

Animal Protection

GRI Standards:

304-2: Significant impacts of activities, products, and services on biodiversity

EXECUTIVE SUMMARY

As a diversified global healthcare leader focused on patients' needs, Sanofi is morally and legally obligated to ensure the quality, safety and efficacy of its medicines, vaccines, medical devices, and consumer healthcare products. Besides the regulatory requirements, the responsible use of animals is essential in the research and production process. Animals remain a small but an integral part of a comprehensive research and testing strategy that includes non-animal methods and clinical research.

Research involving animals poses dilemmas not only for scientists who use animals in medical research but also for society as a whole. At Sanofi, the consensus is that using animals for research is justified when there are clear benefits for human health and when the 3Rs principles (replacement, reduction and refinement of animal use) are applied.

As a key element of Corporate Social Responsibility, Sanofi commits to meet or exceed regulations and standards for the use of animals and to develop alternative approaches.

In this context, Sanofi uses animals only when a non-animal method is unsuited for the required use or not accepted by the authorities (replacement), with the smallest number necessary for quality science (reduction), and implements state-of-the-art practices to promote animal welfare and prevent animal pain

Thierry, Chief Veterinary Officer: "The launch of the Integrated Research and Testing Strategy is very innovative and opens a new era for the implementation of the 3Rs as it sets to upfront the value of the science as a primary goal; The outcome being a reduction of 50% in 10 years. I'm really proud that the executive management has endorsed such decision."

and distress in housing and procedure conditions (refinement). Sanofi authorizes animal use only when the regulatory and scientific merit is established and under strict ethical oversight.

Sanofi promotes a culture of care which fully considers the intrinsic value of animals as sentient beings and which embraces responsible use of animals as a primary value and engages every employee working with animals in that respect. Whenever animals are required, Sanofi will provide high quality programs for care and use.

Any question could be asked to the Chief Veterinary Officer; Please use the form available at the following address: <https://www.sanofi.com/en/contact>

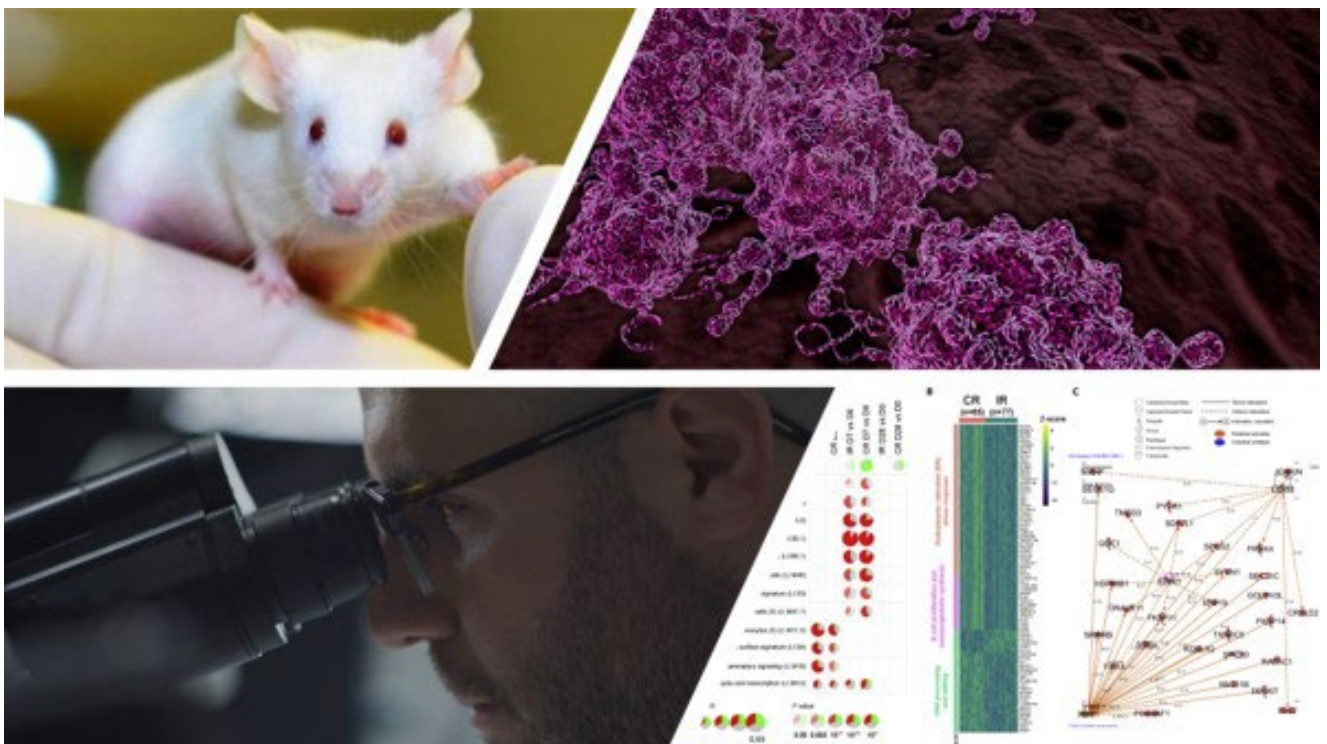


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1. HIGH STANDARDS BEYOND REGULATIONS

1.1. ANIMAL USE IS HIGHLY REGULATED

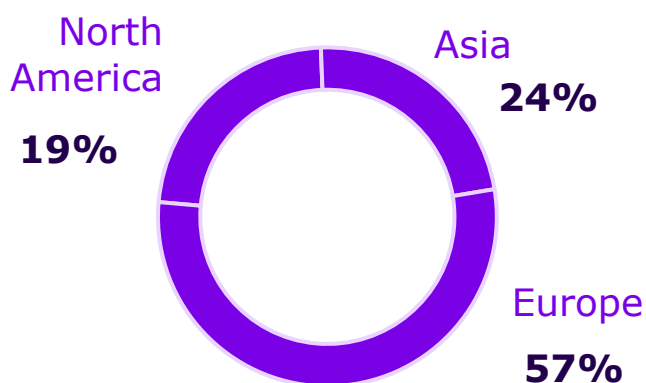
In the last decades, major pieces of regulations and references (Europe, USA, China...) have been set up or updated taking into account the progress in animal welfare knowledge and the increased considerations of the protection of animals by the public (see chapter VII for references).

Use of animals for scientific purpose is a highly regulated area in the countries where Sanofi operates. The regulations encompass all aspects surrounding the use of animals: personnel, facilities, studies and of course, animals.

| Examples of obligations as defined by the European Directive 2010/63 |
|--|
| Ethical review and authorization of projects by independent authority |
| Publication of non-technical summary of projects using animals |
| Implementation and monitoring of the 3Rs |
| Operational expertise by Animal Welfare Bodies |
| Inclusion of genetically-modified animals in the project authorization |
| Restricted conditions for the use of non-human primates |
| Training of the personnel and assessment of competencies |
| Appointment of a designated veterinarian |
| Inclusion of animal breeders and suppliers in the regulation |

Local regulations are mandatory, and compliance is monitored on a regular basis. All Sanofi sites are inspected by the competent authorities. 76% of animal use takes place in the strictest regulatory environments in Europe and Northern America. The other sites, dedicated to quality control of vaccines, are located in Asia and comply with their national regulations.

Breakdown of animal use per region (2021)



1.2. CONSISTENT HIGH STANDARDS ARE APPLIED

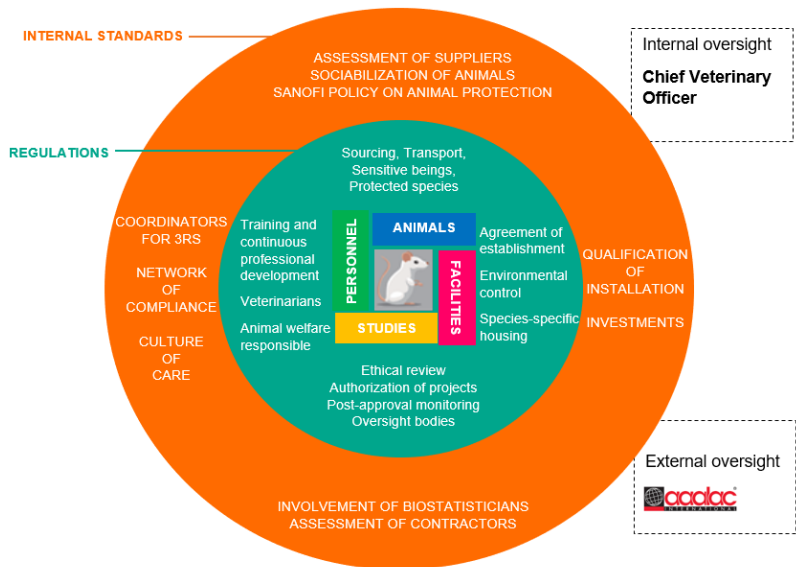
In addition to the legal obligations, Sanofi has set [internal standards to align requirements](#) across the world and to ensure high welfare considerations. All Sanofi sites maintain or seek independent accreditation of their animal care and use programs through recognized expert organizations such as [AAALAC International](#)¹.

Götz, R&D, Germany: "Now, we require that external vendors in the US perform preclinical studies to support human clinical trials in respect with the high European housing standards by default."

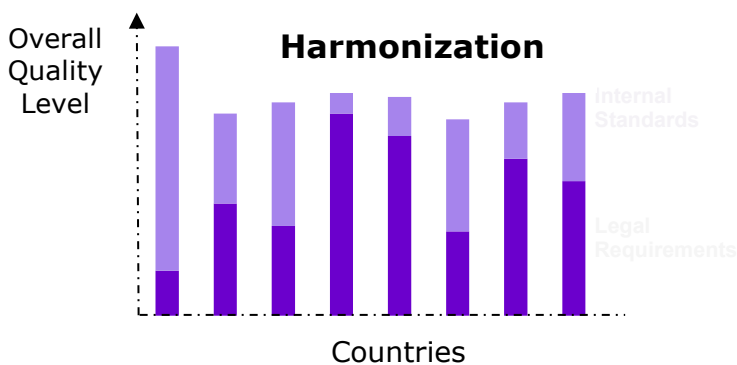
Sanofi applies the same principles to subcontractors and breeders; their animal welfare program is assessed by Sanofi professionals to ensure the consistency of the animal care.

Regulations constitute a first layer of obligations (green circle below) which are completed by specific standards developed by Sanofi (the second layer, the orange circle). The second layer represents how we globally approach high quality standards and apply standardization across the sites.

Compliance with regulations and standards are ensured by local dedicated teams under the oversight of the Chief Veterinary Officer and by accreditation body like AAALAC International.



Sanofi standards complement legal obligations by achieving high quality animal care and use programs.



Legal requirements can differ from countries to countries (dark purple bars; setting internal rules and principles (light purple bars) contribute to increase the overall quality towards more harmonized high standards.

¹ AAALAC International is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs

Breaking news - Marseille Declaration on the global implementation of high standards for animals held and used both internally and externally.

Together we



and signed the Declaration of Marseille on Animal Welfare Standards

Together with other pharmaceutical companies, including Merck and Novo Nordisk, we have announced the joint signing of the Marseille Declaration on the global implementation of high standards for animals held and used by industry for scientific purposes, both internally and externally.

The collaborative work will accelerate the implementation of the highest ethical and animal welfare standards that go beyond local laws for all animals we use internally and externally until replacing animal work by better, cutting-edge alternatives will finally be possible.

[Marseille Declaration](#) available in the Document Center of Sanofi website, Sanofi.com

2. USE OF ANIMALS: A NECESSITY FOR THE BENEFITS OF PATIENTS

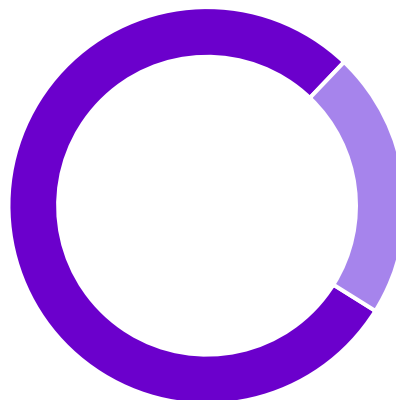
Sanofi is morally and legally obligated to ensure the quality, safety and efficacy of its medicines and vaccines. Although committed to developing and implementing non-animal methods, Sanofi believes the responsible use of animals remains essential in the research and production process. The most reliable scientific models should be used to the benefits of patients; those can be *in silico* (computerized modelization, big data...), *in vitro* (cells and tissues, including human tissues, biochemistry, microbiology, -omics...), *in vivo* (animal models), and in humans (clinical research and clinical trials).

In 2021, 75% of animals were used to support our batch release activity to ensure the safety and efficacy of commercialized vaccines and drugs. 25% of animals have been used for research purposes to better understand diseases and to assess the safety and efficacy of new drugs and vaccine candidates.

Breakdown of animal use per activity (2021)

Industrial Affairs

75%



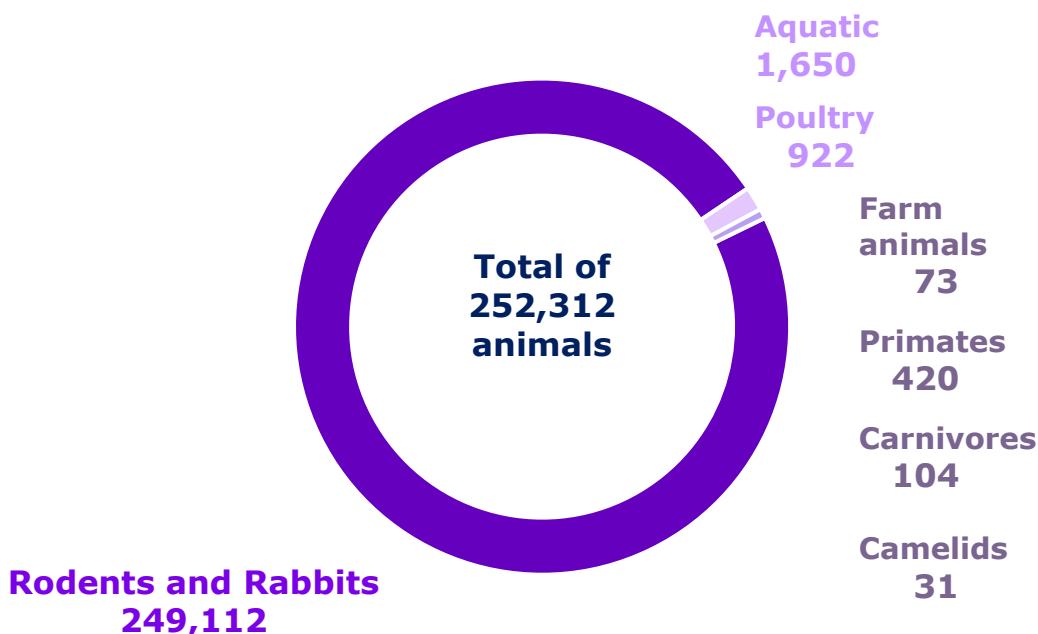
Research & Development

25%



Most animals used (99%) are rodents, rabbits, and aquatic species. About 1% are poultry, farm animals, camelids, carnivores, and non-human primates. The choice of the species is based on a scientific assessment and justifications, which are reviewed by Animal Ethics Committees, responsible for the project approval.

Animal use per species (2021)



Breaking news – New RSV protective therapy thanks to animal studies

Human respiratory syncytial virus (RSV) is a major cause of serious respiratory tract infections in infants and the elderly. In the US alone, approximately 58,000 infants and 177,000 adults over the age of 65 are hospitalized with RSV each year and severe cases cause thousands of deaths annually. Currently the only widely available therapy is the monoclonal antibody Beyfortus (nirsevimab) developed by Sanofi with AstraZeneca to protect newborn infants during their first RSV season. To extend this protection beyond the first season and to protect the elderly, Sanofi is developing innovative vaccines for both populations. In addition to extensive use of in silico modeling and in vitro assays, Sanofi utilizes small numbers of animals to assess the safety and immunogenicity of our vaccine candidates before they proceed to human trials. These in vivo studies are critical for the rapid progression of our infant and older adult RSV vaccine programs.

[Press release](#)

3. A COMPANY-WIDE POLICY ON ANIMAL PROTECTION

3.1. A GLOBAL APPROACH OF ANIMAL WELFARE

In July 2022, animals are used at Sanofi in 15 sites located in 10 countries. We have endorsed a [global policy on animal protection](#) to promote a shared vision of the consideration of animals within the company. In support of our longstanding commitment to the 3Rs, the policy applies to all animals used by Sanofi for research, testing and the production of medicinal products, investigational medicinal products, vaccines, medical devices, and active pharmaceutical ingredients. It also applies to breeders, suppliers and transporters of animals for research, testing and production purposes, as well as to external partners and contractors using animals under Sanofi's sponsorship and in collaboration with Sanofi.



The use of animals is authorized only when regulatory and scientific merit is established, with strict ethical oversight. Our company-wide policy promotes a culture of care that embraces the responsible use of animals as a primary value so that, whenever animals are required, Sanofi and third parties develop quality animal care and use programs. The employees working with animals have been trained and must be committed to providing the best care and attention to the animals.

Good science requires that animals remain in good health and are subject to minimal pain or distress. The animal ethics committee and/or the animal welfare body ensure the oversight of each local animal care and use program.

3.2. ETHICAL OVERSIGHT

When animals are required to support the safety or quality of medicines or vaccines, procedures are performed in accordance with regulations to involve minimal pain or distress.

At every site, an Animal Ethics Committee oversees animal care and use, including effective implementation of the 3Rs at the bench level in an impartial and independent manner. They weigh the objectives of the study and the likelihood of achieving the goals related to the protection and/or improvement of human health against potential animal welfare concerns. All research and testing studies must be covered by an authorization by animal ethics committees and competent authorities, and their decisions are binding.

Members of the ethics committees include senior animal researchers, staff involved in the care and use of animals, at least one veterinarian, and an independent or lay committee member (non-affiliated to Sanofi). Whenever possible, a biostatistician sits on the committee to make sure the study uses the smallest number of animals necessary to produce statistically valid results.

Under the leadership of Sanofi's Chief Veterinary Officer, as a permanent member of the Bioethics Committee, an Advisory Body on Animal Ethics was established in 2017 to address societal issues related to the use and protection of animals. It aims at defining Sanofi's guidelines and positions in animal use and care in line with international recommendations. The Chief Veterinary Officer drives the consistency and cross-fertilization between the veterinarians and animal ethics committees at all sites. To this end, it meets quarterly and has developed global policies. Those positions must be endorsed by Sanofi Bioethics Committee (BEC).

| Policy Title | Description | Approved by the BEC |
|--|---|--------------------------|
| Protection of animals | The Policy on the Protection of Animals states the global quality directive that any person, working under the responsibility or on behalf of Sanofi at all sites, must comply with when using animals. | Version 3 - August 2021 |
| Production and Use of Genetically Modified Animals for Research | The development of new gene-editing technologies, such as CRISPR, is accelerating the capacity to develop new genetically-modified rodent models of human disease. These techniques also represent a significant refinement in the development of animal models. | Version 2 - October 2022 |
| The ethical use of non-human primates in research and quality control of drugs and vaccines | Non-human primate use is usually limited to the late phases of drug discovery of vital research programs, and during the development phase, to assess the efficacy and safety of certain new drugs under specific conditions. | Version 2 - October 2022 |
| Reporting of animal welfare concerns | To ensure that the welfare of laboratory animals is fully implemented, any employees should feel free to express any concern and be empowered to report any animal welfare concern without any negative consequences for both themselves and their career. | December 2019 |
| Rehoming of animals used in research & production | Following the overall trend of reduction of the use of animals, the regulation now encourages rehoming: when animals are healthy and do not represent any risks for neither themselves, the public nor the environment, animals can be offered to start a "second life" in a new home after being part of a project. Appendix: <i>guidance to provide eligibility criteria for adoption</i> | December 2019 |
| Sponsor's responsibilities for externalized animal services and studies | The roles and responsibilities of Sanofi personnel, so-called sponsor, who requests or uses the services of an external partner for the performance of activities relying on the use of live animals are defined to ensure the quality of outsourced studies. Appendix: <i>guidance to help the external partner implementing Sanofi standards related to animal use</i> | April 2020 |
| Ethical considerations during a crisis related to animals used for scientific purpose | To consider critical ethical questions when a crisis starts and needs rapid response and to engage the animal ethics committee become a requirement. The policy are best practices following the former experiences of Sanofi sites during COVID pandemics. | June 2021 |
| The Integrated Research and Testing Strategy (IRTS) | A stepwise strategy to go beyond the 3Rs and to achieve the overall reduction of 50% of use of animals between 2020-2030. | December 2021 |

| | | |
|--|--|----------------------|
| <p>Good practices to ensure independence and impartiality of animal ethics committees of Sanofi</p> | <p>Beyond the regulatory requirements, Sanofi relies on the engagement and the integrity of each Animal Ethics Committee member to ensure the quality of the ethical review and authorization of animal use in respect with best animal welfare practices. Ensuring the quality of the work done by Animal Ethics Committees, in particular the ethical evaluation of projects and procedures, is our societal responsibility.</p> <p>The objective of this policy is to provide criteria and principles to ensure impartiality and independence of Sanofi's animal ethics committees.</p> | <p>December 2022</p> |
|--|--|----------------------|

Due to the global sanitary crisis, animal care and use programs have been adjusted without compromising the welfare of animals. Disaster preparedness plans have been activated, and animal care teams have worked diligently to ensure the best care to animals. Animal ethics committees of the sites have been involved in the management of the situation. The Advisory Body on Animal Ethics has decided to draft a new position on the ethical management of crisis to include all lessons learned and to consider the ethical dimension of operational decisions of remediation plans.

3.3. STRONG COMMITMENTS TO ETHICS AND THE 3RS

3.3.1. The 3Rs

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|---|
| <p>The 3Rs:</p> |
| <p>Replacing use of animals with any other methods when a non-animal method is feasible and accepted</p> |
| <p>Reducing the number of animals necessary to ensure reliable, quality scientific results</p> |
| <p>Refining techniques to promote animal welfare and minimize pain and distress</p> |

For many years, Sanofi has sought to apply the 3Rs when using animals necessary for our research. Our approach is designed to use animals only when a non-animal method is not suitable for the required use or not accepted by the authorities (replacement), with the smallest number necessary for quality science (reduction) while implementing state-of-the-art practices to promote animal welfare and prevent pain and distress in housing, procedures and treatment (refinement).

Animals remain an integral part of a comprehensive research and testing strategy that includes non-animal methods (such as computerized models and in vitro testing) and clinical research. Animal use is also part of many regulatory requirements.



For example, testing vaccines before batch release remains mandatory worldwide for public health reasons and use of animals is justified to ensure the safety and efficacy of commercialized vaccines. For new drugs and vaccines, preclinical packages, which include patient data, computer analysis, in vitro models and in vivo studies are based on last scientific developments and tailored for every project to decipher the mechanism of action and to assess the safety of new candidates before clinical trials: the best options are chosen to address the scientific questions.

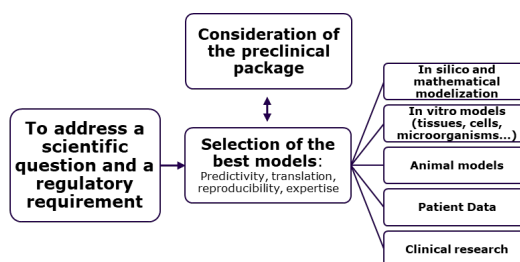
Sanofi has developed an innovative approach, The Integrated Research and Testing Strategy (IRTS), which backs the principles of the 3Rs, in line with regulations, international standards, and our own [Corporate Policy on the Protection of Animals](#).

3.3.2. The Integrated Research and Testing strategy to go beyond the 3Rs

Our company-wide strategy (IRTS) supports our goal of reducing reliance on animal models. It reinforces rigorous, state-of-the-art science as our North Star for selecting the best available, feasible, and translatable models to address scientific questions and adhere to regulatory requirements.

We take proactive measures to reduce the need for animals in research and testing by:

- Ensuring our selection of models is based on sound science,
- Fostering breakthrough innovation for consistent, robust translational research and testing,
- Facilitating regulatory acceptance of novel technologies and models, and
- Educating, training, and communicating with our colleagues and partners to embed IRTS across Sanofi sites and those of our affiliates.



The IRTS helps us uphold our **commitment to the best science and animal welfare** by ensuring we:

- Embed proven new technologies that support our goals;
- Select the best model and preclinical package for each study, so we can decipher the mechanism of action, assess safety, and test the efficacy of every vaccine and medicine;
- Provide a strong rationale for utilizing animal models;
- Adhere to NAMs, continuous reduction of animal use, animal welfare, and going beyond the 3Rs;
- Acknowledge the intrinsic value of animals, openness, and the total number of animals used in research and testing.

Every Global Function and Vaccine Division must set a **clear and ambitious program** aligned with the goals of our IRTS, including:

- Governance, objectives and deliverables;
- Programs to support scientific development of NAMs and scouting new technologies;
- Regulatory science and advocacy to favor regulatory changes, including weight of evidence;
- Active participation in public-private partnerships and collaborations;
- Outreach and awareness-raising programs.

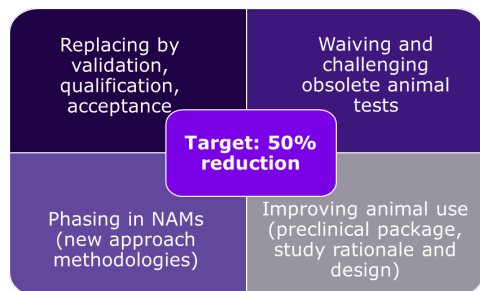
The IRTS policy requires that:

- All models and methodologies are assessed in respect to their scientific validity, complementarity, predictivity and translatability.
- Scientific bodies challenge the status quo about animal models and substitutive methods.
- NAMs are preferred technologies when equivalent models and strategic approaches are available and deliver robust results.
- Animal ethics committees challenge the rationale for using animals (why) and must discuss the conditions of use of animals to reduce and to refine their use (how). Use of animal models is approved only when the expected benefits outweigh the potential harm to the animals.
- The number of animals used is reduced to the minimum, and the experimental procedures are refined; robust experimental design and experimental data quality and integrity should ensure the appropriate use of animals.
- Training program and knowledge sharing about new technologies and models are in place for the teams.

By 2030, we aim to reduce the number of animals used in research and testing by 50%, compared to 2020. We expect to see this reduction on both Sanofi sites and those where studies are conducted on behalf of our company, such as contract research organizations and external partners.

In manufacturing, the use of animals is directly proportional to the production of life-saving drugs and vaccines for patients. That's why our "3Rs" goal in manufacturing centers on finding robust alternatives to the use of animals.

To achieve our 50% reduction target, we will:



- Phase in New Approach Methodologies;
- Challenge and waive obsolete animal tests;
- Replace animal models through validation, qualification, and acceptance by the competent authorities;
- Improve animal use as set out in our preclinical package study rationales and designs.

Internal and external communication actions must be in place to demonstrate Sanofi commitments in a transparent manner. Global progresses regarding the implementation of IRTS will be reported on a regular basis.

4. OUR ANIMAL PROTECTION ROADMAP

To achieve Sanofi objectives of protecting animals, priorities have been defined and progresses are monitored on a regular basis. The roadmap defines the current axes for improvement:

- To develop roadmaps in order to ensure the success of the Integrated Research and Testing Strategy (3Rs), i.e. achieving the 50% reduction goal;
- To maintain the highest standards and to foster a culture of care in respect with Sanofi Policy on the Protection of Animals, beyond regulatory inspections and accreditation;
- To monitor the compliance of third parties (breeders, contract research organizations, not-for-profit collaborations);
- To contribute to regulatory debates, especially those related to the implementation of the European Directive;
- To address societal concerns and to strengthen the ethical considerations about the use of animals through the global Advisory Body on Animal Ethics;
- To improve transparency regarding animal use and to initiate a culture of openness.

Nicolas, R&D, France: "in my role to align animal welfare standards all over the world in complex and evolving societal environments, it is very important to nurture a clear vision to support our ambition on animal protection."

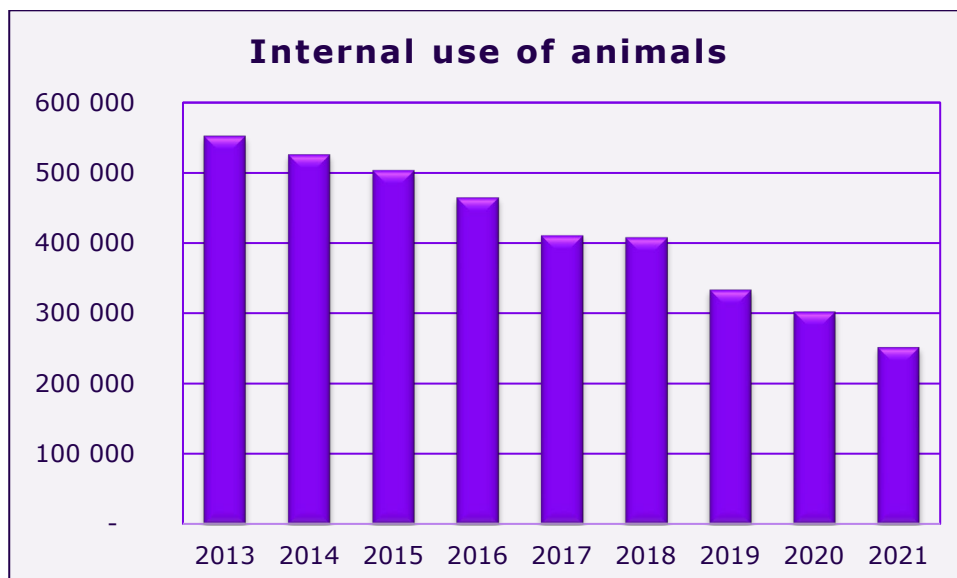
5. ACHIEVEMENTS ABOUT THE 3RS AND ANIMAL WELFARE

There are many examples of outreach within Sanofi and with external partners to increase awareness about animal welfare and the 3Rs. In order to illustrate this, several evidence of commitments and achievements are shared in this section.

5.1. CONSTANT DECREASE OF USE OF ANIMALS WITHIN OUR FACILITIES

Every year, a comprehensive mapping of animal use in Sanofi facilities is conducted, evidencing a constant decrease of use of animals.

Evolution in numbers of animal used across the Sanofi Group, 2013-2022:



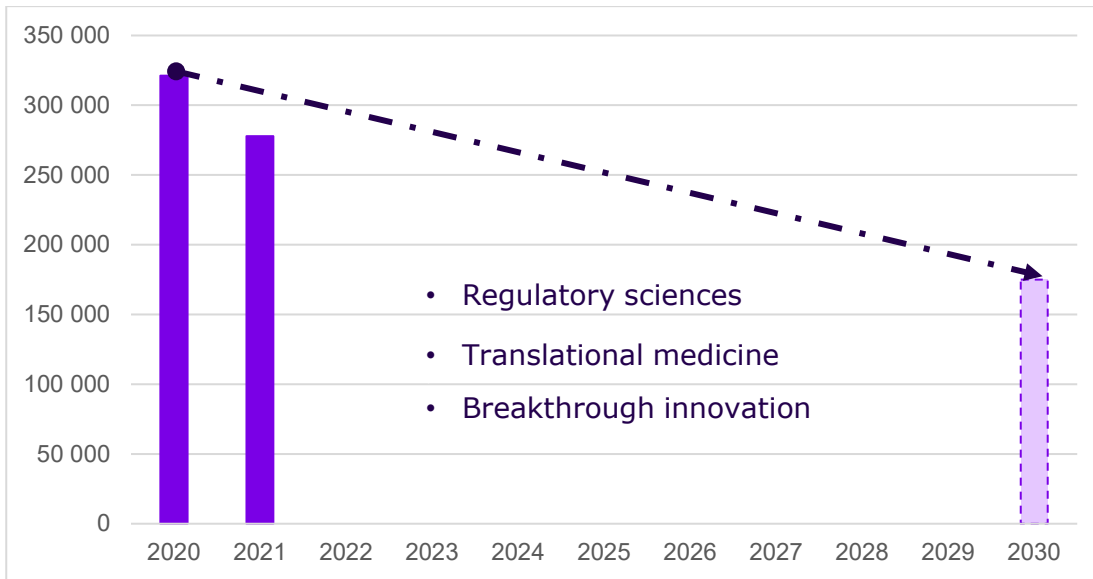
In 2021, Sanofi has maintained its reduction of animal use. Number of animals used on Sanofi sites represents 252,312 animals in 2021. In comparison with the 2020 data, the decrease is of 17%. Since 2013, the drop is of 54%, similar in R&D and in Industrial Affairs. The figure represents evidence of the continuous effort towards the overall reduction.

The Integrated Research and Testing Strategy, which ultimate goal is a reduction of 50% in 10 years. The 50% reduction is calculated by comparing the use of animals in research, development, analytical testing and quality control between 2020 and 2030. It includes animals used by Sanofi (Sanofi sites) and those used on behalf of Sanofi (CROs and external partners). This represents a new performance indicator with a baseline in 2020 of 321,213 animals, corresponding to 302,890 used internally and 18,323 used externally.

Kevin, Industrial Affairs, Global: "Industrial affairs being the first user of animals, I really feel engaged in this unique objective and I consider my self as a key player in this strategy."

| Animal use | 2020 | 2021 | Target 2030 |
|-------------------------|---------|---------|-----------------|
| Internal use | 302,890 | 252,312 | NA ² |
| External use | 18,323 | 25,532 | NA |
| Total | 321,213 | 277,844 | Target: 160,000 |
| Reduction y/y-1 | | -13.5% | NA |
| Reduction y/2020 | | -13.5% | Target: -50% |

² NA : Not applicable

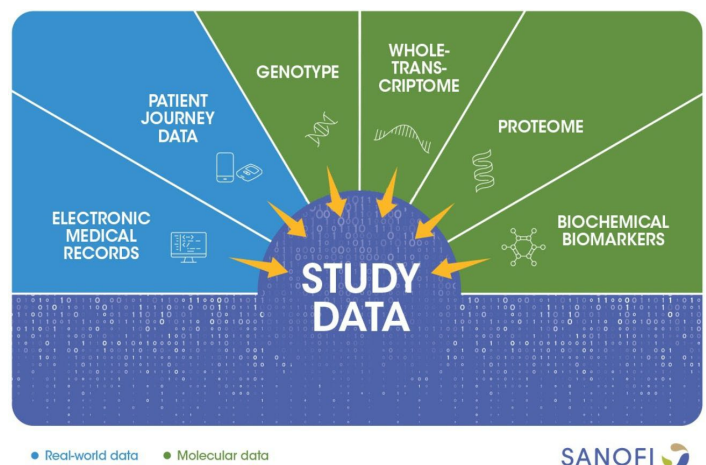


5.2. SCIENTIFIC ADVANCEMENTS AS DRIVERS OF THE NEW APPROACH METHODOLOGIES (NAMs)

The new approach methodologies (NAMs) are fully integrated in the research strategy. Below are some examples of how the NAMs play a vital role and are phased in in the portfolio discovery and development of novel drugs and vaccines for patients. Some scientific approaches are not real replacement as defined by Russel & Burch but represent new, more accurate and predictive translational models of conducting research without using animals. However, the scientific validity and the predictivity must be demonstrated.

- **Therapeutic antibodies** constitute highly potent drugs to address unmet medical needs. In order to accelerate the development of monoclonal antibodies from non-animal sources, ie to use alternative in vitro ways to produce and deliver high affinity and potent lead candidates for all projects in the absence of animal use, from now on, Sanofi has access to a **3rd generation phage-library display platform**. The new platform, which will be integrated into Sanofi’s antibody discovery programs, increases the probability of finding drug-like candidates and a faster affinity maturation step leading to R&D cycle times.
- In asthma, a **precision immunology collaboration** captures the real-world health journeys of asthma patients (patient data), combining Internet of Things (IoT), clinical (clinical research), and genomic data (molecular data) to see the disease with new eyes.

Asthma affects 300 million people worldwide and is the most common chronic condition among children. Asthma attacks, while treatable, can be sudden and severe, and if left unchecked they can be fatal. Sanofi researchers are taking a precision immunology approach to understanding asthma, with the goal of taking asthma diagnosis and treatment to new levels. One example of such work is the **REGAIN study**: a project led by Sanofi and health intelligence company Sema4, leveraging asthma management technology from Cohero Health.



- **Investing in artificial intelligence** has been a priority. As an example, in November 2021, Sanofi has announced the \$180 million equity investment in Owkin’s artificial intelligence and federated learning to advance oncology pipeline on four types of cancer. Owkin, an AI and precision medicine company, builds best-in-class predictive biomedical AI models and robust data sets. With the ambition to optimize clinical trial design and detect predictive biomarkers for diseases and treatment outcomes, this collaboration will support Sanofi’s growing oncology portfolio in core areas such as lung cancer, breast cancer and multiple myeloma.
- **The Quantitative Systems Pharmacology (QSP) model** is able to recapitulate the range of variability seen in patients and to create ‘virtual patients’. This mathematical approach provides mechanistic insight into therapy response and prediction of therapeutic response of patients with different disease severities. QSP model highlights how real-world evidence can be incorporated into mechanistic models to predict the therapeutic response of a more diverse patient population compared with that observed from clinical trial data. The model could also be used for comparability assessment of drugs with different mechanisms of action.
- Sanofi is an active partner of **the Innovative Medicine Initiative, Inno4Vac** is a public-private partnership that addresses scientific bottlenecks in vaccine development. It proposes to develop predictive biological and mathematical models of vaccine performance and bio-manufacturing. Artificial intelligence combined with big data and computational modelling will be used to build an open-access and cloud-based platform for *in silico* vaccine efficacy assessment and development. Controlled human infection models and cell-based human *in vitro* 3D models will be developed to enable early evaluation of vaccine efficacy and prediction of immune protection. A workstream, co-led by Sanofi is dedicated to state-of-the-art infectious models **in human 3D mucosa** (organoïds of respiratory, gastrointestinal, urovaginal tracts).
- For the **quality control of vaccines**, noteworthy is the change of the **potency assays for multivalent pediatric vaccines** which has been a major reduction achievement. Several challenge tests in mice and guinea pigs have been combined in one test, the Single Immunogenicity Assay (SIA). SIA is an immunogenicity test based on the simultaneous quantitation of anti-Diphtheria, anti-Tetanus, and anti-Pertussis antibodies in the serum of immunized guinea pigs. After more than 10 years of development, validation and submission to the many drug agencies, SIA was implemented end of 2020 for one of the vaccines of the multivalent pediatric portfolio. The final objective is to save about 40,000 rodents each year when fully implemented. In addition to the substantial reduction of animals for potency evaluation of pediatric vaccines, this represents a major refinement achievement. Sanofi scientists are still investing to replace the *in vivo* model SIA by non-animal antigenic assays.
- Sanofi is developing the **Monocyte Activation Test (MAT)** for inherently pyrogenic vaccines in the frame of the project of the suppression of the rabbit pyrogen test, both for already commercialized vaccines and new vaccines under development. It will be a challenge to obtain recognition of this method at international level versus Europe, as this method is only described in European pharmacopeia.
- For **rabies vaccine**, an *in vitro* alternative test (G protein ELISA) was approved in Europe on July 19th, 2022, for VERORAB (human rabies vaccine) in replacement of mouse challenge potency assay known as NIH test. It is the first outcome of a project initiated 20 years ago, which, when fully implemented, will lead to a reduction of about 30,000 mice currently used to control the different rabies vaccines every year. This alternative has been developed through a collaboration within EPAA (European Partnership for Alternative Approaches) and is now being disseminated and validated through an international collaborative study (BSP148) under the lead of EDQM (European Directorate for the Quality of Medicines) in order to be used broadly by different laboratories and introduced in European pharmacopoeia for human rabies vaccines.

Breaking news – Sanofi scientists win a Translational Safety Publication Award for an article related to NAMs

The award acknowledged the collaborative works of preclinical safety scientists and bioinformatics.

The article "Accurate in silico simulation of the rabbit Purkinje fiber electrophysiological assay to facilitate early pharmaceutical cardiosafety assessment: Dream or reality?", published in the Journal of Pharmacological and Toxicological Methods in April 2022, has been rewarded by the Safety Pharmacology Society.

In the article, an assessment of mathematical models for early prediction of cardiac risks (including the inter-species differences and the types of tissue) has been done to validate the replacement of animal models.

5.3. REHOMING RESEARCH ANIMALS

Efforts are continuing to offer a new home to animals who have contributed to research programs. The species include ferrets, dogs, pigs, sheep, horses, poultry, llamas and alpacas. Sometimes rats and mice are proposed for adoption. More and more animals are part of the long list of adoption with many great stories. The fate of the animals at the end of the research projects is a concern for animal welfare bodies. When adoption options are limited, all efforts are made to find other projects or research institutions in respect with the strict regulatory obligations.

To facilitate the start in a new living environment, socialization program has been implemented. Since 2020, dogs have been prepared to their new life by animal care takers and veterinarians. Having a formal program has greatly improved the rapidity for the animals to adapt to their new environments.

For llamas and alpacas, a brochure in 3 languages has been drafted to help families to take care of their newly adopted llamas.

With the aim of creating adoption solution for primates, Sanofi has sponsored the building of new large enclosures at le Zoo-Refuge de la Tanière, France. A group of 7 primates has been transferred to this animal sanctuary.

Catherine, Animal Ethics Committee, France:

"I'm proud to be involved in the rehoming program; A way to say "thank you!" to the animals for their contribution. Some would say that's the least we can do, but I'm always amazed by the growing number of goodwill people."

About half of the animals are adopted directly by Sanofi employees and relatives. The other half is adopted thanks to a French animal association, [GRAAL](#) (Groupement de Réflexion et d'Action pour l'Animal). A master agreement has been signed to cover all species in Europe and as the results, there has been an acceleration of rehoming.

In France, Sanofi has contributed to the publication [of guidance documents about the rehoming](#) of research animals (GIRCOR, GRAAL). Those documents are available to the research communities and to the public. With the support of the Ministry of Research and the Ministry of Agriculture, expert groups, including Sanofi veterinarians, are working to share experiences, strengthen adoption programs and accelerate rehoming.

5.4. POLICIES ISSUED BY THE ADVISORY BODY ON ANIMAL ETHICS

In 5 years of activity, the Advisory Body on Animal Ethics (ABAE) has issued 9 corporate policies (list in section 3.2). Two of those policies, rehoming of laboratory animals and sponsors' responsibilities for external studies, have been completed with appendices to facilitate their implementation by Sanofi professionals.

In 2021, the members of ABAE have issued 2 new policies about the ethical management of crisis, using the example of the COVID-19 crisis, and the integrated research

and testing strategy, going beyond the 3Rs. The latter is a major commitment of Sanofi to use the best scientific approach to phase in new approach methodologies (NAMs), which do not require the use of animals (See section 3.3.3 for more details).

Srini, R&D, Global: "With the Policy on the responsibilities of Sanofi sponsors regarding animal studies conducted externally, we make additional continuing efforts to ensure our processes and oversight remain exceptionally vigilant, assuring maintaining highest standards of animal care and use for R&D activities, and requiring assurance of full adherence of all local, state, government and country requirements."

The last approved policy "**Good practices to ensure impartiality and independence of animal ethics committees of Sanofi**",

December 2022 describes the principles each Animal Ethics Committees of Sanofi must apply to ensure the independence and the impartiality of the ethical review. Sanofi relies on the engagement and the integrity of each Animal Ethics Committee member to ensure the quality of the ethical review and authorization of animal use in respect with best animal welfare practices. The principles include:

- The composition to ensure multidisciplinary representation (veterinarians, scientists, biostatisticians, lay members) and the role of unaffiliated members are instrumental. The institutional official must formally appoint the members.
- The management of conflict of interest evidenced by the appropriate documentation must be clear to all members who must recuse themselves if any real or perceived conflict of interest.
- The access to full details of research projects and clear decision process must be guaranteed. All decisions must be based on open collegial discussion and be justified. Expression of minority opinion should be encouraged by the chair of the Animal Ethics Committee and recorded adequately. Any members can freely raise concerns and will not be subject to discipline or discrimination for doing so.
- Any concerns about the integrity of Animal Ethics Committee work and decision should be, anonymously if requested, reported to the chief veterinary officer (CVO) or to the Bioethics Committee or the 'speak up' line of Ethics and Business Integrity. No employee will be discriminated against or subject to reprisal for reporting concerns regarding animal use, care and welfare, or any potential deficiencies or possible violations.

All members of Animal Ethics Committees must be trained on this policy and regular refresher discussions should be organized. The Institutional Official is accountable for the implementation of this policy.

The quality of work of Animal Ethics Committees and the compliance with the principles described in this policy document are overseen by the CVO, as well through regular AAALAC accreditation (every 3 years) or national/regional inspection. The CVO has already performed 5 out of 8 audits of animal ethics committee to assess the performance and the quality of work of Animal Ethics Committees.

Summary of Sanofi position on the use of non-human primates (version 2, Oct 2022)

Although the number is limited, the use of non-human primates is essential to some research and development programs. In fact, in some cases, non-human primates may be the only species where biology, physiology and disease mechanism are similar to that in humans and would ensure the safety and efficacy of the new drug or vaccine. Due their high level of development and sentience, and their behavioral and social complexity, the use of non-human primates in medical research and drug development raises ethical, welfare and conservation questions. Therefore, special considerations are implemented to control the rationale and the conditions of use of non-human primates.

- No great apes, including chimps as well as no endangered primate species, are used by Sanofi and its contractors.
- Non-human primates should be purpose-bred, preferably bred in self-sustained colonies. High ethical standards at breeding centres and by the suppliers should be implemented and periodically audited by Sanofi professionals.
- NHP use is limited to the development of treatments for debilitating or potentially life-threatening clinical conditions in human beings.
- Any use of NHP must be clearly justified and any alternatives, included the use of other species, must be considered.

High ethical and welfare standards are critical to the high level of development and the social nature of primates. Special attention should be paid to the social housing, provision of large enclosures with enriched environments, positive human-animal interaction, and training of non-human primates to experimental conditions, as appropriate.

5.5. OUTREACH AND EDUCATION

Sanofi considers that openness is a key value and is part of our policy on the protection of animals. In 2022, Sanofi is a signatory of 4 openness agreements ([Belgium](#), [France](#), [Germany](#), [UK](#)) and participates to the openness working groups in the US ([U.S. Animal Research Openness \(USARO\) Initiative](#)). Animal care and use programs and 3Rs progresses are openly reported on a yearly basis.

In November 2022, Sanofi has globally participated to the International Biomedical Research Awareness Day; 12 sites in 7 countries have organized local events for the staff and site personnel, most of them being virtual. About 700 people have been able to interact with animal care professionals and to ask any questions about the daily care and use of animals.

To develop ethics competencies, the Advisory Body on Animal Ethics has initiated a series of webinar for members of animal ethics committees. The first priority has been a session focused on the non-animal methods used and in development by Sanofi. Other topics have included the communication and transparency, the good experimental design, and the rehoming with intervention of internal and external experts.

Edith, R&D, Belgium: "It has been a chance to show people about the animal care, facilities and operations. Reaction was "Wow! I Didn't know." In the future, we should expand this BRAD to the whole company."

Sanofi has sponsored several events related to 3Rs:

- The [Global 3Rs Awards](#) by AAALAC International and IQ Consortium to recognize the best scientific publication in 3 regions of the globe;
- The [World Congress on alternatives and animal use in Life Sciences](#). Due to COVID-19 crisis, the congress has been postponed to a virtual event in August 2021; a session on Relevance, Rigor and Reproducibility has been organized by Sanofi R&D;
- The International congress of the Federation of European Laboratory Animal Science Associations (FELASA) which main topics was Communication and Science in June 2022 in Marseille, France. Sanofi

has been very active in the organization and participation to the congress program. Noteworthy was the first ever contest on “[My 3Rs in 3 minutes](#)” sponsored by Sanofi, in which young scientists have presented their 3Rs projects in 180 seconds.

In October 2021, Sanofi scientists have actively participated to the organization of the AFSA and EFPIA workshop “Accelerating Global Deletion of the Abnormal Toxicity Test. Planning common next steps.” As positive outcomes, a [scientific article in the Journal Biologicals](#) (open access) has been published and the South Korea’s Ministry of Food and Drug Safety has introduced an amendment to its Biologicals standard and test method guidelines, and will no longer require the Abnormal Toxicity Test.

6. INSPECTIONS, ACCREDITATIONS, AND AUDITS

6.1. INSPECTIONS IN 2021

Regulatory inspections at Sanofi’s animal facilities are performed on a regular basis by national and local authorities and our programs remain in compliance with animal welfare laws and regulations.

Nonetheless, in July 2021, one site in France received a formal notice following the veterinary inspection, due to findings related to enrichment and refinement. The points have been rapidly addressed and the formal notice was lifted. Full certification was granted after the following inspection performed to maintain the establishment license.

6.2. AAALAC ACCREDITATION OF OUR SITES

As per the Policy on the Protection of Animals, the CVO, the managers, and the veterinarians are committed to ensuring AAALAC accreditation of 100% of our animal care and use programs by 2020. The objective has been successfully reached and the accreditation status have been maintained. Assessment of each program is performed by AAALAC International every 3 years.

In addition to AAALAC accreditation, our Canadian site is CCAC-certified ([Canadian Council on Animal Care](#)).

6.2.1. New accreditation

In 2021, the animal facilities of Kymab, Cambridge UK, a newly acquired biotech company, have been accredited. The animal care and use program is run by a not-for-profit research institute and Kymab uses the services of this institute. The standards in that research institute are fully aligned with Sanofi requirements.

6.2.2. Reaccreditations

Four sites in France have been accredited by AAALAC International in 2021: Alba-La-Romaine, Marcy-L’Etoile, Montpellier, Val-De-Reuil.

In 2022, 2 sites (Frankfurt, Germany and Toronto, Canada) have been reaccredited without any findings. 2 other sites (Ghent, Belgium and Vitry/Seine, France) have been assessed by AAALAC International experts and the final decision by the Council on Accreditation will be made in the 1st quarter of 2023.

Sarvesh, Quality Control, India: “AAALAC gives us the chance for further evaluation towards better animal welfare and find true commitment to humane animal care and use. Quality standards to be accredited to enhance our research outcomes.”

Early 2023, 3 sites (Medchal, India, Shenzhen, China and the new R&D site in Cambridge, MA USA) will be inspected to seek for continuous accreditation.

6.3. CONTRACT RESEARCH ORGANIZATIONS AND BREEDERS EVALUATED IN 2021

Third parties are periodically assessed by Sanofi laboratory animal welfare experts to ensure compliance with the principles of the policy on the protection of animals. With the aim of strengthening the evaluations of third parties, A new global procedure on animal welfare assessment has been issued in 2020.

In 2021, 55 contract research organizations (CROs) or academic institutions and 9 vendors underwent evaluation and were determined to meet requirements to comply with Sanofi's animal protection principles.

JoAnne, R&D, USA: "2020, a challenging year in terms of animal welfare assessments and oversight of our partners. Due to the stay-at-home order, we had to adapt new methods to assure that our Animal Protection Policy was upheld throughout some very trying times. I am extraordinarily proud of how our entire team caught up to meet the challenges and worked together, thus ensuring that critical studies were initiated, and tight timelines were met with confidence regarding animal welfare."

In 2022, the assessment of external partners has been continued and will be reported in 2023. The Marseille Declaration (see section 1.2) should accelerate the global and consistent implementation of the highest standards for the care and use of laboratory animals.

7. REFERENCES

- ETS 123—European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, 1986 and its revised appendices, 2006.
- European Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010, on the Protection of Animals Used for Scientific Purposes.
- United States Animal Welfare Act (Title 7 U.S.C 2131–2159) and United States Animal Welfare Regulations, CFR, Title 9, Chapter 1, Subchapter A, Part 1-4.
- Institute for Laboratory Animal Research—Guide for Care and Use of Laboratory Animals (8th Edition, 2011).
- Federation of Animal Science Societies—Guide for the Care and Use of Agricultural Animals in Research and Teaching (3rd Edition, 2010).
- EFPIA: Putting animal welfare principles and 3Rs into action. European Pharmaceutical Industry 2022 Report Update.