Freeze damage resistant liquid formulations

Comparator: Use without innovation (i.e. current liquid formulations)

Section 1: Summary of innovation

1.1 Example images:

Image source: [a]

Image source: [b]

1.2. Description of innovation:

- Vaccines need to be stored at their proper temperature to maintain their potency, which is commonly at 2-8ºC.
- Vaccines can be exposed to multiple freeze-thaw cycles and long durations of sub-zero temperatures along the different segments of the cold chain. For freeze-sensitive vaccines, this can result in physical, chemical and immunological changes to the formulation, reduced potency of the vaccine, administration of sub-optimal vaccine, local reactions to the vaccine such as sterile abscesses, and increased wastage (if the freeze exposure is identified and the vaccine is discarded) (1).
- Many vaccines are freeze-sensitive, including those containing aluminium adjuvants. When vaccines containing aluminium adjuvant are frozen, the antigen-adjuvant particles agglomerate and sediment which results in the irreversible loss of potency.
- Freeze damaged vaccines can be detected using the “shake test”, but it is not always performed given lack of training and the need for a control vaccine to conduct the test.
- Developing novel freeze stable formulations using different excipients could prevent agglomeration and stabilize the potency of vaccines.
- The addition of excipients such as glycerin, polyethylene glycol 300, or propylene glycol (PG) have been demonstrated to reduce the freeze sensitivity of Hepatitis B vaccine (2) and other vaccines containing aluminum adjuvant including diphtheria, tetanus and pertussis (DTP); and pentavalent (hepatitis B, DTP, *Haemophilus influenza* type b) vaccines (3).

[a] https://www.myelomacrowd.org/wp-content/uploads/2015/05/vials.jpg
[b] https://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/PIDAC/Pages/Infection-Prevention-and-Control-for-Clinical-Office-Practice-Multidose-Vials.aspx

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1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Freeze protection technology Glycerin, polyethylene glycol (PEG) 300, and propylene glycol	**PATH** https://www.path.org/	Studies have demonstrated that the addition of these excipients may stabilize vaccines from freeze damage (4). The freeze protection stabilizers have been successfully applied to vaccines in lab and preclinical studies with hepatitis B, pentavalent, diphtheria, tetanus toxoid and pertussis vaccines.

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- Use of freeze-sensitive vaccines in immunization programmes (such as vaccines formulated with aluminium-salt-based adjuvants, and also IPV) is increasing and various studies have reported that vaccines are frequently exposed to freezing temperatures during storage and transport. Furthermore, freeze-damage can be hard to detect (5–7).
- Efforts to improve freeze resistance of liquid formulations would help to maintain the potency of the vaccines exposed to unintended freezing in the cold chain and help prevent vaccine wastage and/or administration of freeze-damaged vaccines with reduced potency.
- Additional benefits of improving the freeze resistance of vaccines can potentially include protection of antigens exposed to higher temperatures, which has been demonstrated with the addition of the excipient propylene glycol to the hepatitis B vaccine (2).
- Addition of specialised freeze-protection excipients could potentially be used for some non-adjuvanted, freeze-sensitive liquid vaccines (8).
- Identifying freeze exposure is difficult due to the lack of availability of vial-level freeze indicators and insufficient use of the shake test in LMICs.

2.2 Key challenges:

- There are certain challenges related to the innovation, however they do not impact the assessment of innovation in phase I. Please refer to 2.3 (below) for challenges which will be assessed in the phase II, when they are applicable.

2.3 Additional important information

- If the freeze production technology is added during initial vaccine research and development, the benefits can be obtained at minimal cost. Therefore, application of improved stabilisation methods into early vaccine design and development should be encouraged.
- Reformulation of vaccines can be costly and time consuming due to the need to assess the impact of the added excipient on the product via laboratory and clinical studies and to obtain regulatory and WHO prequalification approvals, which can prohibit support and financial investment from donors and interest from manufacturers. At present, there is little incentive for manufacturers to make such investments for currently approved vaccines.
- Each new formulation would require clinical testing, regulatory approval and WHO PQ for licensure, which is time consuming and requires investment.
- Selecting suitable excipients and identifying the concentrations for use, when to incorporate them during manufacturing etc, requires screening, and significant amount testing during the developmental process.

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SECTION 3: Evaluation criteria

3.1 Health impact criteria

Indicator: Ability of the vaccine presentation to withstand heat exposure

*Legend: Green: **Better** than the comparator: The innovation includes features that may increase heat stability; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator: The innovation includes features that may decrease heat stability, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 2.

Ability of the vaccine presentation to withstand heat exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve heat stability?	Neutral	The freeze technology applied to formulations is not expected to improve the stability of vaccines exposed to high temperatures. As such, the innovation would likely have the same heat stability as the comparator. However, it is possible for some excipients to protect against both freezing and high temperatures, but it would depend on the vaccine.

	***No difference** to the comparator*

Indicator: Ability of the vaccine presentation to withstand freeze exposure

*Legend: Green: **Better** than the comparator: The innovation includes features that may increase freeze resistance; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator: The innovation includes features that may decrease freeze resistance, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 3.

Ability of the vaccine presentation to withstand freeze exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve freeze resistance?	Better	The freeze technology applied to freeze-sensitive formulations of vaccines with aluminium adjuvants improves their stability when exposed to freezing temperatures (4).

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Category: *Formulation*

Innovation: *Freeze-damage resistance liquid formulations*

Comparator: *Use without innovation (i.e. current liquid formulation)*

	Better *than the comparator*

3.2 Coverage and equity criteria

Indicator: Ease of use[c]

Legend: Dark Green: ***Considerably better*** *than the comparator: Better for all applicable parameters; Green:* ***Better*** *than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White:* ***Neutral****, no difference with the comparator; Yellow:* ***Mixed****: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red:* ***Worse*** *than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red:* ***Considerably worse*** *than the comparator: Worse for all applicable parameters, N/A: the indicator measured is* ***not applicable*** *for the innovation; Grey:* ***no data*** *available to measure the indicator.*

Table 4.

Ease of use	Parameters to measure against a comparator	Score	Assessment
• *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Does the innovation avoid reconstitution and is that an improvement?**	Neutral	The innovation and comparator both apply to liquid formulations only, so there is no change relative to the comparator.
	Does the innovation require fewer vaccine product components?	Neutral	The innovation only impacts the formulation and therefore vaccines with the innovation have the same number of components as the comparator.
	[d]Does the innovation require additional components or equipment (such as scanners or label readers)?	N/A	
	Does the innovation require fewer preparation steps and less complex preparation steps?	Neutral	The preparation of the vaccine is no different to the comparator.
	Does the innovation improve dose control?	Neutral	The innovation has no impact on controlling the dose of the vaccine.
	Does the innovation improve targeting the right route of administration?	Neutral	The innovation has no impact on targeting the right route of administration.

[c] Ease of use can prevent missed opportunities resulting from the complexity of preparation and administration procedures. It could also impact the ability for lesser trained personnel to administer the vaccine (incl. self-administration). It can be assessed based on usability data from field studies (or based on design of innovation if field studies not available).

[d] This parameter is only assessed for RFID/barcodes, for all other innovations it is not applicable (N/A).

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	No difference *to the comparator*

Indicator: Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities

*Legend: Green: **Better** than the comparator for one of the parameters; White: **Neutral**, no difference with the comparator; Red: **Worse** than the comparator for one of the parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 5.

Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • *Assessment of the potential to reduce stock outs based on the innovation's features*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Does the innovation require fewer components?	Neutral	Improving the freeze resistance of the vaccine does not impact the vial presentation or delivery device, so the number of components remain unchanged.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	The innovation does not impact labelling that facilitates product tracking. There is no change relative to the comparator

	No difference *to the comparator*

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Indicator: Acceptability of the vaccine presentation and schedule to patients/caregivers

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters.*

Table 6.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Painful or not painful	Neutral	The addition of freeze-protecting excipients can increase the osmolality of the vaccine formulation (9), which can influence the pain felt on injection (10).There are no clinical data on this point however.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	Vaccinators and recipients are unlikely to be aware of the freeze resistance properties of the vaccine and the impact it has on the shelf-life, storage or potency. Therefore, this innovation is not anticipated to impact acceptability of the vaccine presentation to patients/caregivers.
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers		

	***No difference** to the comparator*

3.3 Safety criteria

Indicator: Likelihood of contamination

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 7.

Likelihood of contamination	Parameters to measure against a comparator	Score	Assessment
• *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?**	Neutral	Both the innovation and comparator are liquid formulations, so there is no change relative to the comparator.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	Contamination risk during filling the device would be no different to the comparator.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Neutral	Contamination risk based on the preparation steps would be no different to the comparator.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	Contamination risk based on the reuse of the delivery device would be no different to the comparator.
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Contamination risk based use of sterile components would be no different to the comparator.

	No difference *to the comparator*

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Category: *Formulation*

Innovation: *Freeze-damage resistance liquid formulations*

Comparator: *Use without innovation (i.e. current liquid formulation)*

Indicator: Likelihood of needle stick injury

*Legend: Dark Green: **Considerably better** than the comparator: Better for all applicable parameters; Green: **Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; Red: **Worse** than the comparator: Worse for some of the applicable parameters AND no difference for the rest of the parameters; Dark Red: **Considerably worse** than the comparator: Worse for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 8.

Likelihood of needle stick injury • *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	Parameters to measure against a comparator	Score	Assessment
	Does the innovation contain fewer sharps?	Neutral	An improved formulation to impart freeze resistance would have no impact on the actual administration of the vaccine in terms of route, site or depth. There would therefore be no change relative to the comparator.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Neutral	
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	

	No difference *to the comparator*

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3.4 Economic costs criteria

Indicator: Total economic cost of storage and transportation of commodities per dose[e]

*Legend: Dark Green: **Considerably better** than the comparator: Reduces the volume per dose for applicable parameters; Green: **Better** than the comparator: Reduces the volume per dose for either of the applicable parameter, and there is no difference for the other; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the volume for one of the parameter, and increases the volume for the other parameter compared to the comparator; Red: **Worse** than the comparator: Increases the volume per dose for either of the applicable parameters, and there is no difference for the other; Dark Red: **Considerably worse** than the comparator: Increases the volume per dose for both parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 9.

Total economic cost of storage and transportation of commodities per dose	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Does the innovation reduce the volume per dose stored in the cold chain?	Neutral	Improving the freeze resistance of the vaccine does not impact the volume of the vaccine vial.
	Does the innovation reduce the volume per dose stored out of the cold chain?	Neutral	Improving the freeze resistance of the vaccine does not impact the volume of other components stored out of the cold chain.

	***No difference** to the comparator*

Indicator: Total economic cost of the time spent by staff per dose

*Legend: Dark Green: **Considerably better** than the comparator: Reduces time for all applicable parameters; Green: **Better** than the comparator: Reduces time for either, and there is no difference for the other one; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the time for one of the parameters, and increases the time for the other parameter; Red: **Worse** than the comparator: Increases the time for either of the applicable parameters; and there is no difference for the other one; Dark Red: **Considerably worse** than the comparator: Increases time for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

[e] The assessment of the indicator is volume-related and builds upon PATH's VTIA analysis. A directional estimation is made at this stage, and a better evaluation will be done in Phase II with more antigen-specific data.

Table 10.

Total economic cost of the time spent by staff per dose	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Neutral	Improving the freeze resistance of the vaccine does not impact the process of vaccine administration.
	[f]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	There are no additional attributes impacting stock management, relative to the comparator.

	No difference *to the comparator*

Indicator: Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)

*Legend: White: **Neutral**: NO there are no one-time/upfront or recurrent costs and this is not different than the comparator; Red: **Worse** than the comparator: YES there are one-time/upfront or recurrent costs.*

[f] This parameter only applies to barcodes and RFID to capture the benefits for stock management processes, not based on the number of components, but the specific features of the innovation.

Table 11.

Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Are there one-time upfront costs that will be incurred for use of this innovation or recurrent costs that will be incurred for use of this innovation?	Neutral	No. Similar to the comparator, there are no upfront or recurrent costs required with this innovation (other than training costs which would be required with any innovation).
			No difference *to the comparator*

3.5 Secondary criteria on potential breadth of innovation use

Indicator: Applicability of innovation to one or several types of vaccines

Table 12.

Applicability of innovation to one or several types of vaccines • *What vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	The innovation could be applied to all vaccines containing aluminum-salt adjuvant and potentially to other freeze-sensitive vaccines, such as IPV as well. Hepatitis B vaccine is an example of a liquid freeze-sensitive vaccine, which includes an aluminum adjuvant.

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Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combination • *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	The innovation is not expected to facilitate novel combinations of vaccines. It is possible that incompatibility between the excipients and some vaccine components means that it might not be suitable for use with some combination vaccines.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	**Assessment**
Type of study	Literature reviews, range of field studies in LMICs and laboratory testing and preclinical studies.
Inconsistency of results	Low
Indirectness of comparison • *Indicate the setting in which the study was conducted (low, middle or high income setting);* • *Comment if the data is on non-vaccine application of the innovation*	• LMIC setting • Vaccine specific

Overall assessment:	*Moderate*	

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4.2 List of technical experts, manufacturers and/or technology developers interviewed for inputs:

Table 15.

Expert/type	Organisation/contact details	Notes
N/A	N/A	No interviews conducted.

4.3 List of technical experts, manufacturers and/or technology developers that have reviewed and provided feedback/input to the technical notes (TN):

Table 16.

Reviewers	Organisation/contact details	Notes
Fatema Kazi	GAVI, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Developed and reviewed TN
PATH Medical Devices & Health Technologies Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH Debra Kristensen dkristensen@path.org	Reviewed TN
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	External reviewer of TN

4.4 References:

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