ANIMAL PROTECTION

GRI Standards :

N/A

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: *"When looking at all the achievements and progresses in 2019, I'm really impressed by the engagement and the passion demonstrated by the professionals – Globally!*

Enjoy this new version of the factsheet."

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1. HIGH STANDARDS BEYOND REGULATIONS

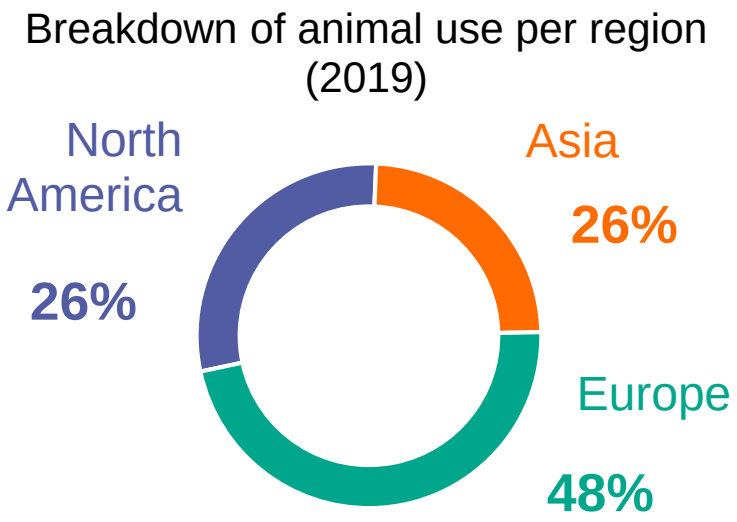
In the last decades, major pieces of regulations and references (Europe, USA, China…) have been set up or updated taking into account the progress in animal welfare knowledge and the increased considerations of the protection of animals by the public (see chapter VII for references).

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
- Implementation and monitoring of the 3Rs
- Creation of 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. 74% 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.



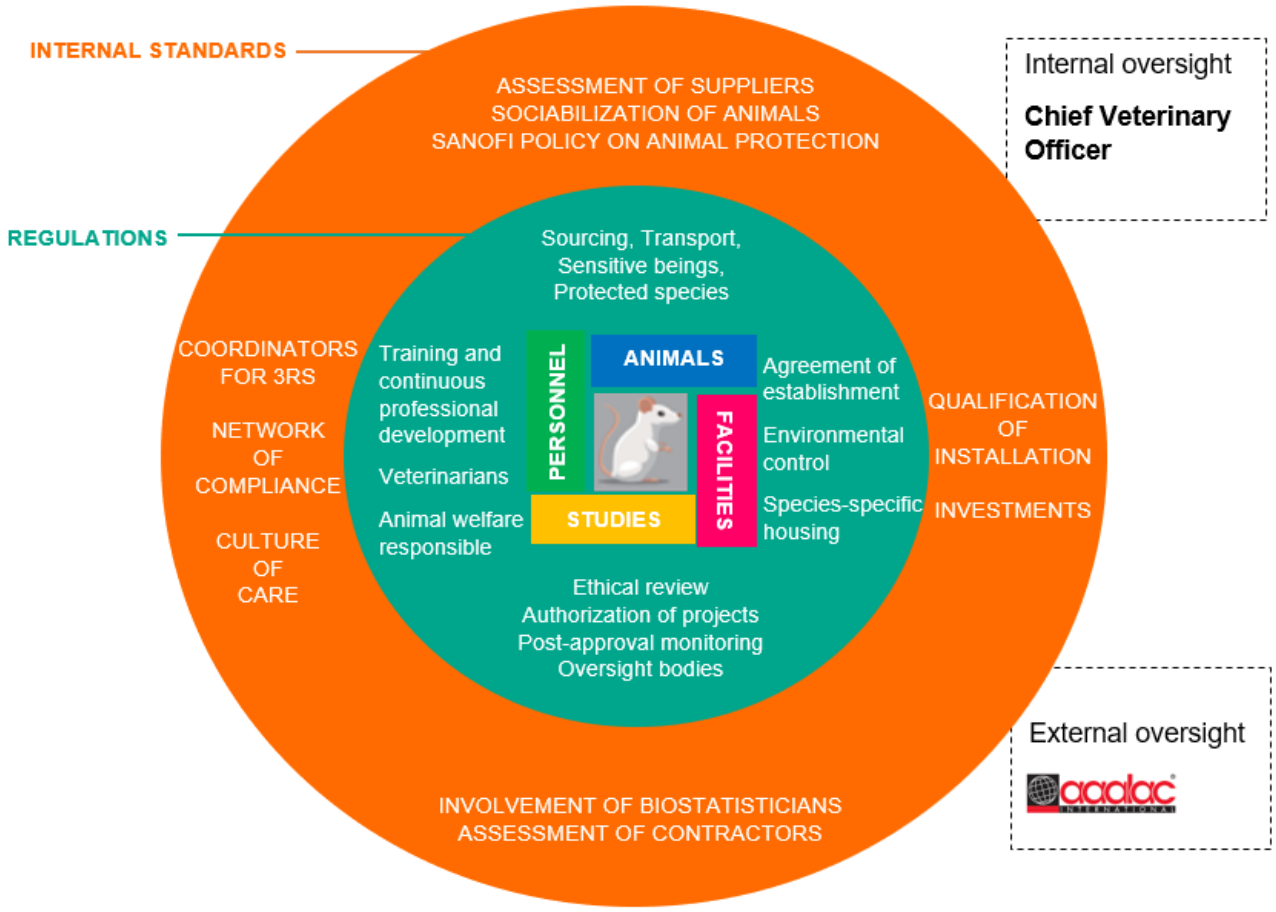
Moreover, in addition to the legal obligations, Sanofi has set internal standards to align requirements across the world and to ensure high welfare considerations. All Sanofi sites maintain or seek independent accreditation of their animal care and use programs through recognized expert organizations 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.

1.1. Animal use is highly regulated

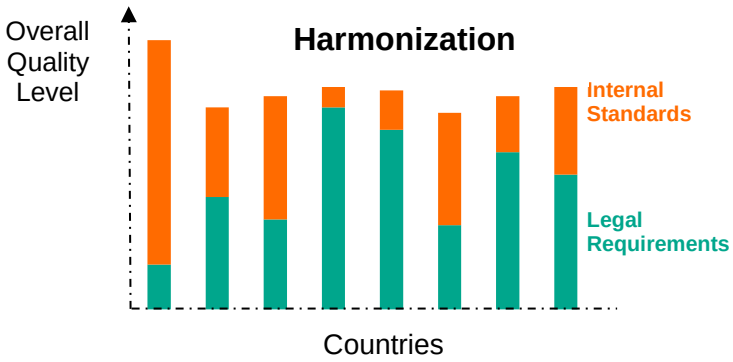
Regulations constitute a first layer of obligations (black circle below) which are completed by specific standards developed by Sanofi (the second layer, the red circle). The second layer represent how we globally approach high quality standards and represent a standardization across the sites.

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:

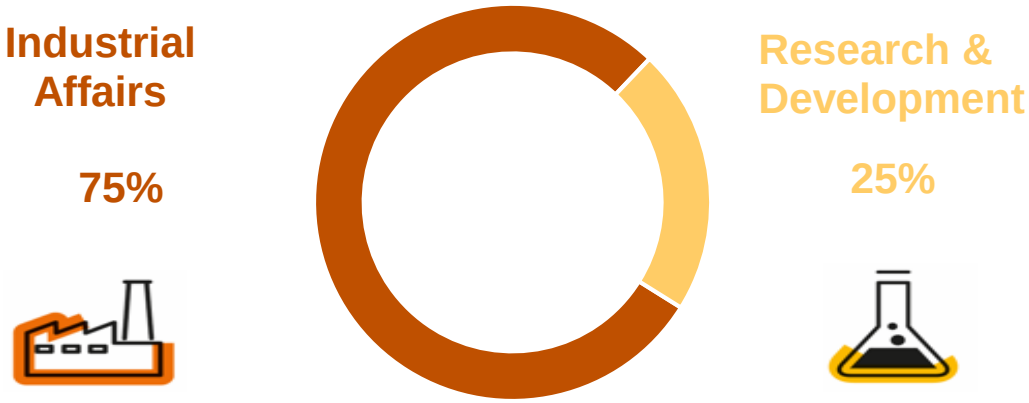


2. USE OF ANIMALS: A NECESSITY FOR THE BENEFITS OF PATIENTS[2]

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).

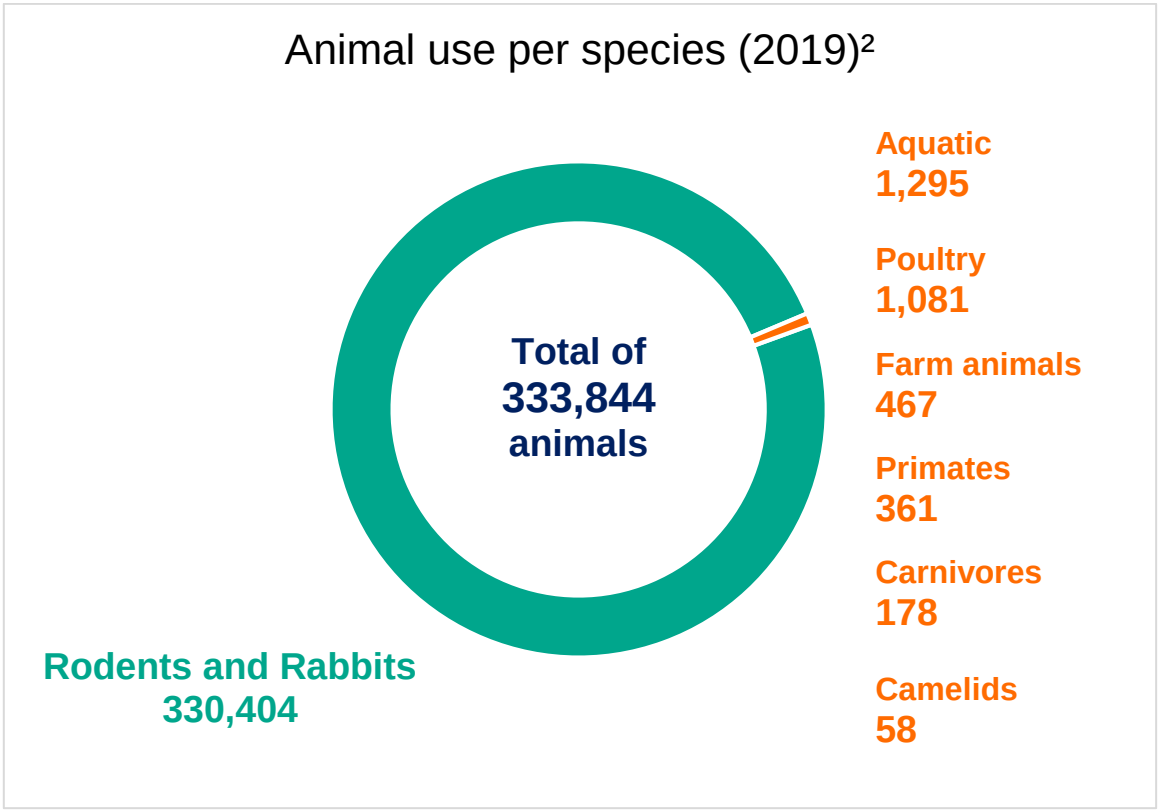
In 2019, 75% of animals were used to support our batch release activity to ensure the safety and efficacy of commercialized vaccines and drugs. 25% of animals have been used for research purposes to better understand diseases and to assess the safety and efficacy of new drugs and vaccine candidates.

Breakdown of animal use per activity (2019)[2]



[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.*

Most animals used (99%) are rodents and rabbits. 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.



3. A COMPANY-WIDE POLICY ON ANIMAL PROTECTION

Animal are used at Sanofi in 17 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. 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 reduce significantly the necessity to use animals in research and production.

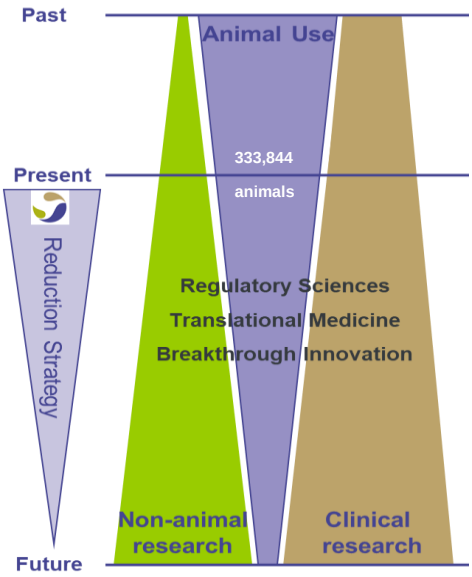


Illustration of the Integrated Research and Testing Strategy towards the relative reduction of animals:

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. To this end, it meets quarterly and has developed global positions, for instance on the use of non-human primates in research and quality control and on the use of genetically-modified animals. Those positions are endorsed by Sanofi Bioethics Committee.

The Chief Veterinary Officer drives the consistency and cross-fertilization between the veterinarians and animal ethics committees at all sites.

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 and compliance of third parties (breeders, CROs, 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"*

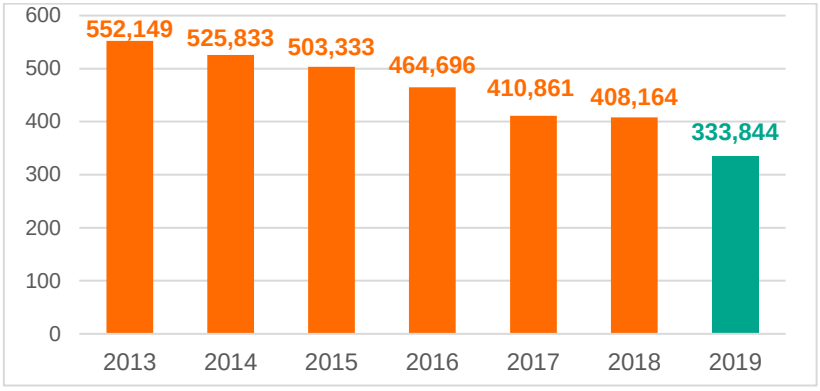
5. ACHIEVEMENTS ABOUT THE 3Rs AND ANIMAL WELFARE

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, 2013-2019:



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. Over a period of 11 months, 333,844 animals have been used. If we extrapolate the data on a 12-month period, the estimate is about 365,000; this represents a decrease of 10% over 2018.

In the period 2013-2018, use of animals in-house has steadily decreased (26%). The decrease is partially due to paying active attention to the 3Rs, with concrete achievements in the quality control of vaccines prior to injection to patients, and to the focus of certain internal research and testing programs. In 2018, the acquisition of 2 companies with preclinical facilities has increased the baseline. It is one of the reasons why the decrease of the use of animals between 2017 and 2018 has slowed down.

As a positive outcome of those reduction efforts, the animal facilities of Industrial Affairs in Frankfurt were closed in June 2018. A cell-based assay has been fully implemented to replace the bioidentity assay for batch release of insulin glargine in rabbits.

Replacement of the rabbit assay for insulin bioidentity:

At the Frankfurt site, Research and Development partnered with Industrial Affairs to develop and validate an in vitro test that has replaced an in vivo test in rabbits. This project involved an extensive effort over several years to ensure equivalency of the test. This new test eliminated the need to use over 2,000 rabbits every year. In late 2016, the team was awarded the Hessian Animal Welfare Research Award from the Hessian Ministry of Environment, in Wiesbaden, Germany and in 2017, the project has been awarded by the Sanofi CSR Award for the 3Rs.

Based on these groundworks, in 2017, the US Pharmacopeia published a new testing guideline for comment with the cell-based bioidentity assay as an alternative to the rabbit bioassay, which will become available to any insulin manufacturers.

While reducing the number of animals, Sanofi is still investing into new facilities: A new building, more than 25 million euros invested, in Marcy-L'Etoile, France has been built to offer better housing conditions for the animals and better protection of the environment. With the closure of 2 older buildings, the total capacity will even decrease for the quality control of vaccines.

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.

- Full replacement by an in vitro model

Each vaccine batch of inactivated poliovirus (IPV) must be tested to ensure completeness of inactivation. The historical method uses primary monkey kidney (PMK) cells. Quality Control team had successfully developed, validated and implemented an alternative assay using an L20B cell line to replace the need for monkey kidneys. The method was transferred to other sites and successfully validated for polio vaccines.

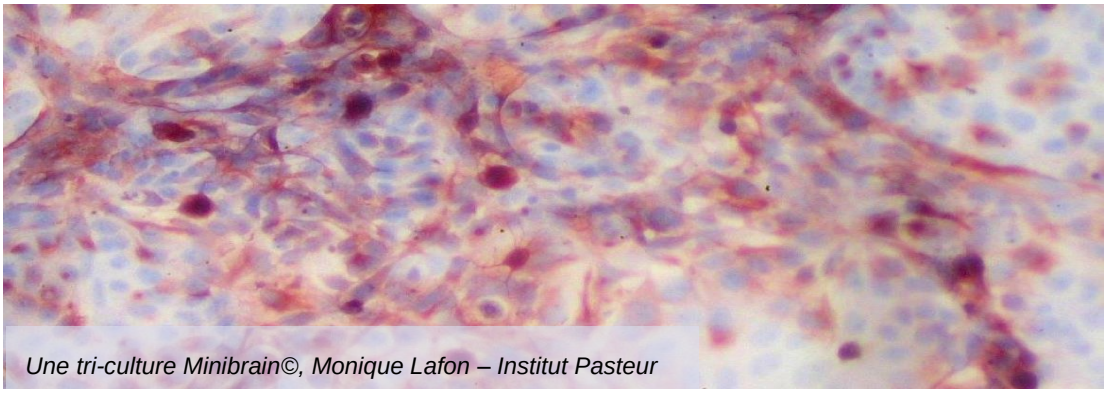
> ***Sarvesh, Quality Control, India:*** *"It's feeling great to work towards reduction of animals by using Single Dilution Assay for Pentavalent vaccine. It motivates us to look for more opportunity for testing more batches with less number of animals and save more children by vaccination."*

- Waiving assays for the quality control

The General Safety Test (GST) in the US Pharmacopeia, also called the Abnormal Toxicity Test (ATT) in Europe, is a test historically intended for the detection of extraneous toxic contaminants in manufactured lots of biologics intended for human use, and its implementation pre-dated Good Manufacturing Practices and the introduction of robust in-process controls and pharmaceutical quality systems. These tests are now generally regarded as lacking scientific rationale, an unnecessary cost and use of animals, and of no added value for the quality control of vaccine batches. As such they are being abandoned in many regulations globally: Sanofi Pasteur goal is therefore to remove these tests from all product licenses.

- Exploring new non-animal models to address scientific questions

Yellow fever live-attenuated vaccine must be evaluated for risks of neuro-virulence using in vivo non-human primate testing, currently the only approved method. The cost and predictive efficacy of this in vivo assay, as well as the principle of the 3Rs, call for alternative methods to be developed. A collaborative project between Sanofi Pasteur and the Pasteur Institute led to a new in vitro compartmentalized system mimicking the blood-brain barrier as well as the cerebral compartment, which allows isolation of a neuro-invasive subpopulation from an initial population followed by its amplification in the cerebral cell culture. Moreover, yellow fever virus strains specific biomarker signatures were identified. As a follow-up of this project a PhD job just began, to compare the in vitro biomarkers with the in vivo situation, and to investigate the neuro-invasiveness mechanisms. As proof of the success and interest of this project, it led to several communications, internally and at international meetings. Beyond the replacement of the in vivo test for yellow fever vaccines, this project will provide new tools for the study of new vaccines and even new therapeutic drugs.



Une tri-culture Minibrain©, Monique Lafon – Institut Pasteur

- Reduction supported by technology development

Micro-sampling is a method to collect a very small amount of blood (typically ≤50 µL) used to measure concentrations of a drug and/or its metabolites, and subsequently calculate the appropriate pharmacokinetics parameters.

Minimizing the volume of blood collection can reduce pain and distress in animals and improve the welfare (refinement) of rodents and non-rodents. It can also reduce or eliminate the number of required animals in satellite groups when used in rodent studies (reduction) whereby drug kinetics assessment is conducted in main study groups. The benefit is particularly notable for mice, since a significant number of these animals have been generally used in satellite groups.

For evaluation at early stage (discovery), micro-sampling method allows serial design studies in rodent (mice and rat) and the possibility to have a full pharmacokinetics profile on the same animal (inter-individual variability assessment). Along with the reduction of animals needed, this approach also improves the statistical power of the study performed.

- Refinement of experimental procedures:

Development of a device for food restriction in small rodents: automated withdrawal of food

In research in diabetes, animal food restriction for a long period is needed doing some physiological experiments. Usually this is done manually late in the afternoon of the previous day. The 16 hours without food are discussed by the Animal Welfare Body as being too much in mice and cause unneeded stress. Fasting the animals at the day of experiment is incompatible with working time of the staff and duration of the tests. The idea has been suggested to build a shelf with a mechanism which elevates the food racks out of the home cages at selectable time point. It should be usable for different species and respectively for a large collective of animals.

Considering the requirements of animal healthcare and laboratory safety together, a system using 16 rodent cages with an electric engine elevating the food racks at any time has been developed. Since 2015 the system is used successful in diverse laboratories and the fasting duration has been adjusted to be minimal without stress to the animals.

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.

For many years, Ablynx® has set up a robust adoption program to ensure the good quality of life of camelids after their stay in our facilities.

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."*

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.

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.

5.4. Policies issued in 2018 and 2019 by the Advisory Body on Animal Ethics

During its 2 first years of activity, the Advisory Body on Animal Ethics (ABAE) has issued 4 corporate policies.

James, Ethics Committee Chair, US: *"It is a great group of people striving to tackle difficult topics, understanding the work to be done to protect the animals we are responsible for"*

Two policies were approved by Sanofi Bioethics Committee in December 2018: Genetic modification to produce animal models of human disease and the ethical use of non-human primates in research and quality control of drugs and vaccines.

Two others were approved in December 2019: Rehoming of animals used in research and production (see section above 5.3) and Reporting animal welfare concerns. T
he latter describes the possibility to any employees to report anonymously animal welfare concerns and to make any suggestions contributing to the improvement of animal wellbeing. All Sanofi sites must have a process in place and must inform employees about the possibility of reporting. Sanofi will investigate any allegation of failure to abide by its principles. If substantiated, such action will provide grounds for disciplinary action. No employee will be discriminated against or subject to reprisal for reporting concerns regarding animal use, care and welfare, or any potential deficiencies or possible violations.

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.

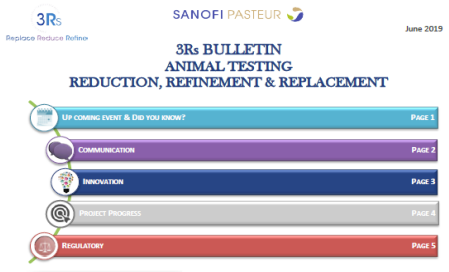
In 2020, the members of ABAE will finalize discussion on an additional new policy about addressing responsibility of Sanofi sponsors for animals used by external partners.

5.5. Outreach and education

In April 2019, for the first time, Sanofi has participated to the International Biomedical Research Awareness Day; 11 sites in 5 countries have organized events for the staff and site personnel. More than 600 people have been able to interact with animal care professionals and to ask any questions about the daily care and use of animals.

BRAD
Biomedical Research Awareness Day

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."*



In order to have a follow-up of all the initiatives the vaccine division of Sanofi issues a quarterly newsletter on the 3Rs. The news cover projects and achievements in R&D and in Quality Control in the field of vaccines.

As science is the driver for the implementation of new technologies, conferences on the human organoid models (3D cell culture, organ-on-a-ship) has been organized in the US, in German and in France. Scientists for different therapeutic areas were trained about the in vitro technologies using human cells.

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 new version of the EFPIA brochure: "Putting animal welfare principles and 3Rs into action", 2019. 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 European Congress on alternatives, EUSAAT, where Sanofi scientists have contributed through oral talks and posters.

6. INSPECTIONS, ACCREDITATIONS, AND AUDITS

6.1. Inspections in 2019

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. All Sanofi sites have been successfully accredited by AAALAC International -one year in advance.

6.2.1. First accreditations

In 2019, the 2 last sites, Ghent in Belgium and Shenzhen in China, have been obtained their first application.

6.2.2. Reaccreditations

Two sites have been accredited in 2018:

- Sanofi R&D Chilly-Mazarin, France
- Sanofi R&D Montpellier, France

Gabi, R&D, veterinarian, Germany: *"I am proud to work towards ensuring that all Sanofi Sites are going the extra step to achieve excellence in animal care by voluntary accreditation process."*

In 2019, 4 accredited units have been inspected to renew their accreditation:

- Sanofi Pasteur, IA, Toronto, Canada
- Sanofi R&D Frankfurt, Germany
- Sanofi and Sanofi Pasteur R&D Boston Hub, US
- Sanofi R&D Vitry, France

6.3. Contract research organizations and breeders evaluated in 2019

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.

Wanyong, R&D, China: *"At the global coordination, we team-up to ensure compliance, good animal welfare, and quality science, wherever the partners are located."*

In 2019, 35 contract research organizations (CROs) or academic institutions and 10 vendors underwent evaluation and were determined to meet requirements to comply with Sanofi's animal protection principles.

End of 2019, an undercover investigation has revealed unethical practices in a CRO located in Germany. As those were in total disagreement with our principles and values, the CRO has been immediately excluded of our list of service provider.

7. REFERENCES

- ETS 123—European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, 1986 and its revised appendices, 2006.
- European Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010, on the Protection of Animals Used for Scientific Purposes.
- United States Animal Welfare Act (Title 7 U.S.C 2131–2159) and United States Animal Welfare Regulations, CFR, Title 9, Chapter 1, Subchapter A, Part 1-4.
- Institute for Laboratory Animal Research—Guide for Care and Use of Laboratory Animals (8th Edition, 2011).
- Federation of Animal Science Societies—Guide for the Care and Use of Agricultural Animals in Research and Teaching (3rd Edition, 2010).
- EFPIA: Putting animal welfare principles and 3Rs into action. European Pharmaceutical Industry 2019 Report Update.