

2014 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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The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

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 European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 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 2013. 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 Commission Expert Group 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 2013

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

Parts I – V also include a description of the methodology, sources and validation process of the entire report, and 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.

Each year, there are around 15 000 downloads of the different sections of the report combined.

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 diseases plan in 2004 for the period 2005-2008 with allocated funding. This first plan, entitled “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 in four yearly waves and funding of 131 centres of expertise, called “*centre de référence maladies rares*” in France (“Reference Centres for Rare Diseases”). 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 for Rare Diseases”), and are the equivalent of regional centres of expertise. Unlike Reference Centres, Competence Centres received no specific funding for their activity and are not evaluated. 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 – MRIS - 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

¹ <http://www.maladiesraresinfo.org>

from corresponding actions that have satisfactorily fulfilled the planned goals. The need to strengthen these 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.

In 2009, the external evaluation of the 131 Reference Centres, planned to take place during the fifth year after their designation, began according to a method (self-evaluation on the third year and external evaluation on the fifth one) which was developed and implemented by the French National Authority for Health (“*Haute Autorité de santé*” – HAS). At the end of the complete process, the designation of all the 131 Reference Centres was renewed.

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 (“*Fondation maladies rares*” – French Foundation for Rare Diseases - FFRD) to coordinate and facilitate research on rare diseases;
- Creation of a National Rare Diseases Databank (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

² http://www.hcsp.fr/docspdf/avisrapports/hcsp20090317_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

be based on the collection of a minimum data set, common to all patients and rare diseases and all the Reference and Competence 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;
- 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;
- Coordination of rare diseases Reference Centres and their regional centers into a limited number (around twenty) of coherent "national networks for rare diseases" (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 anywhere in France. They aim also to allow better coordinated initiatives of the Reference Centres in their research, information and education activities. These French networks would be connected to the future European Reference Networks (ERN) developed for 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 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 helping 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 in 2011 to help implement the plan: one dedicated to draw up a new evaluation process of the Reference Centres, a second one to define the specifications, scope and organisation of the future national networks for rare diseases, a third one to help improve the quality of information, a fourth one to develop the access to NGS, and the last one to help developing 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 might justify the adaptation of the plan during its progress.

An "information and experience sharing meeting" concerning the implementation of the Second Plan was organised on 19 December 2012 for over 300 participants, in particular for all the coordinators of the 131 Reference Centres. The meeting objectives were to share information with the coordinators and patients' association on the progress of the plan. In particular the new evaluation procedures for Reference Centres were presented and discussed, as well as the future national networks for rare diseases and the new method to develop "PNDS" (See section on *Good Practice Guidelines*).

The Steering Committee of the plan held two meetings in 2013 on 19 March and 19 November. These meetings concluded that significant progress has been made to date which is in line with the objectives of the Second French National Plan.

In the area of research, a significant development has been the setting up of a funding process to support Preclinical and Early Clinical Research. This is especially important as France provides sources of funding for basic research (from the "*Agence nationale de la recherche*" – ANR – "National Research Agency", financed by the Ministry for Research) and for academic clinical research (from the "*Programme hospitalier de recherche Clinique*" – PHRC – "Hospital Clinical Research Programme" - financed by the Ministry of Health), but not for research projects that fall somewhere in between basic and clinical research. An annual call for proposals for translational research in health was announced and launched in 2013. It was financed both by ANR and Ministry of Health. Basic research for rare diseases was granted €113 million between 2005 and 2011, representing 327 projects over these 7 years. Clinical research received €9 million (36 projects) in 2010, €8.3 million (23 projects) in 2011 and €8.5 million (21 projects) in 2012.

One of the research priorities of the second plan was to set up a national scientific cooperation structure to coordinate and accelerate rare diseases research. To this end, the French Foundation for Rare Diseases (“Fondation maladies rares” - FFRD⁶) 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 FFRD is an innovative framework gathering all fields of rare diseases research from biomedical research to social sciences and humanities research. Its founding bodies represent a unique alliance of research, care and patients’ organisations, namely the French Muscular Dystrophy Association (“Association française contre les myopathies” – “AFM-Téléthon”), the French Alliance for Rare Diseases (*Alliance Maladies Rares*), the National Institute of Health and Medical Research (INSERM), the Conference of General Directors of the University Hospitals and the Conference of University Presidents. The Executive Committee, composed of representatives from the founding members as well as 8 international experts in the rare diseases field, is supported by International Scientific Committees of leading medical specialists and scientists providing strategic advice. The Foundation operates as a private structure with a sustained source of funding, based on public/private partnerships, and acts a federative and strategic hub to accelerate scientific, clinical and social innovation by stimulating cross-sector cooperation to the benefit of patients affected by rare diseases. With headquarters at the heart of the French national Platform for Rare Diseases (“Plateforme maladies rares”) and seven field coordinators in direct contact with researchers all over the national territory, the priorities of the FFRD are driven by grounded needs and integrated into a national strategy with an international perspective. Its rapid development in 2012 and 2013 has been bringing new synergies to basic, translational and applied research (details in the “research activities” section of this report), with an active bridging of all rare diseases stakeholders leading to:

- Better understand rare diseases (facilitation of researchers’ access to cutting-edge technology, funding resources, R&D expertise);
- Develop new treatments (acceleration of clinical innovation thanks to the early detection of drug candidates, expert consulting and public-private partnerships);
- Improve patients’ care (support of societal advances through the funding of dedicated research, national think tanks on key issues and contribution to acquainted policies).

The implementation of necessary sequencing infrastructures to speed up genetic diagnosis was financed by the Ministry of Health in 2012 and 2013: a total of 34 university hospitals received funds (€9.6 million over 2 years) to obtain necessary equipment to provide new generation sequencing services to speed up standard diagnosis. An in-depth reflexion has been in progress in 2013 to design one national NGS platform for complex diagnosis and research.

Since December 2012, hospitals began one of the key actions of the second plan: coding in the National Database of In-patient Registrations (“PMSI”) all rare disease patients hospitalised in Reference Centres using Orphanet nomenclature. The goal is to begin to use systematically the codes Orpha for better identifying patients in the healthcare system so as to improve knowledge of their healthcare pathways. The pilot study performed in some hospitals found it difficult for coders. The outcomes were analysed by a working group composed of representatives of the Medical Information Coders Society (“Société francophone d’information médicale” – SOFIME), the French National Agency for Technical Coding in Health Information Systems (“Agence technique de l’information sur l’hospitalisation” - ATIH), the National Rare Disease Data Repository (BNDMR) and Orphanet. This group is currently working towards a simpler integration of Orphacodes in the French health information system in order to enable a wider coverage of coding (in- and out-patient clinics).

The initiative to establish a French national rare diseases databank (“Banque nationale de données maladies rares” - BNDMR⁷) in order to have a central data repository on rare disease patients from various existing sources, for health care planning and clinical research, began in 2011. The project is financed by the Ministry of Health. 2012 was dedicated to drawing up the minimum dataset for all rare diseases along with the 131 Reference Centres. The minimum dataset was approved during the Steering Committee meeting on 19 March 2013. A national interoperability framework was also defined in 2013. The project first aims at gathering qualified data from Reference and Competence Centres. The linkage with other national data sources will be enabled in 2015 onwards once patients are identified thanks to the Reference and Competence Centres and the minimum data set. A specific steering committee was created in November 2013 to follow the implementation of the BNDMR.

⁶ <http://www.fondation-maladiesrares.org>

⁷ <http://www.bndmr.fr/>

In the area of health care delivery, improving the way Reference Centres are evaluated is one of the main objectives of the second plan, to ease the reporting carried out by the centres and to create the tools for an accurate assessment on which to base decision on the renewal of the designation and on the allocation of funds. An annual reporting system and a new external evaluation process were defined after 2 years of solid effort by working groups composed of representatives of Reference Centres, patients' associations, French National Authority for Health ("HAS"), French Agency for the Evaluation of Research and Higher Education ("AERES") and Ministry of Health. The new process will be ready to be launched in 2014.

Another main objective of the second plan is to reorganise Reference Centres and group them in a functional way that maximises collaboration and allows better and easier orientation of patients. These "national networks for rare diseases" ("*filiales de santé maladies rares*") will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: Reference and Competence Centres, diagnostic and research laboratories, imaging, health and social care, professionals and patients' associations etc. Preliminary work and surveys in 2012 identified 23 possible groupings of Reference Centres. The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres. At the end of the call, in November 2013, 32 projects have been received. The "Permanent Working Group", planned to monitor the activity of Reference Centres and national networks, held a first meeting on 18 December 2013 and began to examine the submitted projects. The national networks will be designated by the Ministry of Health in early 2014.

Another objective of the plan was to increase the number of "*national diagnosis and treatment protocol*" ("PNDS"). These protocols were identified in the first plan as defining the national standard of care by rare disease (good practice guidelines). Each PNDS was completed with a list of the acts and products (drugs, medical devices) considered as essential for the patients care and therefore which may be reimbursed, including off-label products. The method of production was developed and implemented by the HAS ("French National Authority for Health"), which supervised very closely their elaboration by the Reference Centres. This high quality method was however too complicated to allow rapid publication of a significant number of protocols: in seven years, only 50 PNDS were published. To boost the production to 200 protocols in 4 years, as expected at the end of the second plan, the method was simplified by the HAS⁸ and the task to produce the PNDS was completely delegated to the Reference Centres. However, the production of PNDS remains low: only 2 new PNDS were published in 2013. The PNDS developed with the HAS new method are not yet completed with a list of the acts and products.

One of the burning issues discussed by the Steering Committee of the plan was the off-label use of drugs for treating rare diseases. A survey carried out in 2012 in 50% of the Reference Centres demonstrated that over 500 medicinal products are regularly used off-label, especially in children with rare diseases. A recent French law (December 2011) makes necessary to have "temporary use recommendations" published by the French National Agency for the Safety of Medicine and Health Products ("ANSM") so that off-label products are reimbursed (this clause of the law is not specific for drugs used for rare diseases, and concerns any off-label use). The publication of "temporary use recommendations" requires data to support that the off-label use of the drug has probably a favourable benefit to risk ratio in the absence of any other effective product in this indication. Of course, this is highly difficult for rare diseases as the existence of such data is modest and often absent. The ANSM did not publish any temporary use recommendations in 2013. This new context has been a matter of concern for the professionals and patients. A specific working group has been created to follow this issue and make proposals to help the development of temporary use recommendations.

In conclusion, the second French plan is well on the way and several initiatives delineated in the plan have been implemented. A new leader of the implementation of the plan was named in July 2013. The Steering Committee recognises that the final months of the plan will present challenges as the rare disease community will have to prepare for the future in the context of a constrained budget but also to build on all the improvements resulting from the two national plans.

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

A second National Plan for Cancers⁹ was launched on 2 November 2009 for the period 2009-2013. This plan is the continuation of the first national plan¹⁰ 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

⁸ The HAS published its new method in December 2012: http://www.has-sante.fr/portail/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=3

⁹ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

¹⁰ <http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20032007.pdf>

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 6/100 000 persons per year; or those requiring highly specialised management, owing to their unusual location, or to their occurrence at a specific or complex site.

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 data¹¹. A second report concerning the activity of the "Expert Centres" was published in 2012¹², as well as a document published in French¹³ and in English¹⁴ describing this specific organisation. Other reports on genetic testing and treatment for hereditary cancers were published in 2012: the first one summarised the 2011 activities of French oncogenetic platforms, and the second one focused on molecular genetic testing for targeted therapies in France in 2012¹⁵. In 2013, a report of their scientific council¹⁶ was published including details of specific recommendations and activities in the field to date, as well as an overview of cancer in France¹⁷ and a 2012 activity report¹⁸ concerning the care of adult patients with rare cancers, including details of the number diagnoses, clinical trials and research collaborations in the area.

The final report concerning the implementation of the cancer plan, including a section on the actions in the field of rare cancers, was published in 2013¹⁹.

As for the preparation of the third French National Plan for Cancers (including rare cancers) 2014-2019: recommendations for a third plan for cancers²⁰ in the field were transmitted to the Minister of Health in autumn 2013. A third National Plan for Cancers was then prepared and published on 4 February 2014²¹. Organisation of care for adults with a complex cancer, improvement of the organisation of second opinion in pathology for rare cancers and organisation of care for very rare cancers in children are planned.

French National Plan for Rare Disabilities 2009-2013

A "rare disability" is a French administrative concept which was defined in 2000²²: the definition proposed 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. A plan aimed at rare disabilities²³ (of which rare diseases may be a cause) was adopted on 27 October 2009 for the period 2009-2013²⁴. 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. 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;

¹¹ <http://lesdonnees.e-cancer.fr/>

¹² http://www.e-cancer.fr/component/docman/doc_download/9274-bilan-2011-de-la-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares

¹³ http://www.e-cancer.fr/component/docman/doc_download/4692-cancers-rares-de-ladulte--lorganisation-en-centres-experts

¹⁴ http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

¹⁵ <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#>

¹⁶ <http://www.e-cancer.fr/publications/87-rapports-scientifiques/742-rapport-scientifique-2012-2013>

¹⁷ <http://www.e-cancer.fr/publications/69-epidemiologie/758-les-cancers-en-france-edition-2013>

¹⁸ <http://www.e-cancer.fr/rss-soins/8591-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares-donnees-dactivite-2012>

¹⁹ <http://www.plan-cancer.gouv.fr/accueil/actualites/43-actualites/1204-publication-du-rapport-final-au-president-de-la-republique-du-plan-cancer-2009-2013.html>

²⁰ <http://www.sante.gouv.fr/IMG/pdf/Recommandations-pour-le-3e-plan-cancer.pdf>

²¹ <http://www.e-cancer.fr/publications> (english) <http://www.e-cancer.fr/le-plan-cancer?gclid=CKLYntPlyb4CFbShtAodTDoAcA>

²² <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000765671>

²³ One of the measures of the plan was to compare this concept 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 expert 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>. The 2000 definition of "rare disability" is currently in discussion in France, and may change in 2014.

²⁴ This plan is 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.php?id_article=726

- The development of the offer of services at home and in establishments for patients with rare disabilities.

Several levels of expertise for patients with a rare disability were planned. Three “national resource centres” (“Centres nationaux de ressources pour les handicaps rares” – CNRHR – “National Resource Centres for Rare Disabilities”) were created in 2011 for patients with a severe 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 2013. Inter-regional intermediary teams (“équipes relais”) of these national centres were launched in 2013 with the aim of their complete deployment in 2014-2015. Cooperation between national resource centres and inter-regional teams for rare disabilities and Reference Centres for rare diseases is also underway. A leaflet²⁵ was published describing the national organisation of care in this area.

In terms of improving knowledge, several research projects have been funded by the CNSA, in collaboration with the Institute of Public Health Research.

The Ministry of Social Affairs and Health has asked for an evaluation of the first plan and will announce a second one in 2014 based on various studies conducted during the first one, such as the expert report conducted by INSERM at the request of the CNSA entitled²⁶ “Rare handicaps: context, purposes, perspectives”. It highlights the need to describe rare disabilities with the International Classification of Functioning, Disability and Health (ICF), the utility of creating national and international registries or databases, and suggests strengthening the organisation created by the first plan.

Other French national initiatives related to rare diseases

On 2 May 2013, the third National Plan for Autism for the period 2013-2017 was published by the Ministry of Social Affairs and Health. This plan aimed at improving early diagnosis and early care, structuring healthcare, educational and social pathways for patients, supporting families, improving training for all the professionals in charge of patients, and strengthening research²⁷.

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 handicap²⁸.

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 published²⁹, 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 médical 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. For rare diseases, the on-going limitation of DMP use is the current impossibility to create a DMP for children. Three years after the DMP was launched, there were about 420 000 DMP at the end of 2013.

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo (“Rare Diseases Cohorts”) project for 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 experts in rare diseases;

²⁵ <http://www.cnsa.fr/IMG/pdf/Memos23-WEB.pdf>

²⁶ The expert 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>

²⁷ http://www.social-sante.gouv.fr/actualite-presse/42/brevets/2325/presentation-du-3eme-plan-autisme_15797.html

²⁸ http://www.solidarite.gouv.fr/IMG/pdf/Dossier_de_presse_2JUIN08.pdf; www.cnsa.fr/IMG/doc/Plan_handicap_visuel_1_-2.doc

²⁹ http://www.travail-emploi-sante.gouv.fr/IMG/pdf/Plan_en_faveur_des_personnes_sourdes_ou_malentendantes_-_10_02_2010.pdf

- 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.

The RaDiCo project showed accelerated development in 2013³⁰, and prepared the launch its first call for rare diseases cohort proposals at the beginning of January 2014. The RaDiCo projet has developed very close links with the BNDMR.

In 2011, the web portal “Epidemiology – France”³¹ was launched, aiming to provide a directory of databases to advance research and expertise in the field of health in France. The “Epidemiology – France” 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”; 28 databases classified in “Rare 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 first plan, 131 Reference Centres (“*centre de référence maladies rares*” – CRMR) were named in university hospitals by the Ministry of Health and received a specific funding for their missions. A “coordinator” was designated officially in each Reference Centre. The 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);

³⁰ <http://www.radico.fr>

³¹ <http://epidemiologie-france.fr/>

- 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.

Between 2009 and 2012, the Reference Centres were evaluated over time, first through self-evaluation after 3 years as a designated centre, then through an external evaluation the fifth year. The external evaluation was organised by the HAS published its 2010 activity report in 2011, with one section dedicated to its activity in the evaluation of Reference Centres³². At the beginning of the first plan, a National Consultative Designation Committee (*"Comité national consultative de labellisation"*) analysed the proposals for creation of Reference Centres and 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. The new process has been in progress in 2012 and was definitively specified at the beginning of 2013: each Reference Centre will establish an activity report each year and undergo an external evaluation at 4 years according to modalities still under discussion with the HAS. The second plan has planned the creation of a "Permanent Working Group", which will monitor the annual activity and external evaluation reports, and give an opinion to the Ministry of Health on the renewal of the designation of Reference Centres. It will also monitor the future "national networks for rare diseases". The permanent working group was officially created at the end of 2013, and held its first meeting on 18 December.

A second type of expert centre was designated in 2008, named *"centres de compétences maladies rares"*. 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 patients close to their home, and to participate in the activities of the reference centres they are linked to. Unlike the Reference Centres, the regional centres do not receive dedicated funding for their rare disease activities, and have not to fill an annual activity report and to be evaluated. Currently about 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. These Competence Centres will be included into the future national networks for rare diseases in association with the Reference Centres they are linked to.

In 2013 major steps were made to coordinate individual Reference Centres and group them in a functional way that maximises collaboration across the country. The "national networks for rare diseases" (*"filiales de santé maladies rares"*) will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: not only Reference and Competence Centres, but also diagnostic and research laboratories, imaging, health and social care, professionals and patients' associations etc. The designated networks will receive funds from the Ministry of Health for their coordination activity. A preliminary survey identified 23 possible groups gathering nearly all the 131 Reference Centres (some centres do not fall in any of these groups). The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres: at the end of the call, in November, 32 projects have been received. The Permanent Working Group began to analyse these projects in December 2013. The result of this call is expected in early 2014³³.

In July 2013, the Ministry of Health published a directive concerning the process for succession as coordinator of a Reference Centre, and for the creation or abrogation of a Competence Centre linked to a Reference Centre.

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^{34,35} 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 "Reference Centres" and a network of regional centres for rare adult cancers. Since 2009, 23 national clinical networks 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 Reference Centres have to ensure diagnostic certainty by implementing a systematic second reading of the biopsy specimens, to

³² http://www.has-sante.fr/portail/jcms/c_1070314/rapport-annuel-d-activite-2010

³³ The list of the first 15 accepted "national networks for rare diseases" was published on the website of the Ministry of Health on 28 February 2014. <http://www.sante.gouv.fr/les-filieres-de-sante-maladies-rares.html>

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

³⁵ http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

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 “national resource centres” for rare disabilities have been designated in 2011, and a fourth one in 2013 thanks to the French National Plan for Rare Disabilities 2009-2013³⁶.

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 concerning rare malformation syndromes and developmental defects 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 June 2012, the French General Directorate for Provision of Healthcare launched a position paper³⁷ detailing the conditions for the establishment and renewal of “reference centres” so as to best respond to requests for designation of such centres. This position paper is not specific to rare diseases reference centres.

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 were nominated for a 3-year term, with renewable mandate. The evaluation of the quality of registries was in fact 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 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 began on a possible evolution of the Committee’s missions and the needs of the other registries and databases existing in France for support and evaluation and in April 2013 the committee was dissolved at the same time as the national committee created in 1996 for the evaluation of non-rare disease registries. The InVS, Inserm and INCa launched a call for experts in October 2013 in order to create a Registry Evaluation Committee which will consider, amongst others, rare disease registries. This committee will consist exclusively of experts of registries, epidemiology and public health.

The Second National Plan for Rare Diseases also has foreseen 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 Competence 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 was to build a minimum data set (MDS) common to all rare disease centres of expertise and to all rare

³⁶ http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf; http://www.cnsa.fr/article.php3?id_article=726

³⁷ http://circulaire.legifrance.gouv.fr/pdf/2012/06/cir_35428.pdf

diseases. In 2012, a working group helped to build the MDS along with the 131 Reference Centres, which was discussed and validated by the Steering Committee of the plan in March 2013. The MDS will be entered through an application called BaMaRa (“Banque Maladies Rares” – Rare Diseases Databank), either directly by the centres of expertise, or through their own application if appropriate. To enable data flows between French hospitals and the BaMaRa, a national interoperability framework was defined in 2013. It consists in setting the necessary compatibility elements such as patient identification, data elements and nomenclatures, technical data flows and security. It will help gathering data at the Reference and Competence 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. A steering committee specific of the BNDMR was set up in 2013 including representatives from the concerned ministries and stakeholders, including patients’ associations. In 2013, the BNDMR team also began to develop a specific application named LORD (Linking Open Rare Disease data) to help with rare disease diagnosis coding in hospital health information systems³⁸. This application will be used at national level to help coding RD patients either in hospital information systems or registries.

Each of the national Expert Centres for rare adult cancers is requested to contribute to the epidemiological surveillance and observation of these cancers by establishing a database and collects all the cases. Almost 14 000 cases with a rare adult cancer were registered in 2012 in these databases.

France contributes to several European rare disease registries including EUROCAT, EUROHISTIONET, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EIMD, EUROWABB, EUROTRAPS, CHS, EUROCARE CF, ECFS, INFEVERS, EDMUS, EHN-EUROHISTIONET, ESCORT-HU, SCLS registry, EURORHETT, 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 national 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 disease³⁹.

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 deficiency⁴⁰. 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 national 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 on 23 April 2012⁴¹. Screening for deafness was already performed in 51% of the French maternity hospitals using different methods. National specifications on screening methods have not yet been published in 2013.

Genetic testing

The French Biomedicine Agency (“*Agence de la Biomédecine*”), a public agency operating under the supervision of the Ministry of Health, was created under the Bioethics Law of August 2004. The agency oversees four key areas of human biology and medicine: organ tissue and cell transplantation, assisted reproductive technology, prenatal and genetic diagnosis and human embryo and embryonic stem cell research. On a national level, it provides professionals and researchers with collective answers, guarantees equity of access, ethics and transparency of these activities, organises information and awareness campaigns, and evaluates and publishes

³⁸ This application was launched in early 2014: <http://enlord.bndmr.fr>

³⁹ <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000021763691&dateTexte=&categorieLien=id>

⁴⁰ http://www.has-sante.fr/portail/jcms/c_1069254/evaluation-de-l'extension-du-depistage-neonatal-a-une-ou-plusieurs-erreurs-innees-du-metabolisme-par-spectrometrie-de-masse-en-tandem-1er-volet-deficit-en-mcad

⁴¹ <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000025794966&dateTexte=&categorieLien=id>

its activities in an annual report. Its 2012 annual report was published in 2013⁴². For the fourth consecutive year, the Agency included data on postnatal genetic testing carried out in France culled via a partnership with Orphanet. The number of diseases for which a genetic diagnosis is available is still increasing in 2012: 1526 genetic diseases can be diagnosed.

Guidelines for good practices related to the examination of genetic characteristics in the medical context in order to assure quality of care were finalised in at the end of 2012, and published in the form of an official text on 2 June 2013⁴³. These guidelines describe in particular information to be delivered to patients before and after performing genetic tests.

Tests for 1472 genes and an estimated 1606 diseases are registered as available in France in Orphanet⁴⁴.

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. In 2013, the Alliance has begun reflection and workshops to develop therapeutic patient education programs.

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 France⁴⁵ 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

⁴² http://www.agence-biomedecine.fr/IMG/pdf/rapport_annuel_vdef.pdf

⁴³ http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id

⁴⁴ Data extracted from Orphanet in January 2014.

⁴⁵ <http://www.orphanet-france.fr/national/FR-FR/index/page-d-accueil/?lng=FR>

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 cancers⁴⁶.

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 website⁴⁷. Fourteen 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 2013 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 2012⁴⁸. 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-AFSSAP⁴⁹) 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 professionals⁵⁰. These cards were distributed by the Reference Centre physicians. A simpler model is now envisaged, 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. It is not yet developed.

National Expert Centres for rare cancers are also requested to provide information to patients and their relatives and to develop close links with national and international patients' associations. Twenty patients associations were listed in 2012 in close active collaboration with the expert centres.

⁴⁶ http://www.e-cancer.fr/component/docman/doc_download/9123-cahiers-dorphanet-centres-experts-cancers-rares

⁴⁷ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

⁴⁸ <http://www.maladiesraresinfo.org/services-proposes/89.html>

⁴⁹ 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/>.

⁵⁰ <http://www.sante.gouv.fr/les-cartes-de-soins-et-d-informations-pour-les-personnes-atteintes-de-maladies-rares.html>

In 2010, the website www.droitsdesmalades.fr, which informs all citizens about their healthcare rights, was launched. In addition, the patient organisation *Sparadrap*⁵¹ 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 *Intégrascol* 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 school⁵².

Since 2012, the website of the French Foundation for Rare Diseases (FFRD)⁵³ is integrating information dedicated to rare diseases researchers, including an extensive mapping of funding opportunities (institutional funding, FFRD funding, charities, private and EU/international opportunities). The portal is updated on a regular basis. Further advice is provided by the regional coordinators to better inform researchers about access, specificities and deadlines, guide them towards most adapted funding sources and support their applications, including through access to complementary partners and fulfillments of specific conditions.

Guidelines

During the first national plan up to December 2012, the Reference Centres produced, with the sustained help of the HAS, 50 national good practice guidelines ("PNDS") for diagnosis, treatment and follow-up of patients with rare disease. Each PNDS of this first group were completed with a list of the acts and products (drugs, medical devices) considered as essential for the patients care and therefore which may be reimbursed, including off-label products. In December 2012, the HAS published a new simplified method to develop "PNDS"⁵⁴ to help the Reference Centres draft more quickly the PNDS to boost the production to 200 protocols in 4 years, as expected at the end of the second plan. The task to produce the PNDS is now completely delegated to the Reference Centres, and the HAS will just publish the PNDS on its website. The PNDS developed with the HAS simplified method will be no more completed with a list of the acts and products for patients care. However, the production of PNDS has remained low in 2013: only 2 new PNDS were published. All the PNDS are published on Orphanet, HAS⁵⁵ and Reference Centre websites. The HAS itself has published clinical practice guidelines⁵⁶ for the follow-up of children with deafness under the age of six and their family.

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 disease⁵⁷. Clinical guidelines are available on the dedicated websites of national Expert Centres, concerning most of the rare cancers, such as sarcomas, cutaneous lymphoma, rare head and neck cancers, thyroid carcinoma, rare ovarian carcinoma, thymus carcinoma.

National working groups coordinated by the French Foundation for Rare Diseases have also been working on complementary guidelines, including updated guidance concerning informed consent to the analysis of genetic characteristics, taking into account the rapid evolution of the field through the implementation of NGS at the crossing between research and healthcare. Work has also been undertaken to provide researchers with targeted guidelines on the use of databases in the evolving regulatory context. Consultation of all relevant national learned societies on those key issues is on-going.

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 patients' 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.

⁵¹ <http://www.sparadrap.org/SPARADRAP>

⁵² <http://www.integrascol.fr/>

⁵³ <http://fondation-maladiesrares.org>

⁵⁴ 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

⁵⁵ http://www.has-sante.fr/portail/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=1

⁵⁶ http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite_de_lenfant_-_0_a_6_ans_-_recommandations.pdf

⁵⁷ 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

In 2013, the French Foundation for Rare Diseases organised 3 national workshops designed for rare diseases researchers. A total of 450 participants had the opportunity to meet up with technology platforms and scientific experts in the field of proteomics, animal models and molecular screening, with the objective to boost the development of cutting-edge research projects ahead of the launch of dedicated call for proposals by the FFRD. The FFRD also initiated a reflection on the first national academic training dedicated to rare diseases research. Partner universities have been contacted and details of the objectives, programme and access will be discussed over 2014 for a national implementation as early as 2015.

National rare disease events 2013

To mark the Rare Disease Day 2013 in France, a gathering took place at the Pont des Arts in Paris including the members of the Rare Disease Platform to raise hands in solidarity. Orphanet also marked the day with the launch of their mobile application. From 28 February to 2 March for the third year in a row, an awareness raising campaign was organised on several train lines to raise awareness of this issue amongst the passengers using the service. The Rare Disease Platform also held a press conference on 21 February.

On 12 March, a regional event was organised in Limoges by the Regional Health Agency ("Agence régionale de santé") to bring together healthcare professionals, regional administrative officers and patients' associations, for discussions concerning rare diseases and implementation of the plans in Limousin Region, with presentations from actors in the field and regional decision makers.

On 23 September, Orphanet and the French Rare Disease Alliance organised in Paris their annual forum for patient organisations on the theme of information and communication technologies. This forum has become, over the years, a major event for many patients' organisations, and this year's event was attended by over 100 attendees. The theme for 2013 was "ICT for the collection and sharing of information on rare diseases". The first part was dedicated to the latest news of the French rare diseases community, and then the role of patients and patient organisations in registries and cohorts was discussed. The second part focused on how patients can play a role in data collection by highlighting the benefits and the risks they are exposed to.

On 16 September, a regional event was organised in Marseille by the Rare Diseases Alliance, bringing together more than 150 participants from patients' organisations and from the clinics, research and medico and social care areas with the participation of French Ministry of Health representative.

On 17-18 October, the French Foundation for Rare Diseases supported the organisation of Orphan Drug and Rare Disease Seminar in Marseille organised by Eudipharm, F-CRIN and OrphanDev with the aim to raise awareness among clinical research stakeholders on drug development specificities in the rare diseases field.

On 21 November, a Rare Diseases Conference, organized by the Regional Health Agency, in partnership with the Rare Diseases Alliance and the French Foundation for Rare Diseases, was organised in Rennes in order to inform the public about the availability of regional care, medical resources and technical facilities dedicated to rare diseases patients. This meeting also aimed at bridging teams and dedicated platforms at national and regional levels, raising awareness on latest developments of research as well as addressing social and ethical implications associated with rare diseases.

On 28-29 November, the third edition of the "Rare Conferences", Rare2013⁵⁸, was organised by Eurobiomed in Montpellier with over 300 participants attending the presentations and roundtables to hear about advances in the field of rare diseases.

Each year in December, an annual *Téléthon* is organised by the AFM-Téléthon ("*Association française contre les myopathies*" - French Muscular Dystrophy Association) 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 2013, the 27th edition of the *Téléthon* took place on 6-7 December, raising over 78 million Euros. On the same weekend, the 14th Rare Disease March took place in Paris, organised by the Rare Disease Alliance, bringing together 2000 participants.

Hosted events in 2013

Amongst the events hosted by France in the field of rare diseases were: the European Society of Human Genetics (Paris, 8-12 June 2013), Orphan Drug & Rare Disease Seminar "Accelerating access to therapeutic innovation" (17-18 October 2013, Marseille), 16th International Conference on Behçet's Disease (18-20 September 2013, Paris), 2nd International Symposium on Hypothalamic Hamartomas (20-21 September 2013, Marseille), 2nd International Expert Meeting on Congenital Melanocytic Nevi and Neurocutaneous

⁵⁸ <http://www.rare2013.com/>

Melanocytosis (28-30 September 2013, Marseille), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France), Myasthenia 2013 (1-2 July 2013, Paris), European Human Genetics Conference 2013 (8-11 June 2013, Paris), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France).

The French National Cancer Institute, associated partner of EPAAC (European partnership action against cancer) work package 7 (WP7) organised a workshop on rare cancers in July 2013. The purpose of this workshop was to explore the feasibility and relevance to harmonize clinical practice guidelines at European level in the context of rare cancers (with sarcoma as an example), taking into account the results of the survey which has been conducted in the frame of EPAAC WP7 on existing rare cancer networks and patients groups in Europe. A report of this workshop was presented in Open Forum EPAAC in Slovenia in November 2013⁵⁹.

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;
- The "*Fondation maladies rares*⁶⁰" (*Rare Diseases Foundation*).

Basic research for rare diseases was granted €113 million between 2005 and 2011, representing 327 projects over these 7 years. Clinical research received €9 million (36 projects) in 2010, €8.3 million (23 projects) in 2011 and €8.5 million (21 projects) in 2012.

A specific chapter of the Second National Plan for Rare Diseases is dedicated to research, and several new initiatives have been planned, most of which have already been implemented.

Flagship of the Second National Plan, the French Foundation for Rare Diseases (FFRD) has been actively promoting rare diseases research since its launch in February 2012. The unique cooperative framework is proving to be an efficient design to implement the main objective to accelerate rare diseases research, and more specifically, to bridge all rare diseases stakeholders in order to:

(1) Understand rare diseases

The French Foundation for Rare Diseases carefully selected 7 technology platforms, both public and private, with whom it initiated partnerships in order to fulfil key needs in the area of rare diseases research: by the end of 2013, the FFRD had launched 4 calls for projects to facilitate researchers' access to NGS technologies and identify the genetics underlying rare diseases not characterized to date, as well as 1 call for projects to develop mouse models and study further functional mechanisms involved in rare diseases. A total of 213 projects were received. A selective scientific process involving 150 experts led to the funding of 95 projects all over the national territory (77 NGS and 18 animal models) for a total of over €1.7 million. In parallel to its own sources of funding and call for proposals, the FFRD has also been involved in providing information to the French rare diseases research community on several other funding opportunities both at the French level (nationally and regionally) and at the EU level (such as IMI, COST, FP7, DG SANCO funding programmes for instance).

(2) Develop new treatments

Following a national workshop organised at the *College de France* in July 2013 to enable scientists to share knowledge and experiences in the field of molecular screening of drug candidates, the FFRD launched its first dedicated call for projects in October 2013. A total of 15 high-flying projects are currently under selection, in collaboration with 5 dedicated technology platforms. In parallel, the FFRD actively engaged in anticipating the R&D needs of innovative diagnostic and therapeutic approaches. This led to the detection of 66 promising candidates in 2013, including new molecules, repurposed drugs and innovative medical devices. Guidance is provided at each step of development together with dedicated partners (IP experts, national and EU regulatory agencies, pharma/biotech, investment funds etc.). As an example, a total of 10 procedures of orphan designation have been initiated in 2013

⁵⁹ More than a European sound box: capitalising on the added value of the European perspective in cancer treatment. JM Borrás, J Prades, J-M Bréchet, S Faithfull, A Trama, P G Casali. In: Boosting Innovation and Cooperation in European Cancer Control – Key Findings from the European partnership for Action Against Cancer (EPAAC), ed Jose M Martin-Morena, Tit Albrecht, Sandra Rados Krnel, Ljubljana 2013, pp 117-139.

⁶⁰ <http://fondation-maladiesrares.org/>

with the support of OrphanDev, a national network dedicated to methodological support to clinical studies. Similarly, 5 public-private partnerships were proposed in order to accelerate the pre-clinical and clinical development of academic proofs of concept opening the way to new therapeutic strategies. Finally, the FFRD initiated a think tank of pharmaceutical companies to start working on topics such as databases and registries from the perspective of private contributors, as well as orphan drug economics.

(3) Improve patients' care

As rare diseases scientific and clinical research is tightly linked to societal challenges, the FFRD has been actively promoting humanities and social sciences research. In December 2012, a first dedicated call for proposals was launched, in collaboration with the National Solidarity Fund for Autonomy ("*Caisse nationale de solidarité pour l'autonomie*" – CNSA) and the General Directorate for Health ("*Direction Générale de la Santé*" - DGS) to address three different areas: diagnostic pathway; ethical and societal impact of new technologies in the field of genetics; social, educational and professional integration of patients affected by a rare disease. FFRD regional coordinators supported connections between academic researchers, clinicians and patients' organisations. A total of 77 projects involving 188 research teams and 38 patients' organisations all over France were submitted to the assessment of 88 experts from both the rare diseases clinical and social/humanities fields. In 2013, €643 was allocated to 10 successful projects. The high demand encouraged renewing this call for proposals on an annual basis. At the end of 2013, a similar call for proposals was thus implemented and received 80 letters of intents (involving 257 research teams, 61 patients' organisations) that are currently under selection, with results expected for June 2014. Additionally, the FFRD has been initiating and driving boards of experts at the national levels in order to discuss essential updates, especially in the field of patients' protection and information, including a reflection on a consensus document for informed consent for genetic testing, whose results have been invited to be presented at the national "*Assises de Génétique*" congress, bringing together clinicians, geneticists and all involved learned societies for an update on the clinical genetics developments in January 2014.

In parallel, the FFRD has been actively participating in national and international public health and research policies and frameworks. One main objective is to participate in and promote international collaborations. This includes raising awareness for acquainted international research policies and rare diseases researchers' access to the resulting opportunities, such as dedicated funding lines included in the H2020 programme, as well as an active commitment within international consortia such as E-rare and IRDiRC thereafter described. The FFRD also initiated an innovative cooperation programme with The World Academy of Sciences in order to promote rare diseases research collaborations with emerging countries. This led to the launch of a first joint call for proposals, targeting scientists from the wider Mediterranean and Middle-Eastern areas in October 2013. A total of 90 teams from 17 countries were involved in the submission of 19 international collaborative proposals dedicated to bring together the rare diseases research and clinical communities on key issues. Projects are under international selection, with results expected for the beginning of 2014.

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which was launched at the beginning of 2013 (called "*Programme de recherche translationnelle en santé*" – PRTS, Programme for translational research in Health⁶¹). This call for proposals is not specifically 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-Téléthon (French Muscular Dystrophy Association). In 2013, the AFM-Téléthon (which has been developing a variety of innovative therapeutic approaches over the past 25 years) and the *Fonds National d'Amorçage* (FNA) (which provides public funds towards innovative biotherapies and rare diseases thanks to the French "*Programme d'Investissements d'Avenir*") have moved closer to constitute the first seed fund dedicated to innovative biotherapies and rare diseases. This action forms part of an "*Environmental, Social and Governance*" process. With an initial endowment of €50 million, for a final target of €120 million, the fund aims to create a portfolio of 12 to 15 participants in companies at the seed stage. The amount invested will be between €3 and €10 million per company. The AFM-Téléthon has contributed to a budget of €30 million, and CDC Entreprise, via the FNA, has bestowed €20 million. The fund will target innovative SMEs with strong development potential that have been in existence for less than eight years. They must also follow standards

⁶¹ www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/

that are consistent with the industrial development of therapies such as gene therapy, cell therapy, pharmacological modulation of gene expression, monoclonal antibodies, therapeutic proteins and immunotherapies.

Participation in European projects

French teams participate (have participated) in 151 FP7 rare disease related projects and are coordinating team for 49 projects.

In addition, the French National Cancer Institute participates in The International Rare Cancers Initiative (IRCI), which is a joint initiative between the National Institute for Health Research in the UK, the National Cancer Institute (NCI) in the US and the European Organization for Research and Treatment of Cancer (EORTC). Its objective is to facilitate the development of international clinical trials for patients with very rare cancers. The French National Cancer Institute joined the membership Committee in 2013⁶².

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 2007⁶³ 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. From April 2013, the French Foundation for Rare Diseases is in charge of the E-Rare 2 coordination on behalf of INSERM. France participated in the 5th Joint Transnational Call in 2013, with French teams participating in 9 out of the 12 consortia selected for funding. The E-Rare 2 consortium now brings together 18 ministries and funding national agencies from 15 countries to support projects in translational research on rare diseases across Europe and worldwide. In December 2013, the consortium launched its annual Joint Call 2014 on “innovative therapeutic approaches for rare diseases” with a budget of €13 million.

IRDiRC

In 2013, the AFM-Téléthon (French Muscular Dystrophy Association), the French National Agency for Research (*Agence Nationale de la Recherche – ANR*), and *Lysogene* (all French-based organisations) were committed members of the International Rare Disease Research Consortium (IRDiRC). Since October 2012, the French Foundation for Rare Diseases has been actively involved, together with Orphanet, in the IRDiRC Scientific Secretariat⁶⁴. At the end of 2013, French representatives were also involved in Scientific Committees: 2 members out of 11 were French in the Interdisciplinary Scientific Committee and 3 out of 17 in the Therapy Scientific Committee which was chaired by the French CEO of EURORDIS. In 2013, French scientists also took part in 10 of the 12 established IRDiRC Working Groups.

Orphan medicinal products^{65,66}

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

⁶² <http://www.irci.info/>

⁶³ http://www.e-rare.eu/images/stories/e-rare_final_list_of_funded_projects.pdf

⁶⁴ In February 2014, the French Foundation for Rare Diseases joined the IRDiRC as a funder member and a member of the Executive Committee.

⁶⁵ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelines – 2009 (pp45-49)

⁶⁶ 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. In its annual overview of therapeutic advances for 2012, a particular emphasis was put on new orphan drugs in relation to the development of personalised medicine⁶⁷.

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: the Hospital Clinical Research Programme (“PHRC”). As far as research support is concerned, the French Foundation for Rare Diseases also supported the identification of new molecules with opportunities to become new drugs, through the launch of a first high throughput molecular screening call in 2013 (results to be published mid-2014). It also brought support to research teams in the implementation of all relevant steps to move from a scientific hypothesis to a research protocol (orphan designation – in liaising with OrphanDev, study design, funding etc.).

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 allows 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 French National Authority for Health (“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

⁶⁷<http://www.leem.org/les-essentiels-maladies-rares>

assessment before and delivers its opinion shortly after MA is granted. However, the official process starts after marketing authorisation (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.

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^{68*}, Arzerra, Atriance, Bosulif, Bronchitol, Busilvex*, Carbaglu, Cayston, Ceplene, Cystadane, Dacogen, Defitelio, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Fabrazyme*, Firazyr, Firdapse, Flisint, Gliolan, Glivec, Iclusig, Imnovid, Increlex, Inovelon, Jakavi, Kalydeco, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nexobrid, Nplate, Orfadin, Orphacol, 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: Glybera, Peyona, Plenadren, Procysbi, 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 *TZA ("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*⁶⁹, "*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 Competence 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.

⁶⁸ In February 2014, the French Foundation for Rare Diseases joined them in IRDiRC as a funder member and a member of the Executive Committee.

⁶⁹ Some drugs (*) are no longer considered as orphan medicinal products because they are at the end of the ten-year period of commercial exclusivity.

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.

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 template⁷⁰ 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 has used this data in 2013. No RTU were published by the ANSM in 2013.

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 Insurance⁷¹. 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 (through the “*Maisons départementales des personnes handicapées*”) 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.

On 31 May 2013, a Decree was published concerning the skills and qualifications required of those in charge of giving and coordinating therapeutic education of patients.

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

⁷¹ Article L162-17-2-1 of the Social Security Legal Code.

DEVELOPMENT OF RARE DISEASE ACTIVITIES IN FRANCE IN 2013

National plan/strategy for rare diseases and related actions

Second French National Plan for Rare Diseases 2011-2014

The Steering Committee of the plan held two meetings in 2013 on 19 March and 19 November. These meetings concluded that significant progress has been made to date which is in line with the objectives of the Second French National Plan.

In the area of research, a significant development has been the setting up of a funding process to support Preclinical and Early Clinical Research. This is especially important as France provides sources of funding for basic research (from the “*Agence nationale de la recherche*” – ANR – “National Research Agency”, financed by the Ministry for Research) and for academic clinical research (from the “*Programme hospitalier de recherche Clinique*” – PHRC – “Hospital Clinical Research Programme” - financed by the Ministry of Health), but not for research projects that fall somewhere in between basic and clinical research. An annual call for proposals for translational research in health was announced and launched in 2013.

A total of 34 university hospitals received funds (€9.6 million over 2 years) to obtain necessary equipment to provide new generation sequencing services to speed up standard diagnosis. An in-depth reflexion has been in progress in 2013 to design one national NGS platform for complex diagnosis and research.

The initiative to establish a French national rare diseases databank (“*Banque nationale de données maladies rares*” - BNDMR⁷²) in order to have a central data repository on rare disease patients from various existing sources, for health care planning and clinical research, began in 2011. The minimum dataset was approved during the Steering Committee meeting on 19 March 2013. A national interoperability framework was also defined in 2013. A specific steering committee was created in November 2013 to follow the implementation of the BNDMR.

In the area of health care delivery, improving the way Reference Centres are evaluated is one of the main objectives of the second plan, to ease the reporting carried out by the centres and to create the tools for an accurate assessment on which to base decision on the renewal of the designation and on the allocation of funds. An annual reporting system and a new external evaluation process were defined after 2 years of solid effort by working groups composed of representatives of Reference Centres, patients’ associations, French National Authority for Health (“HAS”), French Agency for the Evaluation of Research and Higher Education (“AERES”) and Ministry of Health. The new process will be ready to be launched in 2014.

Another main objective of the second plan is to reorganise Reference Centres and group them in a functional way that maximises collaboration and allows better and easier orientation of patients. These “national networks for rare diseases” (“*filières de santé maladies rares*”) will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: Reference and Competence Centres, diagnostic and research laboratories, imaging, health and social care, professionals and patients’ associations etc. Preliminary work and surveys in 2012 identified 23 possible groupings of Reference Centres. The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres. At the end of the call, in November 2013, 32 projects have been received. The “Permanent Working Group”, planned to monitor the activity of Reference Centres and national networks, held a first meeting on 18 December 2013 and began to examine the submitted projects. The national networks will be designated by the Ministry of Health in early 2014.

In conclusion, the second French plan is well on the way and several initiatives delineated in the plan have been implemented. A new leader of the implementation of the plan was named in July 2013. The Steering Committee recognises that the final months of the plan will present challenges as the rare disease community will have to prepare for the future in the context of a constrained budget but also to build on all the improvements resulting from the two national plans.

⁷² <http://www.bndmr.fr/>

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

A second National Plan for Cancers⁷³ was launched on 2 November 2009 for the period 2009-2013. The final report concerning the implementation of the cancer plan, including a section on the actions in the field of rare cancers, was published in 2013⁷⁴.

As for the preparation of the third French National Plan for Cancers (including rare cancers) 2014-2019: recommendations for a third plan for cancers⁷⁵ in the field were transmitted to the Minister of Health in autumn 2013. A third National Plan for Cancers was then prepared and published on 4 February 2014⁷⁶. Organisation of care for adults with a complex cancer, improvement of the organisation of second opinion in pathology for rare cancers and organisation of care for very rare cancers in children are planned.

French National Plan for Rare Disabilities 2009-2013

A fourth national resource centre for patients with rare disabilities and severe epilepsy was created in 2013. Inter-regional intermediary teams ("*equipes relais*") of these national centres were launched in 2013 with the aim of their complete deployment in 2014-2015. Cooperation between national resource centres and inter-regional teams for rare disabilities and Reference Centres for rare diseases is also underway. A leaflet⁷⁷ was published describing the national organisation of care in this area.

The Ministry of Social Affairs and Health has asked for an evaluation of the first plan and will announce a second one in 2014 based on various studies conducted during the first one, such as the expert report conducted by INSERM at the request of the CNSA entitled⁷⁸ "*Rare handicaps: context, purposes, perspectives*". It highlights the need to describe rare disabilities with the International Classification of Functioning, Disability and Health (ICF), the utility of creating national and international registries or databases, and suggests strengthening the organisation created by the first plan.

Other French national initiatives related to rare diseases

On 2 May 2013, the third National Plan for Autism for the period 2013-2017 was published by the Ministry of Social Affairs and Health. This plan aimed at improving early diagnosis and early care, structuring healthcare, educational and social pathways for patients, supporting families, improving training for all the professionals in charge of patients, and strengthening research⁷⁹.

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo ("*Rare Diseases Cohorts*") project for duration of 10 years and for a total of €10 million. The RaDiCo project showed accelerated development in 2013⁸⁰, and prepared the launch its first call for rare diseases cohort proposals at the beginning of January 2014. The RaDiCo projet has developed very close links with the BNDMR.

Centres of expertise

In 2013 major steps were made to coordinate individual Reference Centres and group them in a functional way that maximises collaboration across the country. The "national networks for rare diseases" ("*filieres de sante maladies rares*") will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: not only Reference and Competence Centres, but also diagnostic and research laboratories, imaging, health and social care, professionals and patients' associations etc. The designated networks will receive funds from the Ministry of Health for their coordination activity. A preliminary survey identified 23 possible groups gathering nearly all the 131 Reference Centres (some centres do not fall in any of these groups). The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres: at the end of the call, in November, 32 projects have been received. The Permanent Working Group began to analyse these projects in December 2013. The result of this call is expected in early 2014⁸¹.

⁷³ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

⁷⁴ <http://www.plan-cancer.gouv.fr/accueil/actualites/43-actualites/1204-publication-du-rapport-final-au-president-de-la-republique-du-plan-cancer-2009-2013.html>

⁷⁵ <http://www.sante.gouv.fr/IMG/pdf/Recommandations-pour-le-3e-plan-cancer.pdf>

⁷⁶ <http://www.e-cancer.fr/publications> (english) <http://www.e-cancer.fr/le-plan-cancer?gclid=CKLYntPlyb4CFbShtAodTDoAcA>

⁷⁷ <http://www.cnsa.fr/IMG/pdf/Memos23-WEB.pdf>

⁷⁸ The expert 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>

⁷⁹ http://www.social-sante.gouv.fr/actualite-presse/42/breves/2325/presentation-du-3eme-plan-autisme_15797.html

⁸⁰ <http://www.radico.fr>

⁸¹ The list of the first 15 accepted "national networks for rare diseases" was published on the website of the Ministry of Health on 28 February 2014. <http://www.sante.gouv.fr/les-filieres-de-sante-maladies-rares.html>

In July 2013, the Ministry of Health published a directive concerning the process for succession as coordinator of a Reference Centre, and for the creation or abrogation of a Competence Centre linked to a Reference Centre.

Three “national resource centres” for rare disabilities have been designated in 2011, and a fourth one in 2013 thanks to the French National Plan for Rare Disabilities 2009-2013⁸².

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, a reflection began on a possible evolution of the Committee’s missions and the needs of the other registries and databases existing in France for support and evaluation and in April 2013 the committee was dissolved at the same time as the national committee created in 1996 for the evaluation of non-rare disease registries. The InVS, Inserm and INCa launched a call for experts in October 2013 in order to create a Registry Evaluation Committee which will consider, amongst others, rare disease registries. This committee will consist exclusively of experts of registries, epidemiology and public health.

The Second National Plan for Rare Diseases also has foreseen the creation of a National Rare Disease Database (BNDMR). A minimum data set (MDS) common to all rare disease centres of expertise and to all rare diseases was discussed and validated by the Steering Committee of the plan in March 2013. The MDS will be entered through an application called BaMaRa (“Banque Maladies Rares” – Rare Diseases Databank), either directly by the centres of expertise, or through their own application if appropriate. To enable data flows between French hospitals and the BaMaRa, a national interoperability framework was defined in 2013. It consists in setting the necessary compatibility elements such as patient identification, data elements and nomenclatures, technical data flows and security. It will help gathering data at the Reference and Competence 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. A steering committee specific of the BNDMR was set up in 2013 including representatives from the concerned ministries and stakeholders, including patients’ associations. In 2013, the BNDMR team also began to develop a specific application named LORD (Linking Open Rare Disease data) to help with rare disease diagnosis coding in hospital health information systems⁸³. This application will be used at national level to help coding RD patients either in hospital information systems or registries.

Genetic testing

Guidelines for good practices related to the examination of genetic characteristics in the medical context in order to assure quality of care were finalised in at the end of 2012, and published in the form of an official text on 2 June 2013⁸⁴. These guidelines describe in particular information to be delivered to patients before and after performing genetic tests.

Sources of information on rare diseases and national help lines

Orphanet activities in 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. The CNSA decided to maintain the cooperation for three more years in March 2013.

Guidelines

During the first national plan up to December 2012, the Reference Centres produced, with the sustained help of the HAS, 50 national good practice guidelines (“PNDS”) for diagnosis, treatment and follow-up of patients with rare disease. Only 2 new PNDS were published in 2013.

Training and education initiatives

In 2013, the French Foundation for Rare Diseases organised 3 national workshops designed for rare diseases researchers. A total of 450 participants had the opportunity to meet up with technology platforms and

⁸² http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf; http://www.cnsa.fr/article.php3?id_article=726

⁸³ This application was launched in early 2014: <http://enlord.bndmr.fr>

⁸⁴ http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id

scientific experts in the field of proteomics, animal models and molecular screening, with the objective to boost the development of cutting-edge research projects ahead of the launch of dedicated call for proposals by the FFRD. The FFRD also initiated a reflection on the first national academic training dedicated to rare diseases research. Partner universities have been contacted and details of the objectives, programme and access will be discussed over 2014 for a national implementation as early as 2015.

National rare disease events 2013

To mark the Rare Disease Day 2013 in France, a gathering took place at the Pont des Arts in Paris including the members of the Rare Disease Platform to raise hands in solidarity. Orphanet also marked the day with the launch of their mobile application. From 28 February to 2 March for the third year in a row, an awareness raising campaign was organised on several train lines to raise awareness of this issue amongst the passengers using the service. The Rare Disease Platform also held a press conference on 21 February.

On 12 March, a regional event was organised in Limoges by the Regional Health Agency (“Agence régionale de santé”) to bring together healthcare professionals, regional administrative officers and patients’ associations, for discussions concerning rare diseases and implementation of the plans in Limousin Region, with presentations from actors in the field and regional decision makers.

On 23 September, Orphanet and the French Rare Disease Alliance organised in Paris their annual forum for patient organisations on the theme of information and communication technologies. This forum has become, over the years, a major event for many patients’ organisations, and this year's event was attended by over 100 attendees. The theme for 2013 was “ICT for the collection and sharing of information on rare diseases”. The first part was dedicated to the latest news of the French rare diseases community, and then the role of patients and patient organisations in registries and cohorts was discussed. The second part focused on how patients can play a role in data collection by highlighting the benefits and the risks they are exposed to.

On 16 September, a regional event was organised in Marseille by the Rare Diseases Alliance, bringing together more than 150 participants from patients’ organisations and from the clinics, research and medico and social care areas with the participation of French Ministry of Health representative.

On 17-18 October, the French Foundation for Rare Diseases supported the organisation of Orphan Drug and Rare Disease Seminar in Marseille organised by Eudipharm, F-CRIN and OrphanDev with the aim to raise awareness among clinical research stakeholders on drug development specificities in the rare diseases field.

On 21 November, a Rare Diseases Conference, organized by the Regional Health Agency, in partnership with the Rare Diseases Alliance and the French Foundation for Rare Diseases, was organised in Rennes in order to inform the public about the availability of regional care, medical resources and technical facilities dedicated to rare diseases patients. This meeting also aimed at bridging teams and dedicated platforms at national and regional levels, raising awareness on latest developments of research as well as addressing social and ethical implications associated with rare diseases.

On 28-29 November, the third edition of the “Rare Conferences”, Rare2013⁸⁵, was organised by Eurobiomed in Montpellier with over 300 participants attending the presentations and roundtables to hear about advances in the field of rare diseases.

Each year in December, an annual *Téléthon* is organised by the AFM-Téléthon (“Association française contre les myopathies” - French Muscular Dystrophy Association) 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 2013, the 27th edition of the *Téléthon* took place on 6-7 December, raising over 78 million Euros. On the same weekend, the 14th Rare Disease March took place in Paris, organised by the Rare Disease Alliance, bringing together 2000 participants.

Hosted events in 2013

Amongst the events hosted by France in the field of rare diseases were: the European Society of Human Genetics (Paris, 8-12 June 2013), Orphan Drug & Rare Disease Seminar “Accelerating access to therapeutic innovation” (17-18 October 2013, Marseille), 16th International Conference on Behçet's Disease (18-20 September 2013, Paris), 2nd International Symposium on Hypothalamic Hamartomas (20-21 September 2013, Marseille), 2nd International Expert Meeting on Congenital Melanocytic Nevi and Neurocutaneous Melanocytosis (28-30 September 2013, Marseille), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France), Myasthenia 2013 (1-2 July 2013, Paris), European Human Genetics Conference 2013 (8-11 June 2013, Paris), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France).

⁸⁵ <http://www.rare2013.com/>

The French National Cancer Institute, associated partner of EPAAC (European partnership action against cancer) work package 7 (WP7) organised a workshop on rare cancers in July 2013. The purpose of this workshop was to explore the feasibility and relevance to harmonize clinical practice guidelines at European level in the context of rare cancers (with sarcoma as an example), taking into account the results of the survey which has been conducted in the frame of EPAAC WP7 on existing rare cancer networks and patients groups in Europe. A report of this workshop was presented in Open Forum EPAAC in Slovenia in November 2013⁸⁶.

Research activities and E-Rare partnership

National research activities

Flagship of the Second National Plan, the French Foundation for Rare Diseases (FFRD) has been actively promoting rare diseases research since its launch in February 2012. The unique cooperative framework is proving to be an efficient design to implement the main objective to accelerate rare diseases research, and more specifically, to bridge all rare diseases stakeholders in order to:

(4) Understand rare diseases

The French Foundation for Rare Diseases carefully selected 7 technology platforms, both public and private, with whom it initiated partnerships in order to fulfil key needs in the area of rare diseases research: by the end of 2013, the FFRD had launched 4 calls for projects to facilitate researchers' access to NGS technologies and identify the genetics underlying rare diseases not characterized to date, as well as 1 call for projects to develop mouse models and study further functional mechanisms involved in rare diseases. A total of 213 projects were received. A selective scientific process involving 150 experts led to the funding of 95 projects all over the national territory (77 NGS and 18 animal models) for a total of over €1.7 million. In parallel to its own sources of funding and call for proposals, the FFRD has also been involved in providing information to the French rare diseases research community on several other funding opportunities both at the French level (nationally and regionally) and at the EU level (such as IMI, COST, FP7, DG SANCO funding programmes for instance).

(5) Develop new treatments

Following a national workshop organised at the *College de France* in July 2013 to enable scientists to share knowledge and experiences in the field of molecular screening of drug candidates, the FFRD launched its first dedicated call for projects in October 2013. A total of 15 high-flying projects are currently under selection, in collaboration with 5 dedicated technology platforms. In parallel, the FFRD actively engaged in anticipating the R&D needs of innovative diagnostic and therapeutic approaches. This led to the detection of 66 promising candidates in 2013, including new molecules, repurposed drugs and innovative medical devices. Guidance is provided at each step of development together with dedicated partners (IP experts, national and EU regulatory agencies, pharma/biotech, investment funds aso). As an example, a total of 10 procedures of orphan designation have been initiated in 2013 with the support of OrphanDev, a national network dedicated to methodological support to clinical studies. Similarly, 5 public-private partnerships were proposed in order to accelerate the pre-clinical and clinical development of academic proofs of concept opening the way to new therapeutic strategies. Finally, the FFRD initiated a think tank of pharmaceutical companies to start working on topics such as databases and registries from the perspective of private contributors, as well as orphan drug economics.

(6) Improve patients' care

As rare diseases scientific and clinical research is tightly linked to societal challenges, the FFRD has been actively promoting humanities and social sciences research. In December 2012, a first dedicated call for proposals was launched, in collaboration with the National Solidarity Fund for Autonomy ("*Caisse nationale de solidarité pour l'autonomie*" – CNSA) and the General Directorate for Health ("*Direction Générale de la Santé*" - DGS) to address three different areas: diagnostic pathway; ethical and societal impact of new technologies in the field of genetics; social, educational and professional integration of patients affected by a rare disease. FFRD regional coordinators supported connections between academic researchers, clinicians and patients' organisations. A total of 77 projects involving 188 research teams and 38 patients' organisations all over France were submitted to the assessment of 88 experts from both the rare diseases clinical and social/humanities fields. In 2013, €643 was allocated to 10 successful projects. The high demand encouraged renewing this call for proposals on

⁸⁶ More than a European sound box: capitalising on the added value of the European perspective in cancer treatment. JM Borrás, J Prades, J-M Bréchet, S Faithfull, A Trama, P G Casali. In: Boosting Innovation and Cooperation in European Cancer Control – Key Findings from the European partnership for Action Against Cancer (EPAAC), ed Jose M Martin-Morena, Tit Albrecht, Sandra Rados Krnel, Ljubljana 2013, pp 117-139.

an annual basis. At the end of 2013, a similar call for proposals was thus implemented and received 80 letters of intents (involving 257 research teams, 61 patients' organisations) that are currently under selection, with results expected for June 2014. Additionally, the FFRD has been initiating and driving boards of experts at the national levels in order to discuss essential updates, especially in the field of patients' protection and information, including a reflection on a consensus document for informed consent for genetic testing, whose results have been invited to be presented at the national "*Assises de Génétique*" congress, bringing together clinicians, geneticists and all involved learned societies for an update on the clinical genetics developments in January 2014.

In parallel, the FFRD has been actively participating in national and international public health and research policies and frameworks. One main objective is to participate in and promote international collaborations. This includes raising awareness for acquainted international research policies and rare diseases researchers' access to the resulting opportunities, such as dedicated funding lines included in the H2020 programme, as well as an active commitment within international consortia such as E-rare and IRDiRC thereafter described. The FFRD also initiated an innovative cooperation programme with The World Academy of Sciences in order to promote rare diseases research collaborations with emerging countries. This led to the launch of a first joint call for proposals, targeting scientists from the wider Mediterranean and Middle-Eastern areas in October 2013. A total of 90 teams from 17 countries were involved in the submission of 19 international collaborative proposals dedicated to bring together the rare diseases research and clinical communities on key issues. Projects are under international selection, with results expected for the beginning of 2014.

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which was launched at the beginning of 2013 (called "*Programme de recherche translationnelle en santé*" – PRTS, Programme for translational research in Health⁸⁷). This call for proposals is not specifically 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-Téléthon (French Muscular Dystrophy Association). In 2013, the AFM-Téléthon (which has been developing a variety of innovative therapeutic approaches over the past 25 years) and the *Fonds National d'Amorçage* (FNA) (which provides public funds towards innovative biotherapies and rare diseases thanks to the French "*Programme d'Investissements d'Avenir*") have moved closer to constitute the first seed fund dedicated to innovative biotherapies and rare diseases. This action forms part of an "*Environmental, Social and Governance*" process. With an initial endowment of €50 million, for a final target of €120 million, the fund aims to create a portfolio of 12 to 15 participants in companies at the seed stage. The amount invested will be between €3 and €10 million per company. The AFM-Téléthon has contributed to a budget of €30 million, and CDC Entreprise, via the FNA, has bestowed €20 million. The fund will target innovative SMEs with strong development potential that have been in existence for less than eight years. They must also follow standards that are consistent with the industrial development of therapies such as gene therapy, cell therapy, pharmacological modulation of gene expression, monoclonal antibodies, therapeutic proteins and immunotherapies.

E-Rare

From April 2013, the French Foundation for Rare Diseases is in charge of the E-Rare 2 coordination on behalf of INSERM. France participated in the 5th Joint Transnational Call in 2013, with French teams participating in 9 out of the 12 consortia selected for funding. The E-Rare 2 consortium now brings together 18 ministries and funding national agencies from 15 countries to support projects in translational research on rare diseases across Europe and worldwide. In December 2013, the consortium launched its annual Joint Call 2014 on "innovative therapeutic approaches for rare diseases" with a budget of €13 million.

IRDiRC

In 2013, the AFM-Téléthon (French Muscular Dystrophy Association), the French National Agency for Research (*Agence Nationale de la Recherche – ANR*), and *Lysogene* (all French-based organisations) were committed members of the International Rare Disease Research Consortium (IRDiRC). Since October 2012, the French Foundation for Rare Diseases has been actively involved, together with Orphanet, in the IRDiRC Scientific

⁸⁷ www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/

Secretariat⁸⁸. At the end of 2013, French representatives were also involved in Scientific Committees: 2 members out of 11 were French in the Interdisciplinary Scientific Committee and 3 out of 17 in the Therapy Scientific Committee which was chaired by the French CEO of EURORDIS. In 2013, French scientists also took part in 10 of the 12 established IRDiRC Working Groups.

Orphan medicinal products^{89,90}

Orphan medicinal product incentives

Initiatives are in place to stimulate the development of orphan medicinal products: research support is provided through national funding programmes: the Hospital Clinical Research Programme (“PHRC”). As far as research support is concerned, the French Foundation for Rare Diseases also supported the identification of new molecules with opportunities to become new drugs, through the launch of a first high throughput molecular screening call in 2013 (results to be published mid-2014). It also brought support to research teams in the implementation of all relevant steps to move from a scientific hypothesis to a research protocol (orphan designation – in liaising with OrphanDev, study design, funding etc.).

Specialised social services

On 31 May 2013, a Decree was published concerning the skills and qualifications required of those in charge of giving and coordinating therapeutic education of patients.

⁸⁸ In February 2014, the French Foundation for Rare Diseases joined the IRDiRC as a funder member and a member of the Executive Committee.

⁸⁹ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

⁹⁰ 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)

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⁹¹ 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.

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⁹² All websites and documents were last accessed in May 2014.