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

Comparators* : Use without innovation (i.e. current liquid or lyophilized formulation)

Section 1: Summary of innovation

1.1 Examples of innovation types:

Lyophilised formulation

Image source: [a]

Foam-dried, freeze-dried, and spray-dried formulations

Image source: [a]

1.2. Description of innovation:

The controlled temperature chain (CTC) is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen. A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding +40°C and for a defined duration, just prior to administration.[b] An example of a CTC qualified vaccine is the meningococcal A conjugate vaccine, MenAfriVac, which was granted a label variation by the appropriate National Regulatory Authority and WHO for its use in a CTC at temperatures of up to 40ºC for four days.[c]

The innovation being assessed refers to dry formulations that are heat-stable and CTC-qualified. Vaccines with these attributes are able to be exposed to ambient temperatures below a defined threshold temperature without losing their potency and have received regulatory and WHO prequalification approvals to allow CTC storage. Dry formulations vary in their sensitivity to heat and suitability for use in a CTC. Therefore, this innovation only considers a subset of dry formulations that meet these criteria.

Currently all dry vaccine formulations that are commercially available require reconstitution with a diluent and are delivered in a liquid presentation (injectable and oral routes). New delivery technologies, such as

* Single dose vials, rather than multi-dose vials (MDVs) were used for the comparator, because in most cases the innovation being considered is a single-dose presentation. However, when multi-dose vials are commonly used by countries for specific vaccines, a comparison against the multi-dose vial will also be conducted under Phase II for those vaccines if this innovation is prioritised.

[a] Lovalenti, P.M., Anderl, J., Yee, L. et al. Pharm Res (2016) 33: 1144. https://doiorg.ezp.welch.jhmi.edu/10.1007/s11095-016-1860-1.

[b] https://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/

[c] https://www.who.int/immunization/documents/WHO_IVB_13.04_5_6/en/

microarray patches and intra-nasal powder delivery devices) that incorporate novel dry formulations of vaccines are assessed in other technical notes (TN).

Drying vaccines to improve heat stability

Vaccines, in particular live-attenuated vaccines, are unstable when exposed to excessive heat. This results in protein degradation, dissociation of molecules and reduced potency. All of these degradation pathways are exacerbated by the presence of water. Therefore, these vaccines are more stable as a dry product with a low-moisture content of typically less than 3%(1). As a dry product, they are also not freeze-sensitive (2).

Each vaccine antigen has different inherent stability properties, and each dried vaccine formulation will have different stability at specific high-temperatures and will differ in whether it is eligible for CTC and if so, the length of time it can stay in CTC at a particular temperature-threshold. For instance, measles vaccines have moderate heat-stability (VVM14) whereas rabies vaccines (inactivated, but lyophilised) are very heat-stable (VVM30).[d]

Vaccine formulations are highly complex, and customized mixtures of excipients as well as drying methods are required to ensure formulations are stable in terms of pH, ionic strength, osmolality and other chemical/physical interactions, and to maintain vaccine potency(3).

Common drying processes are described below:

Freeze-dried formulations:

- Lyophilization is a complex multi-stage, batch process involving three stages: (I) freezing, (ii) primary drying and (ii) secondary drying to transform a liquid into a dry solid product, resulting in a dried cake in the final container which requires reconstitution before administration (refer to image).
- This method is used on an industrial scale, in particular for live-attenuated vaccines, and can also be used to produce dissolvable tablets for oral delivery (see separate technical note)(4)
- Several compounds/excipients (e.g. sucrose, amino acids, gelatine or serum albumin) are incorporated into the freeze-dried formulation in order protect the formulation against chemical and physical degradation during the freeze drying process(5).
- Lyophilized formulations are freeze-resistant and typically stored within the cold chain(2).

Foam-dried formulations:

- Foam drying is a desiccation process, whereby a solution is transformed into a dried foam structure in one single step. The method involves boiling or foaming of the solution under reduced vapour pressure followed by rapid evaporation, leaving behind a solidified foam structure(6).
- Unlike lyophilisation, there is no freezing step, so it can be used with freeze-sensitive vaccines.

Dry-powder formulations:

- Various processes can produce dry powder formulations – they include spray-drying, spray-freeze drying, and supercritical fluid drying. All of these methods result in the formation of a 'free-flowing' dry-powder with a defined particle size, that does not necessarily need reconstitution before administration (2). While research has been conducted applying these methods to vaccines, there are no commercially available vaccines produced by these methods.
- One-step processes include:

[d] https://www.who.int/immunization/programmes_systems/supply_chain/resources/VaccineStability_EN.pdf

- **Spray drying** is a continuous drying process based on direct contact with hot air at atmospheric pressure that results in the production of a dispersed fine powder(7). It is an established technique commonly used in the food, pharmaceutical and chemical industry.
- **Spray-freeze drying** Involves atomisation, freezing and drying, thus it combines elements of both spray drying and freeze drying. It can be carried out as a continuous process(8).
- **Supercritical fluid drying** is a mild single-step process that can transform fluids into a fine dry powder keeping proteins stabilized.

- Two-step processes include:
  - A combination of first drying the product (i.e. freeze-drying, vacuum drying, foam-drying) and then reducing the particle size to produce a powder form (i.e. milling). However, the additional production step can lead to contamination, damage the vaccine, and increase production costs (9).

CTC qualification

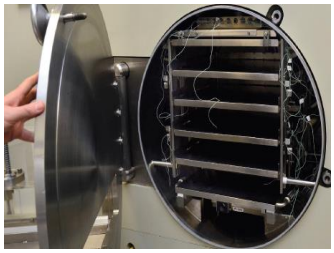
Several licensed vaccines are sufficiently stable for CTC qualification in their current formulation. For these vaccines, manufacturers need to conduct stability testing to support a CTC label indication and obtain a label variation allowing CTC use from the appropriate National Regulatory Authority and WHO. Vaccines in development can be optimized for heat stability as either dry or liquid products (see the Heat-Stable CTC Qualified Liquid Formulations Technical Note) and receive a CTC label indication during their initial licensure - often with minimal investment for this added feature.

For this analysis, we are assuming that the innovation results in a dried, heat-stable vaccine in a single-dose vial that is qualified for use in a CTC, requires reconstitution, and is delivered by injection.

1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Drying processes		
THERM-SB Technology	**Stabilitech** https://www.stabilitech.com/platform-technology/	A technology for thermo-stabilization of vaccines in a lyophilized state, using a specific formulation of sugars and molecules added to the vaccine during the fill-finish process.
Silk derived protein	**Vaxess Technologies** https://angel.co/vaxess-technologies	Uses silk derived protein to stabilize vaccines, with the intent to store and ship vaccines without refrigeration.
LPV platform	**VBI vaccines**	A combination of synthetic lipids in proprietary ratio that can tailored

Product name; Image	**Developer (place); website**	**Brief description, notes**
	Cambridge, MA USA www.vbivaccines.com	for specific formulations, The lipids reduce moisture content during lyophilisation cycles and prevent moisture ingress.[e]
CO2-Assisted Nebulization with a Bubble Dryer® (CAN-BD) technology and novel excipients.	**AKTIV-DRY** https://www.cmocro.com/company/Aktiv-Dry%2C+LLC/index.html	Using Aktiv-Dry's CO2-Assisted Nebulization with a Bubble Dryer® (CAN-BD) technology to prepare thermostable dry powder formulations with novel excipients for stability. They are developing dry wafer formulations for sublingual administration, rapid dissolving micro-powder for parenteral administration using auto-reconstitution devices and dry powder aerosol delivery.
Spray drying process. The ASEPTICSD™ Spray Dryer can be used for the production of sterile pharmaceutical products including vaccines.	**GEA Niro,** Copenhagen https://www.gea.com/en/productgroups/dryers_particle-processing-systems/spray-dryers/index.jsp	Develops and sells spray-dryers and conducts contract spray drying. Has carried out R&D work with vaccines, including Hepatitis B, meningitis A (10) and measles (PATH, unpublished).
Provide drying services (i.e. freeze-drying, spray-drying, vacuum drying)[f]: 	**Intravacc**[g] https://www.intravacc.nl/	Intravacc is a company that has experience in developing thermostable products (for both bacterial and viral vaccines) using a variety of drying methods. They also offer contract services for drying vaccines (11).

[e] https://www.vbivaccines.com/technology/thermostable-platform/
[f] https://www.intravacc.nl/media/1176/20170328-formulating-and-drying-vaccines-v11-zonder-snijlijn.pdf
[g] https://www.intravacc.nl/media/1145/20160712-factsheet-lyophilization.pdf

Product name; Image	**Developer (place); website**	**Brief description, notes**
Photo source: Freeze dryer with temperature sensors.		
Provide drying services (i.e. freeze-drying, spray-drying, vacuum drying)	**PATH** www.path.org	PATH's formulation lab can provide formulation services to improve the thermostability of a vaccine (12).
Preservation by Vaporization (PBV) – a vacuum foam drying technology.	**Universal Stabilization technologies (UST)** https://www.vitrilife.com/	PBV – a technology designed by UST to develop and produce thermostable dry powders of live attenuated vaccines and bacterial vaccines. The heat stable/dry formulations do not require reconstitution with diluent. They can be incorporated into devices for delivery through non-parenteral routes. These formulations can be produced in unit dose format or bulk format.
CTC-qualified vaccines		
MenAfriVac Meningococcal A conjugate vaccine. Lyophilised, intramuscular Photo source: [h] 	**Serum Institute of India Ltd** www.seruminstitute.com	The MenAfriVac vaccine can be used in a controlled temperature chain (CTC), for up to four days at ambient temperatures not exceeding 40°C.[h]

[h] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=196

Product name; Image	**Developer (place); website**	**Brief description, notes**
Schancol Inactivated cholera vaccine. Liquid, oral.  Photo source: [i]	**Shantha Biotechnics Ltd** www.shanthabiotech.com	Shanchol vaccine can be used in a controlled temperature chain (CTC), for up to fourteen days at ambient temperatures not exceeding 40°C.[i]
Gardasil, Human papillomavirus vaccine (quadrivalent). Liquid, intramuscular.  Photo source: [j]	**Merck vaccines** www.merck.com	Use allowed under extended controlled temperature conditions for up to three days below 42°C.[k]

[i] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=249
[j] https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=178
[k] https://extranet.who.int/gavi/PQ_Web/FormAttachment.aspx?ID=2465

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- Heat-stability/CTC-qualification can increase access to difficult to reach populations.
- Heat-stability/CTC-qualification can enable alternative delivery scenarios and simplify supply chain logistics.
- The innovation can alleviate constraints on cold chain logistics and storage (in areas where cold chain storage is limited or not available).
- Improving the heat stability of vaccines can also protect against damage caused by inadvertent heat-exposure.

2.2 Key challenges:

- Dry formulations require reconstitution, which increases the number of components, storage space required, complexity of vaccine preparation, number of sharps, and risk of contamination.
- In multidose presentations, dry formulations without preservative increase vaccine wastage and missed opportunities compared to liquid vaccines as the reconstituted vaccine must be discarded at the end of the vaccination session, making health care workers reluctant to open a vial.

2.3 Additional important information

- CTC qualification can be obtained for vaccines during initial licensure or through a label variation process if stability testing results are available to justify the higher temperature storage recommendations.
- Developing a heat-stable/CTC-qualified dry formulation can be technically challenging for some vaccines and there are constraints depending on the vaccine type and the antigen of interest. There is no single formulation method that will stabilize all vaccines; each vaccine requires a customized approach.
- Freeze-dried formulations are the only dry formulations that are commercially available. Other drying methods (e.g. spray-drying, spray-freeze drying) have been used in the food and pharmaceutical industries, but there are no licensed vaccines produced using these technologies.

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	Compared to current vaccines, heat stable dry formulations that are CTC-qualified are more heat stable. The minimum requirement for CTC qualification is stability at 40°C for at least 3 days, immediately prior to administration. (2)

Liquid	*Lyophilised*	***Better** than both the liquid and lyophilised 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	Lyophilized vaccines are not freeze-sensitive and therefore there is no difference in freeze sensitivity compared to a heat-stable dry presentation. It is possible that vaccines that are freeze-sensitive in liquid formulation might be less sensitive to freeze-damage when in a dry formulation due to the lower moisture content.

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

3.2 Coverage and equity criteria

Indicator: Ease of use[I]

*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 • *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)*	**Parameters to measure against a comparator**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Does the innovation avoid reconstitution and is that an improvement?	Worse	Neutral	A dry presentation is scored neutral compared to a current lyophilized presentation since they both require reconstitution. A current liquid presentation does not require reconstitution.
	Does the innovation require fewer vaccine product components?	Worse	Neutral	A dry presentation has the same number of components compared to a current lyophilized presentation (2) and more components compared to a current liquid presentation (1).

[I] 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).

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)*	[m]**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?	Worse	Neutral	A dry presentation requires the same preparation steps and level of complexity as a current lyophilized presentation and more steps/complexity compared to a current liquid presentation.
	Does the innovation improve dose control?	Neutral	Neutral	A dry formulation has no impact on dose control compared to a liquid or lyophilized comparator.
	Does the innovation improve targeting the right route of administration?	Neutral	Neutral	A dry formulation has no impact on the ability to target the correct route of administration.

Liquid	*Lyophilised*	***Worse*** *than the liquid comparator* ***No difference*** *to the lyophilized 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.*

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

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?	Worse	Neutral	A dry presentation has the same number of components compared to a current lyophilized presentation and more components compared to a current liquid presentation.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neutral	A dry formulation has no impact on labelling similar to the comparator.

Liquid	*Lyophilised*	***Worse*** *than the liquid comparator* ***No difference*** *to the lyophilized 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.

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	A dry formulation would have no impact on pain and be the same as the current presentation.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Better	Better	CTC-qualification could, in theory, increase convenience for caregivers and vaccinees by bringing the vaccine closer to the patient by reducing the burden to travel long distances and taking time off of work for caregivers, thus increasing access for hard to reach populations and increasing coverage. The dry formulation would not impact the administration of the vaccine, but rather the delivery scenario and overall vaccination experience for the caregiver/vaccinee.
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	Better	Better	In 2012, MenAfricVac was successfully delivered to 155,000 people in a campaign in Benin, with the CTC approach enabling an increased coverage of vaccinated people due to reduced logistic burden (13).

Liquid	*Lyophilised*	***Better*** *compared to both liquid and lyophilized 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.*

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?	Worse	Neutral	The risk of contamination while reconstituting is the same compared to a current lyophilized vaccine and worse compared to a current liquid vaccine.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	Neutral	The dry vaccine formulation has no impact on the contamination risk while filling the delivery dice.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Worse	Neutral	A dry presentation requires the same preparation steps and level of complexity as a current lyophilized presentation and more steps/complexity compared to a current liquid presentation.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	Neutral	The dry presentation has no impact on the potential risk of reuse of the delivery technology since it is a formulation-based innovation.
	Does the innovation reduce the risk of use of nonsterile components?	Worse	Neutral	Since reconstitution is integrated into the device, dual-chamber vials eliminate the potential risk of reuse of the reconstitution needle and syringe which is used for conventional reconstitution. Although reconstitution syringes have a reuse prevention feature, they could theoretically be reused. There is a potential risk of reuse of the reconstitution needle and syringe which is used for conventional reconstitution with dry vaccines. Although reconstitution syringes have a reuse prevention feature, they could theoretically be reused.

Category: *Formulations*

Innovation: *Heat stable, CTC qualified dry formulations*

Comparators: *Current liquid/lyophilized formulation*

Liquid	*Lyophilised*	***Worse** compared to the liquid comparator* ***Neutral** compared to the lyophilized 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?**	Worse	Neutral	The innovation has the same number of sharps compared to a current lyophilized vaccine and more sharps compared to a current liquid vaccine.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Worse	Neutral	The innovation has the same number of sharps compared to a current lyophilized vaccine (reconstitution syringe + AD delivery syringe) and more sharps compared to a current liquid vaccine (AD delivery syringe only).

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**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	Neutral	The innovation is a formulation and has no impact on the inclusion of AD features.
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Neutral	The innovation is a formulation and has no impact on the inclusion of SIP features.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Neutral	The innovation would have no impact on the risk of injury after vaccine administration.

Liquid	*Lyophilised*	***Worse*** *compared to the liquid comparator* ***Neutral*** *compared to the lyophilized comparator*

3.4 Economic costs criteria

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

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

[n] 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.

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	Compared to the liquid and lyophilized comparators, CTC-qualified dry formulations could potentially reduce the volume per dose stored in the cold chain at the last mile (just before vaccine administration) (14). This assumes that the diluent used to reconstitute the dry formulation is stored out of the cold chain.
	Does the innovation reduce the volume per dose stored out of the cold chain?	Worse	Neutral	Worse than the liquid comparator because the diluent for the CTC-qualified dry formulation needs to be stored out of the cold chain, while the liquid comparator does not have a diluent. The additional reconstitution syringe will also be stored outside the cold chain. Neutral compared to the lyophilized comparator which also requires a diluent that is stored out of the cold chain.

Liquid	*Lyophilised*	***Mixed*** *compared to the liquid comparator* ***Better*** *compared to the lyophilized 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.*

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?	Worse	Neutral	A CTC-qualified dry formulation requires more preparation steps/complexity compared to a current liquid presentation. A CTC-qualified dry formulation requires the same preparation steps and level of complexity as a current lyophilized presentation.
	[o]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	Neutral	Similar to the comparator, the innovation does not have attributes that save time for staff involved in stock management.

Liquid	*Lyophilised*	***Worse** compared to the liquid comparator* ***Neutral** compared to the lyophilized 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.*

[o] 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**	**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. 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).

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 • *To what types of vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	This innovation could be applied to any vaccine that is currently or can potentially be reformulated into a thermostable dry presentation. Some drying process might not be compatible with aluminum-salt-based adjuvants. Vaccines that are currently liquid and adequately heat-stable would not be appropriate for this innovation since their current liquid format has benefits in terms of ease-of-use and lower costs (i.e. HPV vaccine). The benefits of CTC-qualification are greatest for vaccines that are used in campaigns or special strategies (i.e. meningococcal group A conjugate vaccine). Ebola and MR are other VIPS antigens that could be suitable for this innovation.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combinations • *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	Developing heat-stable dry formulations by **lyophilisation will not facilitate novel combinations**, and might not be suitable for existing combinations, either because of a requirement for adjuvant, or because the stabilising excipients needed for the individual components are not compatible. Drying processes such as **spray-drying** that produce free-flowing powders **should permit novel combinations of vaccines**, because it should be possible to mix incompatible components as powders after drying and maintain stability. **CTC qualification might be more difficult with combination vaccines**, as the individual components will have different stability profiles, and the storage requirements will be limited by the least-stable component.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	**Assessment**
Type of study	The assessment is based mainly on expert opinion. Some data from peer-reviewed publications on drying-processes has been used to assess applicability and status of the technologies.
Inconsistency of results	N/A
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*	All the data assessed has been for vaccine applications

Overall assessment:	*Low to Moderate*	*The quality of data available scores moderate based on the large-scale implementation data available for*

		MenAfriVac use in a CTC and independent expert opinion data.

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

Table 15.

Expert/type	Organisation/contact details	Notes
Jessica White, Senior Technical Officer, Vaccine and Pharmaceuticals Formulation group	PATH, www.path.org, jawhite@path.org	
Manjari Lal, Portfolio Lead, Formulation Technologies, Vaccines and Pharmaceuticals	PATH, www.path.org. mlal@path.org	

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

Table 16.

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

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