Freeze Indicator on primary vaccine containers

Comparators: No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices

Section 1: Summary of innovation

1.1 Examples of innovation types:

Electronic Freeze indicators	Chemical indicators	
Tempmate.®-i1(electronic device)  Image source: [a]	BlindSpotz™ freeze alert technology  Image source: [b]	Temptime FREEZEmarker®– A self-adhesive label  Image source: (1)

1.2. Description of innovation:

- The innovation is a freeze indicator that can be attached to a vaccine primary container. These devices are single-use only and irreversible, so even if the ambient temperature goes back to normal or increases, the alarm or colour change on the freeze indicator will remain unchanged.
- There are two types: electronic indicators and chemical indicators (refer to Section 1.1).
- For detailed explanation about the different indicators refer to Table 1.

[a] Photo source: https://www.tempmate.com/wp-content/uploads/sites/2/tempmate-i1-Datasheet-EN.pdf
[b] Photo source: https://www.tempmate.com/wp-content/uploads/sites/2/tempmate-i1-Datasheet-EN.pdf

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1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Electronic Freeze indicator Tempmate.®-i1 (electronic device)  Image source: [c,d]	**Tempmate** https://www.tempmate.com/temperature-indicator/	Small digital devices that can be programmed to respond to a specific range of temperature settings. When the vaccine has been exposed to freezing temperatures an alarm indicator is activated (a coloured light). This particular device alarms at both a high and low temperature and is too bulky for placement on a primary container at present but could be potentially miniaturized or placed on a separate carton containing a single primary container.
Chemical Freeze indicator FREEZEmarker®  Image source: [e]	**Temptime** (USA) http://temptimecorp.com/temperature-indicators-sensors/freeze-indicator/	Small, chemical freeze indicators composed of microscopic particles dispersed within a colloid. When the temperature goes below a pre-determined threshold, the particles become overcome by the repulsive forces that keep them separate and as a consequence they coagulate irreversibly forming an opaque white color that indicates a freeze event has occurred (1). This particular device is meant for secondary packaging, but could be miniaturized for primary packages. **Before freeze event:** Colloid is clear with a green background and the marker is visible indicating temperature is within range.

[c] Photo source: https://apps.who.int/iris/bitstream/handle/10665/183583/WHO_IVB_15.04_eng.pdf;jsessionid=A88DF7004C2BE8526E68C642D7406583?sequence=1

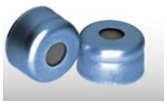
[d] Photo source: https://www.tempmate.com/wp-content/uploads/sites/2/tempmate-i1-Datasheet-EN.pdf

[e] http://temptimecorp.com/temperature-indicators-sensors/freeze-indicator/

Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

Comparators: *No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices*

Product name; Image	**Developer (place); website**	**Brief description, notes**
		 **After freeze event:** Colloid is irreversibly agglomerated and the marker is not visible, indicating exposure to temperatures lower than the threshold. 
Chemical Freeze indicator BlindSpotz™ freeze alert technology The chemical indicator BlindSpotz™ is an example of a technology incorporated in a vaccine vial cap that changes colour following exposure to freezing temperature:  Image source[f]:	**CTI Inks** (USA) https://www.ctiinks.com/blindspotz-freeze-alert	BlindSpotz™ freeze alert (refer to Section 1.1) is a chemical indicator specially designed to irreversibly change colour when vaccine has been exposed to temperatures below 1°C[g]. The technology can be applied to multiple materials including glass, aluminium, paper and plastic. **Before freeze event:**  **After freeze event:** 

[f] https://www.ctiinks.com/blindspotz-freeze-alert
[g] https://www.ctiinks.com/blindspotz-freeze-alert

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- **Helps to safeguard vaccine potency** by individually monitoring freeze sensitive vaccines that may be exposed to temperatures below a specific low temperature threshold and identifying vaccines that may be damaged due to freezing and that should be tested and potentially discarded. An increasing number of expensive freeze sensitive vaccines are being introduced into immunization programmes (2,3).
- **A simple and easy method to signal freeze exposure events** to healthcare providers and logisticians. The devices are easy to interpret, much like the current vaccine vial monitors.
- **Provides individual monitoring of vaccines** including during “last mile” excursions where freeze exposure often occurs. This allows health care workers another data point (along with vaccine vial monitor and expiration date) to confirm the effectiveness of the vaccine prior to administration While standalone freeze indicators and electronic temperature monitoring devices are currently in use in immunization programs, compliance is required to ensure that the temperatures vaccines are exposed to are monitored using these devices during storage and transport. A freeze indicator on a primary container would provide specific information on freeze exposure for that particular container.

2.2 Key challenges:

- **Standalone freeze indicators and temperature monitoring devices** are already in use in immunization programs, especially during vaccine storage, and provide the same or better data than freeze indicators on primary containers. Temperature monitoring devices have the added benefit of helping to identify where freezing is occurring in a vaccine cold chain when used for cold chain assessments. However, these devices are not used consistently during vaccine transport, especially at the last mile and when taking vaccines to outreach sessions.
- **Freeze exposure does not equate to freeze damage**. A vaccine must be physically frozen to incur damage. Even if the freezing points of every vaccine product were identified through laboratory testing, we know that vaccines are unlikely to actually physically freeze at that precise freezing point due to volume, container type, packaging, vibration, supercooling, and speed of temperature change (4). Even if a vaccine’s freezing point is used as the threshold alarm temperature for a freeze indicator, an alarm will often not equate to freeze damage.
- **Use of primary container freeze indicators could result in greater closed vial vaccine wastage** as they will often signal false positive results as described above. When the indicator shows that freeze exposure has occurred, the health worker handling the vaccine must either be willing and able to conduct a shake test (which rarely happens in immunization programs) if the vaccine is formulated with an aluminium salt based adjuvant, send the vaccine for laboratory testing, or discard the vaccine.

2.3 Additional Important information

- **Flexibility to customize the temperature thresholds** of the freeze indicator by the manufacturer, thus providing multiple options for various temperature sensitive vaccines.

- **Freeze prevention is preferable** to monitoring for freeze exposure and many interventions now exist to prevent freezing of freeze sensitive vaccines including: use of WHO prequalified refrigerators with improved temperature control, freeze-preventative vaccine carriers and cold boxes, formulation of freeze stable vaccines, proper ice pack conditioning for vaccine carriers and cold boxes, and tools to raise awareness about how to handle vaccines that are freeze sensitive.
- **Different freeze indicators vary in their accuracy** of performance by ±1°C or ±2°C, thus incorporating further uncertainty in the meaning of an indication of freeze exposure.
- **Specific training to read and interpret** the freeze indicators would be required, including instruction/guidelines. While the freeze indicators are simple to interpret, users may need to know how to interpret them alongside other available temperature indicators used in refrigerators and vaccine carriers and cold boxes.
- There are **labelling challenges** with placing a freeze indicator on a vaccine vial, as there needs to be enough space to visually see the contents as well as other labels/information on the primary container including the existing vaccine vial monitors.
- **Vaccine manufacturers of freeze-sensitive vaccines would need to purchase, validate, and label their products with the new freeze indicator**—a major undertaking and one that the vaccine industry would need to invest time and resources into.

2.4 Evidence

- **Accidental freezing of vaccines is a threat for national immunization programmes** with freezing events occurring more commonly than realized or reported (1), especially in conditions where sub-standard domestic cold chain equipment or unconditioned ice packs in vaccine carriers/cold boxes are used. A 2007 literature review by PATH showed that accidental freeze exposure was pervasive and occurred across all segments of the cold chain (2). Studies in Bolivia and Papua New Guinea have shown that during the process of vaccine distribution, exposure to freezing temperatures occurred, with the greatest exposure during transport (3,4). Freeze-damaged vaccines can result in minor adverse events such as sterile abscesses[h].

Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

Comparators: *No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices*

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	A freeze indicator has no impact on the inherent heat stability of a 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?	Neutral	A freeze indicator monitors freeze exposure but does not impact the inherent freeze sensitivity of vaccines.

	***No difference** to the comparator*

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Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

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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	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 freeze indicator has no impact on reconstitution of a vaccine.
	Does the innovation require fewer vaccine product components?	Neutral	Although the innovation is a freeze indicator incorporated into the vaccine primary container, the user still needs to interact with the freeze indicator and vaccine container separately similar to the comparator.
	[j] **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?	Better	The innovation is less complex than the comparator since it requires that the user to examine a freeze indicator on the primary vaccine container instead of a separate device, which is not attached to the vaccine and can be easily separated. The innovation also makes freeze exposure easier to assess since the freeze indicator is fixed to the vaccine instead of being placed in a container during transport or a refrigerator/cold room during storage where it can be easily separated from the vaccine.

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

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Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

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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**	**Score**	**Assessment**
	Does the innovation improve dose control?	Neutral	This is not a feature of the innovation.
	Does the innovation improve targeting the right route of administration?	Neutral	This is not a feature of the innovation.

	Better *than the comparator*

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Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

Comparators: *No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices*

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?	Better	This innovation is a single-combined indicator that is part of the vaccine primary container, whereas the comparator requires purchase, distribution and tracking of separate freeze indicators. The separate freeze indicators can be reused if they have not been exposed to freezing. Such reuse would require further inventory tracking.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neither the innovation or the comparator include labelling that facilitates product tracking.

	Better *than the comparator*

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Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

Comparators: *No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices*

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**	**Score**	**Assessment**
	Painful or not painful	Neutral	The innovation nor the comparator has any impact on acceptability of vaccine presentation to the vaccinee or caregiver.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	Neutral	

	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.*

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Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

Comparators: *No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices*

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**	**Score**	**Assessment**
	Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?	Neutral	This indicator does not apply to the innovation.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	
	Does the innovation require fewer preparation steps and less complex preparation steps?	Neutral	
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	

	No difference *to the 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 • *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	This indicator does not apply to the innovation.
	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*

3.4 Economic costs criteria

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

*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***

[k] 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 of commodities per dose	Parameters to measure against a comparator	Score	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Neutral	Having a vial level freeze indicator would not impact the volume per dose stored and transported in the cold chain compared to having a standalone temperature monitoring device. The rationale for this assessment is that the temperature monitoring device would still be needed whether or not a vial level freeze indicator is used since the standalone temperature monitoring device serves other purposes such as tracking performance of the cold chain equipment.
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Neutral	Having a vial level freeze indicator does not affect the volume per dose stored and transported out of the cold chain.

	***No difference** to the comparator*

Category: *Labelling*

Innovation: *Freeze indicator on primary vaccine containers*

Comparators: *No freeze indicator on the primary vaccine container and use of standalone freeze indicators and temperature monitoring devices*

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	Score	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Neutral	Having a vial level freeze indicator does not affect the time spent by vaccinators in preparing and administering the vaccine. Whether a vial level freeze indicator or a standalone indicator is used, the health worker has to check the indicators to ensure that vaccines have not been exposed to freezing temperatures.
	[I]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	Having a vial level freeze indicator does not affect the time spent by staff in stock management activities.

	***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.*

[I] 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 *To what types of vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	This innovation could be applied to all freeze-sensitive vaccines as the indicator can be attached to primary containers directly and customized to fit containers of different sizes/shapes. Examples of highly freeze sensitive vaccines on the VIPS priority antigen list that would benefit from this innovation include pentavalent and HPV vaccines.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate vaccine combination *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	No. The use of freeze indicators does not have an influence on the reformulation of vaccines.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	**Assessment**
Type of study	The majority of the data has come from manufacturers' websites, presentations or expert opinion. A small number of peer-reviewed publications were used to validate the use of freeze indicators in the field.
Inconsistency of results	There are too few comparable studies to assess inconsistency of results.
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*

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 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	Working in Tandem Ltd UK julian@workingintandem.co.uk	Reviewed the TN
Renaat Van den Hooff, President & CEO Ted Prusik. Senior vice president	Temptime Corporation 116 The American Road Morris Plains, NJ 07950 973.630.6000	Reviewers of TN

Reviewers	Organisation/contact details	Notes
	General Inquiries info@temptimecorp.com TedP@temptimecorp.com	

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