Heat-stable/controlled temperature chain (CTC) qualified liquid formulations

Comparators: Use without innovation[a] (i.e. current liquid or lyophilised formulation)

Section 1: Summary of innovation

1.1 Example images:

1.2. Description of innovation:

- Historically, vaccines are most commonly formulated and packaged as liquids. Liquid formulations require simpler fill/finish and administration processes than other formulations.
- Heat stable liquid formulations (such as those incorporating stabilizing agents) enable vaccines to be exposed to high temperatures (e.g., a minimum of 3 days at ≤40^{O}C) without losing their potency and can thus be CTC qualified.[b] Such formulations require optimized properties (e.g. buffer, pH, salt concentrations and stabilizing excipients) to prevent denaturing of proteins and reduce the occurrence of damaging chemical reactions caused by increasing temperature.
- Heat-stabilized vaccines will differ in the length of time they can be stored in a CTC and the maximum temperature they can endure while remaining stable and potent, and some vaccines will not be able to be reformulated into a heat-stable liquid.
  Each vaccine will require an individual development process to identify an appropriate stabilizing formulation. High-throughput screening methods can be used to expedite formulation optimisation (1).

1.3 Examples of innovations and developers:

There are currently two liquid vaccines that are thermostable and qualified for CTC use. These are: Merck's Gardasil® 4 (quadrivalent human papillomavirus vaccine) that is labelled to allow use at temperatures up to 42°C for 3 days and Shantha Biotechnics Shanchol™ (oral cholera vaccine) that is labelled to allow use at temperatures up to 40°C for 14 days.

A number of vaccine manufacturers are in the process of qualifying their existing and pipeline liquid vaccines for CTC use.

[a] no comparator or equivalent existing device.
[b] WHO. Controlled Temperature Chain publications and guidance.
https://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/index1.html

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Developers have created approaches to stabilizing formulations, some of which are proprietary, that may be applicable to a variety of vaccines to improve their heat stability in liquid formulations. Examples are shown below in Table 1.

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
A stabilising liquid formulation for hepatitis B vaccines(2,3)	**Aercor Limited**, Cambridge, UK. (http://arecor.com/), PATH, Seattle, WA, USA, and University of Colorado, Denver, CO, USA	Arecor's formulation technology improves the stability of proteins/ and vaccines in aqueous environment such that they can be stored for extended periods of time at ambient temperatures without significant loss of activity. The liquid formulation hepatitis B vaccine was shown to be stable at 37ºC and 45ºC for up to 6 months (3,4).
Stabilising and protecting solutions (SPS)	**Leukocare**, Munich Germany https://www.leukocare.com/improving-vaccines.html	The company specialises in developing protein stabilising solutions to increase the shelf life of proteins in liquid formulations.
Heat stable liquid rotavirus vaccine	**Inventprise**: https://inventprise.com	The innovation is an oral vaccine composed of a micronized freeze-dried particle emulsion with buffering excipients in a non-aqueous liquid. The formulation is stable at 30°C and 40°C for at least twelve months. Extrapolations from the 12-month stability data indicate a shelf life of more than two years at 30°C, and six months at 50°C.

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- A liquid presentation offers benefits over those that require reconstitution as the vaccine requires no preparation and improves safety by eliminating the risk of using the incorrect diluent. Injectable vaccines can be withdrawn directly from the vial with a syringe and oral vaccines can be directly delivered via droppers or tubes.
- Facilitates outreach programmes due to ability to be stored in CTC conditions.
- Compared to a dry presentation, this innovation has a smaller storage footprint as no diluent vial or reconstitution syringe is needed.
- Reduced storage and distribution costs if the stabilised vaccine can be kept in at CTC for part of its shelf life.

2.2 Key challenges:

- Formulating heat-stable liquid formulations is technically challenging and not always possible.
- In general, inactivated vaccines, protein and polysaccharide vaccines are more likely to be heat-stable in contrast to live-attenuated vaccines.

2.3 Additional important information

- Compatible with many existing manufacturing processes thus unlikely to need new equipment.
- Improves vaccine effectiveness and reduces vaccine wastage when cold chain breaks occur due to improved heat stability.
- For manufacturers, vaccine stability could improve bulk production efficiencies and reduce risk of recalls or withdrawals when the cold chain is breached during storage or distribution and reduce shipping and storage costs.
- Heat stable liquid formulations that demonstrate suitability for CTC storage may require additional stability testing to obtain CTC on-label licensure and go through WHO prequalification process. Manufacturers can be reluctant to commit resources for the necessary stability testing and re-licensure (5).
- In cases where reformulation of existing vaccines is required to achieve adequate heat stability, costs to the vaccine manufacturer can be high and would need to include the cost for pre-clinical and possibly clinical testing for regulatory approval.
- Training of vaccinators on general CTC practices would be required. If new delivery strategies are enabled by CTC use, guidelines will have to be developed and users trained.
- Different vaccines may be able to be stored in a CTC for different periods of time, and some vaccines will still need to be kept in the cold chain until use, thus users will need to be trained to understand the different storage parameters for each vaccine. To identify vaccines that have been exposed to excessive temperatures when stored in a CTC, a peak threshold temperature indicator must be used along with a VVM.

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	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation have features that may improve heat stability?	Better	Better	By definition the innovation will improve heat stability and ability of the vaccine to withstand accidental, or intentional (i.e. CTC use) heat exposure. The degree of heat stability will be vaccine and formulation dependent.

Liquid	*Lyophilised*	***Better** than both comparators*

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	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation have features that may improve freeze resistance?	Better	Neutral	Accidental freezing can result in potency loss for freeze sensitive vaccines such as diphtheria, tetanus, pertussis, liquid Haemophilus influenza type b (Hib), hepatitis B, human papillomavirus, and inactivated polio virus(4). The cold chain protects vaccines from heat damage, yet often exposes them to freezing temperatures – especially when vaccines are kept in vaccine carriers or cold boxes with ice or un-conditioned icepacks or in domestic refrigerators. By reducing the need to be stored in the cold chain, a CTC-qualified formulation reduces the likelihood of the vaccine being exposed to freezing temperatures. However, as lyophilised vaccines are freeze resistant (6), there would no difference to this comparator.

Liquid	*Lyophilised*	***Better*** *than the liquid comparator,* ***No difference*** *to the lyophilised 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.*

[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).

Table 4.

Ease of use	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	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	Better	Heat stable liquid formulations do not require reconstitution, so are better than the lyophilised comparator. There would be no difference for liquid vaccines.
	Does the innovation require fewer vaccine product components?	Neutral	Better	
	[d]**Does the innovation require additional components or equipment (such as scanners or label readers)?**	N/A	N/A	
	Does the innovation require fewer preparation steps and less complex preparation steps?	Neutral	Better	
	Does the innovation improve dose control?	Neutral	Neutral	No difference due to the innovation.
	Does the innovation improve targeting the right route of administration?	Neutral	Neutral	

Liquid	*Lyophilised*	***No difference*** *to the liquid comparator* ***Better*** *than the lyophilised comparator*

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

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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**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Does the innovation require fewer components?	Neutral	Better	Compared to AD N&S for liquid vaccines, there would be the same number of components. Whereas, compared to AD N&S, recon syringe and diluent for lyophilised vaccines, there would be fewer components for the innovation.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neutral	Not affected by the innovation

Liquid	*Lyophilised*	***No difference** to the liquid comparator,* ***Better** than the lyophilised comparator.*

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, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

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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**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Painful or not painful	Neutral	Neutral	Unlikely to be affected by the innovation. Vaccines can have different osmolalities according to their formulations, which is linked to the excipients used, and is a factor associated with pain at the injection site (7).
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	Neutral	Not affected by innovation
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	Better	Better	Satisfaction with immunization services may be improved due to increased access to vaccines enabled by use in a CTC.

Liquid	*Lyophilised*	***Better*** *than both liquid and lyophilised comparators.*

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.*

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Table 7.

Likelihood of contamination • *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Parameters to measure against a comparator**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?	Neutral	Better	Overall the innovation will have no impact on contamination risk, other than removing some of the risks associated with reconstitution of currently lyophilised vaccines, assuming suitable heat-stable liquid formulations can be developed and thus reducing the number and complexity of the preparation steps.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	Neutral	
	Does the innovation require fewer preparation steps and less complex preparation steps?	Neutral	Better	
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	Better	
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Neutral	Overall the innovation will have no impact on contamination risk, other than removing some of the risks associated with reconstitution of currently lyophilised vaccines, assuming suitable heat-stable liquid formulations can be developed and thus reducing the number and complexity of the preparation steps.

Liquid	*Lyophilised*	***No difference*** *to the liquid comparator.* ***Better*** *than the lyophilised comparator*

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	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
• *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Does the innovation contain fewer sharps?**	Neutral	Better	As the lyophilised comparator requires additional sharp to reconstitute, the liquid innovation would be better as it would require fewer sharps.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Neutral	Better	No difference exists between the innovation and liquid comparator, however, fewer sharps are used for preparation compared to the lyophilised comparator.
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	Neutral	No difference
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Neutral	No difference
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Neutral	No difference

Liquid	*Lyophilised*	***No difference*** *to the liquid comparator* ***Better*** *than the lyophilised comparator*

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	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Better	Better	With CTC qualification, the volume stored in the cold chain is reduced just before vaccine delivery but there is no difference at the higher levels of the supply chain where the vaccine is still stored and transported in the cold chain.
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Neutral	Better	Compared to a liquid vaccine that is not qualified for CTC use, there is no difference in the volume stored out of the cold chain since an autodisable N&S is still needed for vaccine administration and this AD N&S is stored and transported out of the cold chain. Compared to a lyophilized vaccine, the volume stored out of the cold chain for a liquid vaccine is reduced since no diluent or reconstitution syringe is needed and this reduces the volume stored and transported out of the cold chain.

Liquid	*Lyophilised*	***Better*** *than the liquid comparator.* ***Considerably better*** *than lyophilized comparator.*

[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.

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.*

Table 10.

Total economic cost of the time spent by staff per dose	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Better	Better	Time use may increase for some activities:[f,g] If the vaccine used in CTC has a separate peak temperature threshold indicator (PTTI) rather than one that is integrated on the vaccine vial monitor (VVM) the vaccinator has to check both the separate PTTI and VVM before administering the vaccine to ensure that the vaccine has not been exposed to excessive temperatures. Also, at the end of vaccination sessions, vaccinators have to mark vaccines that have been taken for use in CTC and separate them. For vaccines not in CTC use, the vaccinator only checks the VVM and does not have to mark the vaccines at the end of the day. Time use may decrease for some activities: Most notably, vaccinators may be able to reduce travel time when using vaccines in a CTC since they may be able to avoid returning unused vaccines to health facilities at the end of outreach sessions and in some cases can store the vaccines in their communities during the specified CTC duration. Using vaccines in CTC removes the time needed to prepare icepacks. A heat-stable liquid vaccine in comparison to a lyophilised presentation also offers time savings as it eliminates the need for the reconstitution step. Given there are more points for time saving than time increase, a heat stable

[f] https://apps.who.int/iris/bitstream/handle/10665/86018/WHO_IVB_13.04_eng.pdf;jsessionid=6D44CE229FAEED6BFA00D54CE81A12C9?sequence=1

[g] https://apps.who.int/iris/bitstream/handle/10665/86019/WHO_IVB_13.05_eng.pdf?sequence=1

				vaccine is ranked better than the comparators.
	[h]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	Neutral	Use of a vaccine in CTC or not (comparator) does not impact this parameter.

Liquid	*Lyophilised*	***Better*** *for both liquid and lyophilized vaccine comparators.*

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.*

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**	**Liquid comparator**	**Lyophilised comparator**	**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	Neutral	No. A liquid vaccine with improved heat stability would have no additional upfront/recurrent costs and would be better the comparator.

[h] 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.

Liquid	*Lyophilised*	***No difference*** *to both the comparators*

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	**Assessment**
• *What vaccines/antigens does the innovation apply to, based on technical feasibility?*	This innovation could potentially be applied to any vaccine, but inactivated/subunit vaccines are more likely to be feasible to achieve a CTC-qualified liquid formulation. HPV and hepatitis B birth dose are two VIPS priority antigens that WHO has prioritized for CTC use. The benefits of CTC-qualification are greatest for vaccines that are used in campaigns or special strategies.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combination	**Assessment**
• *Does the innovation facilitate novel combination vaccine products?*	The innovation has no impact on ability to facilitate vaccine combinations.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	Assessment
Type of study	Implementation studies of liquid (HPV vaccine) and dry (MenA) vaccine presentations in a CTC. Laboratory and preclinical testing of thermostable liquid formulations. Economic evaluations of thermostable liquid formulations.
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*	

Overall assessment:	*Moderate to high*	

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 Device and Health Technology Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH Debra Kristensen dkristensen@path.org	Reviewed TN
Julian Hickling Rebecca Jones	Working in Tandem Ltd julian@workingintandem.co.uk	Reviewed TN

4.4 References:

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