Animal Protection

Ethical use of animals in research and production

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, and medical devices. Although committed to developing and implementing non-animal methods and reducing reliance on animal use, Sanofi believes the responsible use of animals remains essential in the research and production process for patients' benefit, besides regulatory requirements. For this reason, the use of animals remains a small but critical part of our comprehensive research and testing strategy along with non-animal methods and clinical studies.

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 and production 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 authorizes animal use only when the regulatory and scientific merit is established and under strict ethical oversight, commits to meet or exceed regulations and standards for the protection 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 improve animal welfare and prevent animal pain and distress in housing and procedure conditions (refinement).

Sanofi promotes a culture of care which fully considers the intrinsic value of animals as sentient beings, 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, at the following address: https://www.sanofi.com/en/contact.

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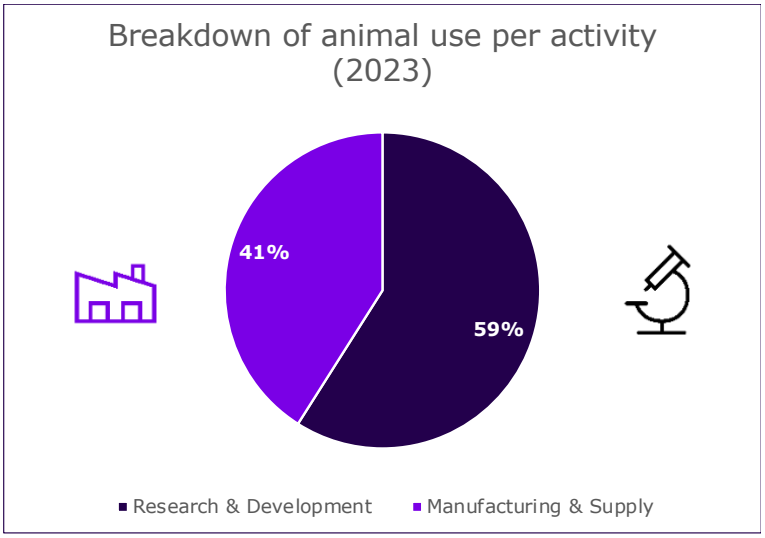
1. The use of animals remains a necessity for the benefits of patients

Sanofi is morally and legally obligated to ensure the quality, safety and efficacy of its medicines, vaccines, and medical devices. Although committed to developing and implementing non-animal methods and reducing reliance on animal use, Sanofi believes the responsible use of animals remains essential in the research and production process for patients' benefit, besides regulatory requirements. The most reliable scientific approach should be used, aiming at a robust assessment of the efficacy and safety of new drugs and vaccines, and generally relies on a combination of models; those can be *in silico* (computer modelling, artificial intelligence, big data…), *in vitro* (cells and tissues, including human tissues, organoids, organs-on-a-chip, biochemistry, microbiology, -omics…), and *in vivo* (animal models), with additional insights from patients' data and from clinical research.

In 2023, for Sanofi globally, approximately 40% of animals were used by the manufacturing and supply sector to support batch release activity that aims at ensuring the safety and efficacy of commercialized vaccines and drugs. Numbers of animals used for this purpose are constantly decreasing. In comparison, although quite steady in numbers, the relative part of animals used for research and development purposes was nearly 60% in support to a better understanding of diseases and to the assessment of the safety and efficacy of new drugs and vaccine candidates.

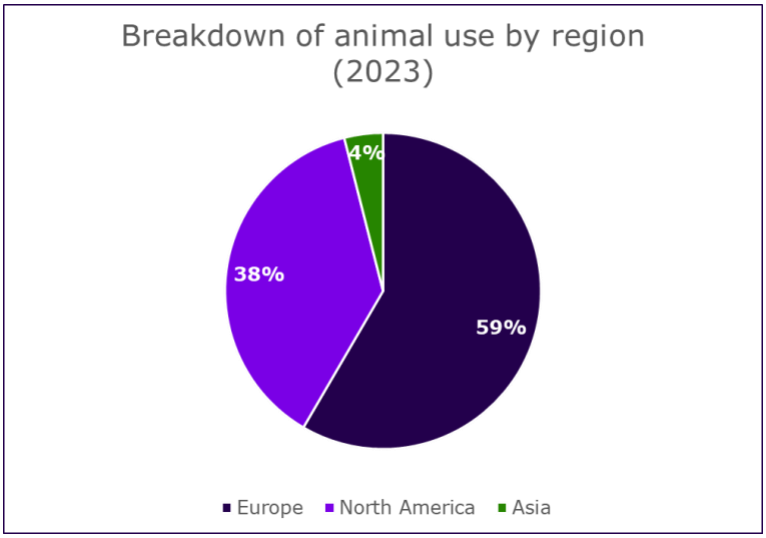


2. *Our company-wide approach towards high animal protection standards*

2.1. TO SUPPORT OUR R&D AND PRODUCTION ACTIVITIES, ANIMALS ARE USED, GLOBALLY

At the end of 2023, animals were used in-house at 12 Sanofi sites located in 7 countries.

In 2023, 96% of animal use in-house took place in Europe and Northern America, to support R&D and manufacturing activities for our drugs and vaccines. The remaining part, mostly dedicated to the quality control of vaccines, was performed in Asia.



2.2. ANIMAL USE IS HIGHLY REGULATED, GLOBALLY

The use of animals for scientific purposes is a highly regulated domain in the countries where Sanofi operates. Several rules apply for the protection of these animals, encompassing all aspects to be fully considered for animal supply and use: animals, personnel, facilities, and studies.

In the last decades, major pieces of regulations and national and international references (in Europe, USA, Canada, China…) have been set up or revised considering advancement in animal welfare knowledge and increasing public interest for the protection of animals (see Main references).

In these countries or regions, legal animal welfare dispositions apply, and compliance is monitored on a regular basis: all Sanofi sites are subject to inspections (frequently unannounced) by the national or local competent authorities and must ensure to constantly meet the legal requirements.

For instance, here are the main applicable legal requirements in European Member States:

Key obligations as defined by the Directive 2010/63/UE
Evaluation and authorization of projects by independent authorities prior animal use
Publication of project non-technical summary and statistics related to animal use
Implementation and monitoring of the 3Rs (To Replace, Reduce, Refine animal use)
Expert committees for project ethical review, for animal welfare, designated veterinarians
Oversight on the creation, maintenance, and use of genetically modified animals
Restricted conditions for the use of non-human primates
Mandatory training of the personnel. Assessment and maintenance of their competencies
Supply of purpose-bred animals from authorized breeders and suppliers
Inspection and authorization of breeders, suppliers and users by competent authorities

Still, disparities exist in the levels of regulatory requirement of the different regions. To address these differences, additional standards are applied consistently across Sanofi activities.

2.3. OUR GLOBAL POLICY TO APPLY HIGH ANIMAL PROTECTION STANDARDS, CONSISTENTLY

To promote a shared vision of the attention to be paid to animals within the company, across geographies and *on top of legal obligations, core animal protection principles are embedded in a global policy*. In support of our longstanding commitment to the 3Rs, the policy applies to all animals used by Sanofi for research, testing and production of medicinal products, investigational medicinal products, vaccines, medical devices, and active pharmaceutical ingredients. It also applies to breeders and suppliers 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.

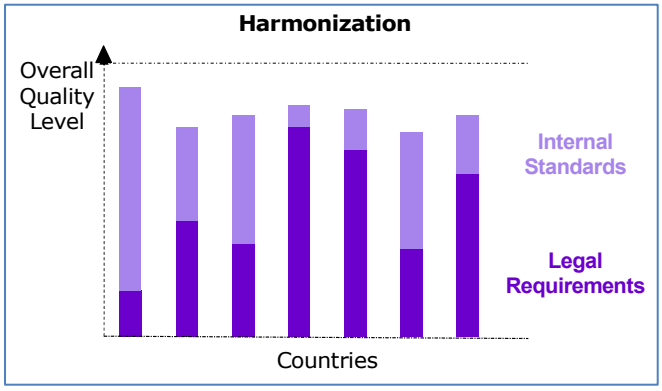
Sanofi standards complement legal obligations to achieve high quality animal care and use programs, globally.

Above regulations which set the minimum applicable standards, Sanofi establishes additional requirements and bodies to embed high welfare principles at all sites, in-house and at breeders and other partners.

Such principles apply to:

- animal species and their sourcing,
- animal facilities, animal housing and care conditions,
- the personnel, and
- the approval and monitoring of studies performed on animals.

As legal requirements can vary from country to country (dark purple bars), establishing internal rules and principles (light purple bars) contribute to increase overall quality and foster harmonization across sites and countries.



2.3.1. Sanofi principles to align standards across the world

As per our *company-wide policy,* the use of animals is authorized only when regulatory and scientific merit is established, i.e., there is a clear expectation that the results will contribute to the protection and/or the improvement of human health, and with strict ethical oversight.

Sanofi supports 3Rs programs fostered by scientific and technological development to proactively replace, reduce, and refine animal use wherever possible.

Good science requires that animals remain in good health and are subject to minimal pain or distress. At each site, an animal ethics committee and/or animal welfare body ensures the oversight of the local animal care and use program. Experts in veterinary medicine and animal welfare, qualified and experienced staff are ensuring humane care and appropriate use of animals on a daily basis.

On top of the legal obligations, to harmonize internal standards across the world and to ensure high welfare considerations, all Sanofi sites seek and maintain independent accreditation of their animal care and use programs through recognized expert organizations such as AAALAC International[1].

In addition, our policy promotes a *culture of care*, i.e., an organizational culture that embraces the responsible use of animals as a primary value, that supports and values caring and respectful behavior towards animals and professionals.

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

[1] AAALAC International is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. https://www.aaalac.org/

2.3.2. Oversight of the ethical use of animals

When animal use is required to support the efficacy, safety or quality testing of medicines or vaccines, procedures are carried out in compliance with ethical principles to minimize pain or distress.

At every site, an animal ethics committee provides oversight of animal care and use, including effective implementation of the 3Rs in designing projects and carrying out procedures. The committee weighs the objectives of the study and the likelihood of achieving the goals related to the protection and/or improvement of human health against the need for using animals and the likely harm to animals. Before being implemented, all research and testing projects must be authorized by animal ethics committees and competent authorities, whose 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 at least one independent or lay committee member (non-affiliated with Sanofi). Whenever possible, a biostatistician sits on the committee, or is called upon by the committee, to make sure the study uses the smallest number of animals necessary to produce statistically valid results.

At the global level, under the leadership of the Chief Veterinary Officer, who is a permanent member of Sanofi 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 guidelines and positions in animal care and use 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, the Advisory Body on Animal Ethics meets quarterly and has developed global policies that are approved by Sanofi Bioethics Committee (Annex I).

As per Sanofi Code of Conduct, any employee who has a concern and believes in good faith that a law, policy, or the Sanofi Code of Conduct has been or is about to be violated has the duty to raise it. This applies to concerns related to animal welfare and appropriate use of animals by Sanofi. In this aim, a dedicated Speak-up Helpline is available, and any question could be asked to the Chief Veterinary Officer using an online form (available at: https://www.sanofi.com/en/contact).

2.3.3. Strong commitment to animal ethics and the 3Rs

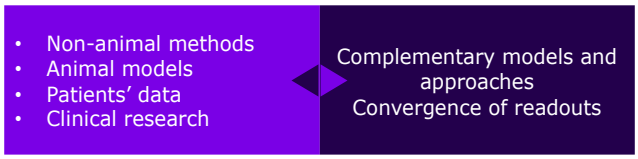
Our policies aimed at fostering an environment of responsible use and humane treatment of animals.

As such they support key principles so that a strong rationale is established before animal use, especially for primates or genetically modified animals, that animal ethics committees operate in an independent and impartial manner, that members of the personnel take full responsibility for animal use, both in-house and at external partners, that 3Rs principles are anchored in the research and testing strategy, and, last but not least, that full consideration is given to the intrinsic value of animal lives – under all circumstances, including crisis situations – and that rehoming of animals is the preferred option whenever possible, after they have been used for science.

When science or regulation necessitates the use of animals, *the 3Rs principles are at the core of every project so as to bring the best of science and innovation together with animal welfare considerations*.

As such, animals can be used 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 improve animal welfare and prevent animal pain and distress in housing and procedure conditions (Refinement).

Rather than being opposed, the use of animal and non-animal models are complementary approaches that inform each other's to address a scientific or regulatory question. The use of animals remains 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.



For new drugs and vaccines, preclinical packages, which include computer analysis of multiple data, *in vitro* models and *in vivo* studies are based on last scientific developments and tailored for every project to decipher the mechanisms of action and to assess the efficacy and safety of new candidates before clinical trials can be performed: the best options are chosen to address the scientific questions, on a case-by-case basis.

In the regulatory field, 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. Thanks to innovation in analytical sciences, and increased consistency in the manufacturing chain, there is increasing room to reduce the numbers of tests required for each product and to replace animal use by synthetic approaches, provided regulatory acceptance by health authorities.

Our *"Integrated Research and Testing Strategy"*, driven by scientific advancement to foster implementation of the 3Rs principles, also includes cross-disciplinary collaboration initiatives to promote acceptance of new approach methodologies by the scientific community and by regulators, worldwide. As per this strategy, Sanofi aims at reducing the number of animals used in research and testing by 50%, between 2020 and 2030.

2.4. OUR PRIORITIES TO FOSTER HIGH ANIMAL PROTECTION STANDARDS

In support of our animal protection strategy, *several priorities* have been defined and progresses are monitored on a regular basis:

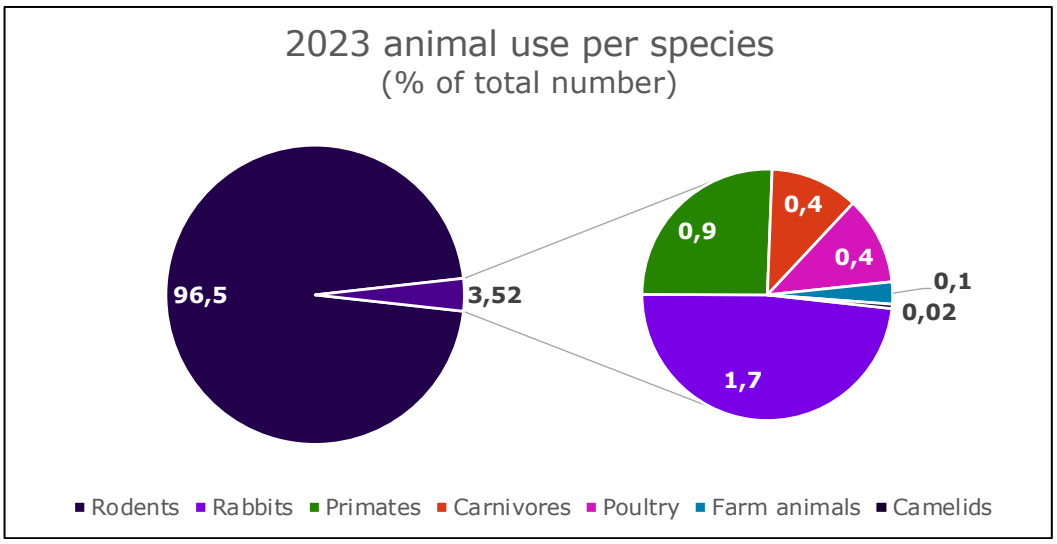
- To develop roadmaps and set objectives in order to ensure the success of the "Integrated Research and Testing Strategy" by reducing reliance on the use of animals;
- To maintain the highest animal care and use standards beyond regulatory inspections and through accreditation, and to foster a culture of care;
- To monitor the compliance of third parties (breeders, contract research organizations, scientific collaborations);
- To contribute to regulatory debates, in relationship with animal protection rules on one side and with regulatory acceptance of non-animal methods on the other side;
- To address societal concerns and to strengthen ethical considerations about the use of animals for scientific purposes;
- To improve communication regarding animal use and to initiate a culture of openness.

Achievements in these various sectors are illustrated in the following section.

3. 2023 facts and figures on our animal protection roadmap

3.1. ANIMAL SPECIES USED TO SUPPORT SANOFI R&D PORTFOLIO AND QUALITY CONTROL

In 2023, most animals used (98%) were rodents and rabbits. Other species used were primates, carnivores, poultry, farm animals, and camelids. The choice of the species is systematically made on scientific and ethical grounds for each project. Justifications are reviewed by animal ethics committees, responsible for the project approval, on a case-by-case basis.

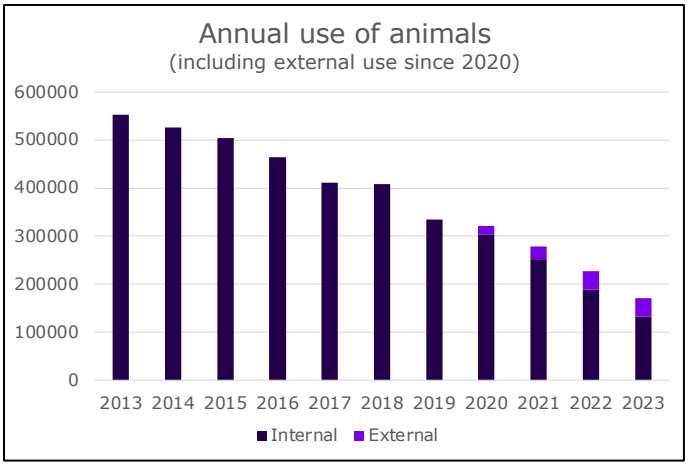


3.2. CONSTANT DECREASE OF ANIMAL USE

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

The total number of animals used at Sanofi sites in 2023 was 132,799[2]. In comparison with figures reported for 2022 (188,821 animals), this represents a reduction of 30%. Since 2013, this total has decreased by 76%.

As per the "Integrated Research and Testing Strategy", Sanofi's aim is to reduce the total number of animals used in research and testing by 50%, between 2020 and 2030. Since 2020, the baseline includes both animals used at Sanofi sites (i.e., internal use) and those used on behalf of Sanofi (at contract research organizations and through collaborations where Sanofi is a sponsor, i.e., external use).



[2] Calculated in accordance with national legislation in each country where we use animals. For European sites, the reference is Commission Implementing Decision 2020/569, available at www.eur-lex.europa.eu.

Annual animal use	2020	2021	2022	2023	...	Target 2030
Internal use	302,890	252,312	188,821	132,799		-
External use	18,323	25,532	37,839	38,302		-
Total	321,213	277,844	226,660	171,101		Target: 160,000
Reduction y/y-1		-13.5%	-18,4%	-24,5%		-
Reduction y/2020		-13.5%	-29,4%	-46,7%		Target: -50%

In 3 years, a significant reduction was achieved. Nevertheless, Sanofi entities maintain their firm intention to continue the reduction trend.

3.3. ACHIEVEMENTS RELATED TO THE DEVELOPMENT AND UPTAKE OF NEW APPROACH METHODOLOGIES

New approach methodologies (NAMs) are integrated in the research and testing strategy. They encompass a variety of developing disciplines that, as stand-alone methods or bridged the one with another, ultimately minimize or replace the use of animals, more particularly in the regulatory testing field. Some of these new scientific approaches do not provide for the full replacement of animal use, but represent new, and often more accurate and predictive translational models of conducting research and testing, with less animal used at the end. In any case, the scientific validity and the predictivity must systematically be demonstrated, on a case-by-case basis in relation to the specific context of use.

Below are some examples of how NAMs play a vital role and are phased in across the development and control testing of drugs and vaccines for patients.

3.3.1. Successful replacement of *in vivo* eye irritation test for the safety assessment of a new vaccine administered by nasal instillation

A new vaccine is being developed in the form of a nasal spray using an atomization device in order to counter Respiratory Syncytial Virus infection in toddler (RSVt). During the development phase, EMA (European Medicines Agency) mandated to assess the eye irritation potential of the vaccine prior to the Phase III clinical trials.

The conventional approach for eye irritation potential is based on *in vivo* instillation of the test compound in 3 rabbits followed by ocular scoring and tissue (histopathology) analysis.

Considering the 3Rs principles and to encourage implementation of new approach methodologies (NAMs), the non-clinical safety department developed a tiered strategy based on available qualified alternative method for ocular testing.

Under this approach, the *in vitro* eye irritation test method was conducted first and demonstrated the absence of eye irritation with sufficient confidence that the *in vivo* study was not deemed necessary.

This approach has been accepted by EMA and is a fitting example where, for a specific context-of-use, the 3Rs principles have perfectly aligned with the development and implementation of NAMs for ocular safety endpoint.

3.3.2. Successful development and implementation of *in vitro* tests to replace animal tests for the quality control of vaccines

For the quality control of vaccines, our company has an overall strategy that ensures reliable and relevant *in vitro* assays are developed to replace animal tests. There is increasing interest to replace animal-based potency assays used routinely to test vaccines, since they are highly variable, costly, and present ethical concerns.

As an example, for DTaP-IPV (diphtheria, tetanus, acellular pertussis, and inactivated poliovirus) vaccines, using the pertactin (PRN) antigen, a PRN antigenicity ELISA test was developed using two monoclonal antibodies with: 1) high affinity to unique PRN epitopes, 2) relevance to human immune responses, and 3) evidence of functionality.

The ELISA method was used to assess the consistency of PRN antigenicity between vaccine batches, and was validated to demonstrate its accuracy, precision, linearity, and specificity. Notably, the PRN antigenicity ELISA method proved to be more sensitive than the mouse-based potency test and to differentiate more effectively between degraded and intact vaccine batches, compared to the *in vivo* test. The PRN antigenicity ELISA method has been proposed and accepted by health authorities as an *in vitro* replacement for the *in vivo* potency test for PRN in DtaP-IPV based formulations.

This work was presented at the 12th World Congress on Alternatives and Animal Use in the Life Sciences in Canada (August 2023) and won the ATLA (Alternatives to Laboratory Animals) *Replacement in Practice Poster Award* with the title "Removing the mouse from the house: An ELISA method to replace mouse-based potency testing for pertactin antigen".

For the quality control of poliomyelitis vaccines, the *in vivo* potency test has been fully replaced by an *in vitro* test for the release of batches. The rat model used for North American vaccines and the chicken model used for European vaccines were replaced by an immunoassay (ELISA), thus avoiding the use of around 10 000 rats and 1000 chickens per year.

Still, some authorities require rat model-based data for the validation of manufacturing process changes. In response to this, our company has developed an alternative approach to characterize the polio antigen and plans to submit it in replacement of the historical *in vivo* model for future process changes.

3.3.3. Replacement of the rabbit blood sugar test for the quantitative determination of the biological activity of insulins with an *in vitro* assay

For insulin batch release, the recent United States Pharmacopeia general chapter requires a nonquantitative bio-identity test either as a rabbit blood sugar assay or as an *in vitro* insulin cell-based assay using in-cell Western (ICW) technology. However, for quantification during stability or comparability studies, the rabbit blood sugar test is still required using a minimum of 24 rabbits to obtain one result.

Based on the 3Rs principle, we sought to qualify the *in vitro* ICW cell-based bioassay approach for quantifying insulin activity. A bridging study with different insulins and stress samples revealed a clear correlation between the *in vitro* and *in vivo* test results. The replacement of the animal-based assay with the quantitative *in vitro* ICW cell-based bioassay for batch quality control saved cost, reduced cycle times while obtaining more meaningful and reliable data, and, above all else, reduced the use of many rabbits[3].

[3] Animals 2023, 13, 2953. https://doi.org/10.3390/ani13182953

3.4. INSPECTIONS, ACCREDITATIONS AND AUDITS

By the end of 2023, 12 Sanofi sites in seven countries were using animals. At 10 of those sites, Sanofi is directly responsible for housing and caring for the animals. These sites are regularly inspected by national and local competent authorities for the protection of animals, and our programs have been found to comply with animal welfare laws and regulations.

In addition, those 10 sites have AAALAC International accreditation, which guarantees high standards in the use and welfare of animals, in line with our voluntary commitment to have independent certification at all Sanofi sites. The other 2 sites, where animals are not housed on Sanofi premises, comply with AAALAC International or equivalent standards.

As part of this continuous process, in 2023, three sites received confirmation from AAALAC International that their full accreditation was renewed, and another site was due to receive the outcome of their assessment in 2024 (following a visit by AAALAC International in fall 2023).

In the course of 2023, per our global procedure on the animal welfare assessment of external partners involving animals, 41 contracted research organizations and 10 universities conducting tests on animals, as well as 7 breeders and suppliers of animals and animal-derived products, were subject to an evaluation and approved by our in-house specialists as entities that comply with our animal protection policy (no critical discrepancies identified).

3.5. MORE ON ANIMAL WELFARE AND THE 3Rs

3.5.1. Rehoming animals used in research

Giving animals a new home after they contributed to research programs is an essential pillar of our commitment to animal welfare. By default, many, if not all, of the species used can be adopted: ferrets, dogs, pigs, sheep, horses, poultry, llamas and alpacas, as well as rats and mice. The fate of the animals at the end of research projects is a topic of concern for our animal welfare bodies. Socialization programs are implemented by animal caretakers and veterinarians to better prepare dogs to their future life and improve their adaptation to a new environment. Decisions are taken on a case-by-case basis, according to legal requirements and the animal's fitness for rehoming as assessed by our veterinarians. When adoption possibilities are limited, and, provided animals meet the legal and ethical conditions for reuse, attempts are made to find other research programs or institutions, so that the animals can be used in other projects in compliance with strict regulatory obligations, thus avoiding the need for additional animal supplies.

In 2023, 58 animals were adopted, either directly by Sanofi employees and relatives or through our close partnership with GRAAL (Groupement de Réflexion et d'Action pour l'AnimaL), adding more animals to the long list of adoptions with many great stories.

3.5.2. Monitoring digital biomarkers to improve animal welfare follow-up in mice

Home-cage monitoring systems enable prolonged or even continuous recording of digital biomarkers, such as locomotor activity. The evaluation of the Digital Ventilated Cages (DVC®) device from Tecniplast® on tumor-implanted animals showed that, based on criteria indicating potential animal welfare concerns, alerts can be generated automatically and be used as an early warning for the staff.

Compared to the daily observation by animal care staff, using the "Animal Welfare Check Alert" allows for a more precocious detection of clinical signs, in circumstances when the animals display ruffled fur or before the animal's movement is hindered by the tumor size. This system provides meaningful additional data in the refinement of the animal's monitoring. We have implemented this welfare monitoring system for almost a year now which provides a concrete complementary advantage to our veterinary follow-up program of mice used to maintain tumor cell lines[4].

[4] Cancers (Basel). 2023 Sep 29;15(19):4798. https://doi.org/10.3390/cancers15194798

3.5.3. Animal-free health monitoring in rodent facilities

To ensure for their welfare as well as for the quality of science, it is essential to maintain laboratory animals in strict environmental conditions and to perform regular checks of their health status. For decades, the health monitoring of rodents has been performed on samples obtained on additional "sentinel animals" housed in the same premises as animals used for research.

Since 2020, for our pharma R&D sites across the world, we have completely switched to a rodent health monitoring method that does not require sentinel animals anymore. The use of new approaches, such as environmental testing (filters placed in sentinel cages without animals or in exhaust plenum of ventilated cage racks) and molecular based diagnoses, allowed us to gradually replace the use of sentinel animals, leading nowadays to avoid the use of 430+ rodents per year.

This program is progressively being expanded at all sites.

3.5.4. Adapting the use of animals to our R&D portfolio needs, example of the Porsolt swim test

The use of animals for R&D purposes is systematically questioned with regards to both moral considerations and scientific validity, with the aim to ensure that patients have always access to medicines, vaccines, medical devices, and other healthcare products whose quality, safety and efficacy has been proved to the highest scientific standards. Using animals is methodically challenged against the use of non-animal alternatives. If animals are used, utmost consideration is given to their care and welfare, especially in situations where animals might experience likely harm due to the complexity or severity of the human condition to be investigated.

In this context, to meet our preclinical portfolio needs, there have been instances in the past where the use of the Porsolt swim test has been authorized on rodents, under strict ethical oversight. However, this test has not been used at Sanofi for several years, consistent with our ethics, standards and procedures described above. Today, Sanofi does not use the Porsolt swim test, has no research projects that involve the use of this test and have no plans for this test to be used in the future, either in-house or at a contract research partner.

Overall, Sanofi is committed to using animals responsibly, and to significantly reducing our reliance on the use of animals as appropriate scientifically valid alternative means become available.

3.5.5. "Together we prioritize animal welfare": Promoting the "Marseille Declaration"

In 2022, Sanofi was one of the initial signatories of the "Marseille Declaration on the worldwide implementation of high standards for animals housed and used internally and externally by the industry for scientific purposes" (Annex II), aiming at extending and accelerating the global and consistent implementation of the highest standards for the care and use of laboratory animals.

In 2023, thanks to continued discussions with other precursors and promotion of the Marseille Declaration principles, four more companies decided to join the initiative, including two more pharmaceutical companies and two contract research organizations, thus launching the momentum for expanding consideration of these fundamental animal welfare principles.

3.6. OUTREACH AND OPENNESS

3.6.1. Improving awareness and communication through openness

Sanofi considers that openness is a key value and is part of our policy on the protection of animals. The Company is a signatory and strong supporter of 4 openness agreements in Europe (Belgium, France, Germany, UK) and supports the openness initiative in the US by appearing on the USARO exemplars webpage (U.S. Animal Research Openness Initiative (USARO)). These are many opportunities to report with other research institutions on the progress of our animal care and use programs, including animal welfare, 3Rs and outreach, on a yearly basis.

In 2023, several Sanofi sites organized events in the framework of the Biomedical Research Awareness Day (BRAD). Locally, professionals involved with animal facility management, animal care and use, animal ethics and welfare committees, and veterinarians hosted presentations and/or booths to interact with their colleagues and other members of the personnel on site, providing information and answering questions about the daily care and use of animals, and the scientific justification for using them.

3.6.2. Openly promoting the phasing-in of New Approach Methodologies to reduce reliance on the use of animals

In the recent years, Sanofi affirmed its ambition to drastically reduce reliance on the use of animals for research, development and production portfolios. To support this aim, internal networking and coordination activities have been on the rise. In addition, relevant external opportunities and forums were used to further express and explain our aspiration to phase in New Approach Methodologies and foster acceptance of non-animal methods.

In the course of 2023, the main illustrations were:

- Oral presentation during the webinar co-organized by EFPIA and RSCPA (respectively, The European Federation of Pharmaceutical Industries and Associations and The Royal Society for the Prevention of Cruelty to Animals, the UK leading animal welfare organization) on June 22, 2023 "How the pharmaceutical industry is working to avoid and replace the use of animals for scientific purposes";
- Oral and posters' presentations during the 12th World Congress on Alternatives and Animal Use in the Life Sciences in Canada (August 2023);
- Active participation to the workshop organized by NC3Rs (The UK National Centre for the 3Rs): "Implementing the 3Rs in WHO biologicals guidelines", in London, September 19-20, 2023, openly and directly engaging with other manufacturers and worldwide health authorities, to foster faster and wider implementation of NAMs for the quality control and batch release testing of vaccines and biological therapeutics;
- Keynote presentation at the annual conference of EPAA (European Partnership for Alternative Approaches to Animal Testing) Conference, in Brussels, on November 15, 2023.

In addition, to promote scientific contribution to the 3Rs, Sanofi provided continued sponsorship to the Global 3Rs Awards Program developed by AAALAC International and the "IQ Consortium" (International Consortium for Innovation and Quality in Pharmaceutical Development) to recognize significant innovative contributions toward the 3Rs of animal research to advance ethical science.

4. Main 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).
- Animals for Research Act, R.S.O. 1990, c. A.22, Ontario, Canada, amended 2024.
- Canadian Council on Animal Care guidelines and policies.
- Experimental Animal Management Regulation, China, 2017
- EFPIA: Putting animal welfare principles and 3Rs into action. European Pharmaceutical Industry 2022 Report Update.

5. Annexes

Annex I: Global policies developed by Sanofi Advisory Body on Animal Ethics and approved by Sanofi Bioethics Committee (BEC)

Policy Title	Description
Protection of animals	The Policy on the Protection of Animals states the global quality directive that any person or *ad hoc* committee, working under the responsibility or on behalf of Sanofi at all sites, must comply with when using animals.
Production and Use of Genetically Modified Animals for Research	The development of 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.
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.
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.
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**: guidance to provide eligibility criteria for adoption*
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 and compliance with Sanofi animal protection principles. ***Appendix**: guidance to help the external partner implementing Sanofi standards related to animal use*
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.
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.
Good practices to ensure independence and impartiality of animal ethics committees of Sanofi	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. The objective of this policy is to provide criteria and principles to ensure impartiality and independence of Sanofi's animal ethics committees.

Annex II: Marseille Declaration on the worldwide implementation of high standards for animals housed and used internally and externally by the industry for scientific purposes (as of December 2023)

First joint pharmaceutical industry declaration on animal housing and use
from Marseille, France; September 2022

Marseille Declaration on the worldwide implementation of high standards for animals housed and used internally and externally by the industry for scientific purposes

The company-signatories of this declaration share common values and believe that the welfare of animals used in the research and production of medicines and vaccines requires the greatest consideration. This work demands application of high and most consistent standards of animal welfare and laboratory animal science regardless of where it is performed.

In this document, the company-signatories state their expectations related to animal welfare practices to be used at their own sites in whatever country and by external partners worldwide when using living animals to conduct studies on their behalf. The company-signatories request that their external partners meet the following criteria or agree on a plan for implementation when using and caring for animals in connection with an existing business relationship.

- Culture of Care: The company commitment and dedication to and engagement of individual employees towards animal welfare is promoted via support of a strong and clearly defined and documented Culture of Care program. Such program is a key asset for a continuously evolving high quality animal care and use program.

- Oversight Bodies: Institutional independent multidisciplinary expert governance or oversight bodies[1] approve all animal use by ensuring the scientific merit and regulatory requirements of in vivo protocols are met. The considerations of the 6 Principles of Animal Research Ethics[2] are applied to ensure that the value and quality of life is considered for each individual animal and the 3Rs and that the quality of the animal care and use program is assessed.

- Continuous Education & Training: A holistic program of professional education and continuous professional development exists for all staff working with animals and conducting animal studies. The training program should be adjusted to the relevant needs of each employee and performed in respect with current best practices. This training program shall define training requirements for all roles that use animals directly or are responsible for animals via management of work or staff.

- Veterinary Care: Appropriate veterinary care to manage animals both at an individual and a colony-wide level. Presence of a competent veterinarian with sufficient authority for rapid intervention and veterinary advice. Institutional commitment to veterinary care is clearly in place and consistent with current best practice in veterinary medicine.

- Housing & Husbandry: Housing and husbandry conditions shall ensure that the basic needs of animals are fulfilled unless required by the objective of an experiment that is unavoidable and can technically and scientifically not be achieved in any other way. The basic needs of animals are species specific and entail at least: species adapted temperature, humidity, and noise; nutritious food and clean water; safe shelter; adequate and species specific stimulation; species specific environmental conditions that allow setting-up functional units (meals, sleep, play/explore, defecation, urination); social species socialization in groups according to species specific needs; provision of veterinary care; sufficient rest to maintain physical and mental health; freedom from harm, pain and fear; freedom from disease, injury and disability; freedom of movement with adequate space to execute physiological movement sequences and behavioral patterns.

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- Environmental Conditions: Controlled species-specific environmental conditions ensuring at a minimum that animal discomfort is prevented and that provisions for animal behavioral and physiologic needs are in place.

- Caging and enrichment program: Caging systems must be designed to meet the fundamental behavioral characteristics of each species, and the environmental enrichment program should be designed around the specific social, behavioral, and nutritional needs of every animal.

- Species: With special attention to the specific needs of dogs, pigs and non-human primates, all signatories are committed to applying and promoting the care and accommodation standards that are consistent with those required by the European Union and United Kingdom. If external partners do not meet these welfare and care expectations, they should provide a specific plan indicating how they will implement their intent to meet this goal. These species should be purpose-bred and NHPs should have a pedigree with individual animal history data provided and should preferably be from self-sustaining colonies.

- Post Approval Monitoring: A formal Post Approval Monitoring program of the site-specific animal care program, including regular program review and vivarium walkthroughs is in place and documented to ensure compliance and appropriate animal use. Relevant performance standards are used to advise the staff about the function of the animal care and use program. A qualified person is appointed who regularly oversees performance of animal activities.

- Risk Management: A program of disaster planning and risk management that covers all risks that may impact the welfare of animals or quality of results is implemented and regularly reviewed.

- Incident Reporting: A formal incident reporting process with a clear program for the development and implementation of corrective and preventative actions and parties responsible for implementation of actions is implemented and successes are documented. All incidents with the potential to impact animal welfare, quality of results, or company reputation must immediately be reported to the relevant sponsor.

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[1]Depending on the local regulation, this may be an Institutional Animal Care and Use Committee, an Animal Ethics Committee, an Animal Welfare (and Ethical Review) Body or other comparable body.

[2]Beyond the 3 Rs to a More Comprehensive Framework of Principles for Animal Research Ethics. David DeGrazia and Tom L. Beauchamp. ILAR Journal, 2019, Vol. 00, No. 00, 1–10

Principles of Social Benefit
(1) The Principle of No Alternative Method
(2) The Principle of Expected Net Benefit
(3) The Principle of Sufficient Value to Justify Harm
Principles of Animal Welfare
(1) The Principle of No Unnecessary Harm
(2) The Principle of Basic Needs
(3) The Principle of Upper Limits to Harm

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Signatory Pharmaceutical Companies

	Merck KGaA, Darmstadt, Germany, 2022 September 9th
novo nordisk®	Novo Nordisk, Bagsvaerd, Denmark, 2022 September 9th
sanofi	Sanofi, Paris, France, 2022 September 9th
NOVARTIS	Novartis AG, Basel, Switzerland, 2022 September 9th
Lundbeck	Lundbeck, Copenhagen, Denmark, 2023 March 27th
LEO	Leo Pharma, Ballerup, Denmark, 2023 March 27th

Signatory Contract Research Organizations

BioReliance	BioReliance, a Brand of Merck KGaA Darmstadt, Germany, 2022 September 9th
	EyeCRO, Oklahoma City, Oklahoma, USA 2023 August 11th
preclinics	Preclinics GmbH, Potsdam, Germany 2023 October 17th