BIOTEAM
Paris Region

How to conduct European clinical trials from the Paris Region ?

Contents

I. France

II. Paris Region: a convergence of resources

III. Appendices

I. France: an environment brimming with opportunity

More information

"Clinical trial refers to any systematic trial of a medicinal product in humans, whether in sick or healthy subjects, designed to demonstrate or verify the effects of such medicinal product and/or to verify any undesirable effects thereof and/or to study the absorption, distribution, metabolism and excretion thereof in order to establish efficacy and safety of use."

According to directive 75/318/EEC of 20 May 1975 *(JOCE L147 of 9 June 1975)*

France has one of the best health care systems in the world according to the World Health Organization. This international acclaim is built upon a highly reputed clinical research sector as well as a strict, but clear and simple regulatory and legislative framework.

France has been one of the driving forces behind European harmonization, initiating advancement in the regulatory sector and playing a strategic role in ethical issues.

As far as clinical trials are concerned, to locate in the Paris Region is to enjoy the advantages of a population 11 million strong, in the leading science and technology belt in Europe offering the resources of Europe's largest hospital platform *("AP-HP", **Assistance Publique-Hôpitaux de Paris**)* in clinical trials as well as a highly developed private medicine sector.

To locate in the Paris Region is also to have easy access to industrial decision makers, since the large majority of pharmas are headquartered here (providing 35,000 jobs), as well as to the 90% of service providers and the 150 specialized biotech firms that have chosen to locate here.

A. An environment brimming with opportunity

- Top-ranking health care system among OECD countries
- Largest pharmaceuticals manufacturer in the European Union
- Third biggest exporter of pharmaceuticals worldwide
- Highest *per capita* medicinal product consumption in the world

1. An extremely favorable market context

The pharmaceutical sector in France is one of the largest and most active in the world. The leading pharmaceuticals manufacturer in the European Union since 1995, France is also the world's third largest exporter of pharmaceuticals. In 2001, medicinal products for human use generated sales of €31.5 billion in France, with export accounting for €13 billion (41%), up 34% from the year 2000.
France allocates 9.5% of its GDP to the health sector, one of the highest proportions in Europe. Each year, companies invest €3.5 billion - or 14.2% of turnover - in R&D, ranking France third among European countries.
The dynamism of the pharmaceuticals sector in France is due in part to a robust and vigorous market. The French are the biggest consumers of medicines in the world, spending $447 *per capita* in 2000, as compared with $300 in Germany, for example.
One of the main reasons for this is the confidence the French have in their health care system, which is considered one of the best. Indeed, a WHO study conducted in 2000 on the overall performance of health care systems as judged by five criteria ranked France in first place among OECD countries. In this same classification, Japan came in 10th, the United Kingdom 18th, Germany 25th, Denmark 34th and the US 37th.

2. A long and exemplary history of drug and vaccine discovery

The Pasteur Institute was founded over a century ago with Louis Pasteur's discovery of rabies vaccine, and since then generations of scientists and researchers have kept France at the forefront. For instance, both the tuberculosis and polio vaccines were developed here. More recently, and despite lengthy debate, Professor Luc Montagnier from the Pasteur Institute was officially named as discoverer of the AIDS virus.
It was also in France, at the Evry Genopole near Paris, that the first map of the human genome was deciphered. In January 2003, Professor Jean Weissenbach's group at Genoscope published the map of human chromosome 14.

Testimony

"The continuum from basic research to innovative medical care is the hallmark, the uniqueness, the strength and the leading mission of our institutions."

From an article in *Le Monde* of 21/12/02 by **L. DEGOS**, Director of the Hematology Institute, **C. HURIET**, President of the Curie Institute, and **T. TURSZ**, Managing Director of Gustave Roussy Institute.

3. A strong willingness on the part of the government

The government is also a strong supporter of biomedical research, making it one of the top priorities in France and in Europe.

In December 2002, French legislators drafted a **bill on innovation** as part of a plan initiated back in 1999 to offer an even more favorable context for the creation of innovative new businesses and to promote R&D. The plan calls for more accessible financing, fiscal and social incentives as well as better protection of intellectual property.

The "Drug and Biotechnology Mission" is one example of how the government is promoting innovation and development of biotech know-how. This mission will fund research on therapeutics, genomics, gene and cell therapy.

Cancer research is also a major focus in France. Research budgets for 2003 have risen 250%. The government's Cancer project aims to create a national cancer institute to coordinate research and clinical trials.

European Union member states have agreed to increase research expenditures to 3% of GDP by the year 2010. The European Commission is rallying against diseases borne of poverty (primarily AIDS, malaria and tuberculosis), allocating €200 million for clinical trials in partnership between Europe and developing countries via the EDCTP *(European and Developing Countries Clinical Trials Partnership).*

4. From basic research to the clinic: an original and efficient structure

In contrast to other countries, the French hospital system places special priority on research *(see opposite).* Practitioners in teaching hospitals devote 50% of their time to research and 50% to clinical activities. When it comes to conducting clinical trials, this twofold competence offers greater accessibility to patients and boosts recruitment potential.

What's more, this umbrella structure facilitates the creation of networks of experts from a wide variety of internationally renowned research institutions including those involved in basic research such as the CNRS *(Centre Nationale de la Recherche Scientifique)*, INSERM *(Institut National de la Santé et de la Recherche Médicale)* and the life sciences division of the CEA *(Commissariat à l'Energie Atomique).*

Organizations like the CNRS and INSERM are taking important steps to promote clinical research, granting physicians a 5-year sabbatical from clinical activities to devote themselves entirely to research.

French teaching hospitals are very open to outside collaborations. Over an 8-year period, 75% of industry-sponsored clinical trials were conducted there *(Légibio survey 2002/2003).*

B. From research to market: considerable advantages for France

1. Medical and scientific know-how backed by solid references

a. Strict training requirements

To guarantee top quality diagnosis and patient follow-up, French clinical trial investigators are required to hold an M.D. degree. This medical qualification, together with the professionalism of Clinical Research Assistants (CRA) who receive both theoretical and practical training, guarantees that clinical trials will be conducted with seriousness and rigour, two critical factors.

b. Competence and expertise that pharmaceutical companies appreciate

Thanks to their extensive clinical trial experience, French investigators have won international recognition in all the major disciplines, from cardiology to oncology to hematology, AIDS and many more. Pharmaceutical companies especially appreciate the strict ethical and regulatory environment in which these investigators work, since they can be assured of meeting their quality standards.

2. A truly enviable position when it comes to clinical trial costs

A soon-to-be-released survey by the French Pharmaceutical Industry Association (LEEM) polled 11 French and foreign-based companies with locations in France, accounting for 44% of the market. France clearly proved to offer an unequalled cost advantage when it comes to conducting clinical trials. In fact, France has the second lowest costs in Europe, just after Belgium, and lower than the United Kingdom, the Scandinavian countries and Germany. As for the oft-cited US, clinical trial costs are half again what they are in France.

Importantly, in France, patients participating in biomedical research with direct individual benefit do not receive payment, which not only lowers costs but also and above all guarantees the quality of the trial data, since there is better compliance with the requirement to not participate in other studies at the same time.

It should also be pointed out that the Conseil National de l'Ordre des Médecins (CNOM) enforces transparency of investigators' fees, thereby avoiding fee competition which can only be a detriment to trial conduct.

More information

Good Clinical Practice (GCP) consists of a set of guidelines governing the design, conduct and reporting of clinical trials so as to guarantee the credibility of the trial data, and protect the rights and safety of the subjects, as well as the confidentiality of the information concerning them. These principles apply to the four phases of drug evaluation.
The current reference in France is the GCP guide version 4 dated 3/7/95, based on the European GCP guide.

Ethics Committees (*CCPPRB - Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale)*, **a key role in France.**

These are independent committees made up of representatives from the medical and paramedical professions as well as persons outside the health fields (legal expert, persons qualified in ethics and social matters), to whom all research projects must be submitted for an opinion. Their role is to examine the study protocol and deliver an opinion on the conditions of validity of the research in respect of the protection of subjects, payment rendered, the scientific relevance of the project, the adequacy of the means in relation to the objectives, and the qualifications of the investigator(s).

Steps necessary for clinical trials launch

1. Before trial start

SPONSOR

Selection of investigators:
> Must be an M.D., registered in the *Ordre des Médecins*
> Research agreement sent to the *Conseil de l'Ordre des Médecins*

Selection of study sites: site authorization required for studies without direct individual benefit. The AFSSAPS* delivers the authorization and the access code to the national file of persons undergoing clinical research.

Partners:
> Hospitals (CIC*)
> Research centers
> GPs
> CROs

Update investigator's brochure

Prepare research protocol

Principal investigator submits study protocol to Ethics Committee (CCPPRB*)
Only a single opinion is required and it is final (response time : 8 days).
In the case of nominative data, CNIL* authorization is required (annual declaration possible).

If the Ethics Committee pronounces in favor, the sponsor sends a **letter of intent** to the AFSSAPS*.

2. During trial start

Obtain signed informed consent of the patients
- Without direct individual benefit (healthy volunteers): voluntary basis, payment possible. Verification in national file of persons undergoing biomedical research.
- With direct individual benefit (patients): voluntary basis, no payment.

CIC: Clinical Investigation Center - CCPPRB: Comité Consultatif pour la Protection des Personnes en Recherche Clinique (Ethics Committee) - AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé (French Medicines Agency) - CNIL: Commission Nationale de l'Informatique et des Libertés (National Commission on Computerized Data Processing and Civil Liberties)

3. Procedural simplicity - France again stands out

This same LEEM study highlighted the simplicity of procedures in France. Not surprising, since for the past 15 years France has enacted strict, straightforward and clear legislation to guarantee the proper organization and conduct of clinical trials. The Huriet-Sérusclat law, enacted in December 1988, lays down the conditions under which research protocols may be undertaken and the role of the different parties (sponsor, investigator) and provides for the legal protection of research subjects.

Institutional Review Boards [Ethics Committees : CCPPRB *(Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale)*] see to it that this law is enforced in order that clinical trials be conducted in a spirit of confidence between sponsors, investigators and patients, and with transparency of methods.

a. Approval of only one Ethics Committee saves time and cuts costs

Unlike other European countries such as the United Kingdom, coordinating investigators of multicenter trials in France are required to obtain the opinion of **only one Ethics Committee** (CCPPRB) and can choose between the different Ethics Committees in their region *(see "More information" page 17).*

All the companies polled in the LEEM survey considered this special feature of the French system to be a major advantage that makes it easier and quicker to set up study sites in France. Less time and lower costs are a winning combination in the race to market.

b. Short timelines

The Ethics Committee is required to issue its opinion in a maximum of 5 weeks (generally about 8 days). **This opinion is final** (in the case of an unfavorable opinion, the protocol cannot be submitted to another Ethics Committee). Ethics Committee approval is the starting point for trial set up. Once approval is obtained, the sponsor can send **the letter of intent** to the Ministry of Health through the AFSSAPS ("Agence Française de Sécurité Sanitaire des Produits de Santé", French Medicines Agency).

c. AFSSAPS : the French drug registration authority

To facilitate administrative procedures, all matters relating to human health products have been merged under the aegis of the AFSSAPS:

- The Marketing Authorization Commission, which delivers the product license,
- The Transparency Commission, which determines the level of reimbursement of the drug by the French health insurance system (100% reimbursement for irreplaceable drugs for serious and debilitating illnesses, 65% for drugs indicated in serious illnesses, 35 % for symptomatic treatments of commonplace benign illnesses),
- The Health Products Economic Committee *(CESP: Comité Economique des Produits de Santé)* serves as an interface between the government and the pharmaceutical company and negotiates the best price in the common interest,
- The Advertising Commission checks that the legally required information intended for the public and for health professionals conforms to the marketing authorization label.

In the year 2000, 683 marketing authorizations were delivered. In 2001, 4340 proprietary medicinal products comprising 7630 presentations were marketed in France.

4. French legislation, a driving force behind European directives

The Huriet-Sérusclat law, which is regularly updated to keep in line with scientific progress, served as the reference for the new European directive of April 2001 *(ref: 2001/20/CE/JOCE No L121 of 01/05/2001),* "on the approximation of laws, regulations or administrative provisions relating to the application of good clinical practice in the conduct of clinical trials". This directive will come into force in 2004 in all the European Member States. However, in contrast to most Member States, implementation of this directive will not incur any major changes in France.

This European harmonization will simplify the conduct of multicenter trials by instituting similar methods throughout Europe. Furthermore, it will apply to candidate countries applying for European Community membership, thereby guaranteeing the same standard of ethics already attained in France.

Testimony

Clinical trials and the AFSSAPS

"The AFSSAPS is the single step for declaring and registering clinical trials conducted in France, whether on medicinal products, gene or cell therapy, medical devices or cosmetics. As laid down in the Huriet law of 1988, all trials must be declared, evaluated and monitored according to their specific requirements. As far as medicinal products are concerned, the AFSSAPS receives more than 1300 clinical trial letters of intent each year, or twice the European average, ***including some 300 phase 1-2 trials on investigational drugs.*** *The pharmaceuticals industry sponsors 80 % of the medicinal product clinical trials conducted in France.*

The AFSSAPS enlists the help of expert groups dedicated specifically to clinical trials. It releases listings of clinical trials in France on serious or orphan diseases in order to help boost recruitment and keep both the public and research sectors informed and up to date."

Doctor Chantal BELORGEY, Head of the Clinical Trials Division of the AFSSAPS

"*The AFSSAPS* *is actively involved with European authorities in developing clinical trial legislation and guidelines. For example,* ***France is the rapporteur or co-rapporteur for preparation of the main guidelines in the forthcoming European directive*** *laying down a harmonized regulatory framework for clinical trial conduct among all EU member states. In addition to clinical trials, France also plays an active role in Community-wide medicinal product evaluation and authorization procedures (CPMP* co-presidency; pharmacovigilance working party and biotechnology working party presidency). As a member of the COMP**, France helps to promote the development of orphan drugs. At the national level, the AFSSAPS makes its scientific services available to pharmaceutical companies during drug development. For instance,* ***some 20 work groups are held each month at the request of firms developing medicinal products, to discuss aspects of clinical or non-clinical development, particularly when there are difficulties interpreting the guidelines or when expert validation of a clinical protocol design is needed.*** *These scientific meetings serve as a cross-link between the different stages of drug development, since during a single meeting the pharmaceutical firm may meet with AFSSAPS groups in charge of clinical trials and in charge of medicinal product evaluation, and can even address matters relating to registration strategy"*

Jean-Hugues TROUVIN, Director of the Medicinal and Biological Products Evaluation Division, AFSSAPS

*Commitee for Proprietary Medicinal Products

**Commitee for Orphan Medicinal Products

More information

Medical devices: G-MED, the most active notified body in Europe (CE marking)

Research on medical devices (prostheses, implantable devices, appliances of all types) must conform to regulatory requirements (in-house expertise, expert review before certification). In France, the G-MED notification body covers all categories of medical devices as well as all conformity assessment procedures required by European directives (CE marking).

G-MED is one of Europe's most active notified bodies for medical device evaluation, delivering 1500 certifications to over 500 European and international companies.

At the international level, G-MED takes part in implementing Bilateral Agreements and mutual recognition between the European Union, the United States, Canada, Australia and New Zealand.

www.gmed.fr

5. Registration procedures have already been harmonized

Despite differences in the quality and organization of health care systems from one country to another, all European marketing authorization procedures are now harmonized (26 January 1998, date at which the European Centralized Procedure came into force).

Access to the Community market must be obtained either through the Centralized Procedure or through the Mutual Recognition Procedure:

- In the Centralized Procedure, the company files the application dossier with the EMEA *(European Agency for the Evaluation of Medicinal Products)* based in London, just 1 hour from Paris by air. If the marketing authorization is granted, it is automatically valid in all EU member states. This procedure is mandatory for all biotechnology-derived products.
- The second possibility is the Mutual Recognition Procedure, one of the strong points of the European system. This procedure allows a medicinal product marketing authorization obtained in one member state, the "reference member state", to be valid in the other member states. Pricing is negotiated at the local level.

The ICH *(International Conference for Harmonization)* is an organization that promotes international harmonization between Europe, Japan and the United States.

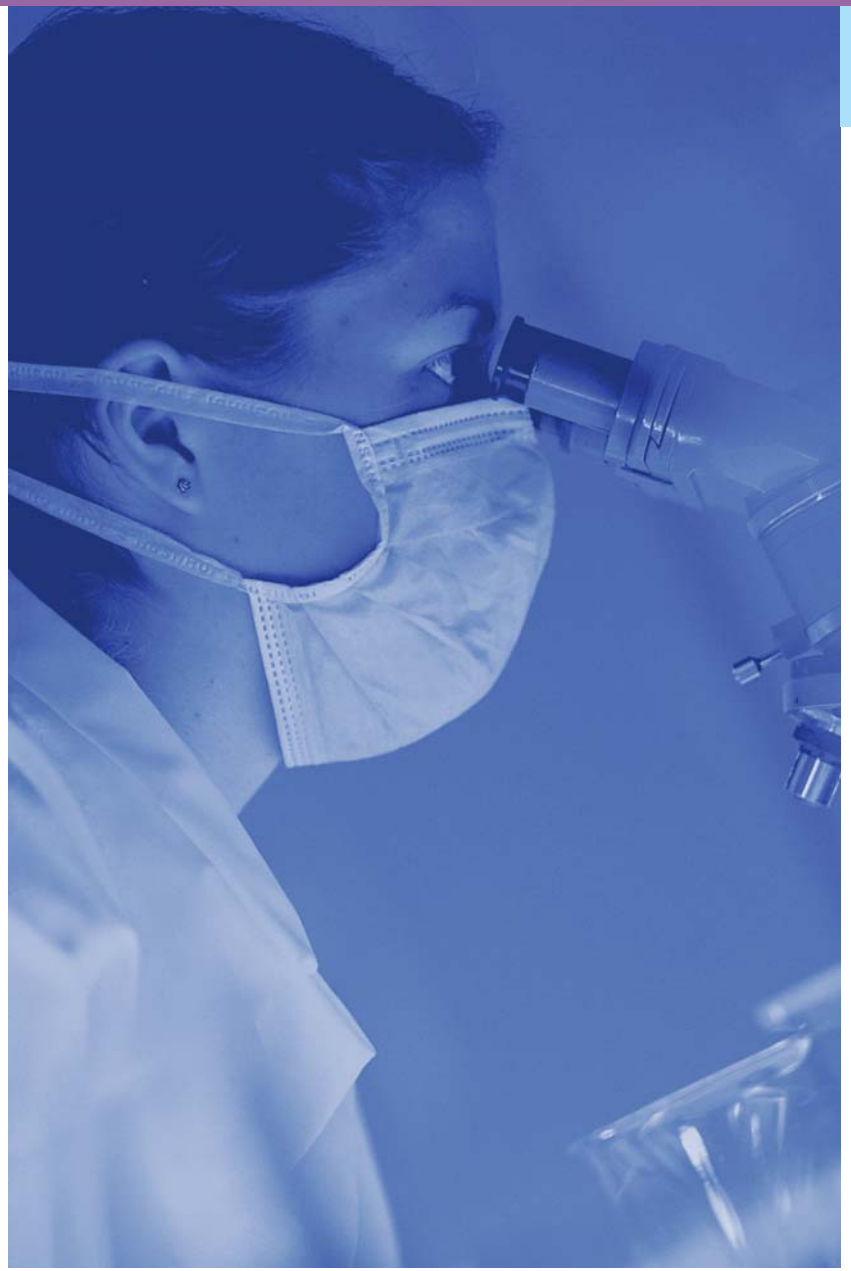
Its mission is to harmonize new drug registration procedures in these three main zones so as to internationalize the pharmaceuticals market while lowering development costs.

In comparison with other member states, the strong market and high population in France are true assets.

Indeed, France is a country that cannot be ignored when developing clinical trials in Europe, whether on new drugs, diagnostic methods or medical devices.

Together, these factors make France a top choice as strategic location in Europe.
As one of Europe's biggest economies (generating over 5% of European GDP), the leading tourist destination in the world, and an economic and financial stronghold of the Franco-German axis underlying the European Union, the Paris Region offers exceptional resources that have made clinical research in France so attractive to pharmaceutical companies:

- A large and highly diverse population of 11 million people
- A medical and scientific platform unequalled in all of France
  (41 state-run hospitals with over 25,000 beds)
- Internationally recognized know-how in a wide variety of fields
- Strong presence of key players:
  - Internationally acclaimed research centers
  - Headquarters of major French and foreign companies
  - Virtually all service providers (90% of CRO nationwide)
  - Headquarters of French regulatory bodies
- Major transportation hub for domestic and international travel
- High speed telecommunications network for data transmission.



II. Paris Region: a convergence of resources

A. The Paris Region, an extraordinary "catchment area" for patients

1. Strong recruitment potential

An article appearing in the March 2002 issue of the American journal *"Applied Clinical Trials"*, titled *"Consider geography"* defines "catchment area" as a combination of criteria favorable to the conduct of clinical trials:

- Size of the population,
- Concentration of the population,
- Diversity of the population.

The article cites the Paris Region as one of four European or North American regions that meet all these criteria :

- 11 million people living in the 8 counties of the Paris Region, or 912 people per square kilometer (over 2000/km² in Paris city limits),
- A truly cosmopolitan region offering high ethnic and cultural diversity for a vast choice of patient profiles.

2. A highly developed medical sector

Accessibility to patients is further enhanced by the high density of medical facilities in the Paris Region. The state-run hospitals alone count more than 25,000 beds and treat over 11 million patients annually.

The number of physicians per 100,000 people is 380 in Paris Region and 400 in Paris city limits as compared to 300 nationally.
Some 42,000 doctors practice in the Paris Region, or close to 24% of the nationwide total. Each year they see 56 million patients for office visits and make 8 million house calls.

Outpatient medicine is a booming sector, making it easy to set up clinical trial programs among private practitioners in the Paris Region. With over 25,000 practitioners in private practice, investigators have access to a high quality network with a large patient population in pathologies such as virology, infectious diseases, asthma, diabetes, hypertension, etc. Networking between GPs involved in biomedical research promotes even easier access to the private medicine sector.

B. A hub of expertise

1. Major research and teaching centers

The Paris Region plays host to a number of internationally renowned research centers and institutions as well as reputed medical schools that all help drive research nationwide:

- Pasteur Institute, the world reference in infectious diseases,
- INSERM *(Institut National de la Santé et de la Recherche Médicale, National Institute for Health and Medical Research),*
- CNRS *(Centre National de la Recherche Scientifique, National Center for Scientific Research),*
- Life Sciences division of the CEA *(Commissariat à l'Energie Atomique, Atomic Energy Commission)* with research laboratories on AIDS and prions, radiobiology and radiopathology, functional genomics, biochips, etc.,
- Gustave Roussy Institute, the largest cancer institute in Europe,
- Curie Institute, a research center entirely dedicated to cancer research,
- National Cancer Genomics Institute of Hôpital Saint-Louis,
- National genome sequencing center in Evry,
- Etablissement Français du Sang,
- Medical ethics and public health laboratory of Hôpital Necker,
- 11 medical schools,
- 2 pharmacy schools (Cochin and Chatenay Malabry).

This makes for an especially dense network of 66,000 researchers and clinicians working in the Paris Region, accounting for 43% of research activities nationwide and focusing on areas such as biomaterials, photonics, bioIT and nuclear magnetic resonance, to name a few.

2. Publications and patents : illustrating the strength of research in the life sciences

In terms of the number of scientific publications, the Paris Region accounts for 2% of all articles published worldwide in 1998 and holds an especially strong position in genetic engineering (2.8% of publications worldwide), pharmacology and pharmacy (2.6%), and cell and molecular biology (2.6%). 51.6% of French patents in the field of "biotechnological therapies and treatments" were filed by researchers and clinicians from the Paris Region.

AP-HP groups alone have authored or co-authored over 2000 original English language articles in peer-reviewed journals.

Testimony

*"In 2001-2002, we carried out a study in **AP-HP hospitals** on 300 patients with septic shock, a major cause of mortality. This study ran counter to the mainstream thinking that previous industry-sponsored trials did not conclusively identify any alternative treatments. **Our study,** which was funded by AP-AP and Germed, **is the very example of a successful institutional trial.** The inexpensive treatment validated in this study has saved many lives and has become an international standard."*

Professeur Djillali ANNANE , principal investigator of the Gerinf-05 study, Hôpital Raymond Poincaré

Also see the article in the *Wall Street Journal* of 21 August 2002 "French Study Finds Steroids Can Help Fight Septic Shock".

Testimony

"The mission of AP-HP's Research and Patent Promotion group *is to promote the innovations developed by AP-HP clinicians, alone or within the scope of industrial research alliances. In the latter case, patents are jointly held. Examples include industrial collaborations with Amgen, Biosphere Medical and Sanofi.*

Technology transfer agreements may also be drawn up with industrial partners.

Results of clinical trials sponsored by AP-HP may be transferred to companies for inclusion in marketing authorization applications to the French Medicines Agency, the EMEA or the US FDA.
One recent example is Takeda."

Florence GHRENASSIA, in charge of Research and Patent Promotion - Assistance Publique-Hôpitaux de Paris

*"**Assistance Publique-Hôpitaux de Paris has set up many international collaborations** for its clinical research activities and participates in research projects cofunded by the European Commission under its Technology Research and Development Program. In particular, AP-HP is a partner in the rare EC-funded trials in orphan diseases, as well as in cardiovascular disease, cancer and gene and cell therapy, for wich AP-HP has won a reputation for excellence."*

Philippe ARHETS, Director of the DRRC European Research Program

3. The AP-HP hospitals (Assistance Publique-Hôpitaux de Paris)

a. The biggest hospital network in Europe

AP-HP is the largest employer in the Paris Region, with 90,000 people working at the 41 internationally acclaimed hospitals (La Pitié Salpetrière, Necker-Enfants Malades, Antoine Béclère, Saint-Louis, Saint-Antoine, Henri Mondor, Paul Brousse, Bichat...). With more than 19,000 medical staff, 3000 hospital physicians including 1000 professors and more than 6000 interns and medical students, AP-HP's staff cover all the major specialties.

AP-HP hospitals provide 25,000 beds; in 2000 they organized over 1 million hospitalizations and 5 million consultations, and treated an emergency every 34 seconds.

The big names in French medicine, all international opinion leaders, teach and practice at AP-HP hospitals.

b. The largest European clinical trial center

AP-HP hospitals represent the largest clinical trial site in Europe. In 2001-2002, 412 active biomedical research projects were undertaken with a cumulative recruitment of 42,200 patients. More than a third of these projects dealt with pathophysiology, another third were drug trials, and 12.2% concerned genetic research studies.

- *Clinical Investigation Centers, dedicated to clinical research*

This important mission of institutional clinical research revolves around eight clinical investigation centers (CIC) in the Paris Region. Born of a partnership between INSERM and AP-HP and based on the French hallmark of continuum between basic and clinical research, these eight centers further reinforce the scientific, technical and logistical resources that the Paris Region has to offer.
The CIC provide investigators with an ideal environment for all the stages of a clinical trial, from project preparation to execution and follow-up. Thanks to the CIC, France and especially the Paris Region rank competitively in phase I and 2 trials.
The centers provide their pharma and biotech partners with: spaces dedicated to clinical research (special facilities, qualified staff), methodological guidelines, technical assistance for regulatory procedures and protocol implementation, assistance with patient recruitment.

Each CIC in the Paris Region has its own speciality: hematology at Hôpital Saint-Louis, cardiology at Henri Mondor and Hôpital G. Pompidou, pneumology at Bichat, neurology at La Pitié Salpétrière, pharmacology at Saint-Antoine and pediatrics at R. Debré and Necker.

● *Promoting cooperation with the pharmaceutical industry*

One of the main goals of AP-HP is to establish industrial partnerships **to promote transparent and formalized cooperation**.

The French Pharmaceutical Industry Association (LEEM) recently signed an agreement with all the French teaching hospital centers, including AP-HP, as well as with the FHF (Fédération Hospitalière de France). This agreement, which took effect on 1st January 2003, is designed to facilitate collaborations which are already in place. Indeed, in 2000 there were 1264 industry-sponsored clinical trials enrolling over 7000 subjects.

This agreement provides for:

- harmonizing the method of calculating hospital added costs,
- standardizing documents.

It is expected to lighten the administrative load and improve communication between partners. It will be an important factor in shortening the time to results and keeping costs down.

Testimony

***"The DRRC** (Regional Clinical Research Delegation) can answer bids for clinical trial sponsorship invited by institutions or the Ministry of Health, particularly under its Hospital Clinical Research Program.*

*Within the scope of its industrial partnerships, the DRRC can also act as sponsor of international multicenter trials. **One example is a trial conducted in partnership with Genzyme; this trial was audited for FDA-compliance prior to commencement.***

This partnership allows several industry-sponsored trials (phase I and IIa) to take place simultaneously in one or more of AP-HP's eight CIC. This type of agreement has been set up with Novartis Pharma, for example.

DRRC partnerships may also be based upon industry cofinancing for trial-related added costs, after review of the clinical research project by the Scientific Expert Panel. Industrial partners can also provide funding for AP-HP-sponsored trials, as in the case of Takara".

Nicolas BEST , General Secretary of the Délégation Régionale à la Recherche Clinique - Assistance Publique-Hôpitaux de Paris.

***"French hospitals** work with the pharmaceutical industry on a daily basis. This priviliged collaboration, which will become even stronger, is their guarantee of access and contribution to pharmaceutical innovation, and continuous training of their staff, and ultimately it benefits patients. It is one of the full-fledged missions of hospital public service".*

Vincent DIEBOLT, coordinator of the "Research, Innovation and Promotion" pole of the Fédération Hospitalière de France.

Testimony

“In the Paris Region, we enjoy wide-ranging expertise in many different therapeutic fields as well as top quality hospital platforms. Easy access to patients and simplified ethics committee procedures promote considerable time savings.
I'm convinced that Japanese companies will find real advantages in locating in Ile de France. Through bridging and ICH E5 guidelines, they can reduce the number of their national trials."

Doctor Jérôme d'ENFERT, Medical Director, Laboratoire Aventis

Doctor d'ENFERT spent three years as **R&D director at Laboratoire Aventis in Tokyo.**

C. Concentration and proximity of key players

1. Paris Region: headquarters of the major pharmaceutical concerns

Attracted by the size of the market, the excellence of its scientific and medical research centers, and the largest hospital system in Europe, many French and foreign pharmaceutical groups have opted to locate in the Paris Region.
In fact, the Paris Region plays host to 40% of the pharmaceutical industry workforce. The three leaders on the French market (private + hospital medicine) - Aventis Pharma, Sanofi-Synthélabo and GlaxoSmithKline - are headquartered here, and companies such as Pfizer, Bayer Pharma, Novartis, UPSA, Astra Zeneca, Servier, Produits Roche, Bristol Meyer Squibb and the Japanese firms Takeda, Chugai and Fujisawa are present as well. Novartis is conducting 85 international clinical trials in France in which 3500-4000 patients are enrolled each year.

"At Sanofi-Synthélabo, second on the French market, 50 new drugs have been developed from France, including 21 currently in phase 2 or 3", notes Monique Couderc, in charge of clinical trials at this company.

In 2002, Aventis France sponsored 149 clinical trials in France involving 3664 investigators and 4552 patients among whom 38% of investigators and 32% of the patients where from the Paris Region *(see opposite)*.
These few examples illustrate the high potential that in the Paris Region has to offer.

2. 90% of CRO located in the Paris Region

Increasingly complex and costly research has led pharmaceutical companies to outsource or subcontract all or part of their clinical trial activities. All the companies in the LEEM survey cited above practice outsourcing; one-third of pre-market authorization monitoring and 80 % of post-marketing data management are subcontracted.

A study by Xerfi showed that the CRO market is a growing sector, with a 30% increase in turnover predicted in Europe for 2003.
Companies can therefore find in the Paris Region a guarantee of a wide choice of service providers, since 90% of CRO are located here, including world leaders like MDS, Quintiles, Parexel, Kendle, Aster Cephac and Thérapharm-Recherches.

3. Centralized administration in the Paris Region

The Paris Region affords sponsors and investigators easy access to all regulatory bodies. Investigators have no trouble finding an Ethics Committee rapidly since the Paris Region counts 14 Ethics Committees in different types of structures.

Also, the registration authorities such as the AFSSAPS are headquartered in Paris and have combined their different commissions to facilitate procedures for French and foreign investigators and sponsors *(see page 8)*.

Testimony

"THERAPHARM Recherches *specializes in clinical research and clinical studies.* ***Our specific positioning stems first from our integral coverage of phase I to IV trials in all of Europe, and secondly from our specific expertise in phase I trials with Japanese subjects.***
Our activity requires that our staff travel extensively in France and Europe to monitor our clinical trials. The Paris Region serves as an ideal hub linking different modes of transportation, with close proximity to the headquarters of all the main European, American and Japanese pharmaceutical groups and less than 2 hours from other major European capitals. THERAPHARM Recherches' strategic location in the Paris Region allows us to rapidly respond to our customers' needs and conduct clinical trials throughout Europe."

Philippe RENOUT, General Manager Associate, THERAPHARM Recherches

D. An outstanding transportation hub

All the companies surveyed emphasized the extensive and excellent transportation network in the Paris Region, perfectly suited to the needs of clinical trials, which involve large numbers of people and often require travel for study monitoring.

As Doctor d'Enfert, the Medical Director of Laboratoire Aventis, notes: *"Transportation facilities in the Paris Region make it easy for our clinical research assistants (CRAs) to be based in Paris and travel domestically or internationally whenever needed"*.

The quality and density of its road, rail and air links make the Paris Region an ideal hub for domestic and international travel.

E. High speed telecommunications networks

A secured, high speed communications infrastructure allows rapid and efficient transmission of clinical trial data.

Lundbeck, a Danish company specializing in nervous system disorders, has already set up its international clinical research center in Paris, and recently decided to locate its worldwide clinical trial data management division in the Paris Region.

Its market potential and innumerable resources make the Paris Region a top choice for clinical development in Europe.

III. Appendices

III. Special thanks to the following people who made important contributions to this document

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France offers many advantages

A conducive market context

> Top-ranking health care system among OECD countries *(WHO survey - 2000)*
> Leading pharmaceuticals manufacturer in the European Union (€31.5 billion in 2001)
> World's third largest pharmaceuticals exporter (€13 billion in 2001, or 41% of turnover)
> Highest per capita medicinal product consumption in the world (€447 per person)

An internationally recognized tradition of excellence in medical research dating back to Louis Pasteur.

A strict, clear and simple legislative and regulatory framework which has served as a reference for European directives.

A system whose simplicity is greatly appreciated by pharmaceutical companies (survey by LEEM, the French Pharmaceutical Manufacturers Association): the opinion of only one Ethics Committee is required for study initiation.

Second lowest clinical trial costs in the European Union after Belgium, far lower than the UK, Germany and the US (LEEM survey).

Paris-Region: a convergence of resources

Easy access to patients

> A large and diverse population of 11 million, with 912 people per square kilometer
> A high density of medical facilities: 42,000 MDs including 24,500 private practitioners (380 physicians per 100,000 people), 77,000 hospital beds including 25,000 in state-run hospitals, 55 million office visits and 8 million house calls annually.

Wide-ranging expertise in many different fields

> Paris Region: location of leading research centers, institutions and universities including INSERM (Institut National de la Santé et de la Recherche Médicale), CNRS (Centre National de la Recherche Scientifique), the life sciences division of the CEA (Commissariat à l'Energie Atomique), Genomics Institute
> The largest hospital system in Europe (41 hospitals, 25,000 beds), the largest European clinical trial site (42,000 patients enrolled in 412 studies), and 8 Clinical Investigation Centers dedicated to clinical research, the only network of its kind in Europe
> Promotion of collaborations between hospitals and industry: a top priority backed by an official master agreement

Concentration and proximity of other key players

> Major pharmas including Aventis, SanofiSynthélabo, GlaxoSmithKline, Pfizer, etc.
> 90% of all CRO (Contact Research Organizations) nationwide
> Presence of administrative bodies: 14 Ethics Committees (CCPPRB - Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale); headquarters of the AFSSAPS *(Agence Française de Sécurité Sanitaire des Produits de Santé)*, the French registration authority.

An outstanding travel hub for easy links with the many parties involved in the conduct of clinical trials.

High speed telecommunication lines for data transmission.

III. BioTeam® Paris Region

BioTeam® Paris Region
A banner, a network of competencies

BioTeam® Paris Region is a network of biotechnologies in the Paris Ile de France region. It promotes the biotechnology industry from Ile de France on an international scale to become a leader in Europe.

The Paris Region is a leading technology park in France with tight links between education, advanced training, research and industry. There are two main locations - Paris and the Essonne county - where our biotechnologies are clustered. Both benefit from a closely knit fabric of research institutes *(CNRS, INSERM, CEA, Centre National de Séquençage et de Génotypage, Institut Pasteur...)*, of great hospitals where clinical trials are carried out (namely *Assistance Publique - Hôpitaux de Paris*), of promising and dynamic companies (sixty in total for both clusters including *Genset, Neurotech, I.D.M., Genodyssée, Hybrigenics, Exonhit Therapeutics, etc.*), and of structures to accommodate and support startups (incubators and nurseries).
This is a consistent environment supported by partners who contribute their competencies in the technological, legal and financial fields.

BioTeam® Paris Region partners are:

> Paris Regional Development Agency in Ile-de-France (PRDA)
> Agence pour l'Economie en Essonne (AEE)
> Paris Développement Agency (PDA)

Jointly they have filed an application for the trademark BioTeam® Paris Region. This network will work with other representative local partners operating in life sciences who wish to become involved in the process. Together, these partners will conduct converging actions to more efficiently promote the biotechnology industry throughout the world.

Objectives

> In the short term - Use the BioTeam® Paris Region banner to enhance the image of Biotechnologies in Ile de France on the international scene
> On the medium term - Expand the BioTeam® Paris Region network, add to it with additional competencies, open it up to all companies from the greater Paris Region.

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