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One Health drives for New Approach Methodologies (NAMs) approaches for Vaccine Batch release

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One Health and Vaccine Batch Release

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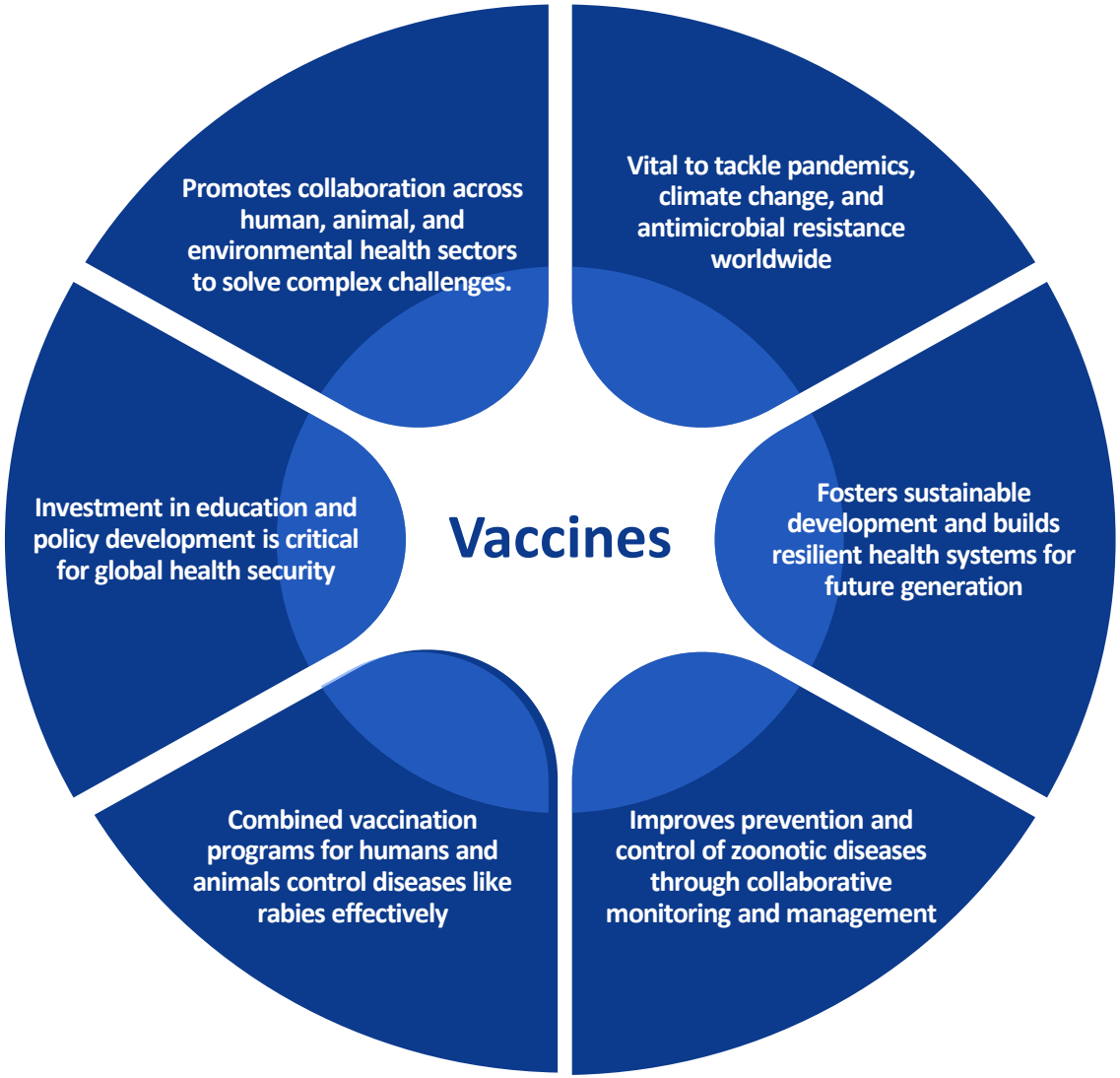
What is One Health and why do vaccines matter?

High Quality Vaccines that provide consistent safety and efficacy globally are critical to support One Health

Cost, supply continuity and speed of development can all be critical factors



Challenge with *in vivo* batch release tests for vaccines

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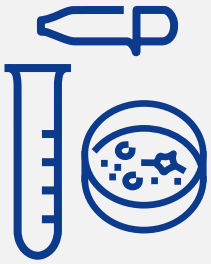

Quality and consistency

In vivo animal release tests have been proven to be highly variable and insufficient to ensure routine product consistency

Animal Use

Animal use is challenging for welfare but also in supply and consistency

Time to release

Time for batch release is much longer with animal tests

Impacts Shelf-life, supply and emergency response time

Quality and consistency

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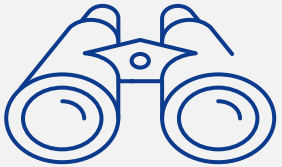
Why *in vivo* release tests are not the gold standard

Quality Validation Data



- Example from Lepto and Rabies
  - Validating transition to *in vitro* both for Lepto and Rabies showed lack of discriminatory power of *in vivo* methods
  - Could reduce antigen content to <5% of target before vaccines failed *in vivo* tests
- In vivo test may show protection in challenge model but provides no guarantee of target species efficacy or duration of protection
- Validating in vivo methods to modern standards can be impossible
- Variability is very high

- Result in lack of batch consistency control and risk of poor vaccine performance

Quality and consistency

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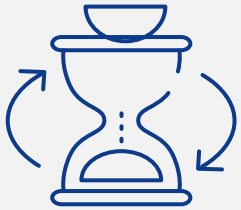
Why *in vivo* release tests are not the gold standard

Consistency



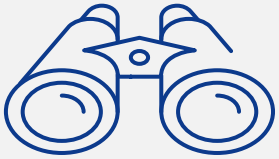
- Poor correlation between outdated approaches to formulation and final product potency
- Lack of ability of in vivo tests to ensure formulation consistency
- Animal consistency in supply and quality is critical but challenging
  - Strain, Age, weight and health status can be critical factors
  - Example – batch recall of vaccine due to failed in vivo potency in GMP stability, vaccine passed at 3 time points, failed and two (recalled) then passed the remaining time points – route cause – the mice

- Result in batch recalls, expended release times and impact on supply

Animal Use

Why *in vivo* release tests are not the gold standard

Welfare



- Challenge with societal acceptance of Animal use
- Severity of challenge model
  - Serology use refinements
- Question of relevance to target species for lab animal release models
- Maintaining welfare standard in test facilities
  - Health status can be a key factor in test outcomes

- Societal concerns over animal use and relevance to Human and other target species safety and efficacy

Animal Use

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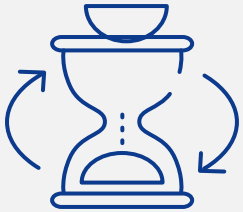
Why *in vivo* release tests are not the gold standard

Availability



- Challenges of availability of the right animals for both manufacturers and medicines control laboratories
- Critical factors
  - Age, weight and sex
  - Strain
  - Sero negativity
- General animal supply challenges will increase based on global drive for NAMs and phasing out animal testing
- Challenges with maintaining animal test facilities

- Delays in release impacting vaccine availability with direct impact on human and animal health

Time and Cost

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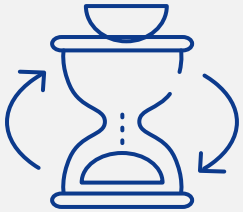
Why *in vivo* release tests are not the gold standard

Time



- Testing time can be weeks vs days for animal test vs *in vitro* approaches
- Longer testing times reduce shelf-life at release
- Issues with animal release tests the biggest reason for vaccine testing issues
- In global supply chains repeat release testing my multiple authorities using more animals and increasing testing time
- Many tests can't be run in EU so need to use other test countries

- Time to release impacts availability, shelf-life and overall, One Health when vaccines not available
-

Time and Cost

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Why *in vivo* release tests are not the gold standard

Cost

- Animal facilities are much higher cost than QC lab space
- Issue of cost is relevant to manufactures and medicines control laboratories
- Overall vaccine cost of goods use of any *in vivo* test is significant vs *in vitro* strategies
- Repeat testing is often required adding time but also cost

- Impact on manufacturing viability, and impact on cost of vaccines to end users which can be critical for key One Health related vaccines

Impact example

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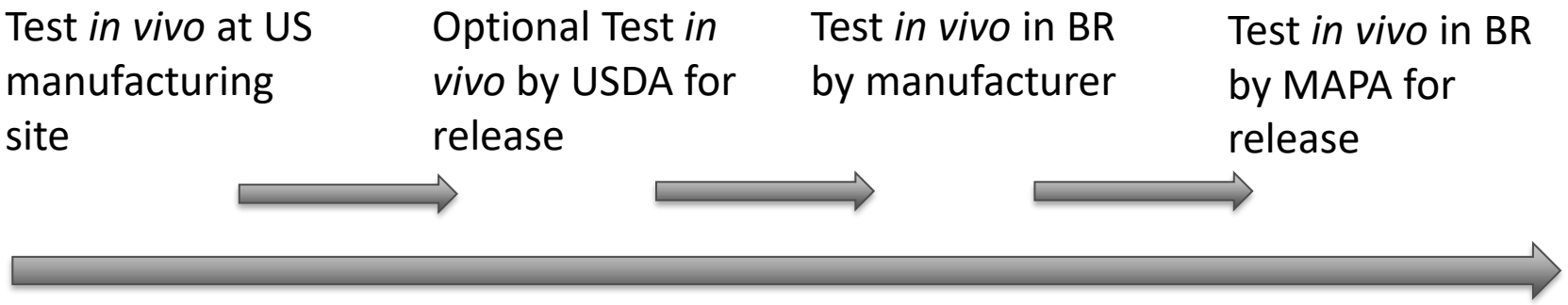
Timeline to release a Veterinary Rabies vaccine in Brazil



US and Brazil (BR) use a different reference and slightly different test method, so US test data not accepted in Brazil – each batch of vaccine can be tested up to 4x *In vivo* in mice

Need for reliance and mutual recognition approaches in the longer term but switching to *in vitro* release potency test would already save time and money

The issue of Reference Standards

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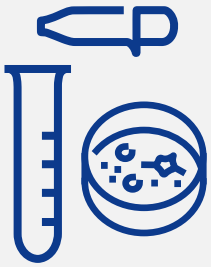

Consistency of References

With only *in vivo* methods it's challenging to ensure reference consistency – example of challenges replacing Rabies references, use of correction factors

Animal Use to Qualify

Can you replace a reference without testing in animals?

Only with good QbD and CQAs in place along with GMP standards

USDA require references to be requalified by animal challenge

Time and availability if issues

Any issue with references (e.g. stability, selection, bridging) can impact supply continuity, vaccine availability and product shelf-life

QbD – Quality by Design
CQAs- Critical Quality Attributes
GMP – Good Manufacturing Practice

What can we learn from Biopharmaceutical approaches

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QbD and CQA approaches to fully characterize products

Biopharmaceutials use fully *in vitro* release approaches with high level of characterization, product understanding and built in quality

For biopharmaceticals

1. Use of extensive biological and physiochemical testing to characterize consistent product as well testing any key excipients
2. QbD and CQA
   A. Use Quality by Design (QbD) to build in QC strategies and refine specifications with increasing batch consistency data
   B. Define critical quality attributes (CQAs) from the start and develop methods to monitor and control these

Vaccines are much more complicated and often less well defined however the same principles can apply – improved characterisation increases consistency and confidence in safety and efficacy – as well as enhancing supply continuity which is critical for One Health

Positive progress

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VAC2VAC

- EU IMI project aiming to support methods and validation approaches to facilitate NAMs for Vaccine release

COVID 19

- All COVID vaccines used in vitro release approaches- critical for speed
- https://www.nature.com/articles/s41541-023-00617-xe

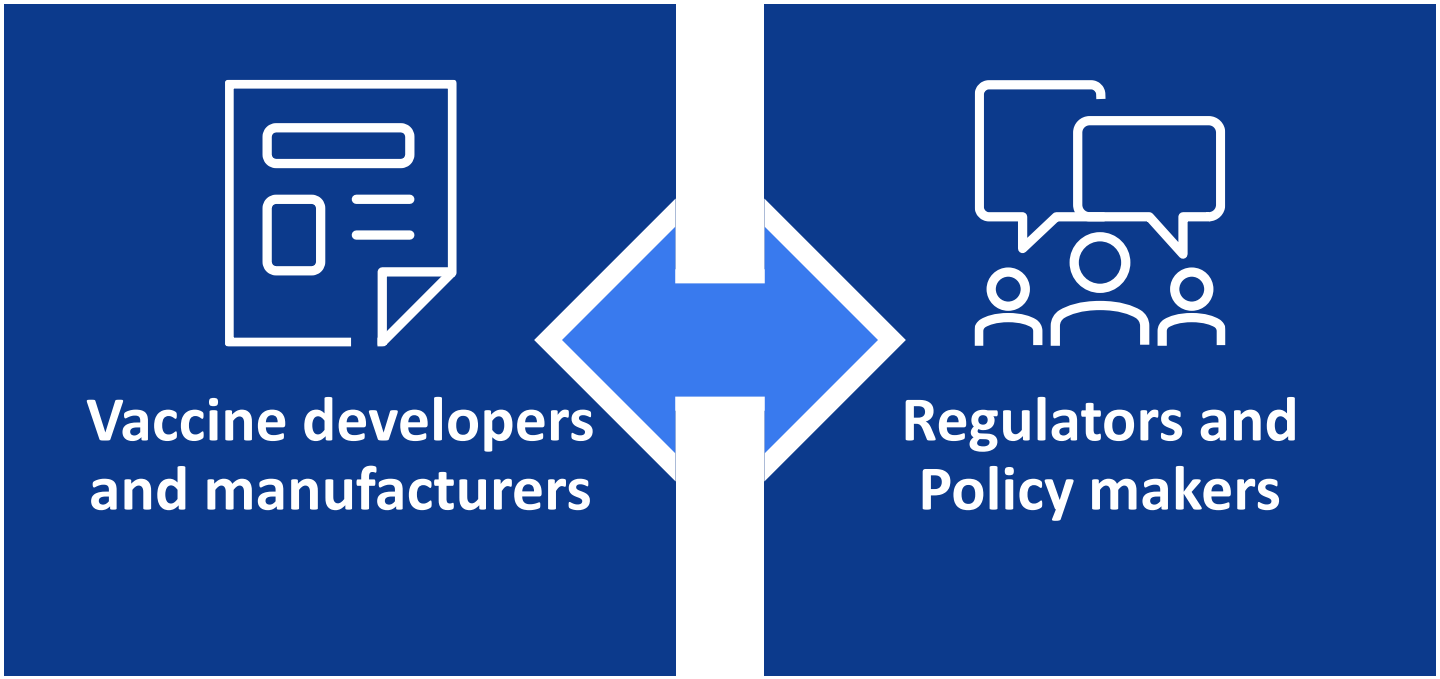
Rabies

- EU has moved to in vitro Glycoprotein ELISA release
- Faster and cheaper
- OMCL Potency test for release still required but using in vitro methods
- Used consistency approach to establish specification

FMD PQ process

- FAO vaccine pre-Qualification for FMDV vaccines
- Vaccine batches pre-qualified by approved lab for release
- Reduces animal testing and repeat testing
- Improves speed of availability for routine and emergency vaccine supply

Communication is key to success



Questions?

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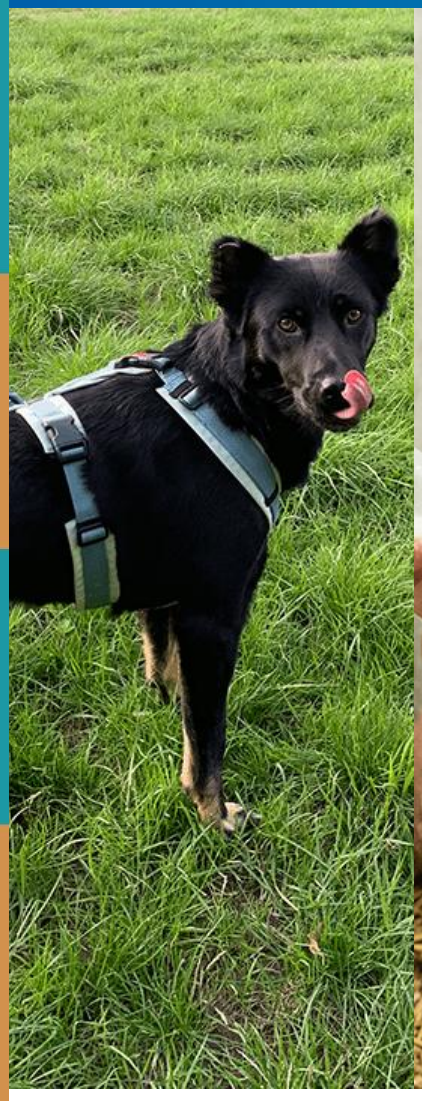


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Working in **~40 countries**

Ten Largest Animal Health Companies
Working in **100+ countries**

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Boehringer Ingelheim

Virbac

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Europe and Africa	European Union	Ireland	Portugal	South Africa
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	France	Netherlands	Switzerland	
	Germany	Nordics	United Kingdom	
Asia and Pacific	Australia	India	Korea	China
	Indonesia	Japan	New Zealand	Thailand
Informal WG or in-development	Sub-Saharan Africa			
	Middle East/ North Africa