Modern science for 3Rs alternative approaches and better quality control of human vaccines

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SANOFI PASTEUR

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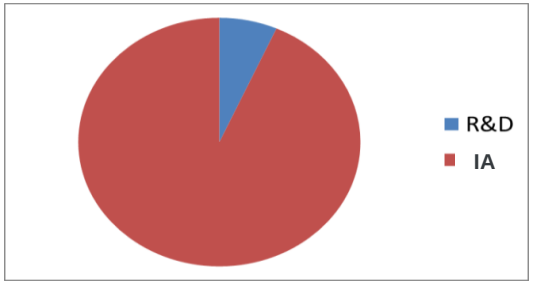
Current animal use for Vaccines

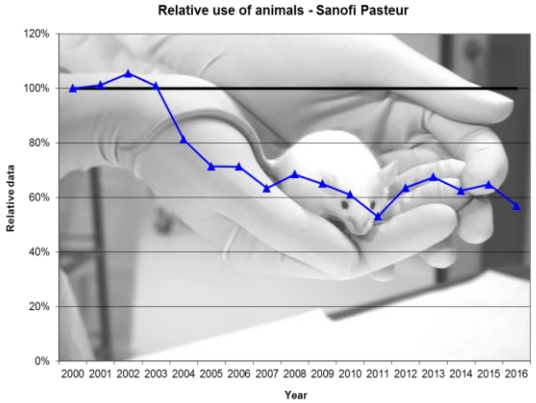
- **Testing of Biologicals has the highest proportion and number of experiments causing severe pain and distress to animals out of various types of experiments (basic research, toxicity testing, etc.)**
- **Animal Use in Vaccine industry**
  - Vaccine development (Research, non clinical evaluation of safety & efficacy)
  - Production
  - Batch control testing (safety and potency testing)
- **Vaccine batch control testing is responsible for ~90-95% of animal use by vaccine manufacturers**
- **In addition, independent Batch Release testing by National Control Laboratories**

Animal Use at Sanofi Pasteur: Current View

- **Sanofi Pasteur: the first user of laboratory animals within Sanofi group (~ 75%)**



- **90 to 95% of animals used in Industrial Affairs**
- **99.4% are rodents**



- **2 fold decrease of number of animals used for marketed vaccine testing since 2003**
- **Stable since 2008 due to increased quality, regulatory requirements and types of vaccines supplied**

Why change?

Animal welfare

- Animals are sentient beings
- Large % of animals used in vaccine QC exposed to severe pain & distress
- Societal concern of animal usage

Science

- *In vivo* models act as a black box
- Relevance to human is sometimes questionable
- Lack of robustness, many factors may affect outcome

Economics

- *In vivo* tests are expensive
- Long cycle times
- High variability can lead to rejection of safe and efficacious vaccines, delays in product release & vaccine shortages

3Rs - Legal basis in Europe

- **EMA/CPMP/SWP/728/95 (adopted 1997): Replacement of animal studies by in vitro models**
- **Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the 66 Community code relating to medicinal products for human use (Consolidated version: 67 05/10/2009); 68**
- **Directive 2010/63/EU on the protection of animals used for scientific purposes on 3 June 2010.**
  - European Directive 2010/63/EU on the protection of animal used for scientific purpose "*Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used …*"
- **Sanofi policy: "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. Sanofi fully adheres to the 3Rs…"**

A clear 3Rs commitment within Sanofi Pasteur

The objective of Sanofi Pasteur, with the support and commitment of its R&D, is to phase out animal use for the manufacturing and control of marketed products in particular for new vaccine registration and reduce the number of animals used for the development of new products


SANOFI PASTEUR

SANOFI PASTEUR'S 3R COMMITMENT

Statement

COMPLEX NATURE AND ESSENTIAL USE OF ANIMALS IN OUR ACTIVITY (Why do we use animals?)

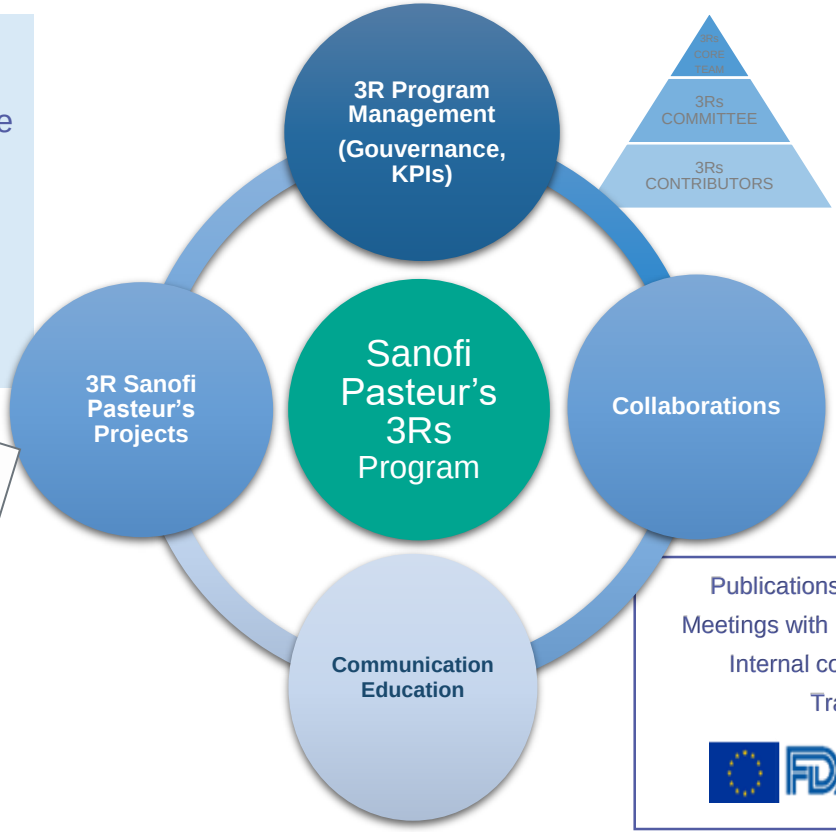
- Compulsory from a scientific and regulatory standpoint and required by the health authorities, in order to ensure the efficacy and safety of the vaccines provided to physicians. As our vaccines are administered to healthy people, including babies, this guarantee of quality is a natural priority.
- Essential for medical and scientific progress: this is a necessary step in new vaccine research and development.

THE 3R RULE HAS LONG BEEN ACTIVE! (What is the current situation?)

- At Sanofi Pasteur, the use of animals is an integral but small part of the global research and analytical control strategy, which favors in vitro methods.
- Our teams include veterinarians, researchers and technicians who have been trained and certified to ensure the best possible conditions for working with and handling animals in our facilities.
- These teams, in conjunction with Sanofi Pasteur's ethics committee and the animal welfare unit, apply the three fundamental principles of the 3R rule:
  - Replace the use of animals with alternative solutions: for example, the use of new mathematical and biomedical models. To that end, in 2010 Sanofi Pasteur acquired Vaxdesign, which has developed a one-of-a-kind technology that reproduces the human immune system in vitro.
  - Reduce the number of animals needed as much as possible: in 10 years, Sanofi Pasteur has more than halved the number of animals needed to develop vaccines. Ongoing attention is paid to refining the standards of care: when the use of animals cannot be avoided, we ensure the best conditions for their breeding, housing and care conditions, with priority given to their well-being and to preventing any suffering under the supervision of the animal welfare unit.

COMMITMENT TO PROMOTING THE USE OF ALTERNATIVE METHODS (What exactly are we talking about?)

- Sanofi Pasteur is committed to an ambitious 3R program under the leadership of the Animal Protection Officer with the aim of continuing to reduce animal use on a steady or even faster pace.
- A 3R network, based on internal and external expertise, has been created to support and promote projects to replace, reduce and refine animal testing. It also seeks to implement the principle of the consistency approach as soon as possible. This entails proving that the quality of the product will be maintained without the use of animals.
- Sanofi Pasteur, with the support and commitment of its R&D department, ultimately aims to eliminate all use of animals in the manufacture and inspection of vaccine batches on the market, in particular for its new vaccines, and to reduce the number of animals used in the development of new products.



imi VAC2VAC
European consortium

WITH AUTHORITIES

3Rs Working Group Biologicals

Group 15

WHO ECBS / OMCL

Publications / Conferences
Meetings with Health Authorities
Internal communication
Training

3R Replace Reduce Refine

Current Limitations to 3Rs for vaccine quality control

Regulatory hurdles

Lack of harmonization of regulatory requirements

Caution of Health Authorities to accept deviations from established guidelines and monographs

Risk aversion – *in vivo* assays used for decades. Animal tests considered as “gold standard”

Complexicity of post-approval changes do not generate strong incentive to develop and implement alternatives to animal testing

Scientific hurdles

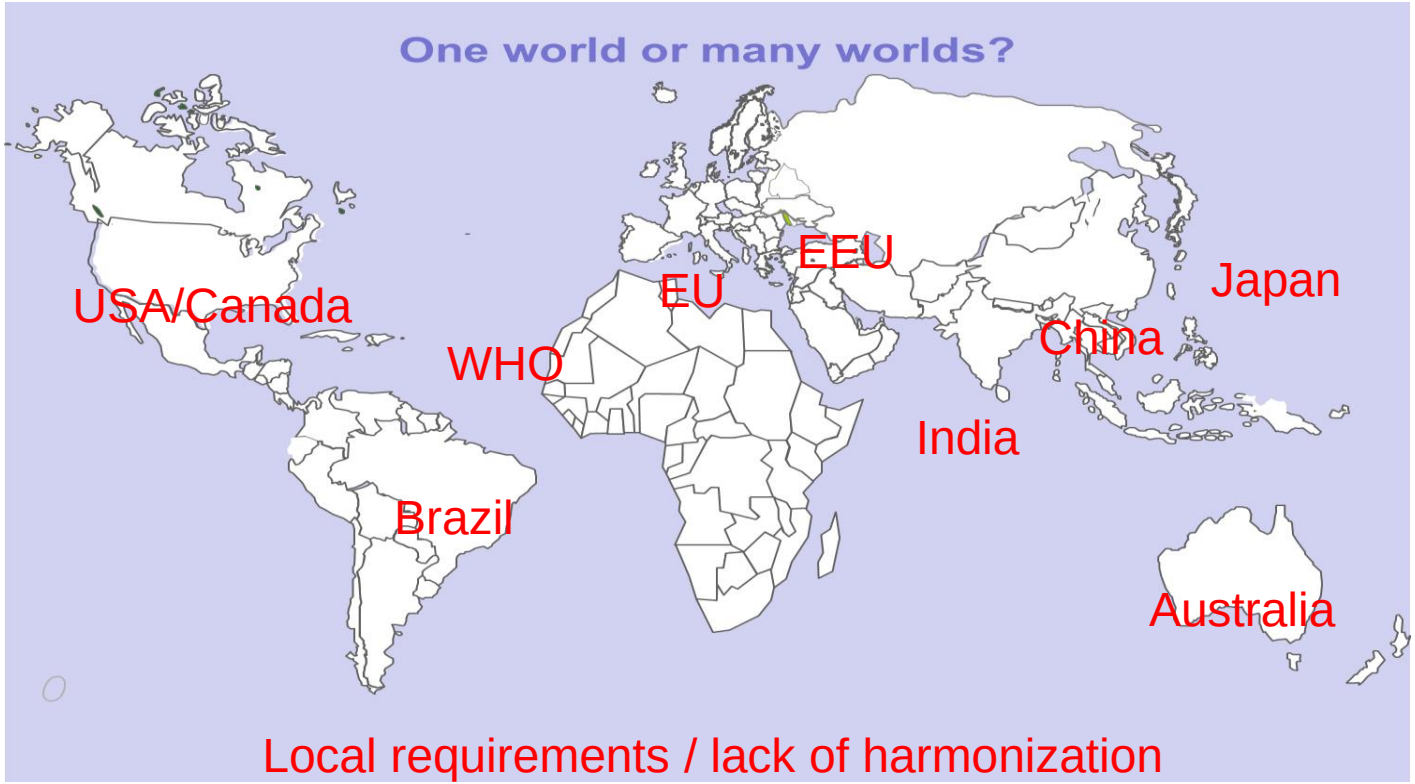
Inherent variability of *in vivo* assays

Historically i*n vivo* assays have not been validated according to current ICH Q2 R1 principles

The product quality attributes will likely be assessed differently when changing from an *in vivo* to an *in vitro* method

1:1 comparison challenging and not necessarily justified

Regulatory hurdles: Many regulatory worlds



Diphtheria and Tetanus potency assays status

Several methods required/recommended depending on the destination

- **Challenge tests**
  Guinea pigs for D
  Mice and guinea pigs for T
  - **Multi-dilution assay**
    
    Potency expressed in IU
  - **One-dilution assay (limit test)**
    
    estimated potency > minimum requirement
  - **In vivo Toxin Neutralisation Test**
    US NIH 
    Functional Ab response above threshold

- **Immunogenicity tests**
  Serology by ELISA or in vitro TNT on Vero cells (for D) or Toxin Inhibition assay (for T)
  - **Guinea Pig model**
    multi- or one-dilution assay
    
  - **Mouse model**
    

Scientific hurdles

- The test methods used for routine QC should be intended to monitor production consistency and ensure comparability of quality attributes between commercial and clinical lots
- The information provided by *in vivo* and *in vitro* methods is different
- An existing *in vivo* method may be substituted by more than 1 *in vitro* method in order to control key qualitative and quantitative attributes measured by the existing test
- New Ph. Eur. general chapter 5.2.14 “Substitution of *in vivo* method(s) by *in vitro* method(s) for the quality control of vaccines” effective since Jan 2018

***In Vivo* assay**	***In Vitro* assay**
Measure Complex functional response	Mimic specific elements of complex in vivo response

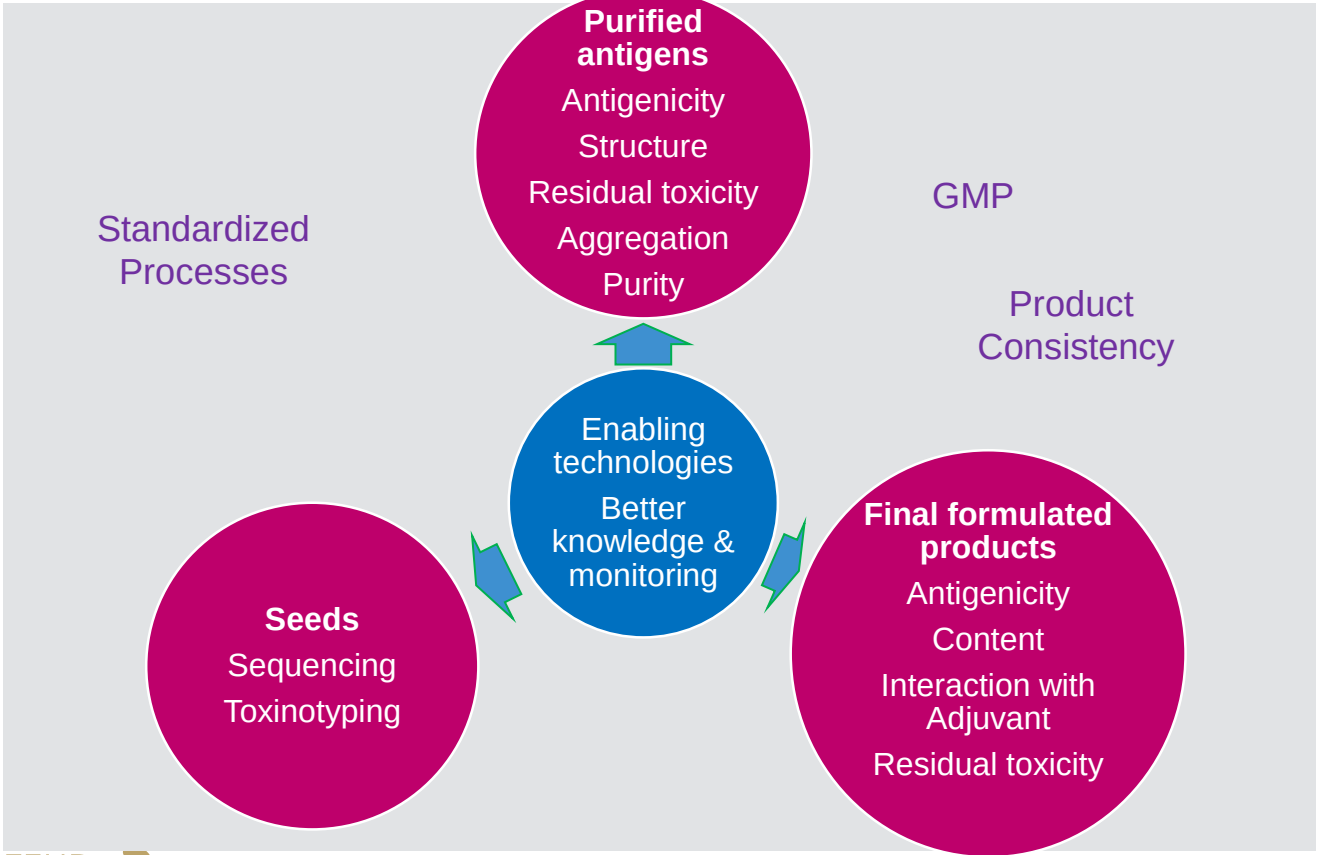
Agreement between methods should not always be expected
Based on the demonstration of the scientific relevance of new test

Time for change…..for consistency approach

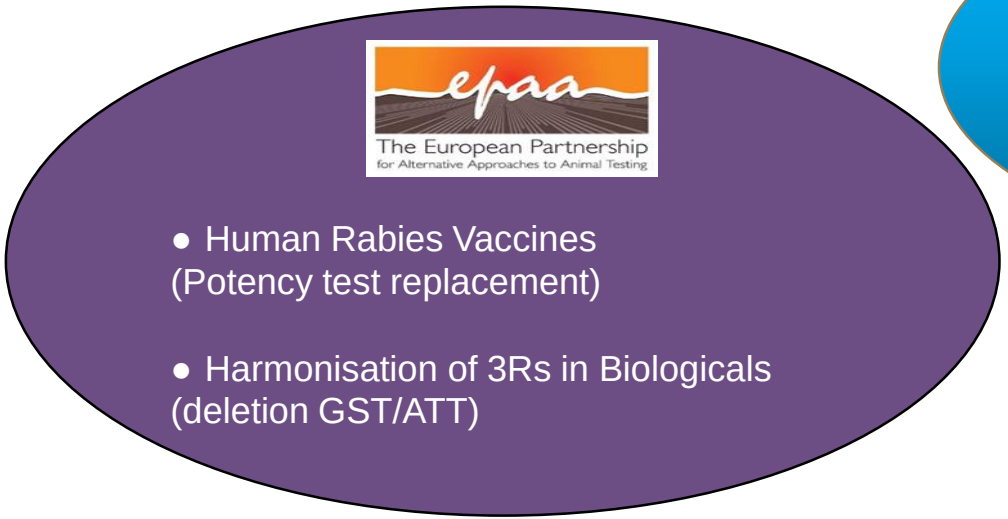
1:1 replacement	Integrated approach
Uniqueness of each batch Emphasis of QC on final product Read out in IU (potency) Comparison to international reference preparation	• Each batch is one of a series • Emphasis on every step of production process (seed lot, in-process, final product) • Read out is: non deviation from consistency • Benchmarking to clinical/ historical batch

'The consistency approach is a concept which includes the strict application of GMP rules and guidelines, process validation and in process and final product tests and is aimed at verifying if a manufacturing process produces final batches which are consistent with one that fulfils all the criteria of Quality, Safety and Efficacy as defined in the marketing authorization, ultimately resulting in replacement of routinely used in vivo tests. *De Mattia et al, Biologicals 39:59-65, 2011*

Perspectives for the future : *in vitro* analyticals tools

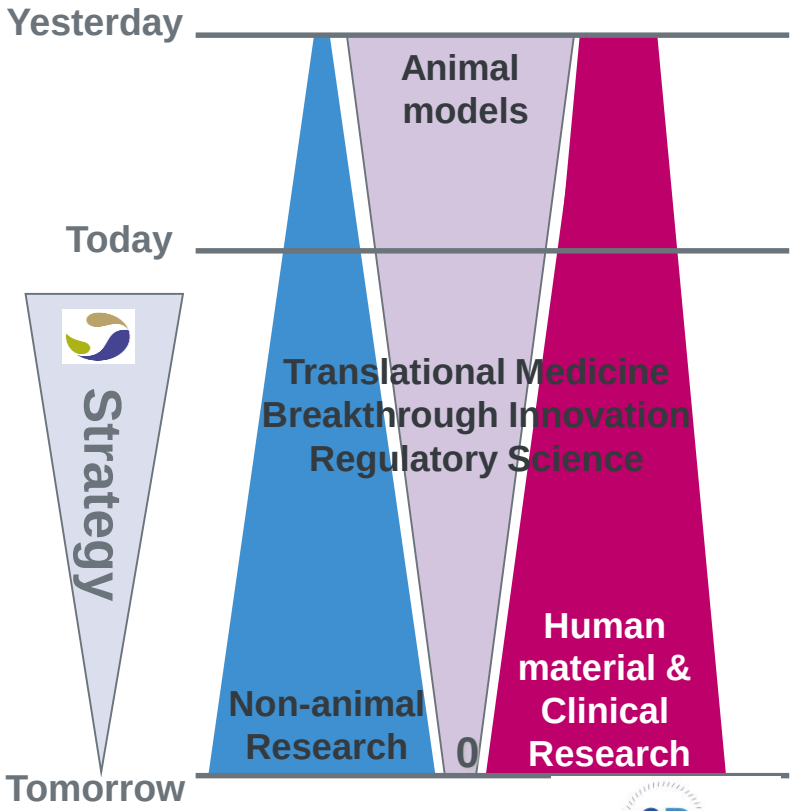


International collaboration is key for success



Integrated 3Rs **S**trategy for new vaccines

- **Yesterday**, animal models were predominant
- **Today**, we use non-animal data, animal model and clinical research to support the development of new products
- **Tomorrow**, the ultimate objective is to replace the use of animals thanks to translational approaches, breakthrough innovations and Regulatory Science



Conclusion

- **Overall reduction in Research and phase out for quality control is a strong commitment**
- **We still need animals for Research and Development of new vaccines**
  - Although progress is being made, this is a long and resource-consuming journey
  - Non-animal methods and animal models are complementary, and the ratio of non-animal ones is increasing
  - Refinement must be maintained when animal are used
- **For existing vaccines,**
  - a change of mindset is necessary to continue replacing *in vivo* by *in vitro* testing: consistency approach
  - Need for a worldwide harmonization and commitment from regulatory bodies

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Thank you