Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use		Product development considerations and assumptions
	Preferred		
Indication for use	Prevention of Zika virus-associated serious complications, in particular congenital Zika syndrome.		Primary goal: Prevention of Zika virus (ZIKV) infections of any severity, in order to prevent or reduce serious complications such as congenital Zika syndrome. For clinical trial endpoints, prevention of clinical illness has been selected. Clinical illness refers to a virologically-confirmed case of ZIKV illness as defined by WHO/PAHO (http://www.paho.org/hq/index.php?option=com_content&view=article&id=11117&Itemid=41532&lang=en) The prevention of ZIKV infection (sterilising immunity) would be an alternative, but durable sterilising immunity might be difficult to achieve based on experience with other flavivirus vaccines. Alternatively or in addition to prevention of clinical disease, the prevention of infection could be estimated by measuring the absence of virus or viral RNA in any specimen including blood, urine, saliva, serum, vaginal secretion, semen or by measuring the absence of an anamnestic immune response to wild-type ZIKV infection immediately post-vaccination with specific serologic tests. The assumption is that a reduction in viraemia below a threshold will reduce likelihood of transmission to the Aedes vectors, prevent/reduce clinical illness, and prevent infection of the foetus and possibly placenta, thereby resulting in prevention of congenital abnormalities. While it is hoped that preclinical models will support this assumption, it will have to be validated through effectiveness studies post-licensure.

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use Preferred	Product development considerations and assumptions
		If prevention of clinical illness, and possibly infection, is not feasible to assess in a controlled clinical trial during a current outbreak, effectiveness will need to be studied post-authorization. Assuming it is infeasible to do so pre-licensure, assessment of effectiveness against the longer-term sequelae of Guillain-Barre Syndrome (GBS) and congenital ZIKV syndrome will be needed post-authorization.
Contraindication	No contraindication for use during pregnancy or in lactating women Hypersensitivity to the active substance or to any of the excipients Relative contraindication: Potential exclusions: pre-existing neurologic or autoimmune disorders, immuno-suppressed individuals, in particular for live-attenuated vaccines.	Pregnant women are not the target population but rather individuals prior to puberty; nevertheless, the theoretical risk of the vaccine may not preclude the exceptional use during pregnancy or in lactating women or inadvertent use in pregnancy.
Target population	Girls and boys below the reproductive age (e.g. <age of 9 years, although girls and women of child-bearing potential could also be considered in catch-up programmes. For non-replicating platforms, alternative age groups could be considered such as during early adolescence.	Ideal target population would be those where programmatic implementations can be combined with other childhood or adolescent vaccinations. Vaccination should be safe regardless of prior flavivirus exposure and vaccination history. Exclusions may need to be formulated in relation to subjects

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use Preferred	Product development considerations and assumptions
		that are at increased risk of developing GBS and related illnesses.
Vaccine platform	Live, attenuated or replication competent viral vaccine platform (e.g. chimeric) with acceptable safety data, ideally using platforms which have a history of supporting licensure of human vaccines. Non-replicating platforms such as inactivated /virus-like particle, subunit vaccines can also be considered from the safety perspective given the potential use in girls or women of child-bearing potential, however, multiple doses may be required in primary vaccination schedules as well as the need for more frequent boosters.	Live vaccines should be accompanied by additional pre-clinical safety data related to neurovirulence, risk of reversion, risk of shedding, risk of persistent infection and mosquito transmission. The development of replication-competent vaccine platforms is likely to achieve longer duration of immunity lasting into reproductive age. A booster dose may be required during adolescence, and there is a theoretical risk that a booster with a live attenuated or replication-competent viral vaccines inadvertently given to pregnant adolescents may be capable of crossing the placenta and infecting the foetus, and for this reason, live vaccines are not recommended for use during pregnancy. That said, live-attenuated vaccines have been given to women of reproductive age (MMR, YF, polio) in situations of increased risk of exposure, and inadvertent vaccination of pregnant women does occur in mass vaccination campaigns, and to date there is no evidence of increased adverse pregnancy outcomes due to immunization with a live-attenuated vaccine[i]. However, the grade of attenuation and absence of neurotropic properties for a live ZIKV vaccine would have to be well-characterized before use due to the pathogenic characteristics of the wild type virus. As such, the safety assessment and regulatory requirements are likely to require additional data compared to a non-replicating vaccine platform (see safety). A

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use Preferred	Product development considerations and assumptions
		large safety data base will be necessary, including reproductive toxicology studies in animal models. A booster with a non-replicating vaccine during adolescence or for women of child-bearing age could be considered. Non-replicating vaccine platforms that either do not use any adjuvant or use a well-characterized adjuvant in currently licensed vaccines, such as aluminium salts (e.g., Alum), would be preferable. The use of other adjuvants may, however, be justifiable if accompanied with superior performance (including durability of protective immunity), safety/reactogenicity, delivery data (e.g. reduced number of doses), and the potential for having data in pregnant populations. Both replicating and non-replicating vaccine platforms need to be assessed for their risk of GBS. Given the low incidence of GBS, such an assessment may only be possible in post-licensure studies in areas where where there is good ascertainment of GBS..
Safety/ Reactogenicity	Safety and reactogenicity at least comparable to WHO-recommended routine vaccines, providing a highly favourable risk-benefit profile, ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination.	It is anticipated the clinical development programme should include demonstration of acceptable safety in representative age groups, and in flavivirus-naive and -exposed subjects in the target population. In addition, data on inadvertent vaccination during pregnancy

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use Preferred	Product development considerations and assumptions
	Low risk of high fever.	should be collected systematically, including safety data ante-partum, during pregnancy, post-partum, and infant follow-up. Such information will be important for recommending bodies to advise on the use of the product in pregnant women. Absence of data supporting safe use of the vaccine in pregnant women must also be stated. Pregnancy registries or equivalent reporting mechanisms should be put in place before roll-out of the vaccine. Adverse event of special interest (AESI) should include: • GBS: Should studies of ZIKV-related GBS implicate a specific antigen in molecular mimicry, study of that antigen and immune responses against it need to be conducted. Should a direct pathogenic effect of the virus be confirmed, specific safety studies will be needed for live-attenuated vaccines. For all vaccine platforms, the risk of GBS will need to be monitored post-authorization. • Autoimmune disorders • Fever ≥ 38°C temporarily related to vaccination • Increased incidence of clinically apparent, severe, or atypical disease following natural flavivirus infection in vaccine recipients For all vaccine platforms, reproductive toxicology in a relevant model (lack of teratogenicity) will need to be conducted.
Measures of Efficacy	Demonstration of prevention of virologically confirmed ZIKV illness, in accordance with proposed WHO/PAHO definition[Error! Bookmark not]	The vaccine should preferentially have demonstrated efficacy against a well-defined clinical endpoint (e.g., prevention of ZIKV-associated disease of any severity compared to control, or

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use	Product development considerations and assumptions
	Preferred	
	defined., ideally in 80% of the population or higher. Acceptable thresholds for efficacy should be informed by updated vaccine impact models, and by market research with key stakeholders. Evidence of prevention of ZIKV infection would be desired, in addition to demonstration of prevention of ZIKV illness. Surrogate of immunity markers obtained from animal models, human challenge studies or cohort studies can be considered.	prevention of viraemia) in Phase 3 trials, ideally stratified by prior exposure to other flaviviruses (in particular dengue). If Phase 3 efficacy trials are not feasible, human controlled infection models (CHIM) could be considered to document efficacy data and immune correlates- If efficacy is demonstrated in a CHIM or if immunological endpoints are used as the basis of authorization, vaccine effectiveness needs to be demonstrated as a post-authorisation commitment. Such data may be essential to guide policy recommendations on the large scale use of the vaccine. If an acceptable analytically validated immunologic correlate or surrogate of protection is identified, it may be possible to base licensure on safety and immunogenicity studies. If a surrogate is used, the efficacy threshold may need to be stratified by known prior exposure to other flaviviruses (in particular dengue). The reduction in congenital abnormalities and the effect on GBS as secondary outcomes, which, due to their low incidence, may only be feasible to assess as a post-authorisation commitment. At a minimum, pre-vaccination serum samples should be collected from all participants in all trials to allow for analysis of safety, immunogenicity, and efficacy by flavivirus exposure at the time of vaccination, although testing may be driven by scientific need.

Annelie
Delete

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use Preferred	Product development considerations and assumptions
Dose regimen	Single-dose primary series is the preferred vaccine characteristics, potentially with a booster dose	It is possible that pre-existing immunity to other locally circulating flaviviruses such as dengue may prime the immune response to a ZIKV vaccine. It would be useful to measure the neutralising antibody titres to ZIKV and such flaviviruses, pre- and post-vaccination to evaluate the need for more than one dose in the primary series and also the need and spacing of booster doses, stratified by prior flavivirus exposure.
Durability of protection	Confers long-lasting protection predicted to be more than 10 year after administering the primary series and can be maintained by a single booster dose	Data on protection may be limited during vaccine development. Post-licensure Zika surveillance and outbreak detection may inform need and timing for booster doses. The role of immunity to other flaviviruses and the potential benefit of cross-protection should be evaluated and considered. Modelling of the immune responses, including assessment of T-cell memory over longitudinal studies, is highly desired. Immune markers could guide the need and timing for boosters.
Route of Administration	Injectable (IM or SC) using standard volumes for injection. Other routes could also be considered such as skin patches.	Standard routes of vaccination are preferred, but oral or sub-lingual delivery would be considered. ID administration could be considered if it constitutes a dose-sparing option and causes no undue safety concern.
Species coverage	Monovalent against ZIKV with documented neutralization of both ZIKV lineages (Asian and African) that infers coverage of all genetic and antigenic lineages.	
Product Stability and Storage	Shelf life of at least 12 months at -20°C. and	Storage at -20°C assumes this is not an alum-adjuvanted vaccine.

Vaccine characteristic	Preferred Product Characteristics (PPC) for Zika Vaccines for Endemic Use Preferred	Product development considerations and assumptions
	Shelf life of at least 6 months at 2-8°C or above. The need for a preservative is determined and any issues are addressed.* VVM: Proof of feasibility and intent to apply a vaccine vial monitor (VVM) to the primary container.	In the case of inactivated vaccines, WHO-approved preservatives for multi-dose vials include thiomersal and 2-phenoxyethanol.[ii,iii] Data on controlled temperature chain are desirable.
Co-administration with other vaccines	The vaccine can be co-administered with other vaccines licensed for the same age and population groups without clinically significant impact on immunogenicity or safety of the Zika vaccine or the co-administered vaccines.	Co-administration with HPV, tetanus, Tdap, MMR, Dengue and YF and JE vaccines, etc. depending on recommended in-country immunization schedule indicated for target population.
Presentation	Vaccine is provided as a liquid product in mono-dose or multi-dose (5-10) presentations with a maximal dosage volume of 0.5mL for i.m. or s.c. administration. Multi-dose presentations should be formulated, managed, and discarded in compliance with WHO's multi-dose vial policy [iii]	In line with Vaccine Presentation and Packaging Advisory Group (VPPAG) generic preferred product profile (gPPP).[iv] Preferred and minimal dose volumes may vary depending on route of administration. See note in 'Product Stability' on preservatives [iv, v]

[i] Global Advisory Committee on Vaccine Safety. Safety of Immunization during Pregnancy: A review of the evidence. Available at http://www.who.int/vaccine_safety/publications/safety_pregnancy_nov2014.pdf

[ii] WHO Policy Statement: Multi-dose Vial Policy (MDVP) 2014. Available at http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf

[iii] http://www.who.int/immunization/newsroom/thiomersal_information_sheet/en/

[iv] Vaccine Presentation and Packaging Advisory Group (VPPAG). Generic preferred product profile (gPPP), Version 2.1, August 2015 Available at http://www.who.int/immunization/policy/committees/VPPAG_Generic_PPP_and_Workplan.pdf?ua=120