MEDICAL ETHICS AND BIOETHICS

GRI Standards :

416-1, 416-2 : Customer Health and Safety

EXECUTIVE SUMMARY

Our R&D and medical activities are guided by Sanofi's ambition to meet the growing expectations of patients and communities.

Anticipating the ethical challenges that may arise at the interface between life sciences, biotechnology, biodiversity, medicine, politics, law and culture, particularly as a result of advances in biology and medicine, is essential. Our medical and R&D practices are constantly challenged by the evolution of scientific and medical innovation, the increasing globalization of our research and medical activities and the importance of complying with regulatory requirements. As such, Sanofi has put in place a strong governance system overseen by the Sanofi Bioethics Committee to ensure a high level of ethics in R&D and medical activities, better stakeholder engagement and greater transparency.

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1. STRATEGIC APPROACH

Through our R&D & medical activities, Sanofi aims to constantly innovate in multiple therapeutic areas while meeting the highest ethical standards. Built on a sound governance system overseen by the Sanofi Bioethics Committee, our strategic approach is designed so that our standards and practices are continuously challenged in response to existing and emerging ethical considerations. We embed this approach in our practices to ensure the responsible use of animals in research and production processes and support ethical conduct in clinical development involving patients and healthy subjects.

For more information on animal welfare, see : Animal Protection factsheet in our Document Center.

1.1. Emerging bioethical challenges and strong oversight

1.1.1. The Sanofi Bioethics Committee

Sanofi recognizes the importance of defining, respecting and continuously revisiting and improving consistent and transparent bioethical standards during all our research and medical activities involving humans and animals.

The Sanofi Bioethics Committee (BEC), created in 2012, is elaborating Sanofi's positions on bioethics policies to ensure high ethical standards in Sanofi R&D and medical activities that adequately address Sanofi stakeholders' expectations and comply with applicable regulatory standards.

The BEC is a multidisciplinary committee chaired by Sanofi Chief Medcial Officer, Ameet Nathwani, with representatives from most of the Sanofi functions, such as R&D, Legal, Medical, GBU and External Affairs. It is a decision-making body regarding Sanofi bioethics policies and the supervisory authority for Sanofi's bioethics matters. It alerts the Sanofi Risk Committee of any potential bioethics risks that must be addressed as part of Sanofi's corporate responsibility. Ultimately, the BEC is responsible for ensuring respect of ethical medical and research principles, including respect of human dignity in all our R&D and medical activities.

- The Bioethics Committee establishes high ethical standards for all Sanofi R&D and medical activities
- Addresses and issues recommendations on bioethical questions, Sanofi employee may encounter in the course of their activities
- Sponsors specific project or working groups to ensure implementation of bioethics related policies
- Informs internal and external stakeholders about Sanofi's position on the ethical implications of biological research
- Helps anticipate ethical challenges that may arise at the interface between the life sciences, biotechnology, biodiversity, medicine, politics, law and culture, in particular due to advances in biology and medicine

It fulfills this role by continually assessing and apprising emerging bioethics issues, discussing potential issues and findings with relevant stakeholders, working with them to devise mitigation plans, and supporting implementation and monitoring of such plans until issues are resolved.

The governance of Bioethics at Sanofi was reviewed with the objective to ensure better consideration of stakeholder expectations and greater transparency. As a result, it was decided to create a new

advisory council composed mainly of people independent of Sanofi and recognized in the field of Bioethics. This Council, named the Advisory Bioethics Council (ABC), is mandated to provide advice on important topics related to Bioethics to enable Sanofi to improve its practices. Sanofi is committed to taking into account their recommendations and to explain the positions adopted on the subjects that will be worked on by the Council. The existing Bioethics Committee continues to develop Sanofi's positions and ensure the operationalization of its policies.

The Advisory Bioethics Council is composed of external bioethicists (three women and four men) representing different generational, academic (doctor, lawyer, philosopher) and cultural backgrounds (Europe, Asia or North America). The Council met for the first time in November 2018 and will continue its reflections in 2019.

1.1.2. Contributing to international initiatives promoting good practices

The Bioethics Committee sponsors external initiatives, such as: TRUST a project that aims to reduce the risk of “ethics dumping”.

In 2015, Sanofi committed to be on the advisory board of an initiative called TRUST (crea**T**ing **R**elationships: eq**U**itable, re**S**ponsible, in**T**ernational), funded by the European Commission “Horizon 2020” program. This project aims to reduce the risk of “ethics dumping,” namely, exporting to other countries research practices that would not be accepted in Europe on ethical grounds, and to actively address the mechanisms to mitigate such a risk.

Since 2017, Sanofi is part of the CIOMS (Council for International Organizations of Medical Sciences)* working group on “Clinical Research in Resource-Limited Settings (RLS)”. The CIOMS is an international, non-governmental, non-profit organization established jointly by the WHO and UNESCO in 1949. The objective of the Working group is “to develop a consensus on relevant scientific issues and propose pragmatic recommendations for improvement of the environment and good practices for randomized controlled clinical trials in RLS” (CIOMS).

1.1.3. Compassionate use policy

The bioethics committee has approved Sanofi policy position on Access to investigational treatments (compassionate use policy)

Individuals participating in our clinical trials may be provided with the treatment being investigated. The purpose of these trials is to discover whether a treatment is safe and effective. We submit a full dossier of evidence from trials and other data to regulatory authorities, who make the final decision to approve the potential treatment. Until the regulatory authority has made this decision, the treatment remains experimental and is not generally available to patients outside of clinical trials. However, patients who are not part of these trials and who meet certain criteria can request access, through their physician, to the investigational treatment. Sanofi has a dedicated website to facilitate access to the compassionate use of our products in development.

1.2. A framework to guide the conduct of clinical research

1.2.1. The ethical challenges in clinical research

As we conduct research designed to develop new healthcare solutions, we must continually examine our practices and processes from an ethical standpoint. Ensuring respect for ethics across our R&D activities requires addressing potential challenges that may arise in response to:

- Social and economic trends
- New biotechnologies
- Scientific advances in other fields
- Public health priorities
- Specific development needs
- Public demand for greater transparency and privacy protection

We must constantly adjust and adapt our practices and processes in light of new developments in all of these areas.

1.2.2. A framework for ethics in clinical trials : 7 key requirements

The purpose of ethical guidelines is to protect patients and healthy volunteers and preserve the integrity of scientific research. The Journal of the American Medical Association (JAMA) has published seven ethical requirements[1] to guide the conduct of research. We use these requirements as a framework for evaluating the ethics of our clinical research studies.

For more information, see : What makes clinical research ethical?

1.2.2.1. Social or scientific value

Sanofi's in-house committees (e.g., the Development Working Group within the R&D organization and Protocol Review Committees) systematically review clinical study protocols, extended synopses and amendments to confirm that the scientific and medical questions the research seeks to address correspond to a clinical need.

1.2.2.2. Scientific validity

To produce rigorous, reliable and valid data, our approach includes a systematic review by Sanofi's internal experts so that the most up-to-date therapeutic guidelines are integrated into our study methodology and evaluation tools. External experts are also consulted when necessary.

1.2.2.3. Fair subject selection

We recruit patients and healthy subjects all over the globe for our clinical trials. In selecting study sites and determining inclusion criteria, we are careful to strike a balance between the quality of local clinical research infrastructures and targeted patient populations to confirm that the disease area and product being investigated correspond to an actual need within the community. As a signatory to the Guiding Principles on Access to Healthcare, our practice is to perform clinical studies in countries where we intend to make the product available, if the development program is successful.

For more information, see : The Guiding Principles on Access to Healthcare

1.2.2.4. Favorable benefit risk ratio

Sanofi continuously assesses the benefit risk profile of all our products in development and marketed products, both prescription medicines and over-the-counter products. To help ensure that healthy

[1] Emanuel E.J., Wendler D., Grady C. "What makes clinical research ethical?" JAMA. 2000; 283: 2701-2711.

subjects and patients are not exposed to a disproportionate risk in relation to the expected benefits of the product being studied, we have a dedicated governance framework that covers all phases of development and commercialization. Several committees and processes are pivotal to this framework, which is overseen by the Benefit Risk Assessment Committee (BRAC) under the direction of Sanofi's Chief Medical Officer.

For more information, see : Pharmacovigilance: Monitoring Product Safety to Protect Patients

1.2.2.5. Independent review

Sanofi only initiates clinical trials once they have received a favorable assessment by the independent ethics committee and by health authorities to protect participants' safety and welfare. The independent ethics committee and the health authorities are informed of any significant study related events or issues that arise during the course of the trial.

1.2.2.6. Informed consent

Sanofi processes are designed to assure that all study participants (patients and healthy subjects, or their legal representatives) enrolled in any clinical trial we conduct have given their free and informed consent to participate in the trial. Study participants must be informed about the purpose of the research so that they can understand the information and are able to make a voluntary decision about whether to enroll. Regardless of a trial's objective, it must be designed to protect the safety of participating subjects and guarantee that they give their voluntary consent based on clear, complete information that is expressed in an understandable, non technical style, especially for trial participants who may be vulnerable for any reason. Informed consent must be obtained prior to any procedure or change in the procedure required by the study protocol and before any data is collected.

The individual informed consent process is the cornerstone of ethical recruitment of participants in clinical trials. The study participant should be the central focus of this process, which is not just about signing forms. Our continuous improvement process looks especially at participants' age, literacy and other factors that may potentially make them vulnerable.

Information that must be provided to participants to help ensure free and informed consent :

1. The purpose and methodology of the study
2. The difference between participation in a study and medical care

   When the investigator is also a treating physician, he must explain that he is acting not in his capacity as a treating physician, but as an investigator. Explaining the experimental nature of the proposed study will help show how this is different from medical care.

3. Study specific constraints, which are added to those related to standard care
4. Potential risks and benefits related to participation in the study
5. Alternatives to participation in the study (especially important if an individual's decision to participate in the trial may have financial implications, such as care provided for free during the study but not under the local health system)

   Study participants must be presented with the choice to either participate in the study or to receive care from the local health system. All the pros and cons of participation (financial and non-financial, such as study specific constraints) must be clearly presented to the participant to enable an informed decision.

6. Compensation for expenses during the study

   The goal is to fairly compensate participants for expenses without creating a situation where this might constitute an undue financial incentive to participate.

7. Measures in the case of an adverse event
8. Participant's post study access to the medicine or vaccine being tested, or alternative treatment
9. Study interruption and withdrawal of consent
10. Access to information before, during and after the study

Respect for participants' privacy and confidentiality of individual data

1.2.2.7. Respect for potential and enrolled subjects

Trial sponsors should ensure participants' privacy is appropriately protected. Moreover, enrolled subjects must be properly informed of newly discovered risks or benefits and results and be given the opportunity to withraw from the trial at any time. Sanofi has organized a number of initiatives to safeguard confidentiality. For example, our Chief Privacy Officer, who is a member of the Bioethics Committee, reviews challenges that may arise in connection with protecting the privacy of persons enrolled in a clinical study. This is especially important with the advent of new technologies, such as electronic forms used to obtain informed consent. The enrollment of potentially vulnerable subjects and patients in a clinical study requires particular attention, especially in pediatric clinical studies or those conducted in countries with fragile health systems.

1.3. Ethics in clinical research: oversight of clinical trial practices

To ensure respect for ethics across our R&D and medical activities, we monitor and audit our processes as we continuously seek to improve them.

1.3.1. Monitoring quality in clinical trials

Maintaining accuracy and quality throughout a clinical study requires an ongoing, active process based on two complementary systems:

Quality control consists of periodic operational checks within each functional department to make sure that clinical data are generated, collected, handled, analyzed and reported in line with requirements. Each investigating site is monitored by a representative of Sanofi two to eight times a year, and more often if necessary

Quality assurance involves the systematic and independent examination of all trial related activities and documents. This includes site audits, vendor audits and system/process audits, as well as inspections and preapproval inspections.

1.3.2. Limiting the risk of misconduct by a clinical investigator

To limit the risk of potential misconduct by a clinical investigator, we utilize central data surveillance and onsite trial site monitoring that provides early detection of any signals that indicate potential deviations, enabling us to implement corrective and preventive actions. We have set up systems to detect, prioritize, assess and mitigate potential risks caused by deviations. In the event of a serious deviation (e.g., data fabrication, scientific misconduct or serious non-compliance at investigator sites), we determine the best course of action according to the severity of the situation. Measures may include an in-depth investigation by a cross-disciplinary panel or termination of the trial for that particular investigator site, and notification of the ethics committees and the health authorities.

1.3.3. Internal clinical audits

We conduct internal audits of our trials, associated systems and contractors to protect participants' safety and ensure continuous improvement and compliance with our quality standards. Our audit strategy relies on a risk based approach where each trial is assigned a risk level:

High risk trials include pivotal trials (i.e., conducted to support the registration dossier) and trials for dose selection. All such studies are included in an audit program with 8-10% of active investigating sites being audited

Moderate risk applies to trials to support dossiers, such as proof of concept, safety studies and important post-marketing trials. Between 50% and 75% of these studies are part of an audit program, with 2-5% of active sites being audited

Low risk trials are subject to system audits. Readiness for an inspection by health authorities is another component of our audit strategy. Various criteria are used to select the sites to be audited (e.g., number of patients enrolled, number of protocol deviations, past experience with that site, etc.). In addition, for cause audits may be carried out in the event of suspected misconduct.

1.3.4. Outsourcing clinical trials

The Quality Management of Outsourcing initiative is a Global Quality initiative implemented to harmonize outsourcing processes across R&D. This initiative pays particular attention to Clinical Research Organizations (CROs). Its continuous improvement objective is to streamline processes across Sanofi and ensure a strong focus on quality that is consistent with our in house practices. It addresses CRO selection, qualification and oversight visibility through a central repository for both the corporate and local levels.

1.3.5. Our commitment to share clinical trial data and documents

Sanofi is committed to sharing appropriate patient level clinical trial data and study reports with qualified researchers. Eligible trials for products that received regulatory approval from US and /or EU agencies, as of January 1, 2014, are available upon request. In addition, Sanofi will review ad hoc requests for studies that are not currently listed on the data sharing site. Requests for clinical trial data are reviewed and approved based on scientific merit, by an independent panel of experts. All patient level data remain anonymous to protect the privacy of patients who participated in clinical trials, in compliance with applicable laws and regulations.

For more information, see : Access to clinical trial data

1.3.6. Our commitment to transparency

Sanofi is committed to being transparent about our medical research and to providing healthcare professionals and patients with all useful information about our development projects and products so that they can make informed medical decisions. Sanofi is ensuring high performance standards in registering our trials and reporting clinical trial results. We respect and follow all relevant governmental regulations concerning the disclosure of clinical trial results.

In addition to those core principles, a new policy on sharing and transparency of clinical data was adopted by our Bioethics Committee in 2017 (link).

Sanofi's clinical trial results are publicly available on the EU Clinical Trials Register or the Sanofi website

2. FACTS AND FIGURES 2018 ON CLINICAL TRIALS

2.1. Overview of clinical trials

For Sanofi Pasteur, our vaccines business, there was a significant increase in the number of trial subjects in North America due to the expanded access program to provide stamaril vaccine for vaccination against yellow fever. For our pharmaceutical activities, a strong pipeline also contributed to a significant increase in the number of key trials.

In 2018, **201** CLINICAL TRIALS were conducted by Sanofi:

161 with Pharmaceuticals

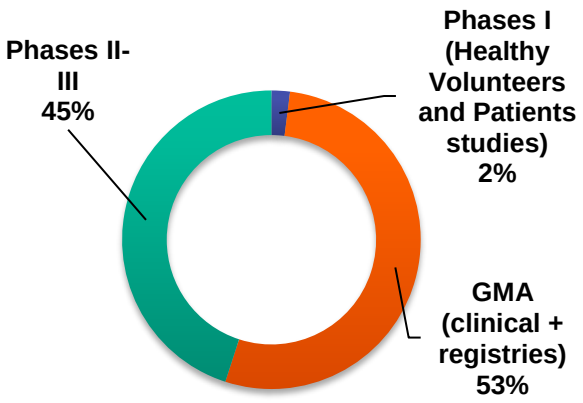
40 with Vaccines

For more information , see our Clinical trials and results.

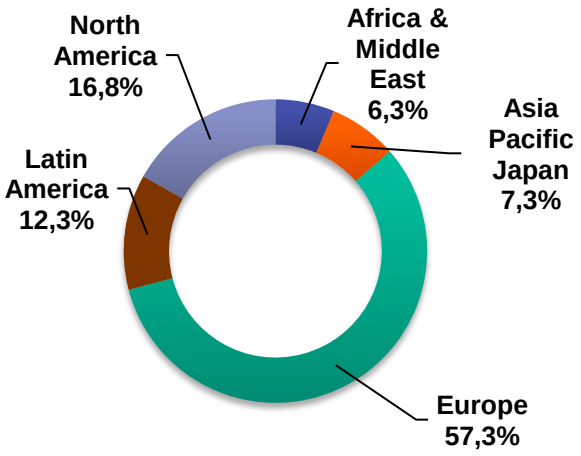
2.2. Pharmaceuticals clinical trials

31,113 subjects enrolled

Graph 1: Pharmaceutical trials 2018, subjects enrolled by phase



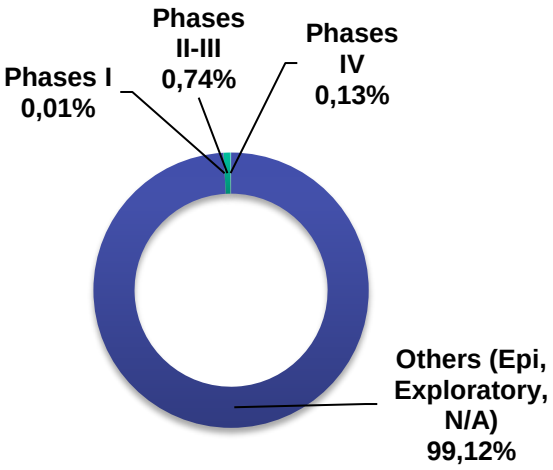
Graph 2: Pharmaceutical trials 2018, subjects enrolled by region



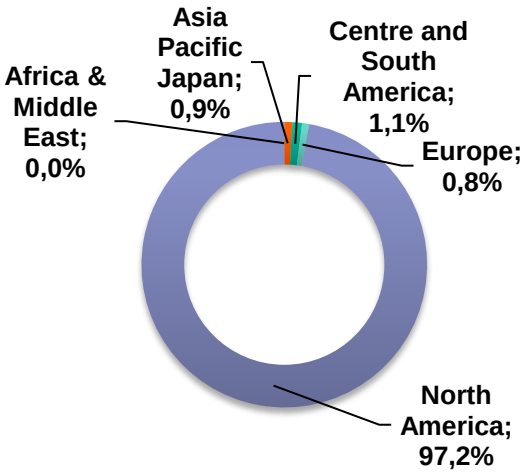
2.3. Vaccines clinical trials

263,059 subjects enrolled

Graph 3 : Vaccines clinical trials 2018, subjects enrolled by phase



Graph 4 : Vaccines clinical trials 2018, subjects enrolled by region



Corrective action in the event of potential misconduct

In the event of a serious deviation, we determine the best course of action according to the severity of the situation. A unique tool supports the required investigations and ensures a consistent approach to deviation management. Cross-functional investigation panels under the lead of Quality are established to address critical and/or major systematic deviations and/or potential misconduct. For deviations with potentially critical impact, a rapid quality notification/quality alert process is in place in order to notify Global Quality management and ensure implementation of corrective and preventive actions, thereby avoiding major or critical impact on data integrity and/or patient safety.

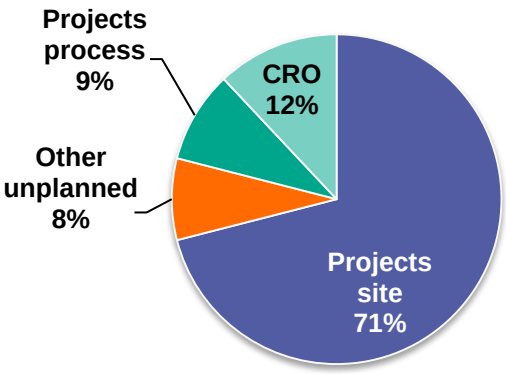
In 2018, for clinical trials sponsored by Sanofi (including Sanofi Pasteur):

- 18 cases were identified requiring in-depth investigations (26 cases in 2017)
- Of the 18 cases, 3 led to a conclusion of misconduct/serious non-compliance, requiring notification to regulatory agencies and in 1 case also to early closure of a non-compliant investigator site (with no impact on patients)
- None of the 18 cases required a rapid quality notification
- No clinical trials were terminated in 2018 due to misconduct.

2.4. Clinical trial audits

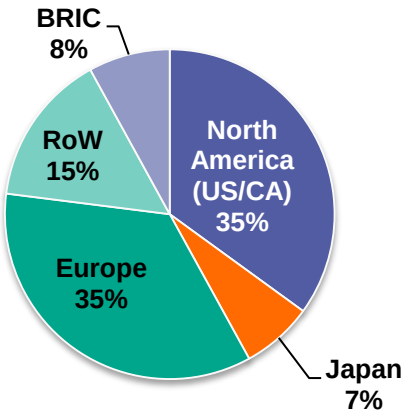
In 2018, Sanofi (including Sanofi Pasteur) conducted 189 audits for our clinical trial activities and related systems/processes and suppliers (CRO), with a strong focus on investigator site audits.

Graph 5 : Clinical trial audits by type



189 AUDITS

Graph 6 : Clinical trial site audits by region



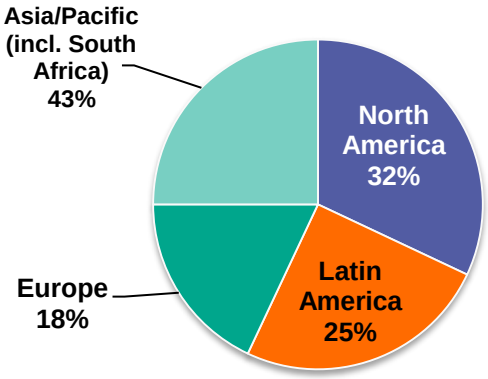
121 AUDITS*

*Pharma investigator site audits only

2.5. Clinical Inspections

Of the 65 inspections[2] by regulatory authorities related to clinical activities carried out in 2018 within the perimeter of Pharmaceuticals and Vaccines, none had critical outcomes resulting in regulatory action from the health authorities

Graph 7: Inspection by regulatory Health Authorities by region



[2] Clinical/GCP inspections only, PV inspections not included

3. HOW DOES CLINICAL TRIAL WORK - INFOGRAPHICS