ANIMAL PROTECTION

GRI Standards:

103 : Management Approach

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 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

Thierry, Chief Veterinary Officer: *"The year 2020 has been disruptive and full of challenges. Thanks to the robustness of animal care and use programs and the engagement of the staff, the crisis has not jeopardized the welfare of animals. Animal care teams have worked diligently to ensure the best care to animals."*

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1. HIGH STANDARDS BEYOND REGULATIONS

1.1. Animal use is highly regulated

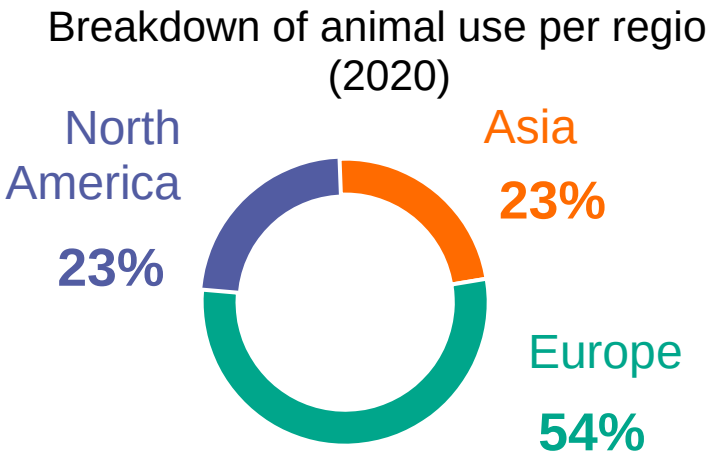
In the last decades, major pieces of regulations and references (Europe, USA, China…) have been set up or updated taking into account the progress in animal welfare knowledge and the increased considerations of the protection of animals by the public (see chapter VII for references).

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. 77% 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.



1.2. Consistent high standards are applied

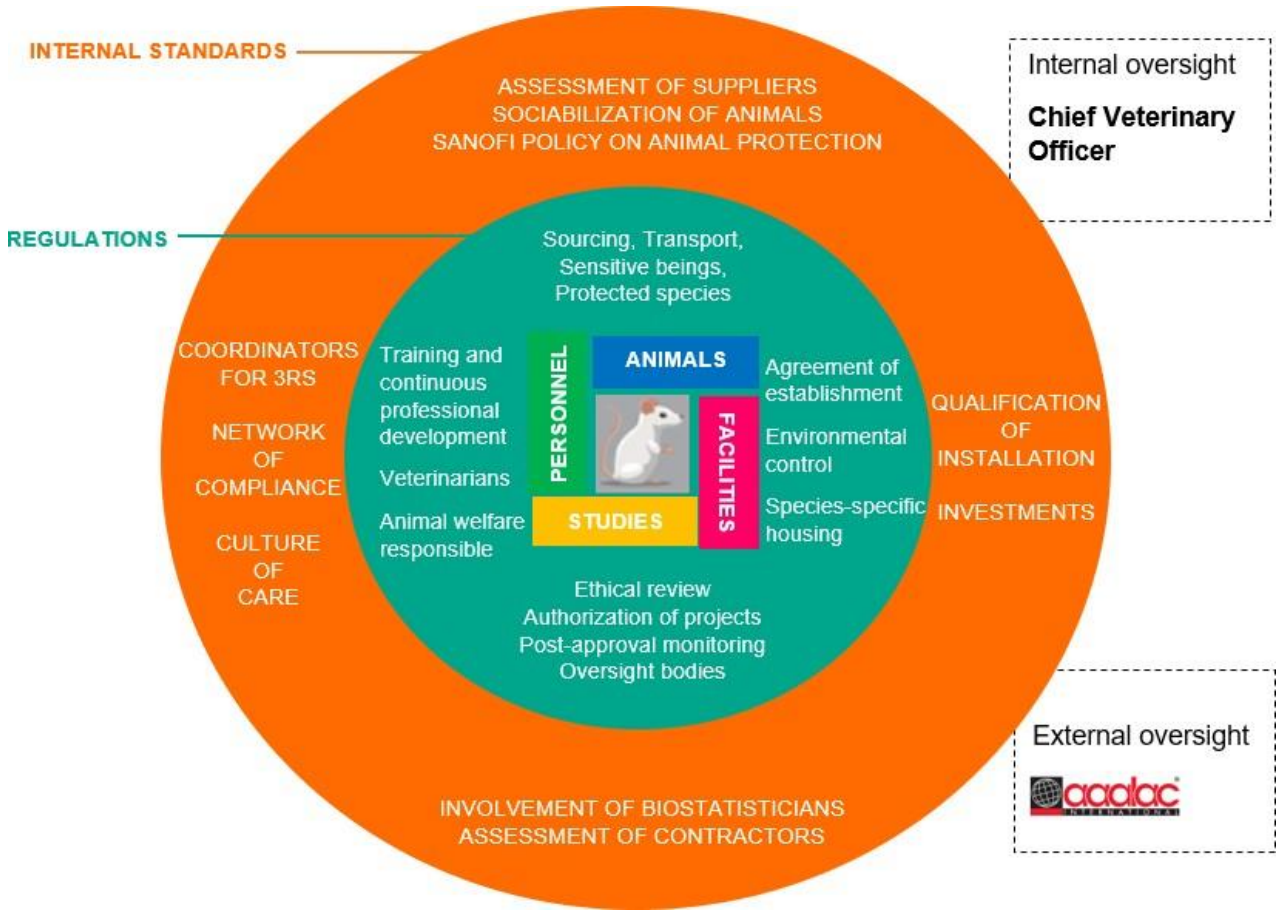
In addition to the legal obligations, Sanofi has set internal standards to align requirements across the world and to ensure high welfare considerations. All Sanofi sites maintain or seek independent accreditation of their animal care and use programs through recognized expert organizations such as AAALAC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

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.

> ***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."*

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.

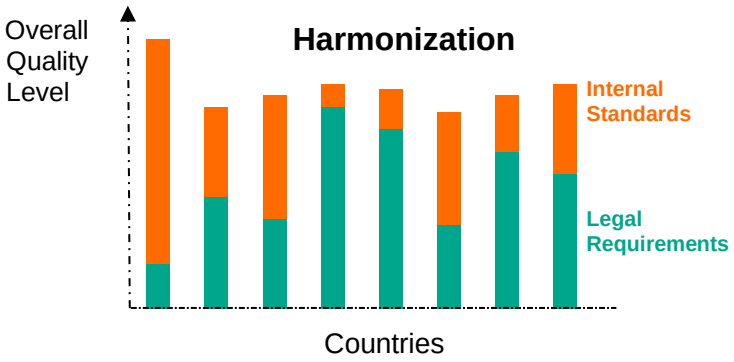
Compliance with regulations and standards are ensured by local dedicated teams under the oversight of the Chief Veterinary Officer and by accreditation body like AAALAC International.



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

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

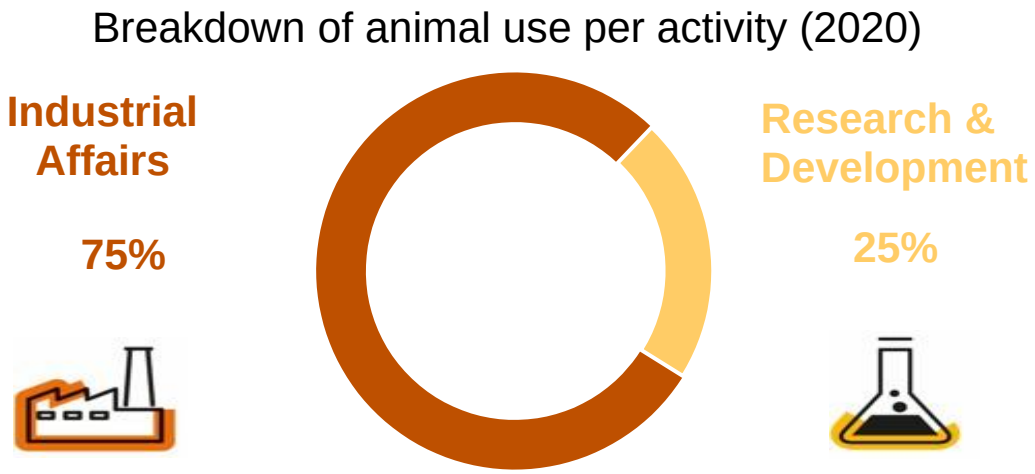
Legal requirements can differ from countries to countries (green bars below); setting internal rules and principles (orange bars) contribute to increase the overall quality towards more harmonized high standards:



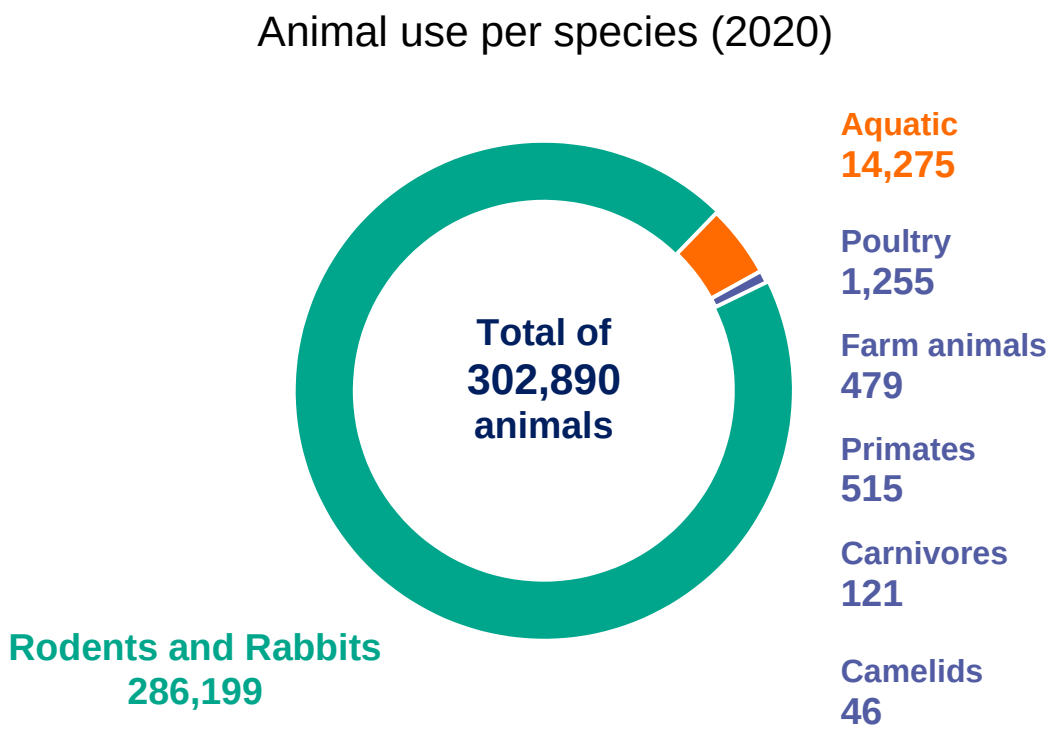
2. USE OF ANIMALS: A NECESSITY FOR THE BENEFITS OF PATIENTS

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).

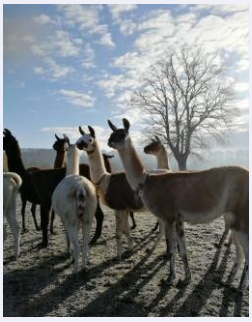
In 2020, 75% of animals were used to support our batch release activity to ensure the safety and efficacy of commercialized vaccines and drugs. 25% of animals have been used for research purposes to better understand diseases and to assess the safety and efficacy of new drugs and vaccine candidates.



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.



Example of therapeutic innovation thanks to animals



The British Pharmacological Society awards Cablivi® (caplacizumab), the first innovative treatment for acquired Thrombotic Thrombocytopenic Purpura (aTTP), Drug Discovery of the Year 2020.

aTTP is a rare and life-threatening blood clotting disorder which can result in severe organ damage and death. It usually presents as a medical emergency where sudden complications like heart attack and kidney failure can occur without warning.

Caplacizumab is the first and only specific therapy approved for the treatment of adults experiencing an episode of aTTP. Caplacizumab uses innovative nanobody technology to provide patients with aTTP rapid protection from blood clots in small blood vessels.

Caplacizumab was developed by Ablynx, which was acquired by Sanofi in 2018. The nanobody technology was originally discovered following identification that Camelidae (e.g. camels and llamas) possess fully functional antibodies which consist of heavy chains only and therefore lack light chains. Due to their small size and unique structure, nanobodies are ideal building blocks which are small, robust and easily adaptable, resulting in a targeted biological therapy.

3. A COMPANY-WIDE POLICY ON ANIMAL PROTECTION

In January 2021, animals are used at Sanofi in 16 sites located in 8 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.

3.1. Strong commitment to the 3Rs

The 3Rs:

- Replacing use of animals with any other methods when a non-animal method is feasible and accepted,
- Reducing the number of animals necessary to ensure reliable, quality scientific results,
- Refining techniques to promote animal welfare and minimize pain and distress.

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 projects 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.

However, a strategy, relying on regulatory sciences, translational medicine, and breakthrough innovation, has been developed to increase the proportion of non-animal methods, including clinical research, to significantly reduce the necessity to use animals in research and production.

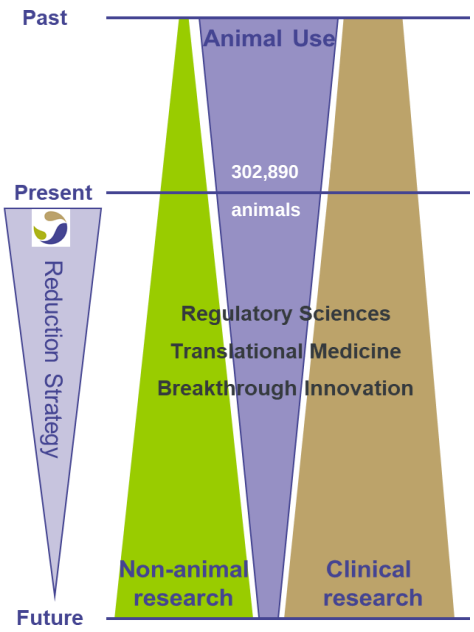


Illustration of the Integrated Research and Testing Strategy towards the relative reduction of animals:

Several decades ago, the development on new drugs and vaccines mainly relied on animal studies. Nowadays, all the projects require and use non-animal data, in vivo studies, and clinical research to assess the safety and the efficacy of new drugs. We strongly believe that, based upon the development of regulatory sciences, translational medicine and innovation, reduction of the ratio animal studies versus non-animal methods is effective and it will accelerate.

3.2. Ethical oversight

When animals are required to help to ensure 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. 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. 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 are endorsed by Sanofi Bioethics Committee (BEC).

Policy	Description	Approved by BEC
• Protection of animals	States a global quality directive that any person, working under the responsibility or on behalf of Sanofi at all sites, must comply with when using animals.	November 2016 Revised May 2018
• Genetic Modifications to Produce Animal Models of Human Disease	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 represent a significant refinement in the scientific development of disease models.	December 2018
• 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.	December 2018
• Reporting of animal welfare concerns	To ensure that the welfare of laboratory animals is fully implemented, any employees should feel free to express any concerns 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: guidance to provide eligibility criteria for adoption*	December 2019
• Sponsor's responsibilities for externalized animal services and studies	To state 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. *Appendix: guidance to help the external partner implementing Sanofi standards related to animal use*	April 2020

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 consider the ethical dimension of operational decisions of remediation plans.

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 improve transparency regarding animal use and the Integrated Research and Testing Strategy (3Rs)
- To continuously assess the compliance with the Sanofi Policy on the Protection of Animals, beyond regulatory inspections and accreditation and to manage the integration of new units acquired by Sanofi
- To ensure support to Sanofi sites by contributing to AAALAC accreditation
- To monitor the compliance of third parties (breeders, contract research organizations, not-for-profit institutions)
- To contribute to regulatory debates, especially those related to the implementation of the European Directive, and initiate a culture of openness
- To address societal concerns about the use of animals through the global Advisory Body on Animal Ethics.

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"*

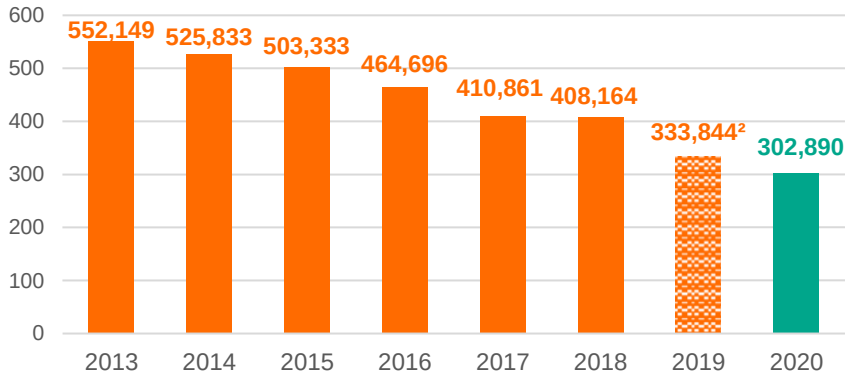
5. ACHIEVEMENTS ABOUT THE 3Rs AND ANIMAL WELFARE

There are many examples of outreach within Sanofi and with external partners to increase awareness of the 3Rs. In order to illustrate this, several evidences of commitments and achievements are shared below.

5.1. Constant decrease of use of animals within our facilities

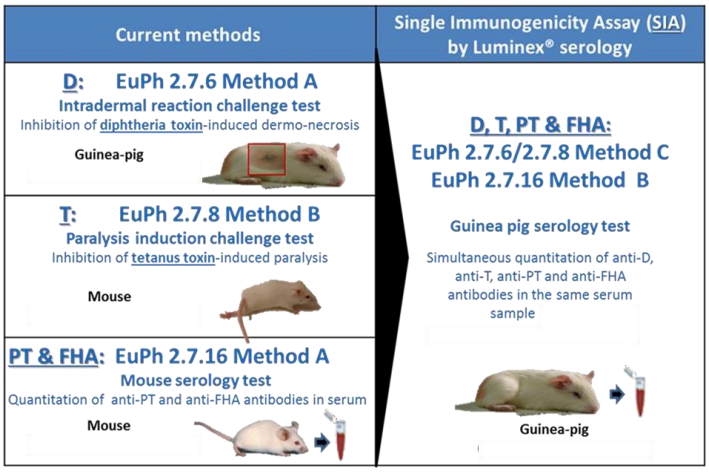
Every year, a comprehensive mapping of animal use in Sanofi facilities is conducted, evidencing a constant decrease of use of animals.

Evolution in numbers of animal used across the Sanofi Group, 2013-2020[2]:



In 2020, Sanofi has maintained its reduction of animal use. Number of animals used on Sanofi sites represents 302,890 animals in 2020. In comparison with the 2019 data (covering a period of 11 months - See footnote[2]), the decrease is of 9% (or 17% if we consider full-year data for 2019).

Since 2013, the drop is of 45%, similar in R&D and in Industrial Affairs. The figure represents an evidence of the continuous effort towards the overall reduction. As an example of the long-term investment in reduction strategy, noteworthy is the change of the potency assays for multivalent pediatric vaccines. 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 extend to the other vaccines and 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.



5.2. Scientific advancements as drivers of the 3Rs

Improving the scientific outcomes is the main priority. This objective converges with ethical principles, i.e. the overall reduction of animal use and more refined models. Thanks to new technologies, regulatory evolution, many initiatives are in progress and some examples of achievements illustrate below the diversity of projects.

[2] In 2019, reporting period has changed to adjust to legal requirements for public disclosure of extra-financial performance indicators. The new period of reporting will be from the 1st of December till the 30th of November. 2019 is the year of transition and the data are from the 1st of January to the 30th of November. If we extrapolate the 11-month data (333,844 animals) to a 12-month period, the estimate is about 365,000

- **Replacement thanks to Artificial Intelligence**

Juliette, R&D, France: "Looking for reduction approaches, I've discovered the world of the 'Non-Animal Methods'. It's a huge sector in Sanofi which needs to be better known. The potential for future development is impressive with rapid improvements of model relevance."

At Sanofi, machine learning is a long-standing expertise. Systematic exploitation of bioassay and ADMET data (Absorption, Distribution, Metabolism, Excretion and Toxicity) guides multidimensional optimization. The historic knowledge hence gathered serves future projects.
Now, multiple In-Silico Models replacing In-Vivo assays are also available for ADME and Safety, such as hERG channel, Nav1.5 and other, Cav1.2 and other, phospholipidosis, genotoxicity (MNT), organ toxicity and phototoxicity.
Combined in vitro and in silico models can predict blood-brain permeability similarly to in vivo studies. A successful ranking of compounds for in vivo pharmacokinetics studies is thus determined, related to brain penetration. This significantly reduces the number of compounds undergoing in vivo studies afterwards.

- **Replacement of animal-derived reagents**

Animal tissues (Blood, cells, organs and tissues, antibodies…) represent important reagents for laboratory activities. Their replacement by non-animal derived source is considered whenever possible. As an example, the replacement of Limulus amaebocytes by recombinant proteins:

Endotoxins, heat-stable lipopolysaccharides from Gram-negative bacteria, are potential contaminants that can be introduced during manufacturing of pharmaceutical products, including vaccines. Parental pharmaceutical products undergo endotoxin testing because endotoxins are pyrogenic in humans and can induce severe physiological reactions. Currently, animal-derived Limulus amoebocyte lysate (LAL) assays are widely used. This requires blood sampling in horseshoe crabs, an endangered species.

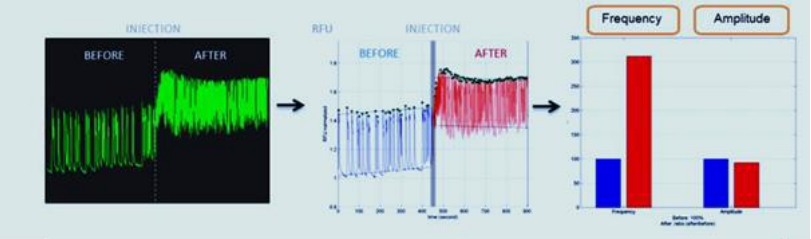
To address the biodiversity issue, assays using recombinant Factor C (rFC), a non-animal-derived reagent, have been proposed as alternatives. The strategy of the vaccine division is to replace the LAL assays by the rFC assay. As some components in the matrices of pharmaceutical products can interfere with these assays, we have compared two LAL- and two rFC-based assays for endotoxin detection in four complex human vaccine matrices. We have demonstrated that both LAL and rFC assays are adequate for testing and releasing four vaccine products. The rFC assays offer a number of benefits (lot-to-lot consistency, more robust, less interference, security of supply), including compliance with the principles of the 3Rs, i.e., replacement, reduction and refinement of animal testing by safeguarding animal welfare and promoting more ethical and sustainable use of animals for testing. After full validation, pending acceptance by drug agencies, they could be considered as suitable replacement assays for the detection of endotoxin in the manufacturing processes of vaccines.

Last minute…

Sanofi scientists have received the Frederick Simon Award for the best Scientific Publication 2020 published in the PDA Journal of Pharmaceutical Science & Technology for the publication "Comparison of Limulus Amoebocyte Lysate and Recombinant Factor C Assays for Endotoxin Detection in Four Human Vaccines with Complex Matrices".

- **Replacement in Safety Assessment - Organoids**

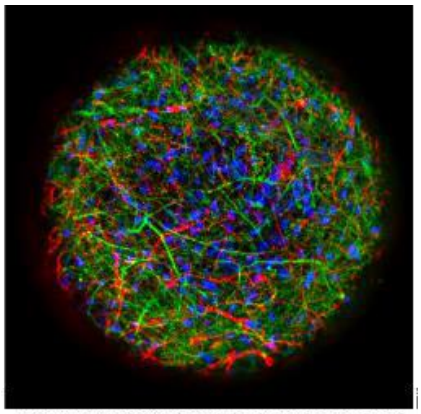
Investigative Toxicology aims at identifying and predicting adverse functional effects prior to first in human studies. The assessment of neurotoxicity remains a major scientific challenge due to the complexity of the central nervous system. Current strategies to evaluate toxicity of chemicals and drug candidates are predominantly based on ex vivo or in vivo animal studies These models have limited predictability for neurotoxicity in humans and are not amenable to high throughput testing. Several non-animal models have been developed and assessed.



Excitatory effect of 4-Aminopyridine, a potassium channel blocker that lead to depolarization state.

An in vitro model based on mice primary neuroglial cultures, able to form a functional network for the explorations of the epileptogenic/ seizurogenic potential of drug candidate which is one of the most major adverse drug reactions causing drug marketing failure. This development has been conducted in collaboration with Cellular Dynamics International and Axiogenesis.

The development of neurotoxicity models based on human iPSC derived neurons in Mimetas' OrganOPlates™ and in MicroBrain 3D©, StemoniX,Inc. OrganoPlate™ is a microfluidic platform which enables high throughput culture of miniaturized organ models. A mixed population of GABAergic and glutamatergic neurons with supporting astrocytes has been cultured in 3D in the OrganoPlate™, closely representing the physiology of the human brain. In Microbrain 3D©, the organoid model has been associated with fast kinetic fluorescence imaging to measure amplitudes and frequencies of the Ca2+ oscillations. The effectiveness of automated imaging assays combined with the organotypic nature of human induced pluripotent stem cell (iPSC)-derived cells opens new opportunities to evaluate the potential drug toxicity of our drug candidates.


Human iPSC-derived neural spheroids composed of a co-culture of active cortical neurons

The in vitro models of the human brain, especially the microphysiological system, reduces the use of animal models has the potential to better predict adverse effects in humans hence improve clinical development success. Up to now, to limit biased conclusions, the results should be considered in respect with other read-outs in an integrated approach.

- **Reduction by using of one species for safety assessment**

An international expert working group representing 37 organisations, including Sanofi collaborated in a data sharing exercise to evaluate the utility of two species within regulatory general toxicology studies. Anonymised data on 172 drug candidates (92 small molecules, 46 monoclonal antibodies, 15 recombinant proteins, 13 synthetic peptides and 6 antibody-drug conjugates) were submitted by 18 organisations. The main focus of this comprehensive review was to explore whether both a rodent and a non-rodent species are required for general toxicology testing or if opportunities to use or reduce to a single species at different stages of development are being fully exploited.

The data did show that for a lot of the compounds that used two species for the first- in-human studies, the toxicities were similar, suggesting that only one species is really required for that stage. This option is already accepted by regulators for biotherapeutic drugs. We hope this paper will

encourage this option to become more widely adopted, and this will be the immediate impacts from this work. For other drug modalities (such as small molecules), changes would be required within regulations and it is likely additional data would be required to support this. Therefore, this is a long-term goal for Pharma Industry and may take many more years before impacts are apparent in practice.

- **Refinement and Science – Model predictivity by using humanized mice**

Monoclonal antibodies (mAbs), nanobodies and Fab fragments are among the fastest growing and most effective therapies for myriad diseases. Multispecific antibodies are an emerging class of novel therapeutics that can target more than one modulator per molecule. The combination of different binding affinities and target classes within multispecific antibodies confers unique pharmacokinetic (PK) properties. Despite their superiority for therapeutic applications, the short serum half-life and rapid renal clearance has hampered their further development to enter clinical trials.

Sanofi scientists have undertaken to design and generate more predictive model through transgenic technologies. This mouse model expresses the human neonatal Fc receptor (FcRn) genes would present an accurate and predictive model for PK profiling of antibodies and other therapeutic proteins. The next step is to characterize and validate the model with reference compounds and establish a standard protocol for conducting PK studies. This transgenic mouse model would also enable prediction of half-life and linear clearance of mAbs and multispecific antibodies in NHPs to guide the design of further pharmacology/safety studies in this species. Our goal is to demonstrate the relevance of the model in predicting in vivo half-life of engineered antibodies, and to show the superiority/equality of the humanized model to predict primate or human PK.

- **Refinement and Welfare – Housing enclosures for rabbits**

Rabbits used by the vaccine have been housed in socially compatible groups in connected cages.

To improve our rabbits housing conditions, several prototype modules have been developed. Ground-floor housing have been initially tested but this type of housing was not compatible with the type of research. A team of animal technologists, caretakers and the designated veterinarian has worked with a supplier for 3 years to design the housing module.

In the final version modules, rabbits are group-housed on solid bottom floor, with bedding and automatic water delivery system. As enrichment, a feeder with non-compacted hay, hiding huts and little toys are provided. Connecting trapdoors between modules allow us to increase the group composition.

The improvement of the animal behaviors, as well as ergonomic working conditions, has been observed by animal caretakers: animals are more relaxed and cooperative. The team has been immediately convinced by the values of these new housing devices. The next step is to consider the modules to house other species as guinea pigs.

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... With the acquisition of Ablynx®, llamas and alpacas are now part of the long list of adoption with many great stories. A brochure in 3 languages has been drafted to help families to take care of their newly adopted llamas.

Noteworthy in 2020 is the socialization program for dogs initiated by animal care takers and veterinarians to facilitate the new social life of beagles. Having a formal program has greatly improved the rapidity for the animals to adapt to their new environments.

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. With the aim of creating adoption solution for primates, Sanofi has sponsored Le Zoo-Refuge de la Tanière, France, to build new large enclosures. A group of 7 primates has been transferred to the 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."*

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

During its 3 first years of activity, the Advisory Body on Animal Ethics (ABAE) has issued 6 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.

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."*

In 2020, a policy on Sponsor's responsibilities for externalized animal services and studies has been approved by the bioethics committee. Its purpose is to state 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. In addition to the animal welfare assessment of external partners involving animals covered by a global procedure, the document highlights several commitments of Sanofi scientists:

- To ensure the absence of relevant non-animal methods to achieve the scientific objectives;
- To establish the scientific merit and legal obligations of using animals;
- To check that the contractor has been approved by animal welfare experts;
- To provide sufficient information to carry out efficient ethical assessment of the project, including the 3Rs by the Animal Ethics Committee of the partner;
- To report any animal welfare incidents or concerns.

Summary of Sanofi position on the use of non-human primates:

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 sentiency, 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 centers 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.

In 2021, the members of ABAE will finalize discussion on 2 additional 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.

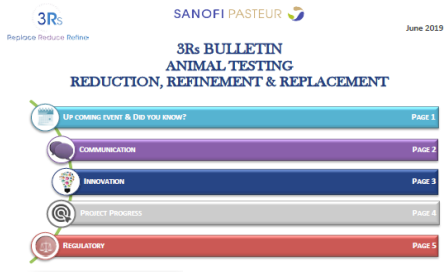
5.5. Outreach and education

In November 2020, Sanofi has globally participated to the International Biomedical Research Awareness Day; 13 sites in 7 countries have organized events for the staff and site personnel, most of them being virtual. About 400 people have been able to interact with animal care professionals and to ask any questions about the daily care and use of animals.

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."*

To develop ethics competencies, the Advisory Body on Animal Ethics has initiated a series of webinar for members of animal ethics committees. The first session has focused on the non-animal methods used and in development by Sanofi.

For scientific and technological developments, the R&D Department of Translational In Vivo Models has organized webinars for scientists and technologists with key external speakers. Bringing up-to-date expertise to the scientists of Sanofi helps maintaining the robustness of preclinical packages and the implementation of good science.



To foster the 3Rs initiatives, the vaccine division of Sanofi issues a periodic newsletter on the 3Rs. The bulletin, open for internal distribution is drafted by the 3Rs core team and scientists contribute to articles. The news cover projects and achievements in R&D and in Quality Control in the field of vaccines, as well as the legal aspects of the acceptance of non-animal methods.

Active collaboration with other pharmaceutical companies and competent authorities fosters the development of good practices and alternative approaches across biomedical research. For example, Sanofi contributed to the last version of the EFPIA brochure: "Putting animal welfare principles and 3Rs into action", 2019 and is participating to the 2021 EFPIA Brochure.

Active participation to collaborative projects will accelerate the development of new technology, like the Microphysiological System (organoid models) working group organized the Innovation & Quality consortium in the US, and the quality of preclinical data, like, the European project EQIPD of Innovative Medicine Initiative.

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; and 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 will be organized by Sanofi R&D. To accelerate the dissemination of 3Rs methods, Sanofi has sponsored a web-based inventory of 3Rs education and training resources developed and maintained by Norecopa, the Norway's consensus platform for 3Rs.

6. INSPECTIONS, ACCREDITATIONS, AND AUDITS

6.1. Inspections in 2020

Regulatory inspections at Sanofi's animal facilities are performed on a regular basis by national and local authorities and results are in compliance with animal welfare laws and regulations; no major issues have been reported.

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 reached one year in advance: all Sanofi sites have been successfully accredited by AAALAC International in 2019.

6.2.1. New accreditation

In 2020, Principia, a biotech company has been acquired by Sanofi. Its animal care and use program is going to be assessed by animal welfare experts of Sanofi.

6.2.2. Reaccreditations

Two sites have been accredited in 2020:

- Sanofi R&D Vitry, France
- Sanofi Pasteur India (official letter received in February 2021)

Due to COVID-19 crisis, the reaccreditation of Sanofi Pasteur France (3 facilities) have been postponed to the first quarter of 2021. This delay does not jeopardize the status of the sites and the quality of animal care and use program.

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."*

6.3. Contract research organizations and breeders evaluated in 2020

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 2020, 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 met the challenges and worked together, thus ensuring that critical studies were initiated, and tight timelines were met with confidence regarding animal welfare."

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.
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