REGULATORY ENVIRONMENT

1. Introduction

Research and development work, pre-clinical tests, clinical studies, facilities, and the manufacture and sale of the Company’s products are and will continue to be subject to the complex legislative and regulatory provisions laid down by the various public authorities in France, Europe, the United States and other countries. The European Medicines Agency (“EMEA”), the Food and Drug Administration (“FDA”) in the United States, l’Agence Française de Sécurité Sanitaire des Produits de Santé (“AFSSAPS”) in France and the equivalent regulatory authorities in other countries impose considerable constraints on the development, clinical trials, manufacturing and sale of products such as those developed by the Company. In case of non-compliance with these regulations, the regulatory authorities may impose fines, seize or remove products from the market or even partially or totally suspend their production. They may also revoke previously granted marketing authorizations, reject authorization applications filed by the Company and undertake legal proceedings. These regulatory constraints are important in considering whether an active ingredient can ultimately become a drug, as well as for recognizing the time and investments necessary for such development.

Although there are differences from one country to another, the development of therapeutic products for human use is essentially subject to identical procedures and must comply with the same types of regulations in all developed countries. To obtain marketing authorization for a product, proof must generally be provided of its efficacy and safety, along with detailed information on its composition and manufacturing process. This entails conducting sizeable pharmaceutical and pre-clinical developments, clinical trials and laboratory tests. The development of a new drug from fundamental research to marketing comprises five steps: (i) research, (ii) pre-clinical trials, (iii) clinical trials in humans, (iv) marketing authorization and (v) marketing.

In France, law No. 88-1138 of 20 December 1988, referred to as the Huriet-Sérusclat law, amended by law No. 2004-806 of 9 August 2004 on public health policy, sets the conditions under which biological research should be organized for the development of drug candidates. This law added Articles L. 1121-1 et seq. to the French Public Health Code in a Section devoted to biomedical research.

2. Regulation of clinical trials

In humans, clinical trials are usually carried out in three phases that are generally sequential, but can also overlap, as described in Section 6.3.2 of this Reference Document. Clinical trials are sometimes necessary after marketing to explain certain side-effects, investigate a specific pharmacological effect, obtain more accurate additional data or explore new indications. Regulatory authorization is needed to carry out clinical trials. The regulatory authorities may block, suspend or require significant modifications to the clinical study protocols submitted by companies seeking to test products.

Clinical trial authorization

European directive 2001/20/EC of 4 April 2001 concerning the application of Good Clinical Practices in conducting clinical trials of drugs for human use, was transposed into French legislation by law No. 2004-806 of 9 August 2004 concerning public health policy and decree No. 2006-477 of 26 April 2006 amending the Article of the French Public Health Code regarding biomedical research, completed by several Ministerial orders dated 24 May 2006. This regulation replaces the declaration system laid down in the Huriet-Sérusclat law of 20 December 1988, which required that a biomedical research protocol be presented to an Advisory Committee for an advisory opinion for the protection of individuals in biomedical research, and a statement by the promoter of the protocol to the AFSSAPS (French Agency for the Safety of Healthcare Products, which became the ANSM in 2012) before the start of clinical trials. From August 27, 2006, when this new legal and regulatory framework was implemented in France, a clinical trial must be authorized by the ANSM and receive a positive opinion from an ethic committee before its starts. The ANSM manages and evaluates biomedical research on health products. In broad terms, the agency evaluates the safety and the quality of the product used in research, with the objective of ensuring the safety of persons involved in the research.

According to Article L. 1123-7 of said code, the Committee gives its opinion on the conditions of validity of the research, notably regarding the protection of participants and their personal information and the method for acquiring their informed consent, as well as the overall relevance of the project, the satisfactory evaluation of benefits and risks and the appropriateness of the resources implemented to meet the objectives. The ANSM can inform the initiator that it has objections to undertaking the research. The promoter may then modify the content of the research project and submit a new application to the ANSM; however, such a procedure may only be applied once. If the promoter does not
modify the content of his application, it is considered as being rejected. According to the terms of the decree of 26 April 2006, the time for examining the application for authorization may not exceed 60 days from the date on which the complete file was received. Lastly, according to Article L. 1123-11, if there is a public health risk or if the ANSM considers that the conditions under which the research is carried out no longer comply with the conditions in the application for authorization or do not comply with the provisions of the French Public Health Code, it may at any time request that the research procedures be modified, and may suspend or even prohibit the research.

The current regulations relating to clinical trials, which are governed by the 2001 Directive cited above, are in the process of being revised.

Following tripartite negotiations with the European Parliament and the European Commission and Council, on December 20, 2013 the Member States (Coreper) approved a compromise text with the European Parliament in relation to the draft Regulation on clinical trials (2012/0192(COD)).

The new legislation takes the form of a European Regulation, allowing the rules for clinical trials to be uniform throughout the European Union.

The new regulation is intended to reduce the administrative formalities and to reactivate patient-based research in Europe. The aim is to restore the European Union’s competitiveness in the field of clinical research and to develop new innovative treatments and drugs which will ultimately benefit patients.

The main changes introduced by the regulation are as follows:

- **The (single) authorization procedure for clinical trials** will allow a quick and detailed examination of the request by the relevant Member States and will lead to one single evaluation result. The authorization request will be filed via a portal associated with a European Union database. The use of this portal will constitute a pre-requisite for examination of the authorization request.

- **The extension of the principle of tacit agreement to the entirety of the authorization procedure**;

- **The improvement of the conditions for conducting multinational clinical trials**;

- **The strengthening of the rules on patient protection and informed consent**;

- **Increased transparency in relation to promoting recruitment of participants in clinical trials and their results**;

- **The possibility for the European Commission to undertake checks in Member States and third countries to verify that monitoring and compliance with the rules are effective**.

The regulation is due to be formally adopted by the Parliament and the Council on March 10, 2014. The text will then be formally adopted in spring 2014 by the Member States. It will apply from 2016.

In the United States, an Investigational New Drug application (“IND”) must be submitted to the FDA and accepted before clinical trials can start on humans. This application contains early research data as well as the pharmaceutical dossier, pre-clinical and clinical data (if any) and includes the clinical protocol. If there is no objection from the FDA, the IND application becomes valid 30 days after it is received. At any time during or subsequent to this 30-day period, the FDA may request the suspension of clinical trials, whether planned or in progress. This temporary suspension continues until the FDA receives the details it has requested. Furthermore, any ethics committee with authority over a clinical site may delay or suspend clinical trials, either temporarily or definitively, if it believes that patient safety is not ensured or in case of non-compliance with regulatory provisions.

In most countries, clinical trials must comply with the Good Clinical Practice standards as defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (“ICH”). These Good Clinical Practices (“GCP”), which were the subject in France of a decision dated November 24, 2006 setting the rules of good practices for biomedical research manipulating drugs for humans and stipulating applicable standards, constitute a set of ethical and scientific quality requirements that must be met during the planning, implementation, registration and notification of clinical trials. Directive
2005/28/EC dated 8 April 2005 also adopted the GCP principles in the context of strengthening the regulatory structure specified by Directive 2001/20/EC. The competent authority designated in each Member Country to authorize clinical trials must take into consideration, among other factors, the scientific value of the study, the safety of the participants and the possible responsibility of the clinical site.

**Conducting clinical trials**

Clinical trials must be carried out in compliance with complex regulations throughout the various phases of the process, based on the principle of informed consent by the patient to whom the products will be administered. Articles L.1122-1 et seq. of the French Public Health Code specify that the patient must be kept informed of the objective, methodology and duration of the research, and also of the expected benefits and predictable constraints and risks associated with the administration of the products undergoing the clinical trials. This information is summarized in a written document given to the patient before any administration of products.

Patients must be kept regularly informed of the clinical trials’ progress and of the overall research results. The personal data gathered for clinical trials must be declared in simplified form to the Commission Nationale Informatique et Liberté (“CNIL”). Patients have the right to access and correct these data in application of law No. 78-17 of 6 January 1978, amended by law No. 2004-801 of 6 August 2004, concerning information systems, files and freedom.

3. **Regulations concerning marketing authorizations**

To be marketed, any given manufactured drug product must obtain a regulatory authorization (New Drug Approval or “NDA”/Biological License Application or “BLA”) in the US and Autorisation de Mise sur le Marché or “AMM” in France) from the competent authority, being the FDA in the USA, the EMEA in Europe and the ANSM in France. Companies apply for an NDA (USA) or an AMM (France) based on quality, safety and efficacy. In Europe, in the USA and in Japan, the dossier is a standard dossier named “CTD”. The file relating to the AMM describes the manufacture of the active substance, the manufacture of the final product and the clinical and nonclinical studies.

In Europe, there are two types of AMM applications: the community procedures when the drug is intended to be marketed in several European countries and the national procedure when the drug is intended to be marketed in one member state only.

**Registration procedures in Europe**

To access the European markets through community procedures, drug products must be submitted to either the centralized procedure, the mutual-recognition procedure or the decentralized procedure.

- The centralized procedure is compulsory for biologicals, new cancer products, drugs with orphan drug status and, since May 2008, drugs targeting auto-immune disorders and other immune dysfunctions. If the marketing authorization is granted by the EMEA, it is automatically valid for all European Union member states.

- In the mutual-recognition procedure, companies apply in one only of the member states. When the authorization is granted in this country, it could be extended to other countries via the mutual-recognition procedure.

- In the decentralized procedure, companies apply simultaneously in all member states and the evaluation of the application is conducted in one of the states chosen as a reference country. If the authorization is granted, it is automatically and simultaneously granted in all other member states.

National procedure has a decreasing interest as community procedures are becoming more and more popular in Europe.

**National procedure**

Conversely, this type of procedure is used less and less as it now only applies to marketing authorization applications that are limited to a national territory.
Since 2008, as a consequence of a European directive, a marketing authorization is now renewed only once, five years after the initial registration. The marketing authorization is then valid for an unlimited period unless the authorities ask the laboratory to undertake a renewal on an exceptional basis (following a problem with pharmacovigilance for example).

It is possible for a drug to be withdrawn from the market, upon the request of the health authorities, if a serious problem arises, in particular a safety-related problem. The marketing authorization is then cancelled.

There can be various reasons for the withdrawal of drugs from the market, with the main ones being reasons of public health, major undesirable side effects and non-compliance with manufacturing rules.

**Registration procedures outside of Europe**

Pharmaceutical firms who wish to market their medicinal drugs outside the European Union submit marketing authorization application dossier to the national authorities of the concerned countries, for instance the Food and Drug Administration ("FDA") for the United States of America and the Kosheisho (Pharmaceutical and Medical Device Agency, PMDA) in Japan.

In order to facilitate the registration in these countries, a worldwide harmonization process of regulation for the development and registration of medicinal drugs is being implemented: the International Conference on Harmonization, or "ICH".

In the USA, the application of a new medicinal drug or NDA, or Biological License Application ("BLA"), is the process used by the FDA to approve a new medicinal drug to be market in the US market. To obtain this authorization, the manufacturer submits all the data and analysis of non-clinical and clinical trials, all the information concerning the product, and the manufacturing process and procedures.

An NDA/BLA should give enough information, data and analysis to allow the FDA to answer major questions such as:

- If the drug is safe and effective for its intended use, and whether its benefits outweigh the risks;
- If the labeling of the drug is appropriate, and if this is not the case, what should it contain; and
- If the methods used in the manufacture and control to maintain quality of the drug are adequate to preserve the identity of the drug, strength, quality and purity.

**Non-classical registration procedures**

Aside from the traditional procedure of granting a marketing authorization, as described above, there are non-classical registration procedures that allow a shorter time-to-market for new medicines.

In Europe, they are:

- Conditional approval: valid only one year instead of five. It is granted only if the benefit / risk ratio is positive, that is if the product responds to unmet medical needs, and if the benefits to public health outweigh the risks associated with uncertainty because of an incomplete evaluation of the drug. This temporary character may be renewed if an appropriate report to support this is provided by the sponsor.
- Approval in exceptional circumstances: a marketing authorization may be granted in exceptional cases, reviewed each year when the dossier for assessment of the drug is not complete.
- Accelerated approval: the evaluation process is accelerated (150 days instead of 210 days) when a drug is of major interest from the standpoint of public health.
- Temporary authorization of use: this is the opportunity, for instance in France (under what is called an Autorisation Temporaire d’Utilisation, or “ATU”) to use a drug that does not have a French or European marketing authorization to treat serious or rare diseases with unmet medical need. The ATU can be granted for a particular patient or for a group of patients. The pharmaceutical company must
justify the presumed efficacy of the drug which the assessment is inadequate, and undertake to submit a proper marketing authorization within a certain timeframe.

In the United States, the Congress adopted a new regulation in 1997 (Food and Drug Administration Modernization Act or “Modernization Act”), intended to facilitate the access to market of new non-toxic and effective drugs, medical devices and biologicals by expediting the review process by the FDA. The Modernization Act establishes the legal framework for the review and accelerated approval of products. As in Europe, these procedures allow a faster development and market access of drugs in serious disease for which no appropriate treatment exists and the medical need is high (cancer, AIDS, Alzheimer's disease, etc.).

The Accelerated Approval is a program that is intended to make promising products for life threatening diseases available on the market on the basis of preliminary evidence prior to formal demonstration of patient benefit. The FDA evaluation is performed on the basis of a surrogate marker (a measurement intended to substitute for the clinical measurement of interest) that is considered likely to predict patient benefit. A result of substitution or marker ("surrogate endpoint") is a result of laboratory or physical sign that is not in itself a direct measure of the patient's feelings, its functions or survival, but which allows to anticipate a therapeutic benefit. The approval that is granted may be considered as a provisional approval with a written commitment to complete clinical studies that formally demonstrate patient benefit. This procedure is equivalent to the “conditional approval” in Europe.

The Priority Review is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the time it takes FDA to review a new drug application is reduced. This procedure is equivalent to the “accelerated approval” in Europe.

The Fast Track Program refers to a process for interacting with FDA to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. The advantages of this process include scheduled meetings to seek FDA input into clinical development plans and to collect appropriate data that will be needed to support approval. Fast Track designation does not necessarily lead to a Priority Review or Accelerated Approval.

The “Breakthrough Therapy Designation” has existed since 2012. It is a process aimed at accelerating the development and examination of drugs which are intended to treat serious illnesses and where the preliminary clinical evidence indicates that the drug may exhibit a substantial improvement over the available therapies with regard to (a) clinically significant criterion (criteria).

A drug which is given the designation “Breakthrough Therapy” can benefit from the following:

- All of the features of the designation “Fast Track”;
- Intensive support on a program for the development of effective drugs, from Phase 1 onwards;
- Organizational commitment involving “senior managers”.

If research or additional studies show that a product presents a risk when it is marketed, the FDA may require its immediate withdrawal. In addition, FDA may withdraw approval for placing on the market for other reasons, especially if the studies after approval are not made with due care

**Orphan drugs**

Orphan drugs are drugs used for the diagnostic, prevention or treatment of deadly or serious rare conditions.

A special authorization procedure is used for orphan drugs.

In the United States, the 1983 Orphan Drug Act brings together various texts that encourage the development of treatments for orphan diseases. The FDA grants the status of orphan drug to any drug aimed at treating diseases affecting fewer than 200,000 people a year in the United States. The Orphan Drug Act also provides the possibility of obtaining grants from the American government to cover clinical trials, tax credits to cover research costs, a possible exemption from application fees when filing for registration with the FDA, and a seven-year exclusivity if a marketing authorization is granted.
In Europe, equivalent legislation has been adopted to promote treatments for rare diseases. Under the terms of Regulation 847/2000/EC of 16 December 1999, as amended by Regulation 847/2000/EC of 27 April 2000, a drug will be considered as an orphan drug if its promoter shows in its submission to the EMEA that it is intended for the treatment of a pathology affecting no more than 5 people out of 10,000 in the European Union and for which there is no satisfactory treatment. If the product obtains orphan drug status, it is granted an exclusive 10-year marketing period during which no similar product may be sold for the same indication, as well as an exemption from regulatory fees and other advantages.

4. The Transparency decree Decree or Sunshine Act à la française

Decree no. 2013-414 of May 21, 2013 “on the transparency of the benefits given by companies manufacturing or marketing products for healthcare and cosmetic purposes that are intended for humans” was published in the Official Journal of May 22, 2013.

It specifies the details of “transparency” and of “public information” with regard to relationships (benefits obtained or agreements entered into) between companies producing or marketing products for healthcare and cosmetic purposes and certain actors in the field of healthcare.

This “transparency” provision, which is derived from the “Bertrand” law of December 29, 2011 on the enhancement of the safety of drugs and healthcare products, specifies that industrial companies that are subject to the publication obligation must now make public:

- information relating to agreements entered into with healthcare professionals and other similar persons (with the exception of agreements governed by Articles L. 441-3 and L. 441-7 of the Code de commerce).
- all of the benefits agreed to, the amount of which is equal to or greater than 10 euros.
- the information will be gathered centrally on a single website which will be managed under the responsibility of the Ministry of Health; the details of the operation thereof were determined by the order of December 3, 2013 by the minister in charge of health.

Industrial companies must forward the information to be published to the authority responsible for the website in accordance with a timescale specified to be:

- within a period of 15 days after the signature of each agreement subject to the publication obligation;
- at the latest on August 1 in respect of the benefits given or paid during the first half of the year in progress and at the latest on February 1 of the following year in respect of the benefits given or paid during the second half of the year in progress.

This website will be accessible for the public to consult from April 1, 2014.