Zika - Vaccine platform specific regulatory considerations

H. Meyer, June 2016
General regulatory consideration on vaccine platforms

- Vaccines are complex biological products
- Each vaccine is described by its specific quality, efficacy and safety profile
- The concept of a vaccine platform, i.e. to build on previous experience with a similar vaccine is currently only defined for flu vaccines
- It requires that a manufacturer has a licensed vaccine with a well established production process, and good knowledge on the clinical performance
- Using the approved manufacturing process a vaccine against the new emerging flu strains is produced
- Safety and efficacy is established during the vaccination campaign
General regulatory consideration on product development

Comparability of batches used in Phase I/II trials (e.g. safety, dose finding), in emergency use campaign and commercial batches (including scale-up) is critical for licensing

- Are the batches intended for the use in clinical trials comparable to the batches investigated in non-clinical toxicity studies
- Is there an anticipated potential safety risk for the patient due to manufacturing changes introduced during development
  - Product and process related impurities
  - Characteristics of the antigen
Any changes to the formulation of the final product should be documented and justified with respect to their impact on quality, safety, clinical properties, dosing and stability of the final vaccine product.

Demonstration of a consistent and validated manufacturing process with a robust control strategy is expected at time of licensure.

Product specifications and acceptance criteria of commercial batches need to be clinically justified.

Stability must be evaluated through all stages of development.

Non-clinical toxicity studies should include reproductive and pre-/post-natal developmental studies.
# Overview on Zika vaccine candidates

<table>
<thead>
<tr>
<th>Institution</th>
<th>Technology</th>
<th>Status &amp; timelines</th>
<th>Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bharat</td>
<td>Inactivated purified virus as priority project; VLP with pRME protein</td>
<td>Preclinical work ongoing, GMP lots 3Q2016</td>
<td></td>
</tr>
<tr>
<td>Bio-Manguinhos / Fiocruz</td>
<td>Inactivated purified; YF17DD chimeric; VLP; DNA</td>
<td>Work initiated</td>
<td>Under consideration</td>
</tr>
<tr>
<td>Butantan</td>
<td>Live dengue recombinant; inactivated purified</td>
<td>Work initiated</td>
<td>Collaboration with US NIH</td>
</tr>
<tr>
<td>US CDC</td>
<td>DNA plasmid expressing VLP; live recombinant adenovirus</td>
<td>Work initiated</td>
<td></td>
</tr>
<tr>
<td>Hawaii Biotech</td>
<td>Insect cell line produced recombinant proteins plus Hydrogel or proprietary adjuvant from collaborator</td>
<td>Work initiated. GMP lots 4Q2016</td>
<td>Under discussion</td>
</tr>
<tr>
<td>InOvio/GeneOne</td>
<td>DNA – electroporation; work initiated</td>
<td>Preclinical work initiated</td>
<td></td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>Lentivirus-vectored, measles vectored</td>
<td>Work initiated</td>
<td>Measles vectored work in collaboration with Themis</td>
</tr>
<tr>
<td>NewLink</td>
<td>Purified Inactivated virus</td>
<td>Work initiated, clinical evaluation 2018</td>
<td></td>
</tr>
<tr>
<td>US NIH</td>
<td>Zika targeted mutation live attenuated (longer-term), DNA, live VSV recombinant</td>
<td>Work initiated</td>
<td>Various</td>
</tr>
<tr>
<td>Novavax</td>
<td>E protein – nanoparticles</td>
<td>Preclinical work initiated</td>
<td></td>
</tr>
<tr>
<td>Replikins</td>
<td>Synthetic replilink peptides</td>
<td>Preclinical work initiated</td>
<td></td>
</tr>
<tr>
<td>Sanofi</td>
<td>ChimeriVax (YF17D); other undisclosed technologies</td>
<td>Work initiated</td>
<td>Under consideration</td>
</tr>
<tr>
<td>Themis Bioscience</td>
<td>Measles vaccine virus vector (live)</td>
<td>Work initiated</td>
<td>Institut Pasteur</td>
</tr>
<tr>
<td>Valneva</td>
<td>Purified inactivated vaccine</td>
<td>Work initiated</td>
<td></td>
</tr>
</tbody>
</table>
Considerations for emergency use

Inactivated vaccines

- Licensed inactivated flavivirus vaccines (TBE, JE) with proven efficacy and acceptable safety profile in all age groups from 1 year onwards
- Traditionally, there is no contraindication for pregnancy and immunocompromised patients (e.g. HIV patients)
- However, non-clinical reproductive and pre-/post-natal developmental studies are required
- Various vaccination and dosing schedules need to be evaluated
- Two doses of vaccine might provide short-term protection, but antibody persistence and further booster immunisations need to be considered
- Production capacity:
  - It is unlikely the required yield of 100 Mio doses per year can be delivered by one manufacturer alone
  - Interchangeability of vaccines?
Considerations for emergency use

Live attenuated / Vector based vaccines

- Attenuation need to be balanced between safety and immunogenicity
  - High level of attenuation might result in a good safety profile but induces a week immune response
  - Low level of attenuation might be associated with neurovirulence, viremia, and undesirable side effects but a strong immune response
- Level of attenuation need to be demonstrated in animal models
- Neurovirulence testing
- Genetic stability in production and clinical use
- Risk of virus shedding and transmission needs to be addressed
- Vector-based platforms: safety data base from other candidate vaccines supportive to judge the risk derived from the vector for approval of clinical trials but not for licensure
Considerations for emergency use

Recombinant derived antigens/VLP

- Extensive physicochemical characterization of the vaccine antigen (e.g. structure, level of posttranslational modifications, particle size and distribution) is expected
- Quantitative and qualitative evaluation of antibody response
  - Antibody response comparable to natural infection?
  - Thorough evaluation in animals and humans
- Various vaccination and dosing schedules need to be evaluated
- Likely to be safe in pregnant women
  - Non-clinical reproductive and pre-/post-natal developmental studies are required
Considerations for emergency use

DNA / RNA vaccines

- Use of a new delivery system or route of administration?
- Training of personnel essential to avoid misuse
- Quantitative and qualitative evaluation of antibody response
  - Antibody response comparable to natural infection?
  - Thorough evaluation in animals and humans
- Various vaccination and dosing schedules need to be evaluated
Consideration for emergency use

Adjuvants:

- Alumn is used since decades in various human vaccines and has a proven safety profile.
- Alumn adsorbed vaccines must not be frozen due to reduced immunogenicity (e.g. Hep B) and higher reactogenicity.
- Other well-known and approved adjuvants system might be considered especially if already shown to be safe in pregnant women.
- Owing to the complexity of novel adjuvanting systems (e.g. MPL, MF59, AS03) same rules and principles apply for manufacturing as for the vaccine antigens.
- Use of novel adjuvants need
  - to be shown to be safe in non-clinical toxicological and safety studies,
  - an extensive safety data base is expected.
- Dose-finding studies should consider various amounts of adjuvants.