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Industry investment on alternative methods

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Business Case to invest in alternatives

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- **Improved animal welfare/reduced animal use**
- **More consistent products delivering quality, safety and efficacy to stakeholders and animals**
- **Better process controls and methods for use in production**
- **Reduced costs and timelines for production**
- **Supply continuity**
- **Sustainability benefits in production**
- **Improved scientific knowledge and expertise arising from alternative *in vitro* assay development.**

Fundamental approach change in development for routine QC testing

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Industry takes an *in vitro* first approach to potency test development for new products

Look to *in vitro* assays as first line – saves animal use from the start

***In vivo* assays as back up or when issues with stability assurance with *in vitro* testing only**

New/Pipeline product considerations

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Generally an *in vitro* approach is taken from the start

Benefits

- **Easier investment decisons**
- **Easier to establish specifications**
- **Direct relationship to safety and efficacy batches**
- **Generally easier to establish references where necesary***

Exceptions:

➢**In case of improved/updated vaccines (with components already licensed): where existing and approved animal models are already available, these might be used to shorten time to market timelines**

➢**Speed to market approach eg for emergency vaccination need with in vitro tests developed as a follow up**

➢**Technical hurdles**

* US requires references to be requalified in target species by challenge every 15 years which adds risk to products every time

Licenced Products

- Existing licensed products are more of a challenge from technical, regulatory and investment perspectives

HOWEVER

- Industry is committed here also for the same drivers as slide 1
- Some major multi-nationals have long term global projects with > several MM $ plus investment in transitioning products away from animal use for batch release testing
- Others are investing on a case by case basis but still based on the same long term approach
- Industry are working internally on projects, through collaborations such as VAC2VAC and working through industry associations to lobby for and encourage change (eg global TABST removal, VICH GL proposal)

Global regulatory acceptance and consistency is critical for success

Licenced Products - Timelines

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Timelines to develop tests

In vitro test development timeline is 2-4 years – dependent on potential critical barriers such as reagents, target ID and on strategy

Registration/approval phase (EU / US): 1 year

Registration/approval markets outside EU/US: can take up to 2 years or longer to get approval in majority of markets (some markets might not approve at all)

- Example - took 1 company 4 years to get global approvals for canine vaccine Lepto ELISA tests

Typical timelines for *in vitro* transition implementation

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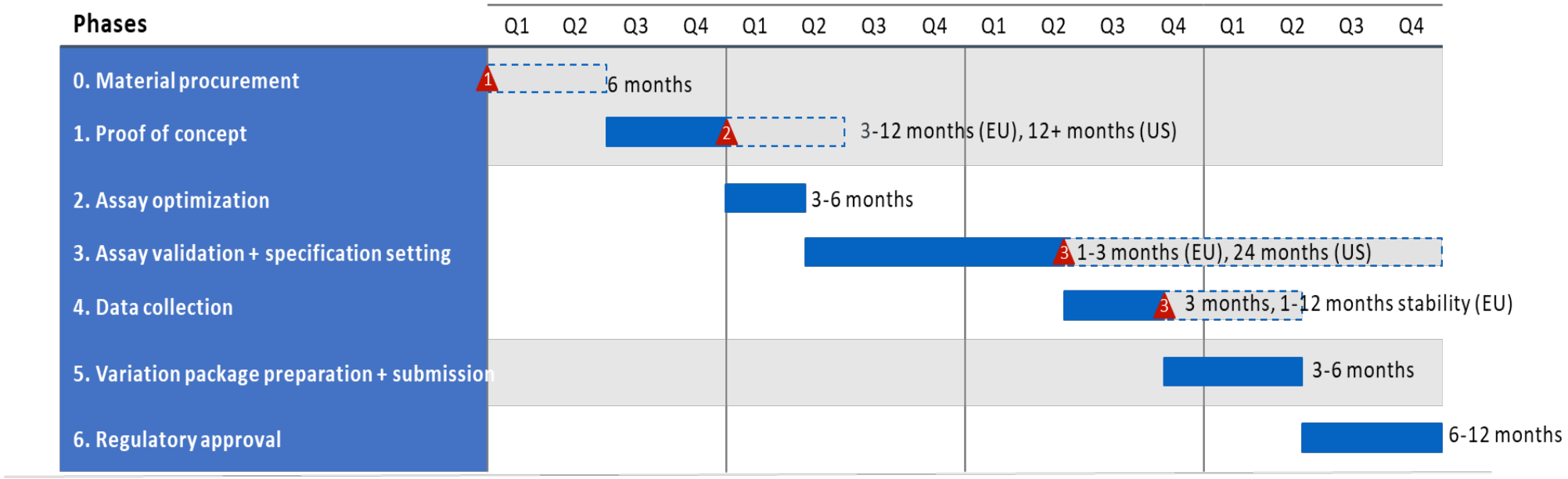

Critical barriers

Average timeline
Potential timeline w/ barriers

1. **Material procurement – biomaterials acquisition / monoclonal generation)** may be required before proof of concept can begin
2. **Proof of concept – antigen recovery is unpredictable,** heavily impacted by interactions between selected adjuvant and antigens
3. **Additional test required –**
   - **US – additional reference qualification test performed by central development team**, cannot begin until ELISA feasibility and stability tests are ready for validation (~24 months)

Note – in the US current approach can require repeating pivotal efficacy studies to set specifications – this can add a further 1-2 years and increases risk. This can be very challenging and complex for old products

Licenced Products - Investment

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Investment – resources needed

- *In vitro* assay development typically needs at least 1 full time equivalent (FTE)/assay during the first 2 years (assay development, validation, specification setting).

- Extra resources are needed for the regulatory process and implementation of the assay into routine QC - both assays may need to be run during validation phase and until all regulatory approvals are in place (FTE and OOP costs for dual testing).

Return on investment needs to be justified case by case

- Animal use reduction benefit
- Consider supply continuity – reduced test failures/repeat testing
- Speed for release tests – days/hours vs weeks/months
- Sustainability
    - Reagent sustainability for generation and long-term supply
    - Environmental – carbon footprint of testing time and animal facilities

Technical considerations

- Adjuvant tests
  - If there is no existing test for adjuvant its not a 1:1 replacement
  - Test for adjuvant is also needed for EU – these can be challenging
- Generation consistency data
  - Need to validate test then generate data
  - Need to understand product consistency to establish specifications
- Need for in-process antigen quantitation tests
  - Many old products are formulated on pre-inactivation titre or other variable methods
  - This can mean that formulation consistency/predictability is variable*
  - *In vitro* antigen quantitation tests often need to be implemented at the same time as *in vitro* potency tests
  - Improves formulation accuracy and support specification setting and reduces risks
- Regulatory needs for relating antigen content to efficacy
  - Need to support specifications
  - Varies across regions depending on acceptance of consistency to set specifications
  - Consistency vs clinical data
  - Relates to reference qualification also

* This is a major risk in the US and needs to be understood

Technical considerations

- Reference qualification differences
  - EU allows in vitro qualification
  - Other regions may require a new animal challenge test to establish the reference
- Justify choice of target epitope
  - For antigen quantitation need to justify biological relevance of target
  - Direct relevance/link to efficacy eg Rabies G protein
  - In Direct link – surrogate used for antigen quantitation
- Changes in product manufacturing might require re-qualification of assay
- Stability indicating properties
  - Need to understand if assays you are using are stability indicating
- Reagents availability

Investment/technical challenges

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- Justifying investment for low volume/limited market products
  - The investment can be bigger than product revenue
  - Collaboration opportunities can be helpful to move these forward

- Multi-valent products where a single animal test supports multiple antigens through serology
  - A new test needs to be developed for each component
  - Animal use is still needed until all antigens are addressed

Experiences so far

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Regulatory

- Approach to spec setting consistency vs clinical data
- Different expectations from different regions
- Challenges justifying relevance of target for *in vitro* test
- Supporting the discrimantory power of the *in vitro* approach (ensuring sub-potent batches would be detected)
- Multiple post *in vitro* methods approved over the last 2 years.
- Health authorities' interaction preceded these submission to increase POS
- HA supportive but technical questions sometimes with commitment to “recalculate specification”
- Basis typically “consistency of production” but questions on correlation received.
    - In Non-EU we are gaining experience.
      Russia and Brazil (*in vivo* batch test in national law)
      India, pending.
      China, frustratingly slow..
      No other show stoppers yet.
      Helpful to have Rabies monograph update (including *in vitro* reference)
- Re-testing by authorities presents challenges

Regulatory/political environment

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EU very open, no legal barriers and big focus on 3Rs/alternatives

US – very open on new products, bigger challenges with existing ones – some legal changes needed (eg TABST/ATT in 9CFR; needs more alignment with VICH GL for exemptions)

AUS – there is significant pressure on manufacturing sites from local animal welfare legislation to stop/reduce animal testing for product release

Other markets - there are still significant challenges in many markets to accept non-animal release testing BUT

- International lobbying is helping
- Initial submission with no animal testing and push back on requests will help
- Messaging on consistency approach and manufacturing quality control
- US and/or EU approval first
- Pre work with NCAs before submission to help facilitate approval especially for new technology methods

Industry needs predictability and global regulatory acceptance to continue to invest in alternatives

EU v US experience - examples

- Difference in level of detail in US outlines vs EU – EU has much more detailed production ranges and in process controls with less HA oversight for batch release. US has less detail in the Outlines but has HA oversight for release of each batch/serial (Many EU countries do still do OBPR control)

- General approach to manufacturing/testing data and potency testing is different

- Higher barriers in proving relevance of target

- More often requests for clinical data to support reference establishment and spec setting so more challenges for old products (focused on outcome-based assessments). US draft guidance in progress that could reduce animal testing required to support the reference for *in vitro* methods.

- Important to work with USDA from early stages for a new potency test approach

Conclusions

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- **Industry are committed to phasing out the use of animals for batch release testing**
- **It will be a long road, but we are making progress**
- **Investing in technology for new products will help progress understanding for existing ones**
- **Early dialogue with regulators helps both for regulatory approval and when re-testing by authorities is required with new tests/technologies**
- **Global consistency of expectations and regulatory acceptance remains a challenge**
- ***In vitro* technology and consistency approach will help us reduce animal use but also produce high quality products with consistent safety and efficacy as well as ensuring vaccine supply continuity**

Questions?