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Date: 27 July 2020

Dear COVID-19 Vaccine Collaborator,

Re: Temptime expands Vaccine Vial Monitor (VVM) types for COVID-19 candidate vaccines

The WHO has published the COVID-19 Target Product Profile (TPP), which sets expectations for the vaccine characteristics: safety, efficacy, and duration of protection (1-3); as well as programmatic criteria (4-7), see table below[1]. Low- and middle-Income countries (LMICs) generally can manage a two-dose vaccine - as opposed to the preferred single-dose[2]; a parenteral administration versus oral/nasal or mono-dose versus multi-dose vial. The challenging characteristic, for LMICs, is Stability and Storage.

Summarized WHO Target Product Profile (TPP) COVID-19 vaccines, Version 3, 29 April 2020

#	Vaccine characteristic	Preferred	Critical or Minimal
1	Safety	Highly favourable benefit/risk profile with only mild, transient adverse events	Safety and reactogenicity whereby vaccine benefits outweigh risks
2	Efficacy	70%	50%
3	Duration of protection	1 year min.	6 months min.
4	Number of Doses	Single-dose	Two dose
5	Route of Administration	Oral / Nasal	Any route
6	Presentation (doses / vial)	Multi-dose for campaigns	
		Multi- or mono- dose acceptable	
		Multi-dose formulated, managed and discarded in compliance with WHO's multi-dose vial policy	
7	Stability and Storage	VVM, proof of feasibility and intent to apply to the primary container	
		Higher storage temperatures and high thermostability	Shelf life of at least 6-12 months. Storage as low as -60 -70°C (Long term: -20°C or higher) 2-week stability at 2-8°C

Stability and storage - WHO counts the VVM among the preferred characteristics for COVID-19[3] vaccines *(see green box above).* The VVM allows the administration of a vaccine confident that it has not been exposed to potentially damaging heat. Even if a vaccine was exposed to an inadvertent heat excursion, the VVM signals if the vaccine could still be used. Use of VVMs can help reduce wastage and increase coverage, as documented in polio and other immunization campaigns.[4]

Some of the COVID-19 candidate vaccines with viral vectors and/or nucleic acid components may likely require frozen or ultra-cold storage at -70°C (see yellow box in table). Financing for the

[1] Summarized TPP https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines
[2] Phase IV clinical studies post introduction needed for additional data on safety and booster dose requirements
[3] Proof of feasibility and intent to apply a VVM to the primary container
[4] Mean wastage rate, was 15.0% in the 1st round and decreased to 8.3% in the 2nd round using VVM, the equates to 6.7% of vaccine wasted, a reduction of -45%. *VVM Impact Study Turkey* O.Z. Asfar, B. Altay
Wastage decrease of 48.8% for OPV, 27.1% for DPT, 55.7% for TT and 23.8% for Hepatitis B with VVM and open-vial policy, *VVM Impact Study, Kingdom of Bhutan*, PATH

creation of an Ultra Cold Chain (UCC) in LMICs, is being put in place by Gavi, in the event this emerges as a requirement, during the clinical development of a lead vaccine candidate. The new Ebola vaccine, which uses a live non-replicating viral vector technology, is stored at -60°C to -80°C and requires specialized ultra-freezers[5]. When needed, the Ebola vaccine is taken out of the freezer, thawed for 4 hours, and then stored at 2-8°C, for only a few days, before being either used or discarded. At the time of the Ebola vaccine development there was no relevant VVM available. However, three new highly reactive VVMs are now under development, and should be available in Q4 2020, for COVID-19 vaccines which need ultra-cold storage and have limited stability at 2-8°C.

VVMs are available in different types, to cater for different vaccine heat stability profiles: VVM2, 2 days stability at 37°C, VVM11, 11 days stability at 37°C etc. The current range includes VVM2, VVM7, VVM11, VVM14, VVM30 & VVM250, and is being expanded to include 3 new VVMs that are more reactive than VVM2 for short shelf life refrigerated storage after removal from Ultra Cold Chain (UCC). The current VVM types and those in development cover the range from weeks at 2° to 8°C to over a year at room temperature. Temptime can develop additional VVM types to meet other product specific needs.

Temptime wishes to ensure that all necessary information about the current and new VVMs is available to relevant decision makers involved in COVID vaccine development, especially those considering LMIC programmatic and logistical needs. A summary of the key information on VVMs for COVID-19 vaccine, manufacturers and other decision makers is as follows:

- There are currently 6 WHO-prequalified VVM types, and 3 new specialized types are in development for short refrigerated shelf life vaccines stored at frozen or ultra-cold storage temperatures.
- VVM capacity is not an issue for COVID-19 vaccines, current annual production (without COVID) is 600 million VVMs, which can be increased by 5 times to 3 billion VVMs depending on the requirements. More than 2 billion VVMs would be available for COVID vaccines.
- 2 billion VVMs on a 5-dose vial would mean VVM supply can meet a Global annual demand of 10 billion doses of COVID vaccines, or 20 billion doses on a 10-dose presentation.
- Applying VVM to vaccines is a well-established procedure. There are over 80 manufacturers who have experience and know-how in applying VVMs, and Temptime has technical staff to support new vaccine suppliers regarding VVM application procedures during the labelling stage of production

The question of COVID-19 vaccine storage requirements is - with a few exceptions - nearly impossible to answer in advance of the establishment of the final formulations, and this may be especially true for the new technologies with limited experience and long-term stability data from previous projects with the same platform. Developers will likely have to be conservative, however some of the more traditional platforms and hopefully even the new technologies will be able to store the vaccine at +2 to +8^{0}C.

[5] The new Ebola vaccine rVSV-ZEBOV, is still-unlicensed and is being used under the expanded access exception

Stability data are usually being generated during the phase III studies and there has been a request for COVID vaccine developers to share relevant information as soon as possible to facilitate planning for the receipt, storage, distribution, and country-wide administration[6].

The application of a VVM, should not slow any of the COVID-19 vaccine developer's critical path, and should help ensure potent vaccines (without heat damage) are administered successfully, offering countries a better chance to overcome this pandemic.
If you require any additional information or have any questions, please feel free to contact me.

Best regards

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[6] Kartoglu et al *Logistical Challenges for Potential SARS-CoV-2 Vaccine and a Call to Research Institutions, Developers and Manufacturers*, Vaccine Volume 38, Issue 34, 22 July 2020, Pages 5393-5395 https://www.sciencedirect.com/science/article/pii/S0264410X20308422?via%3Dihub