Animal Testing Replacement: Global Human Vaccine Manufacturer Perspectives

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AGENDA

1 Sanofi Strategy and Current Situation for QC Analytical Testing

2 Industry key Challenges and Efforts for Worldwide Alignment and Acceptance

3 Conclusion

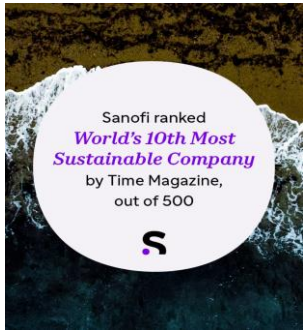
Sanofi Strategy and Current Situation for QC Analytical Testing

Sanofi's Integrated Research and Testing Strategy (IRTS) as a sustainability fundamental

Lays out Sanofi guidelines to affirm **rigorous & state-of-the-art science**

- to **select** the best available, feasible, and translatable **models**
- to address **scientific questions**
- to adhere to **regulatory requirements**,

With the aim to **stop using live animals**



Improving animal use by preclinical package, study rationale and design

+

Phasing in NAMs (New Approach Methodologies)

+

Replacing by qualification, validation, acceptance

+

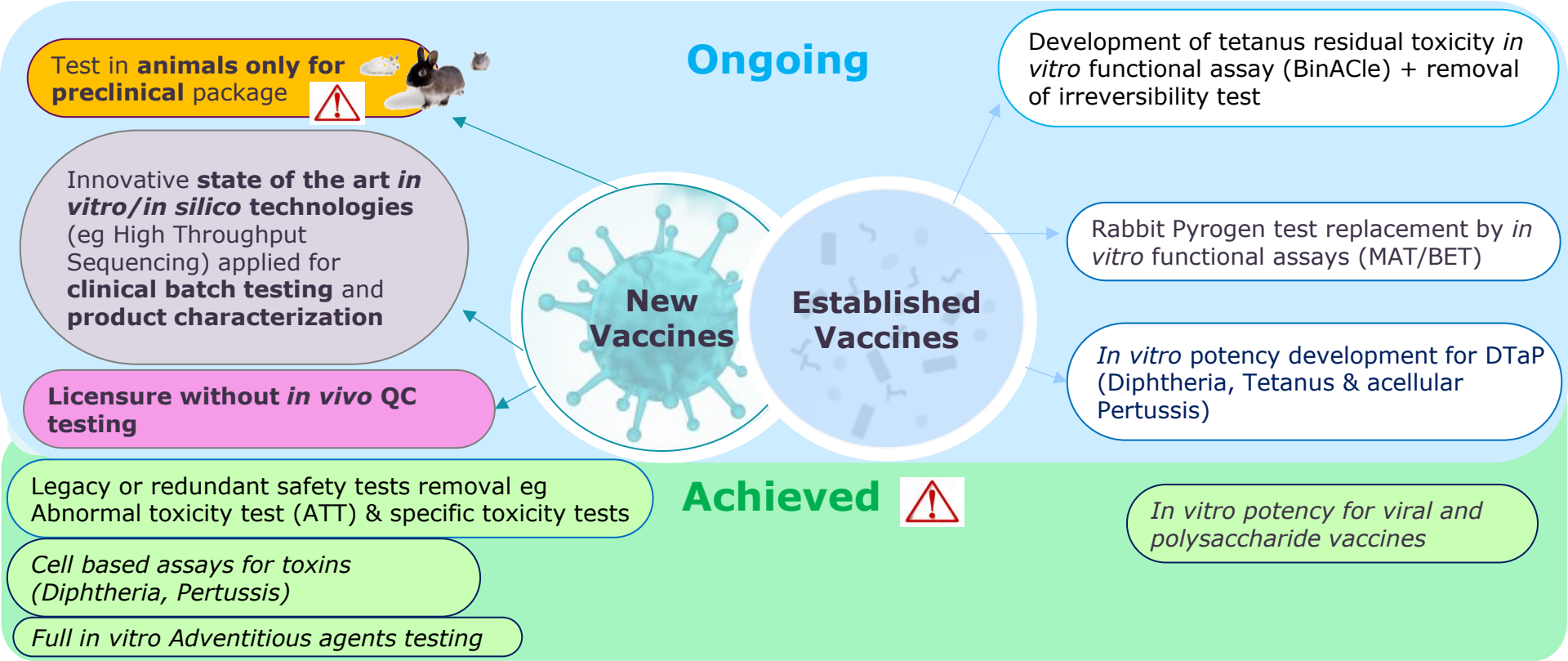
Waiving and challenging obsolete tests

=

Objective of 50% global reduction of animal use:

- **Between 2020 and 2030**
- **Internal and external use**

Sanofi's strategy for vaccines : aiming at Quality Control with scientifically relevant non-animal based analytical testing



Specific animal based testing requirements (National/Regional Pharmacopoeias, Importation)

Sanofi's strategy for vaccines with non-animal-based quality control has several benefits

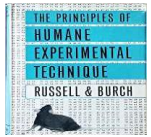
- **Analytical Performance**

automation

RELEVANCE (state of the art technology and scientific value)
RELIABILITY (less variability, invalid and false OOS)
REDUCED CYCLE TIME (faster time to market and improved availability for patients)

- **Regulatory Compliance (EU Directive 2010/63, European Pharmacopoeia, other local regulations)**

3Rs



Reduction	Refinement
• **Minimize the number** of animals per experiment	• **Minimize suffering** and improve animal **welfare**

- Replacing challenge potency tests by **serological methods**
- Using **single-dilution** method design instead of multi-dilution design
- Use of **humane endpoint** for lethal or invasive assay

Replacement

- **Avoid** or **replace** the use of animals

Replacing *in vivo* assays : Developing and implementing ***in vitro* alternatives** using **animal free reagents**

The 4th R

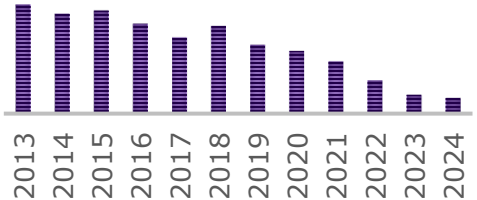
edqm

Removal

- **Removing/ not performing unjustified tests** : redundant, unnecessary

* European Directorate for the Quality of Medicines

- **85% decrease of animal use for quality control between 2013 & 2024**



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Overview of current of animal-based testing replacement and removal situation

Safety

- **No routine ATT** following global deletion of GST/ATT worldwide (CFR, WHO, Ph. Eur., other national Ph done or ongoing) but **some exceptions**…
- **No routine Specific toxicity** testing on drug product but **some exceptions** …
- Test for **Adventitious agents based on a risk assessment** and with **no animal test**
- **Ongoing development** of alternative assay for **residual tetanus toxin** on toxoid

Potency

- **Only remaining *in vivo* routine potency testing** is applied to **DTaP combination vaccines** (serological with single dilution or challenge assay according to destination)
- **Immunoassays** have been **developed** through a **Public-Private consortium** (IMI-Vac2Vac)
- **Ongoing validation**, **submission** and **presubmission consultation with HAs** for alternative antigenicity assays

Pyrogenicity

- Testing according to a **risk-assessment**
- **Few remaining RPT replacements with BET** are under worldwide approval for products with an endotoxin risk only BET
- **Ongoing validation of MAT** for inherently pyrogenic vaccines in order to replace the RPT
- **Ongoing strategy to replace horseshoe crab** blood lysate reagents by recombinant reagents for products, **achieved partially for pharmaceutical water**

ATT : Abnormal Toxicity Test GST : General Safety Test RPT : Rabbit Pyrogen Test BET : Bacterial Endotoxin Test DTaP : Diphtheria Tetanus Acellular Pertussis MAT: Monocyte Activation Test

Industry key Challenges and Efforts for Worlwide Alignment and Acceptance

Remaining challenges due to heterogenous legislations : Specific testing requirements and Post Approval Change management

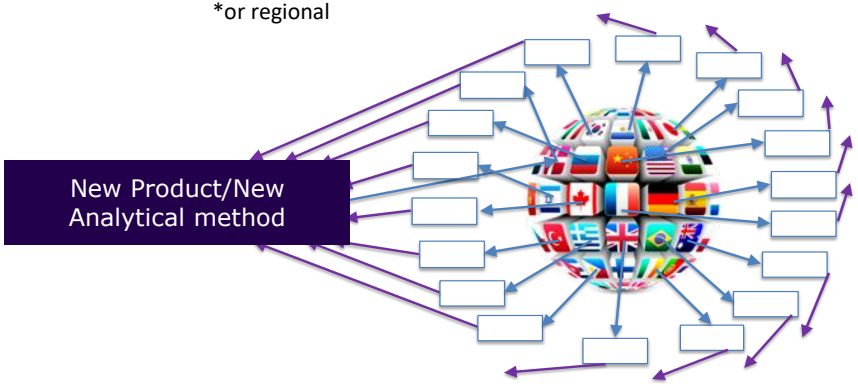
- A Post-Approval Change application for an alternative method takes up to 5 years
- Specific testing requirements impact both manufacturer, authorities and patient supply

Global Company

1 product (single quality, efficacy and safety) for 1 worldwide market
Ideally : 1 regulatory requirement

National* Regulatory Approvals

*or regional



Reality:
1 product with 100+ regulatory approvals and various testing requirements

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Remaining specific in vivo QC testing due to non alignment

Legacy products

- **At manufacturer site per destination (eg RPT, challenge potency assay for D&T, mouse histamine sensitization assay)**
  → Batches allocated to specific market OR systematic duplicative testing
- **On importation by manufacturer**
  → In manufacturing country or in destination country **(eg specific toxicity, ATT)**
- **On importation by Health Authority (eg ATT, RPT, challenge potency assay vs serological for DTaP)**

Products under licensure

- **Clinical batch release** or **as additional characterization assay**
- **Representative set of GMP batches to establish consistency**
  → prior to licensure or post licensure (**eg RPT, ATT, in vivo potency**)

Impacts

COMPLEXITY for manufacturer

- **Multiple** QC profiles according to destination
- **Multiple** methods & reagents, specific animal model & reference standard, staff training & qualification

RESOURCE & MATERIAL CONSUMPTION for manufacturer and NCL

- **Additional** resource needed and logistical burden increase, including reagents management
- **Redundant** testing & **duplicative** testing

ADDITIONAL TIME FOR RELEASE (manufacturer & NCL testing) +++

INCREASED RISKS for not releasing or delaying release

- **Non-compliance** to 3Rs related legislation (& CROs in EU become rare)
- Enhanced risk of **OOS (Out of specifications) and invalid results** due to inherent animal variability
- Risk of **discrepant result/conclusion** on batch acceptance between manufacturer/NCL & between NCLs

What are we doing to promote worldwide acceptance and alignment?

Early Collaboration

Networking

Knowledge Sharing

- Public Dissemination (Workshops, Congress, Publications Reports, Interviews)
- Contribution to new analytical tools & standards (Consortia, Collaborative studies)
- Analytical Standardisation (Control Laboratories)
- Pharmacopoeias WHO Guidances Revisions
- Health Authorities Scientific & Presubmission meetings
- Associations Specific Networks

Some examples of industry & regulatory collaborative efforts

Contribution to new analytical tools & standards (Consortia, Collaborative studies)

- Co-development or development of analytical methods with available reagents
- Multi-laboratory validation through collaborative studies
- Testing Material and reagents provided by manufacturers
- Examples: BSP 148 rabies potency ELISA , BSP 136 Binacle, IMI-V2V consortium

Analytical standardization

(Control Laboratories)

- Analytical method transfer from manufacturer to NCLs
- Standardized methods and testing profiles through control laboratories network eg OMCL network, WHO-NNB, WHO-GNP
- Example: OCABR setting standardized release testing

Health Authorities Scientific & Presubmission meetings

- Early and very upstream collaboration and exchange with HAs through meetings, briefpacks
- More and more Multi authority meeting → shortens timelines and facilitates acceptance

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BSP : Biological Standardization Program NCL : National control Laboratory
WHO GNP : WHO GLOBAL NETWORK OF NATIONAL QUALITYCONTROL LABORATORIES FOR PHARMACEUTICALS (WHO-GNP)
WHO NCL NETWORK FOR BIOLOGICALS (WHO-NNB)

Some examples of industry & regulatory collaborative efforts

Pharmacopoeias
WHO
Guidances
Revisions

- Participation to Pharmacopoeia Expert Groups (regulators & industry)
- Proposal for revisions
- Submission of data
- Reviewing and commenting drafts
  - ❑ Example: Ph. Eur. chapter 5.2.14 & ongoing DTaP door opener; CPC annual specification improvement projects; MRBP revision for Flu with removal of animal tests; HTS for adventitious virus detection in Pharmacopoeias & ICHQ5A(R2)

Trade associations
Specific networks

- Multisakeholder cross-sectorial collaborations:
  - ❑ EPAA
  - ❑ NGOs (AFSA, NC3Rs)
  - ❑ EFPIA/Vaccines Europe, IFPMA
  - ❑ ICMRA, WHO-NNB, WHO-GNP
  - ❑ EMA 3Rs WP/ Quality WP/ Biologics WP
  - ❑ IABS
- Example : NC3Rs/Gates Foundation project to review WHO guidelines

Public
Dissemination

- Publications
- Conferences
- Workshops
- Open and transparent communication

EPAA : European Partnership for Alternative Approaches NGO : Non Governmental Organization
EFPIA : European Federation of Pharmaceutical Industries & Associations
IFPMA : International Federation of Pharmaceutical Manufacturers & Associations
WP : Working Party

Let’s also talk about reliance & reduced in country testing

TRS 1033 - Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations

World Health Organization

Reliance for post-authorisation changes: pilots for the pharmaceutical industry | European Medicines Agency (EMA)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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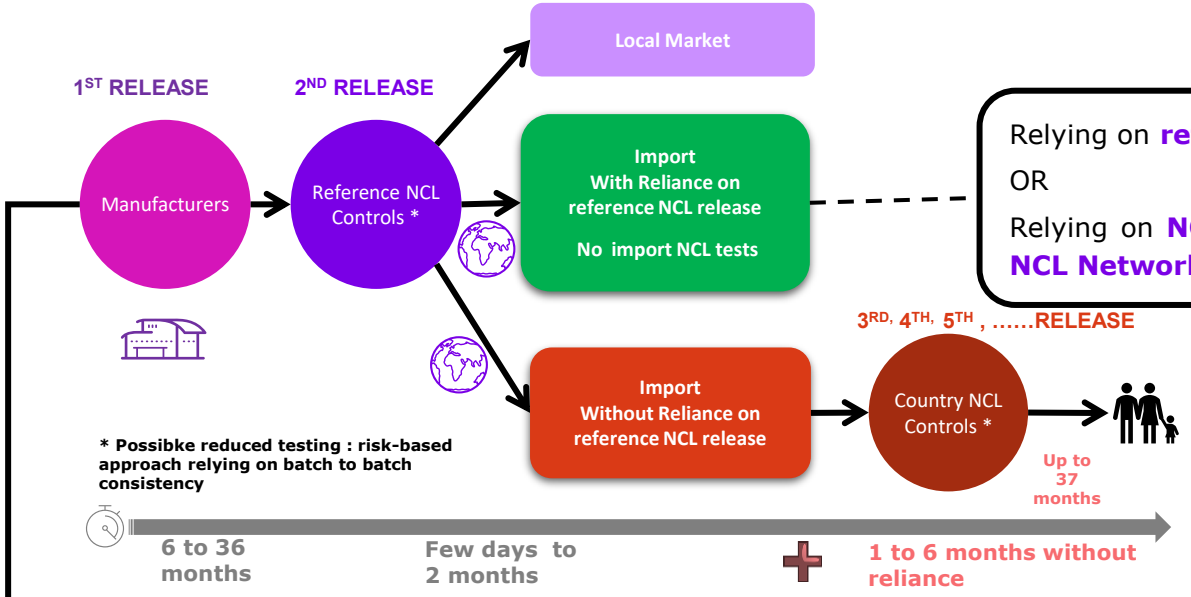
Reliance approach for Global Batch Release



Relying on **reference NCL release certificate**

OR

Relying on **NCL Certificate of Analysis shared by WHO NCL Network** for Biologics (TRS 978 Annex 2)

More and more countries are implementing laws enabling reliance mechanisms and risk- based approaches to replace or reduce importation tests

Manufacturing according to **PQS: Pharmaceutical Quality System (GMPs, validated process, process controls, annual product review)**

PQS and manufacturing **inspected by independent NRAs**

PIC/S

Pharmaceutical Inspection Co-operation Scheme


Reliance-Based Waivers Become the Predominant Trend in In-Country Testing of Pharmaceutical Products

Reliance approach for Post Approval Change

Several pilots have shown **"proof of concept" :**

- **Reduced** time for approval **(2-4 years to 6-10 months)** with predictable timeline
- Country **decision sovereignty** maintained
- **Streamlined workload** for agencies

Based on **transparency & trust :**

- **Voluntary participation**
- 1 standard dossier/**1 set of requirements**
- **1 tool** to share documentation (CTD, Q&As, assessment report)

Worldwide Regulatory Reliance: Results of an Executed Chemistry, Manufacturing, and Control Post-Approval Change Pilot

Cynthia Ban, Jamie Graham, Lyne Le Palaire, Priya Persaud, Franziska Brehme, Olivier Faure, Allison Rameau and Ana Luisa Silva

PDA Journal of Pharmaceutical Science and Technology May 2025, 79 (3) 295-302; DOI: https://doi.org/10.5731/pdajpst.2024-003023.1

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-024-00677-8

DIA

ANALYSIS

Unleashing the Power of Reliance for Post-Approval Changes: A Journey with 48 National Regulatory Authorities

Francesca Mangia[1] · Yameng (Melly) Lin[1] · John Armando[2] · Kareny Dominguez[1] · Vera Rozhnova[1] · Susanne Ausborn[1]

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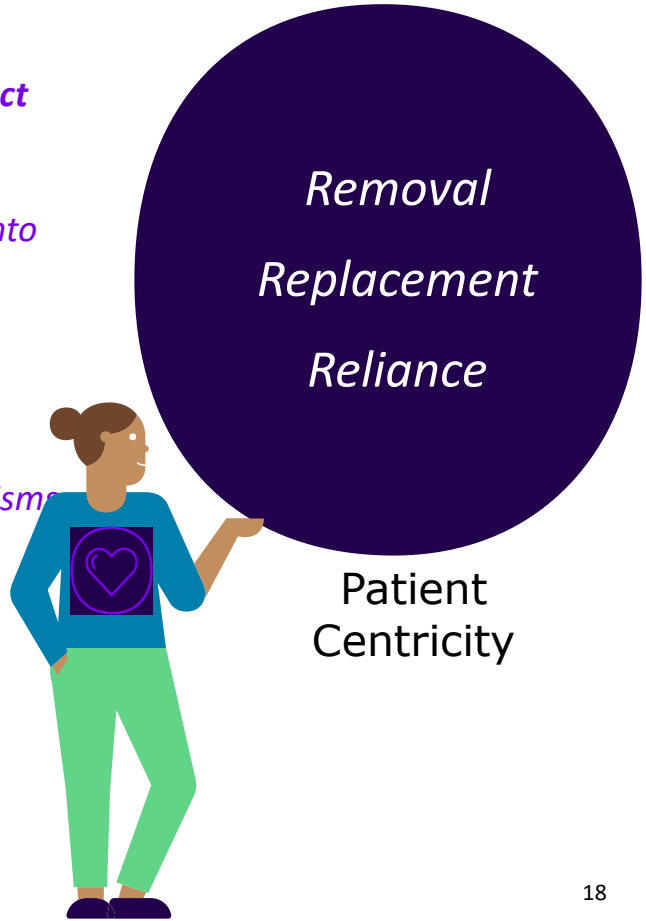
Conclusion

- *Transition to non-animal-based QC testing allows to **better assess product quality***
- *Global momentum and willingness to **phase-out animal testing** taking into consideration product Overall Control Strategy*
- *Some remaining **challenges** for non animal QC testing acceptance and **harmonization** but we are almost there*
- *Key success factor is building **trust and collaborative space** and mechanisms*
- *Next step: preclinical landscape with phasing in of NAMs*



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Emmanuelle Coppens is a Sanofi employee and may hold shares and/or stock options in the company.

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