cardiovascular/metabolism/diabetes) thus account for 77% of patients recruited in France (n=20,321/26,392). With 31 patients recruited per centre and a recruitment speed of 17.1 patients/centre/month, the field of vaccines/infectious disease, which carries out a very specific type of study, has had an effect on overall productivity in France in comparison with the 2006 survey. Outside this field, the other treatment areas have experienced a slight increase of 2% in the number of patients recruited per study and per centre in comparison with the 2006 survey (47 patients/study compared with 46 in 2006, and 6.3 patients/centre compared with 6.2 in 2006) and a 36% reduction in recruitment speed (0.9 patients/centre/month compared with 1.4 in 2006).

3.2. International data comparison

19 companies (compared with 17 in 2006) had access to international data which enabled them to compare France with other countries according to quantitative criteria (8 of these were American companies, 5 were European and 6 French).

3.2.1 Quantitative analysis

Of the 457 studies considered, 385 phase II and III studies (84%) were analysed, involving 77 countries, 29,708 centres and 312,835 patients. The scope of this analysis is broader than that of the 2006 survey, with a 49% increase in the number of studies (385 studies, compared with 258 in 2006) and a 71% increase in the number of

centres (29,708 centres compared with 17,345 in 2006), a 2.3-fold increase in the number of patients (312,835 patients compared with 137,989) and stability in the number of investigating countries (77 countries compared with 74). The largest number of studies with French participation is still within haematology/oncology, followed by cardiovascular/metabolism, diabetes (figure 2). In terms of trial phases, France appears to be proportionally more in demand for early-phase trials with respect to the average for all countries (Phase IIA: 20% compared with 13% and Phase IIB: 17% of studies, compared with 13%).

3.2.1.1 Recruitment levels

France took part in all 385 studies as, by definition, only studies involving France were included in the analysis. In this sample, France still has 8% (n=24,343) of all patients recruited worldwide, like Germany, and has been overtaken by the two countries that recruit the largest number of patients, which are Eastern Europe (18%, compared with 15% in 2006), which has itself overtaken the United States (13% compared with 17% in 2006) (table III). A more in-depth analysis of Eastern Europe shows that Poland, Russia, the Czech Republic and Hungary are responsible for 70% of patient recruitment within this geographical region. France is in 3rd place when analysis is confined to French pharmaceutical companies, which confirms that there is a "national preference". When European pharmaceutical companies are considered, France (7% of patients) is outstripped by Eastern Europe (19%), the United States (10%), Germany and other Western European countries (9%) and the United Kingdom (9%), which was not the case in the 2006 survey. France recruited 6% of patients recruited into studies run by American pharmaceutical companies, and was therefore behind the United States (18%), Eastern Europe (16%), Scandinavia (8%), other Western European countries (9%) and, appearing for the first time in this survey, Latin America (8%) and Asia (9%).

The weighting of Europe is also significant because of study selection criteria, with over 63% of all patients recruited in Europe, which has increased very slightly since the 2006 survey (Table III). Within Europe, the slight reductions in France's (12% compared with 14% in 2006) and Germany's patient numbers (12% compared with 15% in 2006) were to the benefit of Eastern Europe (29% compared with 25% in 2006) and the United Kingdom (8% compared with 5% in 2006). Italy remained stable at 5%. Analysis including the populations of the various countries enabled a ratio to be defined for each country, expressing the number of patients recruited per million inhabitants (Table IV). All countries saw an increase in this ratio compared with the

2006 survey. With a ratio that is 1.6 times higher than the Europe-wide ratio, France is the second highest recruiter in Europe behind Scandinavia.

This survey shows an increase in the number of patients recruited per study for all countries (74 compared with 53 in 2006) and Europe-wide (70 compared with 46 in 2006). Although France has improved the mean number of patients recruited per study (63 compared with 46 in 2006), it is still below the European average (table III). The United Kingdom improved its performance in terms of patients recruited per study by a factor of 2.2. All countries have also experienced an increase in the number of patients recruited per centre (9.5 patients/centre, compared with 7.7 in 2006). France recruited fewer patients than the average for European countries (7.6 patients/centre compared with 9.8) in spite of a 21% increase in patients recruited per active centre when compared with 2006 (7.6 patients/centre compared with 6.3 in 2006) (table III).

Analysis by trial phase shows that the number of patients recruited per active centre, over all countries, increased for all trial phases (table V). France is in second position for phase IIA trials.

Breakdown by therapeutic area shows an average number of patients recruited per active centre, for all countries combined, of 24.8 for vaccines/infectious disease, 16.2 for cardiovascular/metabolism/diabetes, 11.7 for inflammatory diseases/rheumatology, 7.7 for the central nervous system/geriatrics/Alzheimer's and 5 for haematology/oncology. France occupies an important position in haematology/oncology (5.6 patients/centre, 4th place) and vaccines/infectious disease (29.2 patients/centre, 4th place). France is below the average for other countries in the fields of inflammatory diseases/rheumatology (8 patients/centre, 8th place), the central nervous system/geriatrics/Alzheimer's (5.7 patients/centre) and is still in last place for cardiovascular/metabolism/diabetes (8 patients/centre).

3.2.1.2 Speed of recruitment

Mean recruitment speed increased by 47% over all countries between the 2006 and 2008 surveys (2.5 patients/centre/month compared with 1.7 in 2006) and by 65% throughout Europe (2.8 patients/centre/month compared with 1.7 in 2006). Recruitment speed in France has increased by 57% (2.2 patients/centre/month compared with 1.4 in 2006). Within Europe, France is now ahead of the United Kingdom which doubled its recruitment speed (2.1 patients/centre/month, compared with 1.0 in 2006), but is outrun by countries which have improved their performance to a striking extent, such as Scandinavia (3.8 patients/centre/month compared with

1.8 in 2006), Germany (3.4 patients/centre/month compared with 1.3 in 2006) and Spain (2.2 patients/centre/month compared with 1.6 in 2006).

Since the last survey, recruitment speed for all countries combined has increased for phase III trials (IIIA: 2 patients/centre/month compared with 1.8 in 2006 and IIIB: 3.7 patients/centre/month compared with 1.2 in 2006) and phase IIB trials (5.8 patients/centre/month compared with 2.4 in 2006) and has reduced for phase IIA studies (1 patient/centre/month compared with 1.9 in 2006). France followed this trend, with the exception of phase IIA trials, for which patient recruitment speed has been stable since 2006 (IIA: 1.5 compared with 1.6; IIB: 2.8 compared with 2.2; IIIA: 1.7 compared with 1.2 and IIIB: 3.4 patients/centre/month compared with 1.1 in 2006). Analysis by therapeutic area shows that recruitment speed in France is lower than the average for other countries (vaccines/infectious disease: 16.6 compared with 19.2; cardiovascular/metabolism/diabetes: 1.4 compared with 2.7; inflammatory diseases/rheumatology: 2.0 compared with 2.6; central nervous system/geriatrics/Alzheimer's: 0.7 compared with 1.5 and haematology/oncology: 0.6 patients/centre/month compared with 0.9 in 2006).

3.2.2 Qualitative analysis

Eleven companies answered the qualitative questionnaire. The qualitative performance indicators, represented by scores between 0 and 5, are given in table VI and involve France, Germany, Eastern Europe, the United Kingdom and the United States.

This survey confirms once again that France is a key European market (with a score of 4.6). Since the last survey, the perception of the significance of the German and United Kingdom markets has also increased (table VI). In contrast to the 2006 survey, France has now overtaken the United States on the criterion "administrative simplicity" and has regained its 2004 score. The quality of medical treatment in France is still appreciated, even though France has been overtaken on this criterion in this survey by the United States. The organisation of clinical research in France is perceived as being as good as that in Germany and the United Kingdom. In terms of pharmaceutical companies' perception of the productivity of clinical research in France, this has made progress on the criteria "recruitment speed" and "consistency with recruitment aims".

4. Discussion

Data from the Leem surveys, which is exceptionally wide in scope, provides a precise view of the state of clinical research in France and thus enables its position among the international competition to be monitored.

Like previous surveys, this survey is broadly representative (19 companies, representing 61.9% of the market) and there is a base of 14 companies which provided data for both the 2006 and 2008 surveys, which ensures that robust comparisons can be made[2-4]. The deliberate decision to take into account only studies with French participation in each of the Leem surveys provides reinforcement for the place of France in comparison to that of other countries, and it also enables comparison of other countries' performance for the same studies.

For data that were specific to France, this new survey shows that France has successfully implemented the European directive, although with some delay. Time taken to CPP approval has remained stable (median time to approval 50 and 49 days) over the last two surveys in 2006 and 2008, although the new CPPs, which are structured in two college (scientific and community-based) and which have a broader scope, were only established at the end of 2006, and in parallel their numbers were reduced to 40 (there had been 48 CCPPRBs previously – "ethics committees for the protection of research subjects") and their funding was adjusted[7]. The relevant authority, Afssaps, successfully launched a pilot phase at the end of 2004- early 2005, which anticipated the new regulations. The average Afssaps response time of 58.7 is highly satisfactory, as the directive requiring a period of 60 days was only implemented in September 2006. Further confirmation that Afssaps is performing well is provided in the mean period of 41-day that was published in its 2007 annual report.

France's success in transposing the Directive has also been recognised by the parent companies of these pharmaceutical companies. In the qualitative section of the survey, France occupied first place in terms of administrative simplicity, which it had previously taken in 2004 but had lost in 2006 because it took too long to transpose the directive in comparison to other countries.

Conversely, there is still room for improvement to the complexity of administrative processes: the heterogeneity among CPPs, which was noted in 2006, still persists and demonstrates that probably there is still insufficient co-ordination. At Afssaps level, although average performance in terms of response times is admirable, there is still work to be done to improve these times for all studies, particularly early-stage trials and first administration in humans.

In tandem with implementation of the new European legislation, clinical research organisation in France has made progress, as demonstrated by the perceptions that parent companies have of this organisation. The 15-day reduction in time to signature of hospital contracts (125 days compared with 140 days) also bears witness to this. Improvements in recruitment speed and better consistency with recruitment aims are also positive indicators. The establishment of CeNGEPS may be considered to be one of the key factors in this improvement. Since it was created in March 2007, CeNGEPS has provided a new dynamism in hospital research. However, funding has only been granted for the current year 2008, so the full impact of this facility for organising clinical research may only be fully appreciated in the survey planned for 2010.

Other areas for improvement emerge clearly on reading this survey. Parent companies' perception of the quality of investigators and the importance of opinion leaders has reduced in comparison with the 2006 survey. This deterioration may be explained by the lack of resources experienced by investigators when carrying out clinical trials, in terms both of time and of personnel. The fact that pharmaceutical companies sponsored trials have not been taken into account by MERRI until now is an additional factor which could be responsible for the lack of mobilisation of resources. In addition, as at CPP level, there is a high level of observed heterogeneity among DIRRC and there are indisputably significant "reserves" of productivity. This can partially be explained by the insufficient development of community-hospital networks and clinical investigation networks on a national scale. Specific funding for such networks was granted in 2008 by CeNGEPS, and this will undoubtedly help to improve performance, as will the information campaigns about clinical trials, aimed at the general public, that may be carried out in 2009.

In terms of international comparisons, these surveys show that the percentage of patients recruited by France (8%) has remained stable with respect to other countries. However, this apparent stability, when the scope of the study is taken into account (studies with French participation), must not be allowed to obscure the reduction in the number of studies involving France. More than half of international studies carried out by the companies involved did not have presence in France (56% in 2008 compared with 30% in 2006).

This reduction is also reflected in the number of clinical trials authorised by Afssaps, which fell from 1,148 in 2006 to 1,000 in 2007. In other European countries, 1,400 trials were approved in 2007 in Germany, 1,230 in the United Kingdom and 750 in Italy.

There is lively competition between European countries, but the performance of the Scandinavian countries remains unrivalled. Eastern Europe and the United Kingdom have also made good progress. The main finding of these surveys has been a change in geographical distribution, with an ever greater role played by Asian and Latin American countries. These new countries have undoubtedly, like Eastern Europe before them, contributed to improved efficiency in terms of numbers of patients recruited and recruitment speed, while maintaining the quality of studies. Comparison between the 2006 and 2008 surveys shows that France has made progress on these criteria, but much less quickly than many other countries.

Today, therefore, French clinical research is in a precarious position. However, it does have many assets, among which one of the most important is its relative position in early-stage trials (proof of concept and phase IIA). In addition, performance is satisfactory in the field of cancer, which covers 39% of studies carried out in France. Factors responsible for this good position[9] include the development of CICs and the cancer plan, which established translational research as a priority. In the virology field (HIV, hepatitis), France is also well-placed, which is in part the result of the voluntarist policy established by ANRS. In the major fields of treatment, such as degenerative nervous system disorders, diabetes and vaccines, it is essential to provide reinforcement to translational research facilities so that France may remain competitive in areas in which it provides added therapeutic value, in other words the early phases of clinical research[10,11]. Finally, the new research tax credit is undoubtedly a positive influence on France's attractiveness[12].

5. Conclusion

This survey confirms that France is a key European market. The progress that has been made in organisation and simplification of the process by which clinical research is implemented complements the recognised quality of the infrastructure and medical treatment.

Action that has been begun to strengthen France's attractiveness as a venue for clinical research should be continued in the face of growing international competition and a reduction in relative investment levels in France.

Leem (French Association of Pharmaceutical Companies) is making 5 propositions for continued action to assist clinical research in France:

1- Support a voluntary regulatory policy, particularly at Afssaps level, and especially for early-stage trials and at CPP level, with an harmonisation of processes.
2- Organise clinical research more efficiently, supported by CeNGEPS and the new hospital reforms, by simplifying administrative procedures, developing clinical investigation networks shared between communities and hospitals, and taking pharmaceutical companies clinical research into account in MERRI
3- Make clinical research even more professional, by developing new career paths in hospitals (ARC, TEC etc), by establishing hospital-based teams that are dedicated to clinical research, by emphasising the importance of clinical research in hospital-based careers and by giving a much more important role to clinical research, both in basic training and in continuing medical training
4- Pursue the construction of an environment that promotes medicine and science, supported by the efforts made in improving healthcare quality, by sharply increasing international recognition of French medical experts, by improving the visibility of centres of excellence and translational research facilities and by maintaining an attractive research tax credit system
5- Improve the image of clinical research in the general public's eyes, using campaigns led by the DGS with support from CeNGEPS

Implementation of these measures is indispensable if we are to improve the attractiveness of France in the field of clinical studies, which are an essential link between research and patients. These should also be included in a broad-scope action plan to promote Life Sciences.

Abbreviations

AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé (French Agency for the Safety of Healthcare Products), **ANRS:** National Agency for Research into AIDS and viral hepatitis; **ARC:** Clinical Research Assistant; **CeNGEPS**: National Centre for Management of Health Products Trials; **CIC:** Centre for Clinical Investigation; **CPP:** Ethics Committee; **CRO:** Contract Research Organisation; **DIRRC:** Inter-regional Delegation for Clinical Research; **FMC:** Continuing Medical Training; **GIP:** Public Interest Group; **MERRI:** General Missions for Education, Research, Reference, Innovation and appeal; **TEC:** Clinical research technician.

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Table I: Share of French market of 19 companies participating in the survey, according to country of origin

Country of origin	Participating companies[a]	Share of French market 2008 survey[b] (*2006 survey)* [4]
France	Ipsen, Pierre Fabre, Sanofi-Aventis[3], Sanofi Pasteur, Servier, SPMSD (Sanofi Pasteur MSD)	22.1 % *(22 %)*
EUROPE (excl. France)	AstraZeneca[5], Boehringer Ingelheim[15], GSK (GlaxoSmithKline)[2], Novartis[4], Roche[8]	21.3 % *(16.7 %)*
United States	Abbott[13], Amgen[14], BMS (Bristol-Myers Squibb)[11], Lilly[10], MSD (Merck Sharp & Dohme)[7], Pfizer[1], Schering Plough, Wyeth[9]	18.5 % *(22.4 %)*

[a]: *World pharmaceutical company classification*

[b]: *GERS data (Group for the Collection and Publication of Statistics) 2007*

New participants: firms which did not take part in the 2006 survey

Table II: Breakdown of studies and patients by DIRRC (Inter-regional clinical research delegation - Data sent by 11 pharmaceutical firms (225 studies and 6197 patients).

DIRRC	Number of studies* implemented per DIRCC (% carried out in France)	Number of studies begun per DIRCC (% carried out in the DIRCC)	Number of patients recruited (% patients)	Ratio No. of patients recruited/million inhabitants	Mean number of patients/study	Mean number of patients/centre
Ile-de-France	142 (22%)	35 (25%)	1886 (30%)	154	13.3	11.4
Grand Ouest	99 (15%)	17 (17%)	843 (14%)	76	8.6	8.6
Sud-Méditerranée (Soutl Mediterranean)	94 (14%)	19 (20%)	841 (14%)	113	8.9	8.2
Rhône-Alpes Auvergne	88 (13%)	8 (9%)	609 (10%)	77	6.9	7.0
Sud-Ouest (South-West)	85 (13%)	16 (19%)	728 (12%)	94	8.5	8.6
Nord-Ouest (North-West)	82 (12%)	22 (27 %)	711 (11%)	74	8.6	8.2
Nord-Est (North-East)	76 (11%)	5 (7%)	579 (9%)	69	7.6	5.8
TOTAL	666 (100%)	-	6197 (100%)	-	-	-

* : one study may involve several DIRRCs.

Table III: Comparative levels of recruitment by country (or geographical region) as shown in the 2008 and 2006 surveys (France participated in all studies)

		Studies (n)	Patients recruited [n (%)]	Patients/study (n)	Patients/active centre (n)
France[a]	2008	385	24,343 (8%)	63	7.6
	2006	*258*	*11,637 (8%)*	*46*	*6.3*
Other Western Europe[b]	2008	280	28,099 (9%)	43	7.8
	2006	*186*	*11,642 (8%)*	*30*	*7.4*
Germany	2008	255	23,904 (8%)	94	8.3
	2006	*169*	*12,725 (9%)*	*66*	*6.8*
Eastern Europe[d]	2008	243	56,764 (18%)	75	13.0
	2006	*127*	*21,108 (15%)*	*65*	*10.4*
Spain	2008	222	12,475 (4%)	56	8.1
	2006	*135*	*6,377 (5%)*	*47*	*6.5*
Italy	2008	221	14,644 (5%)	66	7.8
	2006	*120*	*5,755 (4%)*	*48*	*6.6*
United Kingdom	2008	173	16,873 (5%)	98	8.1
	2006	*103*	*4,609 (3%)*	*45*	*5.6*
Scandinavia/Northern Europe[c]	2008	172	20,599 (7%)	61	13.1
	2006	*145*	*10,479 (8%)*	*33*	*7.4*
EUROPE[e]	2008	**385**	**197,701 (63%)**	**70**	**9.8**
	2006	***258***	***84,332 (61%)***	***46***	***7.5***
Canada	2008	191	14,695 (5%)	72	6.5
	2006	*126*	*6,517 (5%)*	*47*	*6.2*
Australasia/South Africa[f]	2008	185	9,653 (3%)	38	6.7
	2006	*122*	*8,062 (6%)*	*49*	*8.3*
United States	2008	181	40,433 (13%)	197	5.7
	2006	*138*	*23,132 (17%)*	*168*	*6.1*
Latin America[g]	2008	161	23,341 (7%)	64	11.4
	2006	*93*	*7,944 (6%)*	*38*	*9.1*
Asia[h]	2008	135	22,658 (7%)	68	11.1
	2006	*50*	*4,997 (4%)*	*58*	*11*
Middle East[i]	2008	74	4,354 (1%)	47	7.5
	2006	*47*	*3,005 (2%)*	*55*	*8 9*
All countries	2008	**385**	**312,835 (100%)**	**74**	**9.5**
	2006	***258***	***137,989 (100%)***	***53***	***7.7***

Table III: (continued)

a The total numbers (385 studies in 2008 and 258 in 2006) represent all studies carried out in France and in Europe
b Other Western European Countries: Andorra, Austria, Belgium, Greece, Ireland, Luxemburg, Malta, Netherlands, Portugal and Switzerland
c Scandinavia/Northern Europe (Denmark, Finland, Iceland, Norway and Sweden)
d Eastern Europe: Armenia, Bosnia Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Serbia & Montenegro, Slovakia, Slovenia and Ukraine
e Europe: all countries on the continent, particularly Western and Eastern Europe and Scandinavia
f Australasia/South Africa: South Africa, Australia and New Zealand
g Latin America: Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Panama, Peru, Dominican Republic, Uruguay and Venezuela
h Asia: China, North Korea, South Korea, Hong Kong, India, Indonesia, Japan, Malaysia, Nepal, Philippines, Singapore, Taiwan, Thailand, Vietnam
i Middle East: Saudi Arabia, Egypt, Israel, Lebanon, Morocco, Pakistan, Tunisia, Turkey

Table IV: Geographical distribution of recruited patients in relation to the general population (per million inhabitants).

Country or geographical region	Number of patients recruited (per million inhabitants)	
	2008	***2006***
France[a]	400	*190*
Other Western Europe[b]	391	*191*
Germany	285	*155*
Scandinavia/Northern Europe[c]	833	*419*
Spain	308	*148*
Eastern Europe[d]	178	*72*
Italy	252	*99*
United Kingdom	277	*78*
EUROPE[e]	**274**	***123***
United States	133	*78*
Canada	443	*204*
Australasia/South Africa[f]	141	*119*
Latin America[g]	46	*17*
Asia[h]	6	*2*
Middle East[i]	11	*16*
All countries	**60**	***29***

a The total numbers (385 studies in 2008 and 258 in 2006) represent all studies carried out in France and in Europe
b Other Western European Countries: Andorra, Austria, Belgium, Greece, Ireland, Luxemburg, Malta, Netherlands, Portugal and Switzerland
c Scandinavia/Northern Europe (Denmark, Finland, Iceland, Norway and Sweden)
d Eastern Europe: Armenia, Bosnia Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Serbia & Montenegro, Slovakia, Slovenia and Ukraine
e Europe: all countries on the continent, particularly Western and Eastern Europe and Scandinavia
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h Asia: China, North Korea, South Korea, Hong Kong, India, Indonesia, Japan, Malaysia, Nepal, Philippines, Singapore, Taiwan, Thailand, Vietnam
i Middle East: Saudi Arabia, Egypt, Israel, Lebanon, Morocco, Pakistan, Tunisia, Turkey

Table V: Comparison of number of patients recruited per active centre, by study phase and country (or geographical region) in the 2008 and 2006 surveys.

	Number of patients/active centre 2008 (2006)			
	Phase IIA	**Phase IIB**	**Phase IIIA**	**Phase IIIB**
France[a]	6.2 (4.7)	6.5 (7.2)	7.9 (6.7)	9.5 (5.8)
Germany	5.2 (5.8)	10 (7.2)	7.2 (6.5)	12.5 (7.1)
Scandinavia/Northern Europe[b]	3.1 (7.2)	17.1 (8.1)	14.3 (7.9)	14.8 (6.3)
Spain	4.8 (4.2)	6.5 (6.6)	7.5 (6.8)	14.2 (6.5)
Eastern Europe[c]	5.7 (10.8)	14.5 (10.6)	14.3 (10.4)	12.1 (10.0)
Italy	3.7 (5.0)	6.0 (5.8)	9.7 (6.3)	7.6 (8.1)
United Kingdom	2.6 (4.1)	6.9 (5.7)	7.9 (5.7)	14.1 (6.1)
United States	3.8 (3.8)	5.1 (5.6)	6.2 (7.2)	7.6 (5.3)
Latin America[d]	16.1 (8.1)	6.0 (5.7)	11.8 (11.7)	12.0 (8.0)
Asia[e]	5.3 (3.0)	9.7 (5.7)	10.2 (12.1)	17.6 (11.6)
All countries	**5 (6 .6)**	**8.8 (7.2)**	**10 (8.3)**	**12.2(7.4)**

a The total numbers (385 studies in 2008 and 258 in 2006) represent all studies carried out in France and in Europe
b Scandinavia/Northern Europe: Denmark, Finland, Iceland, Norway and Sweden
c Eastern Europe: Armenia, Bosnia Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Serbia & Montenegro, Slovakia, Slovenia and Ukraine
d Latin America: Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Panama, Peru, Dominican Republic, Uruguay and Venezuela
e Asia: China, North Korea, South Korea, Hong Kong, India, Indonesia, Japan, Malaysia, Nepal, Philippines, Singapore, Taiwan, Thailand, Vietnam

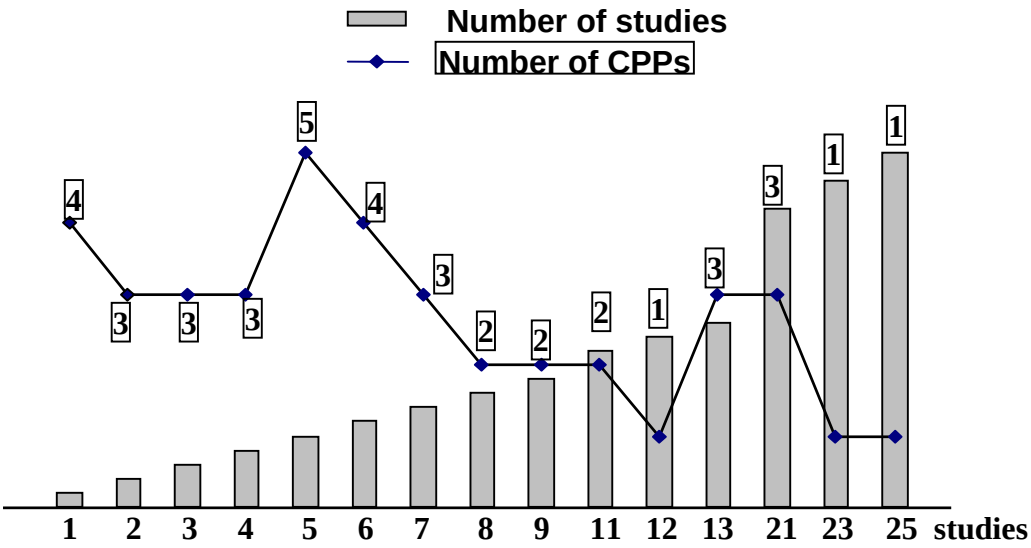
Table VI: Qualitative indicators by country or geographical region (expressed as a mean score[a])

	France	Germany	United Kingdom	Eastern Europe[b]	United States
	2008 (2006)	2008 (2006)	2008 (2006)	2008 (2006)	2008 (2006)
Attractiveness of market					
Size of market	4.6 (4.1)	4.6 (3.8)	4.5 (3.8)	2.6 (2.1)	5.0 (4.3)
Importance of registration authorities	4.3 (3.9)	4.2 (3.5)	4.5 (3.8)	2.0 (2.0)	4.8 (4.1)
Infrastructure quality					
Importance of opinion leaders	3.9 (4.2)	4 .0 (4.0)	4.4 (4.0)	2.3 (2.2)	5.0 (4.2)
Simplicity of administrative authorisation process	3.3 (2.8)	3.3 (3.3)	3.1 (2.5)	2.6 (2.5)	3.2 (3.4)
Quality of medical treatment	4.3 (4.2)	4.3 (4.0)	3.4 (3.3)	2.5 (2.4)	4.7 (3.8)
Clinical research organisation levels	3.4 (2.9)	3.4 (3.3)	3.4 (3.3)	2.6 (2.9)	4.7 (3.7)
Productiveness of clinical research					
Attractiveness of development costs	2.8 (2.7)	2.3 (2.4)	1.6 (2.2)	3.8 (3.7)	1.3 (1.8)
Quality of investigators	3.3 (3.3)	3.5 (3.5)	3.3 (3.2)	3.6 (3.4)	3.5 (3.1)
Speed of recruitment	3.1 (2.7)	3 (3.1)	2.7 (2.4)	4.2 (3.8)	2.7 (2.4)
Consistency with recruitment aims	3.4 (2.7)	3.2 (3.3)	2.8 (2.6)	4.1 (3.8)	3.0 (2.8)

a score calculated for each criterion, from 0 (least good) to 5 (best)

b Eastern Europe: Armenia, Bosnia Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, the Czech Republic, Romania, Russia, Serbia & Montenegro, Slovakia, Slovenia and Ukraine

Figure 1: How the 319 studies are distributed between 40 ethics committees (CCP)



The number in a box corresponds to the number of CPPs that have dealt with this number of studies (so 4 CPPs have each dealt with just one study, 3 CPPs have dealt with 2 studies each, 3 CPPs have dealt with 3 studies, and so on).

Figure 2: Distribution of studies by therapeutic area and by country (expressed as a % of studies).