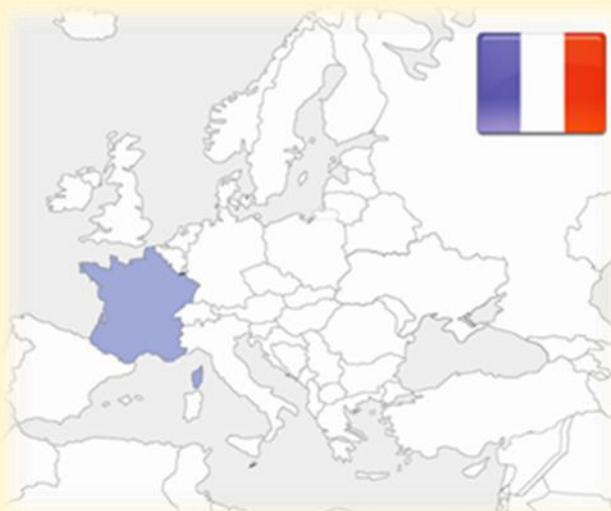


2013 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE



STATE OF THE ART OF RARE DISEASE ACTIVITIES IN FRANCE

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More information on the European Union Committee of Experts on Rare Diseases can be found at www.eucerd.eu.

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ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG - Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area
EMA - European Medicines Agency
ERN - European reference network
EU - European Union
EUCERD - European Union Committee of Experts on Rare Diseases
EUROCAT - European surveillance of congenital anomalies
EUROPLAN - European Project for Rare Diseases National Plans Development
EURORDIS - European Organisation for Rare Diseases
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
IRDiRC – International Rare Diseases Research Consortium
JA - Joint Action
MA - Market Authorisation
MoH - Ministry of Health
MS - Member State
NBS - New born screening
NCA - National Competent Authorities
NHS - National Health System
PDCO - Paediatric Committee at EMA
RDTF - EC Rare Disease Task Force
WG - Working Group
WHO - World Health Organization

GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2012. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2012

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Each part contains the following description of the methodology, sources and validation process of the entire report, and concludes with a selected bibliography and list of persons having contributed to the report.

The present document contains the information from Parts II and V of the report concerning France. A list of contributors to the report and selected sources are in annex of this document. For more information about the elaboration and validation procedure for the report, please refer to the general introduction of the main report.

RARE DISEASE ACTIVITIES IN FRANCE

Definition of a rare disease

Stakeholders in France accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 people.

National plan/strategy for rare diseases and related actions

First French National Plan for Rare Diseases 2005-2008

France was the first EU country to set up a comprehensive rare disease plan in 2004 for the period 2005-2008 with allocated funding. This first plan, subtitled “Ensuring equity in the access to diagnosis, treatment and provision of care”, included 10 objectives:

- Increase knowledge of the epidemiology of rare diseases;
- Recognise the specificity of rare diseases;
- Develop information on rare diseases for patients, health professionals and the general public;
- Train health professionals to better identify rare diseases;
- Organise screening and access to diagnostic tests;
- Improve access to treatment and quality of healthcare provision for patients;
- Continue efforts in favour of orphan medicinal products;
- Respond to the specific needs of accompaniment of patients suffering from a rare disease and develop support for patients’ organisations;
- Promote research and innovation on rare diseases, in particular on treatments;
- Develop national and European partnerships in the domain of rare diseases.

The first national plan provided for the official recognition, funding and evaluation of 131 centres of expertise, called “*centre de référence maladies rares*” in France (“Reference Centres”). This national network was completed in 2008 by the recognition of a second level network of 500 centres working in close connection with the Reference Centres. They are called “*centre de compétences maladies rares*” (“Competence Centres”), and are the equivalent of regional centres of expertise; they received no specific funding. New rare disease research networks and research projects were supported by a national call for proposals. Information on rare diseases, orphan medicinal products and related fields was developed by Orphanet (established in 1997, but whose budget was increased significantly thanks to the plan). A national helpline for patients (called “*Maladies Rares Info Services*”¹, French “Rare Disease Information Service Helpline”) was developed. Several new information products for health professionals were developed such as emergency guidelines, developed by Orphanet, and specific clinical practice guidelines (called “*protocole national de diagnostic et de soins*” – PNDS – “*national diagnosis and treatment protocol for a rare disease*”), developed by the Reference Centres; all these guidelines are published on the Orphanet website. Emergency cards to be used by the patients if necessary were also developed by the French Ministry of Health.

Funding for this first national plan was provided within the general health system budget with ad hoc funding on the basis of rare disease projects (over €100 million for the duration of the plan).

Evaluation of the first plan

The first French National Plan for Rare Diseases underwent intense scrutiny when its four-year term ended in 2008. The main goal of the evaluation was to provide data to serve for the elaboration of a second national plan, initially expected in 2010. An Evaluation Committee consisting of health, economics and sociology experts, under the authority of the French Council for Public Health, measured the initial objectives of the plan against the corresponding actions undertaken during the four years of the plan. The official evaluation report was rendered to the French Minister of Health in May 2009. The document provided an analysis of the accomplishments, advances, and shortcomings of each of the ten objectives of the plan. A series of propositions and recommendations for the elaboration of a second plan was also provided.

Throughout the evaluation, the Evaluation Committee underscored the satisfaction of the different stakeholders towards the overall results of the plan. The objectives judged most pertinent – access to information (Orphanet and *Maladies Rares Info Service*), new healthcare organisation (Reference Centres), research funding, orphan product accessibility, and partnerships with European institutions – have benefited from corresponding actions that have satisfactorily fulfilled the planned goals. The need to strengthen these

¹ <http://www.maladiesraresinfo.org>

successful actions was underlined in the evaluation. However, some objectives – specifically those concerning epidemiology, professional training for rare diseases, and screening and diagnostic programmes – were considered insufficiently developed. The strategies to meet these goals needed to be reformulated taking stock of the difficulties encountered and planning actions to overcome obstacles.

The tenth objective of the plan, “Develop national and European partnerships in the field of rare diseases”, received an overall favourable evaluation with propositions formulated to enhance and encourage European collaboration. Furthermore, the Evaluation Committee proposed the development of measures to bring non-European industrialised and developing countries into the fold. Indeed, throughout the evaluation of the plan, the necessity for European and international-level coordination and resource-sharing was emphasised.

The Evaluation Committee’s report² was completed by a self-assessment report³ drawn up by the Steering Committee of the plan within the Ministry of Health. These two reports and the testimonies of rare disease health professional, industry and patients’ organisation stakeholders who had contributed to the first plan were presented and discussed at the final meeting of the Follow-up Committee of the plan.

On 30 September 2010, the French Alliance for Rare Diseases (“*Alliance Maladies Rares*”), in collaboration with EURORDIS, organised a national conference on rare diseases⁴ in the context of the Europlan project. The theme of the conference was “The French plan in the European landscape”. This conference gathered a large range of stakeholders and focused on lessons drawn from the first plan for the benefit of other European countries.

Second French National Plan for Rare Diseases 2011-2014

The second French National Plan for Rare Diseases⁵ was elaborated during 2009-2010 by the Ministry of Health with the collaboration of the Ministry of Higher Education and Research from the results of the evaluation of the first plan and from the conclusions of seven working groups, which had gathered during 34 meetings 184 representatives of health professionals, rare disease experts, researchers, patients’ organisations and administration. The second plan was launched on 28 February 2011 on the occasion of Rare Disease Day, with a budget of €180 million for the period 2011-2014. The ten objectives of the first plan have been consolidated into three main objectives:

- Improve the quality of care for rare disease patients;
- Develop research on rare diseases;
- Amplify European and international cooperation in the field of rare diseases.

These three objectives encompass actions such as:

- Quality assessment and networking of the existing French Reference Centres;
- Improvement of access to genetic diagnosis;
- Development of neonatal screening of rare diseases;
- Proper use and facilitated access to drugs, orphan medicinal products and any other medical product necessary for the patients;
- Information and training of health professionals;
- Information for patients;
- Strengthening of research.

The second plan includes 15 measures and 47 specific actions. The key measures of the plan are:

- Creation of a Foundation for Scientific Cooperation on Rare Diseases (called the “*Fondation maladies rares*”⁶) to coordinate and facilitate research on rare diseases;
- Creation of a National Rare Disease Database (called “*Banque nationale de données maladies rares*” - BNDMR) to allow mapping of patients’ needs and delivered healthcare, and to facilitate their recruitment for clinical and epidemiological studies and clinical trials. The national registry BNDMR will be based on the collection of a minimum data set, common to all patients and rare diseases and all the reference and regional centres;
- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature for the patients’ follow-up;

² http://www.hcsp.fr/docspdf/avisrapports/hcspr20090317_maladiesRares.pdf

³ http://www.sante.gouv.fr/IMG/pdf/Evaluation_interne_Plan_National_Maladies_Rares_2005-2008.pdf

⁴ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_france_europlan.pdf

⁵ http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf

⁶ The “Fondation maladies rares” was created on 6 February and launched officially on 29 February 2012: <http://www.fondation-maladiesrares.org>

- Access to next-generation sequencing (NGS) technology for genetic diagnosis. Most of the French academic laboratories will be equipped at the end of the second year of the plan with NGS facilities to optimise genetic diagnosis of a large set of rare diseases. Various levels of NGS will be implemented during the plan for speeding up and maximal diagnosis coverage;
- Restructuring of rare disease reference and regional centers into a limited number (around twenty) of coherent “national clinical networks” (called “*filières de santé maladies rares*”), gathering all rare disease relevant stakeholders and centered on a homogeneous group of rare diseases. These networks aim to allow a better and easier orientation of patients towards appropriate diagnosis, treatment, social care and follow-up. These future French clinical networks should be connected to the future European Reference Networks (ERN) concerning rare diseases.
The additional actions foreseen in the plan to improve the quality of care are:
 - Creation of a “permanent working group” for the monitoring of Reference Centres and the future national clinical networks;
 - Measures to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed out of their marketing authorisation;
 - Enhancement of rare disease clinical practice guidelines (“PNDS”) development;
 - Training of medical doctors and paramedical professionals;
 - Better coordination of health care and social care;
 - Improvement of information for rare disease patients supporting Orphanet and *Maladies Rares Info Service* and the creation of a European unique number for rare disease help lines.

The implementation and the follow-up of the plan is the mission of a dedicated Steering Committee (called “*Comité de suivi et de prospective*” – Follow-up and Prospective Committee) which held its first meeting on 19 May 2011 and meets at least once a year. This committee is chaired by the General Director for Provision of Healthcare in the French Ministry of Health. Five thematic working groups reporting to the Steering Committee were established to help implement the plan. They include a “permanent working group”, dedicated at first to the definition of a new evaluation process of the Reference Centres, and later to the monitoring of Reference Centres and their future national clinical networks, as well as four temporary working groups: one dedicated to defining the specifications, scope and organisation of the future national clinical networks, one to help improve the quality of information and healthcare, one to develop the access to NGS, and the last one to help develop the National Rare Disease Database. The Steering Committee is in charge of the follow up of the plan, its implementation according to schedule, the effective involvement of relevant bodies and institutes, as well as the survey of new methods for diagnosis, prevention, treatment and care for rare disease patients which would justify the adaptation of the plan during its progress.

Since 1 December 2012, hospitals – in priority Reference Centres – began one of the key actions of the second plan: coding in the National Database of Inpatient Registrations (“PMSI”) all hospitalised rare disease patients using systematically Orphanet nomenclature. The goal is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways.

An “information and experience sharing meeting” was organised on 19 December 2012 concerning the implementation of the Second Plan for over 300 participants, in particular for all the coordinators of the Reference Centres. The meeting objectives were to share information with the coordinators on the progress of the plan. In particular the new evaluation procedures for Reference Centres were presented and discussed, as were the future national clinical network organisation and the new method to develop “PNDS” (*See section on Good Practice Guidelines*).

Second French National Plan for Cancers (including rare cancers) 2009-2013

A second National Plan for Cancers⁷ was launched on 2 November 2009 for the period 2009-2013. This plan is the continuation of the first national plan⁸ which covered the period 2003-2007, during which pilot projects targeting an organisation of expert centres for rare cancer patients were supported. The six main domains concerned by the plan are: research, observation, prevention, screening, care, and “living with and after cancer”. A specific action of the plan is dedicated to the development of specialised expert centres for rare cancer patients, labelled “reference centres for rare cancers”. The term “rare cancers” applies to the following cancers: those which are diagnosed in fewer than 3/100 000 persons per year; or those requiring highly specialised management, owing to their unusual location, or to their occurrence at a specific or complex site.

⁷ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

⁸ <http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20032007.pdf>

The National Cancer Institute (*"Institut national du cancer" – INCa*) published a report entitled "The Situation of Cancer in France in 2011". This report gives an overview of the measures in place for cancers, including rare cancers, and gives key facts and figures concerning the cancer patients in France. It was published at the same time on the INCa site and on a new web portal on cancer data⁹. The INCa also released at the end of 2011 a first report on the expertise activity for rare adult cancers, including updates on organisation, collaborations, translational research and clinical trials, survey of cases in national databases, and elaboration of recommendations amongst other actions¹⁰. A second report concerning the activity of the "Expert Centres" was published in 2012¹¹, as well as a document published in French¹² and in English¹³ describing this specific organisation.

The INCa published two new reports on genetic testing and treatment for hereditary cancers in 2012. The first one summarises the 2011 activities of French oncogenetic platforms. The second one focuses on molecular genetic testing for targeted therapies in France in 2012¹⁴.

French National Plan for Rare Disabilities 2009-2013

A plan aimed at rare disabilities (of which rare diseases may be a cause) was adopted on 27 October 2009 for the period 2009-2013¹⁵. The National Solidarity Fund for Autonomy (*"Caisse nationale de solidarité pour l'autonomie" – CNSA* - in charge of funding for the autonomy of the elderly and disabled people) is in charge of its implementation. A "rare disability" is a French notion¹⁶: the definition proposed by the plan is the coexistence of a prevalence of no more than 1 in 10 000 people, a rare combination of severe deficiencies or diseases (vision or hearing disability, dysphasia, severe epilepsy etc.), complex care and rarity of competent professionals. The main objectives of the plan are:

- The centralisation and dissemination of information on rare disabilities in collaboration with Orphanet;
- The consolidation, development and evaluation of specialised expertise at national level;
- The reinforcement and organisation of the identification of rare disabilities and multidisciplinary functional evaluation across France;
- The creation of inter-regional relays;
- The development of the offer of services at home and in establishments for patients with rare disabilities.

Several levels of expertise for patients with rare disabilities are planned. Three national "resource centres" were created in 2011 for patients with a visual or hearing deficiency associated with other deficiencies or diseases. A fourth national "resource centre" for patients with rare disabilities and severe epilepsy was created in 2012. Inter-regional relays of these national centres will be created during 2013. Cooperation between national "resource centres" and inter-regional teams for rare disabilities and "reference centres" for rare diseases is also planned.

Other French national initiatives related to rare diseases

On 16 May 2008, the French Ministry of Health announced the second National Plan for Autism for the period 2008-2010. This plan aimed at improving the diagnosis and the treatment of patients with autism, children and adults, their access to social and educational services, and the information of health professionals. In 2011, the evaluation of this plan began in the perspective of a next third plan¹⁷.

⁹ <http://lesdonnees.e-cancer.fr/>

¹⁰ <http://www.e-cancer.fr/toutes-les-actualites/360/6714-synthese-de-lactivite-2010-des-centres-experts-cliniques-pour-cancers-rares-de-ladulte>

¹¹ http://www.e-cancer.fr/component/docman/doc_download/9274-bilan-2011-de-la-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares

¹² http://www.e-cancer.fr/component/docman/doc_download/4692-cancers-rares-de-ladulte--lorganisation-en-centres-experts

¹³ http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

¹⁴ <http://www.e-cancer.fr/toutes-les-actualites/360-les-soins/7283-genetique-moleculaire-des-cancers-deux-nouveaux-rapports-sur-la-prise-en-charge-personnalisee-des-patients#>

¹⁵ Called "Schéma national handicaps rares" ("National Scheme for Rare Disabilities"): http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf; http://www.cnsa.fr/article.php3?id_article=726

¹⁶ One of the measures of the plan was to compare this notion with other concepts used in France or in other countries. The INSERM (French National Institute for Healthcare and Medical Research) set up an expert working group in charge of analysing this notion. The expertise report has been published in May 2013: <http://www.inserm.fr/actualites/rubriques/actualites-societe/handicaps-rares-contextes-enjeux-et-perspectives-une-expertise-collective-de-l-inserm>

¹⁷ The third plan has been launched on May 2013: <http://www.social-sante.gouv.fr/actualite-presse,42/breves,2325/presentation-du-3eme-plan-autisme,15797.html>

In June 2008, a national plan concerning visual handicap (of which rare diseases may be a cause) for the period 2008-2011 was published. This plan aimed at improving treatment, social care, mobility and social integration of people with visual handicap¹⁸.

In February 2010, a national plan concerning deafness and hearing-impairment (of which rare diseases may be a cause) for the period 2010-2012 was published¹⁹, with 52 measures including: improvement of the prevention and screening of hearing disorders; better support of deaf and hearing-impaired people through their life; and enhanced access to social life.

The “*dossier medical personnel*” (“personal medical record” - DMP) is a national healthcare tool for sharing and exchanging information about individual patients. The DMP has been developed by the French Shared Healthcare Information Systems Agency (“*Agence des systèmes d’information partagés de santé*” - ASIP Santé) for the Ministry of Health. It is a secure electronic health record accessible on the Internet with full patient control of what it contains and what physicians may access. The aim is to provide physicians with a holistic picture of patients with complex conditions such as chronic diseases, and among them, rare diseases. It is thus expected to support the coordination of the different specialists, GPs and centers of expertise involved in the follow-up of patients and improve the quality of care. Two years after the DMP was launched, there were 250 000 DMP at the end of 2012.

The French National Authority for Health (“*Haute Autorité de santé*” – HAS) and the French Biomedicine Agency (“*Agence de la biomedecine*”) signed a collaboration on 14 December 2010²⁰ to work together during 3 years on a project to improve healthcare in four fields in which the Agency is principally involved: organ donation, transplants, medically assisted reproduction and human genetics. The French Biomedicine Agency follows the different tests performed by French laboratories and publishes an annual report. This report communicates only diagnostic activities related to routine patient’s results excluding research genetic testing. It provides critical information to support rare diseases plan decision process at national level and gives a complete overview of genetic labs practice and technological evolutions and, to some extent, encourages genetic labs networking.²¹

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo (“Rare Diseases Cohorts”) project for a duration of 10 years and for a total of €10 million. The RaDiCo project finality is to create and follow selected cohorts of rare disease patients in the perspective of better annotating the phenotypes, better understanding the genotype-phenotype relationship, the natural history of rare diseases, and improving physiopathological, therapeutic or prognostic research. The RaDiCo program is dedicated to set up a platform pooling all the resources needed for rare disease cohorts in order to:

- Establish a common set of meaningful rare disease data/indicators collected from all the Reference and competence centres;
- Provide appropriate resources to clinicians/biologists expert in rare diseases;
- Be able to integrate rare disease data from different sources, requiring the development or improvement of the interoperability of different databases (data standardisation and harmonisation);
- Use common standards for data (including data description, data quality, interoperability, data exchange etc.);
- Ensure the long-term sustainability of these actions.

The RaDiCo project will take advantage of this platform to facilitate the emergence and the design of clinical and translational research programs on rare diseases in partnership with industry. Expected results of the above-mentioned actions are:

- Provision of methodological expertise to analyse rare disease data;
- Anticipation of future needs such as integration of data from systems biology and “omics” approaches.

The research programs resulting from this integrated view of rare diseases are:

- Economic and socio-economic aspects of rare diseases;
- Setting up a collection of induced pluripotent stem cells (iPS) for all rare diseases investigated in France.

In 2011, the web portal “Epidemiology – France”²² was launched, aiming to provide a directory of databases to advance research and expertise in the field of health in France. The “Epidemiology – France”

¹⁸ http://www.solidarite.gouv.fr/IMG/pdf/Dossier_de_presse_2JUIN08.pdf; www.cnsa.fr/IMG/doc/Plan_handicap_visuel_1_-2.doc

¹⁹ http://www.travail-emploi-sante.gouv.fr/IMG/pdf/Plan_en_faveur_des_personnes_sourdes_ou_malentendantes_-_10_02_2010.pdf

²⁰ http://www.has-sante.fr/portail/jcms/c_1007980/la-haute-autorite-de-sante-et-lagence-de-la-biomedecine-sengagent-pour-ameliorer-la-qualite-des-soins

²¹ www.agence-biomedecine.fr

²² <http://epidemiologie-france.fr/>

portal was created under the auspices of the Strategic Council for the Health Industries (“Conseil stratégique des industries de santé” - CSIS), in collaboration between:

- AVIESAN (“Alliance nationale pour les sciences de la vie et de la santé” - French National Alliance for Life Sciences and Health);
- The French Ministry of Economy, Finances and Industry (General Directorate for Competitiveness, Industry and Services - DGCIS);
- The LEEM (“Les entreprises du médicament” - French pharmaceutical industry association).

This portal aims to :

- Improve the availability of information;
- Locate existing skills and data by theme;
- Encourage transparency;
- Contribute to cooperation between research networks;
- Reinforce research quality;
- Foster the generation of new research projects;
- Promote partnerships and collaboration and increase value of health data.

It brings together information on approximately 493 databases and includes a search by the theme “Rare Diseases”; 25 databases classified in “Rares Diseases” are included in this portal with theme including mostly nationally designated registries.

Centres of expertise

The first National Plan for Rare Diseases (2005-2008) launched a structured organisation of healthcare for rare disease patients. A designation process was created to name centres of scientific and clinical expertise in the field of rare diseases. Four waves of designation took place between 2004 and 2007. By the end of the plan, 131 reference centres were named in university hospitals by the French Ministry of Health and received a specific funding for their missions. These designated centres have 6 main missions:

- To facilitate diagnosis and define the course of treatment. Each centre has a double role: it is an expert centre for one or several diseases for which it is designated, and it is a resource centre for patients referred to it.
- To define, publish and update national clinical practice guidelines for rare diseases (“PNDS”) in collaboration with the French National Authority for Health (HAS);
- To coordinate research and participate in epidemiological surveillance in collaboration with the French Institute for Public Health Surveillance (“Institut de veille sanitaire” – InVS);
- To participate in training and information programmes for health professionals, patients and their families, in collaboration with the French national Institute for Prevention and Health Education (“Institut national de prévention et d’éducation pour la santé” – Inpes);
- To coordinate networks of health professionals and social workers;
- To be the contact point for patient organisations and social workers.

Up to the end of 2012, the Reference Centres were evaluated over time, first through self-evaluation after 3 years as a designated centre, then through an external evaluation after 5 years. The external evaluation was organised by the HAS which published its 2010 activity report in 2011, with one section dedicated to its activity in the evaluation of Reference Centres²³. During the first plan, a National Consultative Designation Committee (“Comité national consultative de labellisation”) analysed the results of the external evaluation and gave advice to the Ministry of Health. This Committee has not been continued. The second national plan has planned a revision of the evaluation process, for which a “permanent working group” was created in 2011. The new process has been in progress in 2012 and will be definitively specified at the beginning of 2013. The evaluation process will be modified: each reference centre will establish an activity report each year and undergo an evaluation at 5 years according to modalities still under discussion. When the new process will be published, the missions of the “permanent working group” will evolve towards the analysis and the follow-up of the annual activity and 5-year evaluation reports of the reference centres. This working group will also monitor the development of the future national clinical networks.

A second type of expert centres was designated in 2008, named “centres de compétences”. These regional centres were proposed by each reference centre and designated by French Regional Hospital Agencies (“Agences Régionales d’Hospitalisation” – ARH). The aim of these regional centres is to assume responsibility for diagnosis, treatment and follow-up of the patient close to their home, and to participate in the activities of the reference centres they are linked to. The regional centres have not received dedicated funding for their

²³ http://www.has-sante.fr/portail/jcms/c_1070314/rapport-annuel-d-activite-2010

rare disease activities. They have not been included in the evaluation process of the reference centres, and will still stay out of the future evaluation process in progress. Currently 500 regional centres have been named corresponding approximately to 1 expert centre per region for each of the 18 groups of rare diseases identified in Orphanet reports. The regional centres will be included into the future national clinical networks in association with the Reference Centres they are linked to.

In June 2012, the French General Directorate for Provision of Healthcare launched a position paper²⁴ detailing the conditions for the establishment and renewal of “expert centres” so as to best respond to requests for designation of such centres. This position paper is not specific to rare diseases centres.

Rare cancers have been excluded from the first national plan for rare diseases (2005-2008) since a national plan for cancer including measures for rare cancers was already in place. The French National Cancer Institute (INCa) published a report^{25,26} on the organisation of healthcare for rare adult cancers. This organisation was one of the key actions of the Second National Cancer Plan for the period 2009 -2013: this includes the creation of a system of national “Expert Centres” and a network of regional centres for rare adult cancers. Since 2009, 23 national “Expert Centres” for 23 groups of rare adult cancers and four anatomical pathology networks - in charge of the double reading of sarcoma, rare malignant neuroendocrine tumours, malignant mesothelioma and lymphoma - have been set up and financed. Among their missions, these Expert Centres have to ensure diagnostic certainty by implementing a systematic second reading of the biopsy specimens, to assure a multidisciplinary expert discussion of the patient file for the choice of initial and subsequent treatments, and to facilitate the enrolment of patients in appropriate clinical trials.

Three “resource centres” for rare disabilities have been designated in 2011, and a fourth one at the end of 2012, in the Framework of the French National Plan for Rare Disabilities 2009-2013.

In 2011 the university hospitals of Angers and Nantes, in association, with the French Alliance for Rare Diseases (“*Alliance Maladies rares*”), created a platform to support rare disease patients in the Pays de la Loire Region. This unique platform (called “*Plateforme régionale d’information et d’orientation sur les maladies rares*” – PRIOR – Regional platform for information and guidance concerning rare diseases) consists of a team including neurologists, a dermatologist, a psychologist, an occupational therapist, a social worker and a coordination assistant. It aims to help patients to find their way in the health and social care system. In Montpellier and the Languedoc-Roussillon Region, a network was created by the Reference Centre in association with the French Alliance for Rare Diseases to provide support to patients with developmental disorders and training sessions for professionals of health and social sector.

In 2012, the Assistance Publique - Hôpitaux de Paris, the consortium of university hospitals of Paris, organised several meetings to set up closer links and common procedures between Paris Reference Centres and community social services which assess needs and meet requirements of rare disease patients with disabilities.

Registries

A National Rare Disease Registry Committee was created in October 2006 as part of objective 1 - “Improve knowledge of epidemiology of rare diseases” - of the first National Plan for Rare Diseases. The Committee aims at:

- Proposing a policy for registries based on healthcare and epidemiological research needs;
- Giving an opinion on whether to create new registries or maintain existing registries, and on the management of registries;
- Evaluating the quality of registries submitted to the Committee after a call for proposals each year: only registries recognised as good quality registries (from then on called “qualified registries”) may receive a national public funding from Inserm, InVS or INCa);
- Helping to diffuse and valorise information produced by qualified registries.

Members of the Committee include official members (representatives of French Institute For Public Health Surveillance, French National Institute of Health and Medical Research, Ministry of Health, Ministry of Research etc.), professionals with expertise in the field of rare diseases, registries or public health, as well as two representatives of patients’ organisations. They are nominated for a 3-year term, with renewable mandate. Until now, the evaluation of the quality of registries has been the only activity of the Committee. In 2008, 6 national registries were qualified by the Committee for the period 2009-2011, and three new national registries in 2010 for the period 2011-2013. In 2011, seven national registries already qualified obtained a new

²⁴ http://circulaire.legifrance.gouv.fr/pdf/2012/06/cir_35428.pdf

²⁵ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

²⁶ http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

qualification for the period 2012-2015, and one registry were qualified for the period 2012-2014. In 2012, one register was qualified for 3 years (2013-2015). At the end of 2012, 12 national registries were qualified: thalassemia, Gaucher disease, histiocytosis, congenital neutropenia, Pompe disease, cystic fibrosis, biliary atresia, esophageal atresia, arterial pulmonary hypertension, hereditary immune system disorders, SDH-dependant hereditary paraganglioma, and inherited deficiencies of coagulation. In 2012, a reflection has begun on the questions of a possible evolution of the Committee's missions and the needs of the other registries and databases existing in France for support and evaluation.

The Second National Plan for Rare Diseases also foresees the creation of a National Rare Disease Database (BNDMR). Its primary objective is to describe the demand of care for rare diseases at a national level, as well as the offer of care, and to assess whether the offer matches the demand. A secondary objective is to help recruiting patients for clinical trials or rare diseases cohorts (RaDiCo project). The reference and regional centres for rare diseases will be the primary data providers as well as diagnostic laboratories (genetic, cytogenetic, etc.) or existing rare disease registries if appropriate. To achieve these objectives, the first step is to build a minimum data set (MDS): this MDS will be common to all rare disease reference centres and to all rare diseases. In 2012, a working group helped to build the MDS, which will be discussed and validated by the Steering Committee of the Plan at the beginning of 2013. The MDS will be entered through an application called BaMaRa ("Banque Maladies Rares"), either directly by the reference centres, or through their own application if appropriate. It will help gathering data at the reference centre level and linking this information to biobank data and other national databases (medico-economic databases, national health insurance databases etc.). A data warehouse, the National Rare Disease Database (BNDMR), will host several types of de-identified national rare disease data sets in accordance with the Data Protection Act.

The French Institute for Public Health Surveillance (*InVS*) has already analysed some data collected via a range of available sources (The National Database of Medical Mortalities - CépiDC, The National Database of Inpatient Registrations – PMSI etc.) in order to build epidemiological indicators for a few rare diseases. This work has been cited in the Second National Plan for Rare Diseases and the first results are available online²⁷.

France contributes to several European rare disease registries including EUROCAT, EUROHISTIONET, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EIMD, EUROWABB, EUROTRAPS, CHS, EURO CARE CF, ECFS, INFEVERS, EDMUS, EHN-EUROHISTIONET, ESCROT-HU, SCLS registry, VALID and TREAT-NMD. In the domain of rare cancers, France contributes to European clinicobiological databases, as CONTICABASE (soft tissue and visceral sarcoma), CONTICAGIST (gastrointestinal sarcoma tumours), ENS@T-ACC (adrenal cortical carcinoma) and ENS@T-pheo (pheochromocytoma).

Neonatal screening policy

A neonatal screening programme exists in France for all newborns for the following four diseases: cystic fibrosis, phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, as well as for sickle cell anaemia only for newborns at risk of developing the disease.

In 2010, an assessment of the opportunity to extend neonatal screening to one or more inborn metabolic errors of metabolism by tandem mass spectrometry in the general French population began. The first results were published in 2011 by the French National Authority for Health (HAS). The HAS has recommended the extension of the neonatal screening programme to medium chain acyl-CoA dehydrogenase deficiency²⁸. The decision to put this recommendation into practice has not yet been taken. That requires reorganising first the neonatal screening programme because tandem mass spectrometry cannot replace all the existing screening techniques, and cannot be used in all the laboratories currently participating in the programme. Furthermore the HAS is still working on the possibility of extending the programme to other inborn metabolic errors and on the generalisation of sickle cell anaemia screening to all newborns in France.

Neonatal screening programme for deafness (of which rare diseases may be a cause), on which the HAS had given recommendations in 2007, was approved in April 2012. Screening for deafness was already performed in 51% of the French maternity hospitals using different methods. National specifications on screening methods will be published in 2013.

Genetic testing

The French Biomedicine Agency ("*Agence de la Biomédecine*"), a public organisation operating under the supervision of the Ministry of Health, was created under the Bioethics Law of August 2004. Its overriding

²⁷ <http://www.invs.sante.fr/surveillance/index.htm> (Section "Maladies Rares")

²⁸ http://www.has-sante.fr/portail/jcms/c_1069254/evaluation-de-lextension-du-depistage-neonatal-a-une-ou-plusieurs-erreurs-innees-du-metabolisme-par-spectrometrie-de-masse-en-tandem-1er-volet-deficit-en-mcad

function is to “guarantee equity, ethics, and transparency for the activities under its responsibility and for anticipated developments”. The Biomedicine Agency published its 2011 annual report²⁹ in 2012. For the third consecutive year, the Agency included data on postnatal genetic testing carried out in France culled via a partnership with Orphanet. The annual report revealed that 387 059 tests were performed in France in 2011. In the domain of molecular genetics (including pharmacogenomics), diagnostic tests were undertaken for 1 012 diseases of a total offer of 1 282 diseases for which testing is possible in France. Of these 1 282 diseases, 726 tests are available in only one French laboratory. As in previous years, two non-rare disease indications (haemochromatosis and non-rare thrombophilia) represented over 40% of the total analyses conducted in 2011.

In the arena of prenatal diagnosis (PND), of the 42 082 cases examined in 2010, 7 141 certificates were issued for a medical termination of pregnancy (MTP). Of these, 668 pregnancies were pursued although a MTP had been issued. Among MTP cases, 44% were performed for malformations or malformation syndromes, 38.5% for chromosomal abnormalities, 6.2% for genetic abnormalities, 2.7% for maternal conditions, and 0.8% for involved infections. Ultrasound is the most performed prenatal examination tool in France. Unregulated by law, its practice does not fall within the competence of the Biomedicine Agency. Biologically, PND involves sampling either the foetus and/or its annexes (amniotic fluid, chorionic villi, foetal blood), or the mother's blood. Among the 74 629 foetuses studied by cytogenetic analysis, 3 849 were affected. Among 2 728 foetuses studied by molecular genetics, 534 anomalies were detected. Biochemistry and foetal serum markers resulted in 27 diagnoses of hereditary diseases: 50 in endocrinology (abnormal genital or genotype-phenotype discordance, abnormal thyroid or 21-hydroxylase deficiency); 251 involved neural tube defects and 550 detected trisomy 21 (determined by serum markers on 660 629 women tested). The only non-invasive prenatal genetic diagnosis involves the analysis of foetal DNA circulating in the maternal blood, which yielded 5 921 diagnoses in 2009. The number of foetal Rh determination using this technique is increasing: from 384 cases in 2005 to 5 359 in 2009. Finally, assisted procreation procedures employing pre-implantation genetic diagnosis in 2009 led to the birth of 59 children in France (versus 71 in 2008).

The French Bioethics Law of August 2004 stipulated the prohibition of embryonic research, but allowed the possibility of research under certain conditions for a maximum of five years following the publication of the decree. The moratorium period expired in February 2011. Between September 2004 and February 2011, 173 permits to conduct such research were issued, of which 71 were for research protocols, 24 involved the conservation of embryonic stem cells and 46 the importation of embryonic stem cell lines. The revised Bioethics Law of July 2011 maintains the possibility of French scientists to conduct research under certain conditions. The Biomedicine Agency did not issue any new authorisations in 2011 after the end of the moratorium.

In 2006 a programme supporting the structuring of molecular genetics, including the development of 28 hospital-based platforms, was established in France. Amongst the services these platforms perform is molecular testing to identify genetic mutations in tumours, the identification of biomarkers for potential targeted therapies, diagnosis refinement, and prognosis establishment. The INCa reports show that the platforms' turnover is robust and growing, especially in the areas of haematology and solid tumours. Some 144 000 patients underwent molecular testing in 2010, versus 102 000 in 2009. The platforms have a catalogue of 60 tests available, as well as 14 determinants for access to targeted therapies already established or under development. Few new molecular tests were added in 2010, with the exception of IDH1 and IDH2 mutations in gliomas. Thus, the increased activity involves molecular tests already available in 2009. The second report³⁰ on molecular genetic testing for targeted multidisciplinary treatment, summarises the 2011 activities supported by INCa to bring targeted therapies to more patients. In 2010, 61 000 patients underwent testing and were offered a tailored treatment strategy, up from 42 874 patients in 2009 and 31 965 in 2008. Both of the new INCa documents report on activities stemming from specific measures of France's Cancer Plan (2009-2013) that seek to ensure equal access to treatment, and develop molecular genetics platforms for hereditary cancers.

The final text of the Bioethics Law³¹ was adopted on 23 June 2011 and published in July 2011. The text includes indications on how to inform family members in the case of genetic disease, as well as the delivery of tests proposed to pregnant women. The legislation on research using embryos will remain unchanged.

²⁹ http://www.agence-biomedecine.fr/IMG/pdf/ra_biomed_2011_bd_web.pdf

³⁰ http://www.e-cancer.fr/component/docman/doc_download/8310-molecular-genetic-testing-for-equal-access-to-targeted-therapies-in-france-in-2011

³¹ <http://www.service-public.fr/actualites/001820.html>;

<http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000024323102&dateTexte=&oldAction=rechJO&categorieLien=id>

National alliances of patient organisations and patient representation

The *Alliance Maladies Rares* (French Alliance for Rare Diseases) is the national umbrella organisation dealing with rare diseases. It plays a major role in organising working groups, communicating on rare diseases, offering support to organisations of patients and families, and contributing to the development of the French National Plans for Rare Diseases and their evaluation. The Alliance played a major role in the elaboration of the first and second National Plan and in the evaluation of the Reference Centres. The Alliance celebrated its 10 anniversary in 2010 and marked the occasion with a meeting of its members on 15 February 2010 in Paris: the Alliance's new website was launched as were the forthcoming information documents created by the Alliance. In 2011 the Alliance launched a practical guide and made it available for its members and in centres of expertise for rare diseases. The guide is intended to patients and their families, and provides information on the organisation and availability of expert care and the services. The guide also gives information on the rare disease patients' organisations in France. The Alliance also launched an awareness raising campaign aimed at children via the newspaper for children called *Le Petit Quotidien*; information packs for teachers were also made available to help classes understand what is a rare disease and life for children with such a condition.

The *Alliance Maladies Rares* and other patients' organisations have received some public funding during the first and second National Plans for their various support activities and awareness campaigns.

Seventeen patients' organisations in the field of rare cancers collaborate daily with the existing rare cancer national expert centres. Several have been involved as soon as the designation of these centres. They play a major role in diffusing high quality information both on the healthcare services available and on access to innovative treatments.

Sources of information on rare diseases and national help lines

Orphanet activities in France

Concerning actions to improve public information, financial support for the French Rare Disease Platform ("*Plateforme Maladies Rares*", established in 2001 in Paris), and more particularly for the Orphanet web portal, has been reinforced under the two National Plans. The French Ministry of Health has supported strongly the launch of the Orphanet Joint Action financed by the European Commission.

Orphanet was established in 1997 and is the reference for all rare disease information in France. The team, hosted by the French National Institute of Health and Medical Research (Inserm) in Paris, is in charge of collecting data on services for rare diseases (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patients' organisations) in France, and of coordinating the activity of Orphanet's external teams across Europe, as well as maintaining the encyclopaedia and inventory of rare diseases. The team also maintains the Orphanet France³² national website. Recent new Orphanet features include the encyclopaedia for patients in French, emergency guidelines, a search by sign facility and a national entry point for France in French. Since 2003, Orphanet also edits a twice-monthly newsletter concerning political and scientific news in the field of rare diseases and orphan medicinal products entitled *OrphaNews France*.

In December 2009, Orphanet signed a partnership with the National Solidarity Fund for Autonomy (CNSA) and leads a project, in the framework of both the National Plan for Rare Disabilities and the National Plan for Rare Diseases, to develop and make available the information concerning the disabilities caused by rare diseases. Orphanet will introduce specific chapters on disability in the General Public encyclopedia concerning rare diseases responsible for disability. In addition to this, the disabilities associated with rare diseases will be indexed with the WHO's ICF (International Classification of Functioning, Disability and Health), in order to allow rare diseases to be found when searched by any kind of disability. The first 3-year cooperation has been an opportunity to develop information on some crucial aspects of rare diseases that have not yet been specifically addressed before in Orphanet. This information will be useful to patients, families and professionals dealing with disabilities. The CNSA decided to maintain the cooperation for three more years in March 2013.

The INCa signed an agreement with Orphanet to share information on organisation for rare cancers. Recently, Orphanet published a document describing the clinical networks (national and regional expert centres) for rare cancers³³.

Official information centre for rare diseases

Orphanet is the official source of information on rare diseases in France.

³² <http://www.orphanet-france.fr/national/FR-FR/index/page-d-accueil/?lng=FR>

³³ http://www.e-cancer.fr/component/docman/doc_download/9123-cahiers-dorphanet-centres-experts-cancers-rares

Information on rare cancers organisation is available on the INCa website³⁴. Ten national expert centres have elaborated dedicated websites with high quality information available for the patients.

Help line

The help line *Maladies Rares Info Services* provides support and information on rare diseases. It is the first health information service in France to have a quality certification (ISO 9001). This service launched in 2011 and has continued in 2012 to propose a series of Internet chat sessions on the first Monday of each month: each session has a theme and Internet users can ask the team questions during the hour-long sessions. *Maladies Rares Info Services* also implemented a “rare diseases barometer”. The purpose of this barometer is to collect objective data on the issues to which patients are confronted. Data were collected by means of qualitative and quantitative surveys targeting users of the information and support service. The results of the first round of these surveys were published in 2012³⁵. The service also launched a forum for its users in 2012.

The AFM (*Association française contre les myopathies*, French Muscular Dystrophy Association) provides a help line for information on neuromuscular diseases.

Other sources of information on rare diseases

The French National Agency for the Safety of Medicine and Health Products (“*Agence Nationale de Sécurité du Médicament et des Produits de Santé*” – ANSM, ex-AFSSAP³⁶) has published on its website since 2009 a registry of clinical trials on medicinal products conducted in France including those on rare diseases, an updated list of compassionate use authorisations (cohorts) with respective summary of product characteristics and leaflet, updated list of medicinal products available within nominative temporary use authorisations (ATU) with specific information if applicable and other general information on hospital preparations.

During the first National Plan for Rare Diseases, the French General Directorate for Health (“*Direction Générale de la Santé*” - DGS) in the Ministry of Health has produced some information cards to be used in case of emergency by rare disease patients. These cards were developed in close collaboration with health professionals, Reference Centres and patient organisations. Each card had two parts: a first one with information about the patient’s health status intended for healthcare professionals, and a second one with brief general information on his/her disease for the patient and for non-specialist healthcare professionals³⁷. These cards were distributed by the Reference Centre physicians. During the second plan, a simpler model will be developed, just specifying some information on the patient and on his/her disease (name of the disease, Orpha number, Reference Centre, what to do and not to do in case of emergency) to be used in case of emergency.

In 2010, the site www.droitsdesmalades.fr, which informs all citizens about their healthcare rights, was launched. In addition, the patient organisation *Sparadrap*³⁸ has published an informative guide concerning children’s rights when they are admitted into healthcare facilities, including issues such as consent to participate in research and financial aid.

The website *Intégrascal* gives information on chronic diseases, in particular rare diseases, for teachers and education professionals in charge of pupils with chronic disease or disabilities. This website free of access contains brief medical and educational information useful for education professionals to adapt teaching to the children with the aim of better integration into school³⁹.

Good practice guidelines

Since the beginning of the first national plan, the Reference Centres produced, with the help of the HAS, 49 national good practice guidelines (“PNDS”) for diagnosis, treatment and follow-up of patients with rare disease. These guidelines are published on Orphanet, HAS⁴⁰ and Reference Centre websites. The HAS itself has published clinical practice guidelines⁴¹ for the follow-up of children with deafness under the age of six and their

³⁴ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

³⁵ <http://www.maladiesraresinfo.org/news/observatoire-maladie-rare-maladies-rares.html>

³⁶ The AFSSAPS was given a new name and new missions on 1 May 2012, following the French law reinforcing the monitoring of safety of medicinal and other health products, published on 29th December 2011: *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (French National Agency for Medicine and Health Products) <http://www.ansm.sante.fr/>.

³⁷ <http://www.sante.gouv.fr/les-cartes-de-soins-et-d-informations-pour-les-personnes-atteintes-de-maladies-rares.html>

³⁸ <http://www.sparadrap.org/SPARADRAP>

³⁹ <http://www.integrascal.fr/>

⁴⁰ http://www.has-sante.fr/portail/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=1

⁴¹ http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite_de_lenfant_-_0_a_6_ans_-_recommandations.pdf

family. At the end of 2012, the HAS published a new simplified method to develop “PNDS”⁴² to help the Reference Centres draft more quickly the PNDS.

Concerning rare tumours, two national good practice clinical guidelines were published with the quality label of HAS and INCa respectively in 2010, the first one concerning surgical practices in digestive neoplasia, including peritoneal pseudomyxoma, and the second one gestational trophoblastic disease⁴³. Clinical guidelines are available on the dedicated websites of national expert centres, concerning cutaneous lymphoma, rare head and neck cancers, thyroid carcinoma, rare ovarian carcinoma, thymus carcinoma.

Training and education initiatives

All health professionals, medical doctors, midwives, nurses and paramedics follow two hours of training during their undergraduate medical studies on the topic of rare diseases. Every year, 3rd year medical students at the Necker-Cochin faculty of medicine in Paris are offered an optional 30-hour training course on rare diseases during which experts in the field and representatives of rare disease patient organisations are present.

The Paris-based Institute of Myology organises an annual Summer School in Paris: this offers the possibility to train in myology via a condensed 10-day course.

National rare disease events 2012

Each year in December, an annual *Téléthon* is organised by the AFM (*Association française contre les myopathies*) over 30 hours to raise funds. The funds raised go towards rare disease research, information services (including the French Rare Disease Platform), awareness campaigns, patient care and patient organisations. In 2012, the 26th edition of the *Téléthon* took place on 8-9 December, raising 81 million Euros. On 8 December 2012: the AFM launched a new English language website to present the aims of the organisation and the projects the AFM is funding. Each year, to coincide with the *Téléthon*, the *Alliance Maladies Rares*, in association with the AFM and the *Fondation Groupama pour la santé* (Groupama – one of the major French mutual insurance companies – Foundation for Health), organises a Rare Disease March (*Marches des Maladies Rares*) involving patients and patients’ organisations. In 2012, the annual Rare Disease March gathered around 2 000 people in Paris. The *Téléthon*⁴⁴ and Rare Disease March⁴⁵ aim to raise awareness about rare diseases in addition to the Rare Disease Day which is celebrated each February.

On 29 February 2012, on the occasion of the Rare Disease Day, the *Fondation maladies rares* (Rare Diseases Foundation) was officially launched at the French Academy of Sciences with a dedicated evening event which gathered 150 participants and welcomed speeches from its founding members. A press release also acknowledged the creation of the Foundation, a unique alliance of actors from research, care and patients’ organisations devoted to speeding up and stimulating research in rare diseases. In addition to this, the *Alliance Maladies Rares* and Orphanet organised an awareness-raising day with the French railway company SNCF: they were present on a number of high speed trains leaving Paris for other major towns. On the same day in Paris, members of the Rare Diseases Platform came together in front of the Eiffel Tower to raise their hands in support of patients for the Rare Disease Day. A range of activities were organised in towns across France by patients’ organisations to raise awareness of the Day and rare diseases in general.

In September 2012, Orphanet held its 13th Forum for Patient Organisations in Paris, in collaboration with the *Alliance Maladies Rares*. The sessions centred on clinical and emergency online guidelines for rare diseases developed by Orphanet and on personal electronic medical records in the French healthcare system, as well as advances in the area of research, and the recent launch of the French Rare Disease Foundation.

Hosted events in 2012

Amongst the events hosted by France in the field of rare diseases were: EUCERD/Eurogentest workshop on coding rare diseases and describing phenotypes (27 -28 September 2012, Paris), International Symposium on Hepatic Glycogen Storage Diseases (4-6 April 2012, Lyon), Sixth International Alkaline Phosphatases Symposium (16-19 May 2012, Huningue), European Working Group on Gaucher Disease Meeting (28-30 June 2012, Paris), World Federation of Hemophilia World Congress (8-12 July 2012, Paris), Mechanisms of Intellectual Disability: From Genes to Treatment (3-7 October 2012, Roscoff), 7th World Rett Syndrome Congress (22-26 June 2012,

⁴² http://www.has-sante.fr/portail/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=2

⁴³ http://www.has-sante.fr/portail/jcms/c_1147273/fr/tableau-des-recommandations-de-bonne-pratique-ayant-obtenu-le-label-methodologique-inca-has?xtmc=&xtcr=2

⁴⁴ <http://www.afm-telethon.fr/le-telethon/le-telethon-2011>

⁴⁵ <http://www.alliance-maladies-rares.org/article/marche-des-maladies-rares-2011-98>

Paris, France), OroDysmorphology course (24 May 2012, Strasbourg), ESH-ENERCA Training Course: Diagnosis and Management of Very Rare Anaemias (3-4 February 2012, Paris). The IRDiRC held its Executive Committee Meeting on 25-26 September 2013 in Evry, and the Interdisciplinary Group held a meeting on 9-10 November 2012 in Paris.

Research activities and E-Rare partnership

National research activities

In France, public funding is available for rare disease research projects from:

- The National Agency for Research (*Agence Nationale de la Recherche – ANR*) for basic research;
- The General Directorate for Provision of Healthcare (*Direction Générale de l'Offre de Soins – DGOS*) of the Ministry of Health for clinical research via funding of the "PHRC" ("*Programme Hospitalier de Recherche Clinique*" – Hospital Clinical Research Programme) sponsored by National Health Insurance of the French Social Security System;
- The INSERM for translational research;

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which will be launched at the beginning of 2013 ("*Programme de recherche translationnelle en santé*" – PRTS, Programme for translational research in Health⁴⁶). This call for proposals is not specific for rare diseases. The first objective of this programme is to select and fund research projects at the interface between basic research projects currently funded by ANR and clinical research projects currently funded by PHRC.

In addition, some charities, private foundations or patient organisations provide funding for research, such as the AFM.

The "*Fondation maladies rares*⁴⁷" (*Rare Diseases Foundation*) was approved by a decree of the French Ministry of Research and Higher Education on 6 February 2012, and officially launched on 29 February 2012. The creation of this rare diseases research foundation is a measure delineated in the research objectives of the second French Plan for Rare Diseases 2011-2014. The Foundation is a private, non-profit structure endorsed by both the French Ministry of Research and the French Ministry of Health to coordinate, federate and fund rare diseases research. Its main aim is to accelerate and promote technological, medical and social innovations to the benefit of the rare disease patients. The Foundation gathers French rare disease research into one cooperative structure that operates with a sustained source of funding to bring a new synergy to fundamental, clinical and translational research. Its funding bodies represent a unique alliance of research, care and patient organisations. The funding bodies are: the AFM (French Muscular Dystrophy Association), the French Alliance for Rare Diseases Alliance (*Alliance Maladies Rares*), the French National Institute of Health and Medical Research (Inserm), the Conference of General Directors of the University Hospitals and the Conference of University Presidents. The Foundation is administrated by an Executive Board, composed of representatives from each of the funding members and eight renowned experts in research and academia. Furthermore, the Foundation benefits from the guidance of a Scientific Committee composed of French and International leading medical specialists and scientists in the rare diseases field, encompassing both biomedical and social and human sciences fields. The Foundation is based in the "*Plateforme Maladies Rares*" in Paris. It consists of a team of twelve people, including seven Regional Delegates, who ensure the linking of actors as well as the development of rare diseases research programmes.

In 2012, several activities have been developed around 6 main objectives that structure the Foundation working programme:

1. Boosting research by facilitating access to technology platforms and launching calls for tenders;
2. Developing research in social and human sciences applied to the rare diseases field;
3. Supporting the setting up and development of preclinical and clinical trials;
4. Participating in and developing European and international rare diseases dedicated research programmes;
5. Being involved and proactive in the public health and research policies and frameworks;
6. Supporting and valorising rare diseases data collection according to state of the art national and international frameworks.

As far as calls for proposals are concerned (Point 1), the French Rare Diseases Foundation is offering funding opportunities both for biomedical research and social and human sciences. In the biomedical field, three different project calls were launched to increase access to High Throughput Sequencing in May 2012,

⁴⁶ www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/

⁴⁷ <http://fondation-maladiesrares.org/>

September 2012 and February 2013 respectively. A total of 55 projects have been funded in 2012 with the aim to identify new genes responsible for rare diseases. The Foundation works in close collaboration with state of the art public and private technological platforms and is establishing partnerships to facilitate general access to resources for rare diseases research, also outside its own funded calls. New themes for calls for proposals, especially designed according to the needs identified from the extensive regional coverage of research teams, will be implemented on a regular basis. In addition to exome and genome sequencing calls for proposals, the Foundation also funds animal models through bi-annual calls for proposals (the first call will be launched on mice models in February 2013) as well as the screening of innovative molecules.

In addition to the calls for projects, an important milestone has been reached in 2012 with the online release of an extensive mapping of funding opportunities for rare disease research (including institutional funding, charities, private, and EU and international funding). This unique and regularly updated portal, established by the Foundation in collaboration with the ANR and the DGOS, gives a better visibility to researchers seeking funding. Of note, this provides, within a single platform, information to the French rare diseases community on funding opportunities available at the French regional and national levels as well as at the EU level (including for instance programmes such IMI, COST, FP7, DG SANCO). Information is relayed and extended locally by the Regional Delegates.

In December 2012, a first call for proposals was also launched in the field of human and social sciences (Point 2) jointly by the Foundation, the French National Solidarity Fund for Autonomy (CNSA) and the General Directorate for Health (DGS) to support human and social sciences research while encouraging cross-disciplinary studies by involving patients' organisations and clinicians together with dedicated academics. This call for proposals addressed three different areas: the diagnostic pathway; new technologies in the field of genetics and consequences for patients including ethical issues; and the social, educational and professional pathways for rare disease patients. More than 70 projects have been submitted to this first call for proposals underlying the need of additional calls to be launched on a regular basis.

The Foundation aims to boost clinical trials in rare diseases (Point 3) by identifying and supporting innovative medical devices as well as molecules with therapeutic benefit. Dedicated new public-private partnerships are under development. The objective is to provide guidelines, methodological support and search for partners in the development of preclinical and clinical studies linking academia and industry.

In order to promote French research, increase international collaborations and influence global related policies (Point 4), the Foundation has been actively involved in a number of international programme. In 2012, the Foundation, together with Orphanet, has been awarded the scientific organisational support of the International Rare Diseases Research Consortium (SUPPORT-IRDiRC, coordinated by Orphanet) and has joined the integrated infrastructure programme RD-Connect as an official partner in order to assess the project's impact and the appropriateness of the implementation of shared databases with the needs of the international research community. The Foundation also supported the collaborative Mediterranean Myology School initiative of Saint-Joseph University, (Beirut, Lebanon, by funding three traveling grants, hence promoting expertise sharing in the Mediterranean area.

Beyond workshops jointly organised with French National Alliance for Life Sciences and Health (*Alliance nationale pour les sciences de la vie et de la santé - Aviesan*) on timely themes including proteomics and model organisms, the Foundation has initiated collective initiatives (Point 5), in 2012, on rare diseases issues, such as a think-tank of pharmaceutical companies and awareness actions together with the international business school ESSEC, that are to be continued in 2013.

Since its setup, the Foundation has been working closely with the representatives of the national data collection programme respectively initiated by the French Ministry of Health and the French Ministry of Higher Education and Research, namely the National Rare Disease Database (BNDMR) and the RaDiCo Project (Point 6).

In September 2012, the French Institute of Rare Disease Biotherapies was launched, grouping together the actions of Genethon, the French Muscular Institute, I-Stem and the Genetic Therapy Pole of Nantes under the coordination of the AFM, to cover all the stages of research. The Institute will bring together hundreds of experts and researchers.

In the scope of the Second French National Plan for Rare Diseases, €9.6 million were dedicated by DGOS in 2011-2012 to upgrade next generation sequencing platforms.

Other funding opportunities for rare diseases research in 2012 included grants and calls launched by the following organisations/institutes: Agence nationale de sécurité du médicament et des produits de santé (ANSM), International Fund for research on Congenital Adrenal Hyperplasia, Fondation Jérôme Lejeune, Fondation Thierry Latran, Fondation des Entreprises du Médicament, Fondation Imagine, Association Française de l'Atrésie de l'œsophage, Association Française de l'Ataxie de Friedreich, Association pour l'information et la

recherche sur les maladies rénales génétiques (AIRG-France), Institut de Recherche en Santé Publique (IReSP), Association Française du Syndrome de Rett (AFSR), Fondation Motrice, and l'Agence de la biomedicine.

Organisation into expert centres for rare adult cancers contributes to promoting research on these rare cancers through multicentre research studies, either basic, translational or clinical, at national or international level. Therefore, in 2011, 46 new clinical trials were initiated or ongoing and 16 finalised, with a total of more than 800 patients with a rare cancer included in a clinical trial.

Participation in European projects

France participates, or has participated, in European rare disease research projects including: ARISE, ANTEPRION, ANTIMAL, ALPHAMAN, AUTOROME, BIOMALPAR, BALANCE, BIO-NMD, BRAINCAV, BNE, CARDIOGENET, CAV-4-MPS, CUREFXS, CELLPID, CLINIGENE, CONTICANET, CONTICABASE, CHEARTED, CRUMBS IN SIGHT, CUREHLH, CRANIRARE, DSDLife, DARTRIX, ELAST-AGE, EDEN, EPOKS, EMINA, ERMION, EVI-GENORET, EPINOSTICS, EUROBFNS, EuroGeBeta, ENRAH, ENCCA, ENS@T-ACC, EUROMICS, EUNEFRON, EMSA-SG, EUMITOCOMBAT, EURAMY, EUREGENE, EuRenOmics, EURO CARE-CF, EUROAGENTEST, EUROAGENTEST2, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROAS, EURO IRON1, EURO-LAMINOPATHIES, EURORETT, EURO-CDG, EURO-SCAR, EUROSCA, EURSPA, EUROTRAPS, EUROWABB, ENCE-PLAN, EUROSARC, ESPOIR, EUSTAR, EPOKS, EURO-PADNET, EURIOFNET, FAD, GETHERTHAL, GENESKIN, GENEGRAFT, GRIP, GENOMIT, GENOSTEM, HMA-IRON, HSCR, HEMO-IPS, HAEIII, HUE-MAN, IPF-AE, IMPACTT IMMOMEK, INNOVALIV, INHERITANCE, INTREALL, IMMUNOPRION, KINDLERNET, LEISHMED, LYMPHANGIOGENOMICS, MANASP, MILD-TB, MITOCIRCLE, MM-TB, MTMPATHIES, MTMPATHIES2, MPCM, MITOTARGET, MYASTAID, MYORES, MYELINET, NEUROBID, NEOTIM, NEUPROCF, NMD-CHIP, NOVSEC-TB, NM4TB, NEUROSIS, NEUROPRION, NEUROMICS, NOVELPID, NEMMYOP, NEUTRONET, NSEuroNet, OCTIPS, OVERMYR, OSTEOPETR, PODONET, PEMPHIGUS, RARE-G, RATSTREAM, RAPOSDI, RD-CONNECT, RISCA, SKIN-DEV, STRONG, SKINTHERAPY, STEM-HD, SIOPEN-R-NET, RHORCOD, RDPLATFORM, SUPPORT-IRDIRC, TB CHINA, TRANSPOSMART, THERAPEUSKIN, TUB-GENCODEV, WHIPPLE'S DISEASE, WHIM-Thernet and WHIMPath.

E-Rare

The *GIS Maladies Rares* was the coordinating partner of the E-Rare for Research Programmes on Rare Diseases, and organised the first joint transnational call in 2007⁴⁸ for research on rare diseases, with the participation of 6 countries and a total of 13 funded consortia (French research teams participated in each of these funded projects/consortia). France took part in the 2nd E-Rare Joint Transnational Call in 2009 and is represented in 11 of the 16 consortia selected for funding, with funding totalling around €2 million. France also took part in the 3rd transnational call launched at the start of 2011 in the context of E-Rare2: French research teams have been funded to participate in 13 of the projects selected for funding. France participated in the 4th Joint Transnational Call in 2012, with French teams participating in 7 out of the 11 consortia selected for funding. Starting April 2013, the Rare Diseases Foundation will be in charge of E-Rare 2 coordination on behalf of Inserm.

IRDIRC

The AFM (French Muscular Dystrophy Association) and French National Agency for Research (*Agence Nationale de la Recherche*) are committed members of the International Rare Disease Research Consortium.

Orphan medicinal products^{49,50}

Four institutions are involved in the field of orphan medicinal products on the French market: the French National Agency for the Safety of Medicine and Health Products (ANSM, ex-AFSSAPS), the French National Authority for Health (HAS), the French Economic Committee for Health Products (*Comité Economique des Produits de Santé* – CEPS), and the Ministry of Health.

The LEEM (French Pharmaceutical Industry Association) is a constituted professional organisation that represents the pharmaceutical industry in France, i.e. the companies whose missions are research, development, manufacturing and marketing of medicinal products. Rare diseases became priority action in the LEEM's strategy in 2002: a rare disease working group made up of key stakeholders in the public and private sectors meets regularly to discuss: innovative therapies for rare diseases (and how to bring these therapies to

⁴⁸ http://www.e-rare.eu/images/stories/e-rare_final_list_of_funded_projects.pdf

⁴⁹ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

⁵⁰ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (pp12-14)

patients), the provision of health care for rare disease patients, the communication of information on rare diseases and treatment, ways to create the correct conditions for optimal and innovative clinical treatment and ways to support the national plan for rare diseases. The LEEM organises a workshop dedicated to orphan medicinal products every year. Since 2001 the LEEM evaluates the advances made in clinical research in France, including clinical research in the field of rare diseases. The LEEM presented its annual overview of therapeutic advances with an edition covering 2012. A particular emphasis was put on new orphan drugs in relation to the development of personalised medicine⁵¹.

Orphan medicinal product committee

There is no orphan medicinal product committee currently in France, apart from the multistakeholder group at the LEEM (see above).

Orphan medicinal product incentives

Initiatives are in place to stimulate the development of orphan medicinal products: research support is provided through national funding programmes: *GIS Maladies Rares*, the Hospital Clinical Research Programme (“PHRC”). During orphan medicinal product development, free scientific advice is available from the ANSM; and budgetary incentives (from 2001) are available in the form of a tax exemption. Other incentives measures, such as free early advice and fast track process of the assessment for reimbursement by the Transparency Committee (CT) are performed by the HAS.

Free scientific advice is available for medicines from the ANSM as well as CT and compassionate use authorisation (cohort ATU) from the ANSM. The HAS is performing early meetings at the national level, the European level (within the EUNETHTA network of Health technology agencies) on request of pharmaceutical industry or on its own request. These scientific meetings aim to let the marketing authorisation (MA) owner know what data the HTA bodies expect especially concerning the relative effectiveness assessment in usual care.

Sponsors of orphan medicinal products are exempted from taxes to be paid by companies:

- tax on the turnover of medicinal products if under €20 millions;
- tax on the promotion of medicinal products, based on their promotion costs if turnover under €30 millions;
- taxes paid in France by the companies on their sales (there is no turnover threshold for these taxes);
- the safeguard clause for medicinal products whose turnover is under €30 millions;
- tax on direct sales for medicine whose turnover is under 30€ millions;
- tax on the distribution of medicines for medicine whose turn over is under 30 € millions.

These are some of the initiatives aimed at stimulating research by the pharmaceutical industry into rare diseases in addition to the provisions of the European Regulation on Orphan Medicinal Products.

The public authorities decided in 2010 to abrogate the framework agreements which exempt orphan medicinal products from certain regulations, and recommended price cap for orphan medicinal products costing more than €50 000 per year and per patient. An obligation to treat all affected patients was also proposed.

A law adopted by Parliament on 22 March 2011 will allow non-profit organisations to become pharmaceutical establishments and will give the status of medicine to gene-therapy products. As a direct result, the Généthon Bioprod non-profit laboratory, inaugurated in November 2010, will be able to produce products for gene-therapy for clinical trials.

Orphan medicinal product pricing policy

Before any pricing, all drugs including orphan medicinal products are assessed by the Transparency Committee of the HAS for reimbursement purpose. This committee provides the Ministry of Health and National Health Insurance with an opinion about the pertinence of reimbursement and the level of copayment, and specifies the added value of the drug, which is the basis for price definition. For innovative drugs (new therapeutic modality, presumably efficient and well tolerated, and covering an unmet medical need), often including orphan medicinal products, the Transparency Committee performs a fast track assessment before MA and delivers its opinion shortly after MA is granted. However, the official process starts after MA. This fast track reduces the usual timelines, which is of 90 days after MA, to 15 days.

After that step, an Industry-government agreement via the French Economic Committee for Health Products (CEPS) is defined, which sets the rules for the pricing of reimbursed medicines in France.

⁵¹<http://www.leem.org/les-essentiels-maladies-rares>

HAS also provides early dialogues for medicines that are under development in order to answer questions that the sponsor wants to ask about the way the development should go to *in fine* provide most adequate evidence of clinical interest for the patient and the public health. This is particularly adapted to orphan drugs that usually bring innovation for a limited population in a situation where the need is not covered.

Orphan medicinal product market availability situation

According to the registry of the French National Agency for the Safety of Medicine and Health Products (ANSM) website, the availability of orphan medicinal products in France can be represented as follows:

- Orphan medicinal products with valid market authorisation and with mention of commercialisation: Adcetris, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Ceplene, Cystadane, Dacogen, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Flisint, Gliolan, Glivec, Increlex, Inovelon, Jakavi, Kalydeco, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nexo-Brid, Nplate, Orfadin, Pedeia, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Signifor, Siklos, Soliris, Somavert, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Votubia, Vpriv, Vyndaqel, Wilzin, Xagrid, Yondelis, Zavesca.
- Orphan medicinal products with valid market authorisation without mention of commercialisation: Bronchitol, Glybera, Mepact, Peyona, Plenadren, Revestive, Xaluprine.

Orphan medicinal product reimbursement policy

Orphan medicines can be dispensed in out-patient or in-patient settings through one of the two corresponding lists: list for medicines reimbursed by National Health Insurance and available in community pharmacies, and list for hospital pharmacies. Within the hospital list, the drugs are generally funded through *GHS (Groupes H*, a diagnostic-related group system established by the *T2A ("tarification à l'activité"*, Hospital Activity-Based Payment) policy. However, some expensive drugs used in hospitals are fully reimbursed to the hospitals by the National Health Insurance. These drugs are listed in a specific list (called "*liste hors GHS*") established by the French Ministry of Health. Some of the drugs available in hospital pharmacies can be made available to outpatients (retrocession list) and paid for by the National Health Insurance. Within the 68 orphan medicinal products that have been granted MA in Europe, 3 have not requested reimbursement and within the 65 medicines remaining, all but two have been granted a positive advice for reimbursement in France.

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*⁵², "*particular prescribing conditions are in place for: drugs for hospital use, drugs with hospital prescription, drugs with initial hospital prescription, drugs with prescription only by specialists, drugs with a particular follow up during the treatment.*" From 1 January 2010, the Ministry of Health and the French National Health Insurance made it mandatory for the first prescription of an orphan medicinal product to be validated by a relevant Reference Centre when available, or by the regional centre directly linked to the relevant Reference Centre.

Other initiatives to improve access to orphan medicinal products

Compassionate use for individual patients takes the form of either cohort use (cohort Temporary Authorisation for Use) or named patient supply (nominative Temporary Authorisation for Use) prior MA granted both by the ANSM. Patients can also be treated with drugs before these drugs have received MA through clinical trials or hospital preparations. Reimbursement measures are in place for compassionate use. Innovative drugs are eligible for an *ATU ("Autorisation temporaire d'utilisation"* - Temporary Authorisation for Use) from the ANSM if there is a public health need.

This process was modified in 2012 following the law reinforcing the monitoring of safety of drugs and other healthcare products, published on 29 December 2011 (Law N° 2011-2012). The new law maintains the possibility of an *ATU*, in particular in the case of rare diseases. The drug must fulfil the following criteria: the treatment cannot be postponed; there is no alternative therapeutic to the drug; the efficacy and security of the drug are strongly presumed from the results of clinical trials (cohort *ATU*) or from scientific published data and knowledge (nominative *ATU*); the patient cannot be treated within a clinical trial. The *ATU* is given for a limited period, but renewable. A therapeutic protocol and data collection concerning safety and efficacy are mandatory for both cohort and nominative *ATU*.

⁵² Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p14)

This law also introduced the concept of “temporary recommendation of use” (“recommandation temporaire d’utilisation” - RTU) developed and published under the responsibility of the ANSM. The aim of RTU is to provide a framework for the prescription of a medicinal product beyond the indications of its MA when no other medicinal product with a MA or a cohort ATU is available for the considered indication. The development of RTU is possible when the ANSM considers the available data are sufficient to presume a favourable benefit risks ratio. Prospective data collection concerning safety and efficacy of the drug is mandatory when a RTU is published. In November 2012, the ANSM published a template⁵³ for the follow-up of patients and collection of data if RTU are available. In order to help the ANSM to prepare the development of RTUs for rare diseases, the Ministry of Health asked the Reference Centres in July 2012 to carry out an inventory of their prescriptions out of the MA of the medicinal products that could be eligible for RTU. The questionnaire was returned by 70% of the Reference Centres. The data were compiled by the ministerial authorities and sent in November 2012 to the ANSM which is now exploiting them.

In hospitals, Temporary Treatment Protocols (“*Protocoles temporaires de traitement*” - PTT) may also be used to extend the indication for a drug or device with reimbursement permitted. Temporary Treatment Protocols are limited to expensive drugs used only in hospitals and registered on a special list.

In 2006, the law for the financing in 2007 of French Social Security system planned a derogative pathway for exceptional coverage of off-label use of medicinal products and of non-covered medical devices or services by the National Health Insurance⁵⁴. Orphan or non-orphan medicinal products used off-label, medical devices or services intended for rare diseases are in particular concerned. The complete reimbursement is allowed for a limited renewable period by the Ministry of Health after the HAS has given a positive opinion. Since the law of the 29 December 2011 reinforcing the monitoring of safety of drugs and other healthcare products, the ANSM must publish a RTU before the HAS is allowed to advise the complete reimbursement of a medicinal product used off-label.

The ANSM also established a national public register of clinical trials on medicines conducted in France, which is regularly updated.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Respite care services are available for patients whose care is demanding temporary relief of their relatives: this is only partially reimbursed for some rare diseases. Therapeutic recreational programmes are available mostly within hospital organisations and patient organisations or local institutions, and are mostly fully reimbursed. Social assistance community centres (“*Centres communaux d’action sociale*” - CCAS), social assistants within hospital structures, and services provided by patient organisations all aim to assist the integration of patients with rare disease into daily life. These services are financed either by government or community budgets or patients’ organisations. The AFM has a number of administrative, medical and social coordinators who assist families with their specific needs.

On 9 February 2010 an interministerial observatory was created to evaluate the accessibility of public buildings, housing, work places, transport and footpaths/roads to all persons.

⁵³

http://www.legifrance.gouv.fr/jopdf/common/jo_pdf.jsp?numJO=0&dateJO=20121122&numTexte=13&pageDebut=18412&pageFin=18414

⁵⁴ Article L162-17-2-1 of the Social Security Legal Code.

DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2012 IN FRANCE

Second French National Plan for Rare Diseases 2011-2014

Since 1 December 2012, hospitals – in priority Reference Centres – began one of the key actions of the second plan: coding in the National Database of Inpatient Registrations (“PMSI”) all hospitalised rare disease patients using systematically Orphanet nomenclature. The goal is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways.

An “information and experience sharing meeting” was organised on 19 December 2012 concerning the implementation of the Second Plan for over 300 participants, in particular for all the coordinators of the Reference Centres. The meeting objectives were to share information with the coordinators on the progress of the plan. In particular the new evaluation procedures for Reference Centres were presented and discussed, as were the future national clinical network organisation and the new method to develop “PNDS” (*See section on Good Practice Guidelines*).

Second French National Plan for Cancers (including rare cancers) 2009-2013

The National Cancer Institute (“*Institut national du cancer*” – INCa) published a report concerning the activity of the expert centres in 2012⁵⁵, as well as a document published in French⁵⁶ and in English⁵⁷ describing this specific organisation.

The INCa published two new reports on genetic testing and treatment for hereditary cancers in 2012. The first one summarises the 2011 activities of French oncogenetic platforms. The second one focuses on molecular genetic testing for targeted therapies in France in 2012⁵⁸.

French National Plan for Rare Disabilities 2009-2013

A fourth national “resource centre” for patients with rare disabilities and severe epilepsy was created in 2012. Inter-regional relays of these national centres will be created during 2013. Cooperation between national “resource centres” and inter-regional teams for rare disabilities and “reference centres” for rare diseases is also planned.

Other French national initiatives related to rare diseases

The “dossier medical personnel” (“personal medical record” - DMP) is a national healthcare tool for sharing and exchanging information about individual patients. Two years after the DMP was launched, there were 250 000 DMP at the end of 2012.

Centres of expertise

Up to the end of 2012, the Reference Centres were evaluated over time, first through self-evaluation after 3 years as a designated centre, then through an external evaluation after 5 years. The new process has been in progress in 2012 and will be definitively specified at the beginning of 2013. The evaluation process will be modified: each reference centre will establish an activity report each year and undergo evaluation at 5 years according to modalities still under discussion. When the new process will be published, the missions of the “permanent working group” established by the plan will evolve towards the analysis and the follow-up of the annual activity and 5-year evaluation reports of the Reference Centres. This working group will also monitor the development of the future national clinical networks.

In June 2012, the French General Directorate for Provision of Healthcare launched a position paper⁵⁹ detailing the conditions for the establishment and renewal of expert centres so as to best respond to requests for designation of such centres. This position paper is not specific to rare disease centres.

⁵⁵ http://www.e-cancer.fr/component/docman/doc_download/9274-bilan-2011-de-la-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares

⁵⁶ http://www.e-cancer.fr/component/docman/doc_download/4692-cancers-rares-de-ladulte--lorganisation-en-centres-experts

⁵⁷ http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

⁵⁸ <http://www.e-cancer.fr/toutes-les-actualites/360-les-soins/7283-genetique-moleculaire-des-cancers-deux-nouveaux-rapports-sur-la-prise-en-charge-personnalisee-des-patients#>

⁵⁹ http://circulaire.legifrance.gouv.fr/pdf/2012/06/cir_35428.pdf

In 2012, the Assistance Publique - Hôpitaux de Paris, the consortium of university hospitals of Paris, organised several meetings to set up closer links and common procedures between Paris Reference Centres and social services which assess needs and meet requirements of rare disease patients with disabilities.

Registries

A National Rare Disease Registry Committee was created in October 2006 as part of objective 1 - "Improve knowledge of epidemiology of rare diseases" - of the first National Plan for Rare Diseases. In 2012, one register was qualified for 3 years (2013-2015). At the end of 2012, 12 national registries were qualified: thalassemia, Gaucher disease, histiocytosis, congenital neutropenia, Pompe disease, cystic fibrosis, biliary atresia, esophageal atresia, arterial pulmonary hypertension, hereditary immune system disorders, SDH-dependant hereditary paraganglioma, and inherited deficiencies of coagulation. In 2012, a reflection has begun on the questions of a possible evolution of the Committee's missions and the needs of the other registries and databases existing in France for support and evaluation.

The Second National Plan for Rare Diseases also foresees the creation of a National Rare Disease Database (BNDMR). Its primary objective is to describe the demand of care for rare diseases at a national level, as well as the offer of care, and to assess whether the offer matches the demand. To achieve these objectives, the first step is to build a minimum data set (MDS): this MDS will be common to all rare disease reference centres and to all rare diseases. In 2012, a working group helped to build the MDS, which will be discussed and validated by the Steering Committee of the Plan at the beginning of 2013. The MDS will be entered through an application called BaMaRa ("Banque Maladies Rares"), either directly by the reference centres, or through their own application if appropriate. It will help gathering data at the reference centre level and linking this information to biobank data and other national databases (medico-economic databases, national health insurance databases etc.). A data warehouse, the National Rare Disease Database (BNDMR), will host several types of de-identified national rare disease data sets in accordance with the Data Protection Act.

Neonatal screening policy

Neonatal screening programme for deafness (of which rare diseases may be a cause) was approved in April 2012. Screening for deafness was already performed in 51% of the French maternity hospitals using different methods. National specifications on screening methods will be published in 2013.

Genetic testing

The French Biomedicine Agency ("*Agence de la Biomédecine*"), a public organisation operating under the supervision of the Ministry of Health, was created under the Bioethics Law of August 2004. The Biomedicine Agency published its 2011 annual report⁶⁰ in 2012. For the third consecutive year, the Agency included data on postnatal genetic testing carried out in France culled via a partnership with Orphanet. The annual report revealed that 387 059 tests were performed in France in 2011. In the domain of molecular genetics (including pharmacogenomics), diagnostic tests were undertaken for 1 012 diseases of a total offer of 1 282 diseases for which testing is possible in France. Of these 1 282 diseases, 726 tests are available in only one French laboratory. As in previous years, two non-rare disease indications (haemochromatosis and non-rare thrombophilia) represented over 40% of the total analyses conducted in 2011.

Sources of information on rare diseases and national help lines

Official information centre for rare diseases

Orphanet is the official source of information on rare diseases in France.

Information on rare cancers organisation is available on the INCa website⁶¹. Ten national expert centres have elaborated dedicated websites with high quality information available for the patients.

Help line

Maladies Rares Info Services implemented a "rare diseases barometer". The purpose of this barometer is to collect objective data on the issues to which patients are confronted. Data were collected by means of qualitative and quantitative surveys targeting users of the information and support service. The results of the first round of these surveys were published in 2012⁶². The service also launched a forum for its users in 2012.

⁶⁰ http://www.agence-biomedecine.fr/IMG/pdf/ra_biomed_2011_bd_web.pdf

⁶¹ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

⁶² <http://www.maladiesraresinfo.org/news/observatoire-maladie-rare-maladies-rares.html>

Good practice guidelines

Since the beginning of the first national plan, the Reference Centres produced, with the help of the HAS, 49 national good practice guidelines (“PNDS”) for diagnosis, treatment and follow-up of patients with rare disease. At the end of 2012, the HAS published a new simplified method to develop “PNDS”⁶³ to help the Reference Centres draft more quickly the PNDS.

National rare disease events 2012

In 2012, the 26th edition of the *Téléthon* took place on 8-9 December, raising 81 million Euros. On 8 December 2012: the AFM launched a new English language website to present the aims of the organisation and the projects the AFM is funding. In 2012, the annual Rare Disease March gathered around 2000 people in Paris. The *Téléthon*⁶⁴ and Rare Disease March⁶⁵ aim to raise awareness about rare diseases in addition to the Rare Disease Day which is celebrated each February.

On 29 February 2012, on the occasion of the Rare Disease Day, the *Fondation maladies rares* (Rare Diseases Foundation) was officially launched at the French Academy of Sciences with a dedicated evening event which gathered 150 participants and welcomed speeches from its founding members. A press release also acknowledged the creation of the Foundation, a unique alliance of actors from research, care and patients’ organisations devoted to speeding up and stimulating research in rare diseases. In addition to this, the *Alliance Maladies Rares* and Orphanet organised an awareness-raising day with the French railway company SNCF: they were present on a number of high speed trains leaving Paris for other major towns. On the same day in Paris, members of the Rare Diseases Platform came together in front of the Eiffel Tower to raise their hands in support of patients for the Rare Disease Day. A range of activities were organised in towns across France by patients’ organisations to raise awareness of the Day and rare diseases in general.

In September 2012, Orphanet held its 13th Forum for Patient Organisations in Paris, in collaboration with the *Alliance Maladies Rares*. The sessions centred on clinical and emergency online guidelines for rare diseases developed by Orphanet and on personal electronic medical records in the French healthcare system, as well as advances in the area of research, and the recent launch of the French Rare Disease Foundation.

Hosted events in 2012

Amongst the events hosted by France in the field of rare diseases were: EUCERD/Eurogentest workshop on coding rare diseases and describing phenotypes (27 -28 September 2012, Paris), International Symposium on Hepatic Glycogen Storage Diseases (4-6 April 2012, Lyon), Sixth International Alkaline Phosphatases Symposium (16-19 May 2012, Huningue), European Working Group on Gaucher Disease Meeting (28-30 June 2012, Paris), World Federation of Hemophilia World Congress (8-12 July 2012, Paris), Mechanisms of Intellectual Disability: From Genes to Treatment (3-7 October 2012, Roscoff), 7th World Rett Syndrome Congress (22-26 June 2012, Paris, France), OroDysmorphology course (24 May 2012, Strasbourg), ESH-ENERCA Training Course: Diagnosis and Management of Very Rare Anaemias (3-4 February 2012, Paris). The IRDiRC held its Executive Committee Meeting on 25-26 September 2013 in Evry, and the Interdisciplinary Group held a meeting on 9-10 November 2012 in Paris.

Research activities and E-Rare partnership

National research activities

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which will be launched at the beginning of 2013 (“*Programme de recherche translationnelle en santé*” – PRTS, Programme for translational research in Health⁶⁶). This call for proposals is not specific for rare diseases. The first objective of this programme is to select and fund research projects at the interface between basic research projects currently funded by ANR and clinical research projects currently funded by PHRC.

The “*Fondation maladies rares*”⁶⁷ (*Rare Diseases Foundation*) was approved by a decree of the French Ministry of Research and Higher Education on 6 February 2012, and officially launched on 29 February 2012. The creation of this rare diseases research foundation is a measure delineated in the research objectives of the second French Plan for Rare Diseases 2011-2014. The Foundation is a private non-profit structure endorsed by

⁶³ http://www.has-sante.fr/portail/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=2

⁶⁴ <http://www.afm-telethon.fr/le-telethon/le-telethon-2011>

⁶⁵ <http://www.alliance-maladies-rares.org/article/marche-des-maladies-rares-2011-98>

⁶⁶ www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/

⁶⁷ <http://fondation-maladiesrares.org/>

both the French Ministry of Research and the French Ministry of Health to coordinate, federate and fund rare diseases research. Its main aim is to accelerate and promote technological, medical and social innovations to the benefit of the rare disease patients. The Foundation gathers French rare disease research into one cooperative structure that operates with a sustained source of funding to bring a new synergy to fundamental, clinical and translational research. Its funding bodies represent a unique alliance of research, care and patient organisations. The funding bodies are: the AFM (French Muscular Dystrophy Association), the French Alliance for Rare Diseases Alliance (*Alliance Maladies Rares*), the French National Institute of Health and Medical Research (Inserm), the Conference of General Directors of the University Hospitals and the Conference of University Presidents. The Foundation is administrated by an Executive Board, composed of representatives from each of the funding members and eight renowned experts in research and academia. Furthermore, the Foundation benefits from the guidance of a Scientific Committee composed of French and International leading medical specialists and scientists in the rare diseases field, encompassing both biomedical and social and human sciences fields. The Foundation is based in the “*Plateforme Maladies Rares*” in Paris. It consists of a team of twelve people, including seven regional delegates, who ensure the linking of actors as well as the development of rare diseases research programmes.

In 2012, several activities have been developed around 6 main objectives that structure the Foundation working programme:

1. Boosting research by facilitating access to technology platforms and launching calls for tenders;
2. Developing research in social and human sciences applied to the rare diseases field;
3. Supporting the setting up and development of preclinical and clinical trials;
4. Participating in and developing European and international rare diseases dedicated research programmes;
5. Being involved and proactive in the public health and research policies and frameworks;
6. Supporting and valorising rare diseases data collection according to state of the art national and international frameworks.

As far as calls for proposals are concerned (Point 1), the French Rare Diseases Foundation is offering funding opportunities both for biomedical research and social and human sciences. In the biomedical field, three different project calls were launched to increase access to High Throughput Sequencing in May 2012, September 2012 and February 2013 respectively. A total of 55 projects have been funded in 2012 with the aim to identify new genes responsible for rare diseases. The Foundation works in close collaboration with state of the art public and private technological platforms and is establishing partnerships to facilitate general access to resources for rare diseases research, also outside its own funded calls. New themes for calls for proposals, especially designed according to the needs identified from the extensive regional coverage of research teams, will be implemented on a regular basis. In addition to exome and genome sequencing calls for proposals, the Foundation also funds animal models through bi-annual call for proposals (the first call will be launched on mice models in February 2013) as well as the screening of innovative molecules.

In addition to the calls for projects, an important milestone has been reached in 2012 with the online release of an extensive mapping of funding opportunities for rare disease research (including institutional funding, charities, private, and EU and international funding). This unique and regularly updated portal, established by the Foundation in collaboration with the ANR and the DGOS, gives a better visibility to researchers seeking funding. Of note, this provides, within a single platform, information to the French rare diseases community on funding opportunities available at the French regional and national levels as well as at the EU level (including for instance programmes such IMI, COST, FP7, DG SANCO). Information is relayed and extended locally by the Regional Delegates.

In December 2012, a first call for proposals was also launched in the field of human and social sciences (Point 2) jointly by the Foundation, the French National Solidarity Fund for Autonomy (CNSA) and the General Directorate for Health (DGS) to support human and social sciences research while encouraging cross-disciplinary studies by involving patients’ organisations and clinicians together with dedicated academics. This call for proposals addressed three different areas: the diagnostic pathway; new technologies in the field of genetics and consequences for patients including ethical issues; and the social, educational and professional pathways for rare disease patients. More than 70 projects have been submitted to this first call for proposals underlying the need of additional calls to be launched on a regular basis.

The Foundation aims to boost clinical trials in rare diseases (Point 3) by identifying and supporting innovative medical devices as well as molecules with therapeutic benefit. Dedicated new public-private partnerships are under development. The objective is to provide guidelines, methodological support and search for partners in the development of preclinical and clinical studies linking academia and industry.

In order to promote French research, increase international collaborations and influence global related policies (Point 4), the Foundation has been actively involved in a number of international programme. In 2012, the Foundation, together with Orphanet, has been awarded the scientific organisational support of the International Rare Diseases Research Consortium (SUPPORT-IRDIRC, coordinated by Orphanet) and has joined the integrated infrastructure programme RD-Connect as an official partner in order to assess the project's impact and the appropriateness of the implementation of shared databases with the needs of the international research community. The Foundation also supported the collaborative Mediterranean Myology School initiative of Saint-Joseph University (Beirut, Lebanon), by funding three traveling grants, hence promoting expertise sharing in the Mediterranean area.

Beyond workshops jointly organised with French National Alliance for Life Sciences and Health (*Alliance nationale pour les sciences de la vie et de la santé - Aviesan*) on timely themes including proteomics and model organisms, the Foundation has initiated collective initiatives (Point 5), in 2012, on rare diseases issues, such as a think-tank of pharmaceutical companies and awareness actions together with the international business school ESSEC, that are to be continued in 2013.

Since its setup, the Foundation has been working closely with the representatives of the national data collection programme respectively initiated by the French Ministry of Health and the French Ministry of Higher Education and Research, namely the National Rare Disease Database (BNDMR) and the RaDiCo Project (Point 6).

In September 2012, the French Institute of Rare Disease Biotherapies was launched, grouping together the actions of Genethon, the French Muscular Institute, I-Stem and the Genetic Therapy Pole of Nantes under the coordination of the AFM, to cover all the stages of research. The Institute will bring together hundreds of experts and researchers.

In the scope of the Second French National Plan for Rare Diseases, €9.6 million were dedicated by DGOS in 2011-2012 to upgrade next generation sequencing platforms.

Other funding opportunities for rare diseases research in 2012 included grants and calls launched by the following organisations/institutes: Agence nationale de sécurité du médicament et des produits de santé (ANSM), International Fund for research on Congenital Adrenal Hyperplasia, Fondation Jérôme Lejeune, Fondation Thierry Latran, Fondation des Entreprises du Médicament, Fondation Imagine, Association Française de l'Atrésie de l'œsophage, Association Française de l'Ataxie de Friedreich, Association pour l'information et la recherche sur les maladies rénales génétiques (AIRG-France), Institut de Recherche en Santé Publique (IReSP), Association Française du Syndrome de Rett (AFSR), Fondation Motrice, and l'Agence de la biomedicine.

E-Rare

France participated in the 4th Joint Transnational Call in 2012, with French teams participating in 7 out of the 11 consortia selected for funding.

Orphan medicinal products^{68,69}

The LEEM (French Pharmaceutical Industry Association) presented its annual overview of therapeutic advances with an edition covering 2012. A particular emphasis was put on new orphan drugs in relation to the development of personalised medicine⁷⁰.

Initiatives to improve access to orphan medicinal products

Compassionate use for individual patients takes the form of either cohort use (cohort Temporary Authorisation for Use) or named patient supply (nominative Temporary Authorisation for Use) prior MA granted both by the ANSM. Patients can also be treated with drugs before these drugs have received MA through clinical trials or hospital preparations. Reimbursement measures are in place for compassionate use. Innovative drugs are eligible for an ATU ("*Autorisation temporaire d'utilisation*" - Temporary Authorisation for Use) from the ANSM if there is a public health need.

This process was modified in 2012 following the law reinforcing the monitoring of safety of drugs and other healthcare products, published on 29 December 2011 (Law N° 2011-2012). The new law maintains the possibility of an ATU, in particular in the case of rare diseases. The drug must fulfil the following criteria: the treatment cannot be postponed; there is no alternative therapeutic to the drug; the efficacy and security of the

⁶⁸ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

⁶⁹ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (pp12-14)

⁷⁰ <http://www.leem.org/les-essentiels-maladies-rares>

drug are strongly presumed from the results of clinical trials (cohort *ATU*) or from scientific published data and knowledge (nominative *ATU*); the patient cannot be treated within a clinical trial. The *ATU* is given for a limited period, but renewable. A therapeutic protocol and data collection concerning safety and efficacy are mandatory for both cohort and nominative *ATU*.

This law also introduced the concept of “temporary recommendation of use” (“recommandation temporaire d’utilisation” - RTU) developed and published under the responsibility of the ANSM. The aim of RTU is to provide a framework for the prescription of a medicinal product beyond the indications of its MA when no other medicinal product with a MA or a cohort *ATU* is available for the considered indication. The development of RTU is possible when the ANSM considers the available data are sufficient to presume a favourable benefit risks ratio. Prospective data collection concerning safety and efficacy of the drug is mandatory when a RTU is published. In November 2012, the ANSM published a template⁷¹ for the follow-up of patients and collection of data if RTU are available. In order to help the ANSM to prepare the development of RTUs for rare diseases, the Ministry of Health asked the Reference Centres in July 2012 to carry out an inventory of their prescriptions out of the MA of the medicinal products that could be eligible for RTU. The questionnaire was returned by 70% of the Reference Centres. The data were compiled by the ministerial authorities and sent in November 2012 to the ANSM which is now exploiting them.

In hospitals, Temporary Treatment Protocols (“*Protocoles temporaires de traitement*” - PTT) may also be used to extend the indication for a drug or device with reimbursement permitted. Temporary Treatment Protocols are limited to expensive drugs used only in hospitals and registered on a special list.

In 2006, the law for the financing in 2007 of French Social Security system planned a derogative pathway for exceptional coverage of off-label use of medicinal products and of non-covered medical devices or services by the National Health Insurance⁷². Orphan or non-orphan medicinal products used off-label, medical devices or services intended for rare diseases are in particular concerned. The complete reimbursement is allowed for a limited renewable period by the Ministry of Health after the HAS has given a positive opinion. Since the law of the 29 December 2011 reinforcing the monitoring of safety of drugs and other healthcare products, the ANSM must publish a RTU before the HAS is allowed to advise the complete reimbursement of a medicinal product used off-label.

⁷¹

http://www.legifrance.gouv.fr/jopdf/common/jo_pdf.jsp?numJO=0&dateJO=20121122&numTexte=13&pageDebut=18412&pageFin=18414

⁷² Article L162-17-2-1 of the Social Security Legal Code.

LIST OF CONTRIBUTIONS⁷³

Contributions in 2010

Ségolène Aymé (*INSERM, SC11 – Director of Orphanet*)
Florence Suzan (*Institut national de veille sanitaire*)
Paul Landais (*Necker Children's Hospital*)
Jean Donadieu (*Armand-Trousseau Children's Hospital*)
Sophie Koutouzov (*GIS Maladies Rares*)
Odile Kremp (*Direction Générale de la Santé*)
Guillaume Le Henanff (*Direction de l'Hospitalisation et de l'Organisation des soins*)

Contributions in 2011

Ségolène Aymé (*INSERM, SC11 – Director of Orphanet*)
Alain Garcia (*Ministère du travail, de l'emploi et de la santé*)
Odile Kremp (*Direction Générale de la Santé*)
Florence Suzan (*Institut national de veille sanitaire*)
Paul Landais (*Necker Children's Hospital*)
Jeanne-Marie Brechot (*Institut national du cancer*)
Annie Lorence (*Afssaps*)
Valérie Drouvot (*DGOS*)
Sophie Koutouzov (*GIS Maladies Rares*)

Contributions in 2012

Ségolène Aymé & Odile Kremp (*INSERM, US14 –Orphanet*)
François Meyer (*Haute Autorité de Santé*)
Anne d'Andon (*Haute Autorité de Santé*)
Catherine Rumeau-Pichon (*Haute Autorité de Santé*)
Brigitte Lefeuvre (*Direction Générale de la Santé*)
Patrick Cayer-Barioz (*Direction Générale de la Santé*)
Frédérique Pothier (*Direction Générale de la Santé*)
Rosemary Ancelle-Park (*Direction Générale de la Santé*)
Patrice Dosquet (*Direction Générale de la Santé*)
Lydia Le Bris (*Direction Générale de la Cohésion Sociale*)
Jacqueline Patureau (*Direction Générale de la Cohésion Sociale*)
Thomas Heuyer (*Plateforme Maladies Rares*)
Aymeric Audiau (*Alliance Maladies Rares*)
Hélène Dollfuss (*Vice President, Research, National Rare Disease Plan 2011-2014*)
Nathalie Leporrier (*Agence de la Biomédecine*)
Christine Bouveresse (*Institut de Veille Sanitaire*)
Charles Persoz (*Institut National de la Santé et de la Recherche Médicale*)
Annie Lorence (*Agence Française de Sécurité Sanitaire des Produits de Santé*)

Contributions in 2013

Serge Amsellem (*RaDiCo Project*)
Aymeric Audiau (*Alliance for Rare Diseases*)
Ségolène Aymé (*INSERM, Orphanet Joint Action*)
Christine Bouveresse (*Institute for Public Health Surveillance*)
Patrick Cayer-Barrio (*General Directorate for Health, Ministry of Social Affairs and Health*)
Anne d'Andon (*National Authority for Health*)
Patrice Dosquet (*General Directorate for Health, Ministry of Social Affairs and Health*)
Thomas Heuyer (*Rare Disease Information Service Helpline*)
Céline Hubert (*Rare Diseases Foundation*)
Chrystel Jouan-Flahault (*French Pharmaceutical Industry Association*)
Paul Landais (*National Rare Diseases Database*)
Lydia Lebris (*General Directorate of Social Cohesion, Ministry of Social Affairs and Health*)
Pascale Levy (*Biomedicine Agency*)
Hélène Marie (*National Solidarity Fund for Autonomy*)
Arlette Meyer (*General Directorate for Health, Ministry of Social Affairs and Health*)
Catherine Paclot (*General Directorate for Health, Ministry of Social Affairs and Health*)

⁷³ The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

Charles Persoz (French National Institute of Health and Medical Research)

Catherine Rumeau-Pichon (National Authority for Health)

Audrey Tranchant (Rare Diseases Foundation)

Validated by: Alain Garcia (EUCERD Representative France, Ministry of Social Affairs and Health)

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⁷⁴ All websites and documents were last accessed in May 2013.