Dual-chamber delivery devices

Comparator* : Single dose vial, diluent, reuse prevention recon N&S and autodisable (AD) needle and syringe (N&S)

Section 1: Summary of innovation

1.1 Examples images:

Dual-Chamber delivery device: Vetter Lyo-Ject® Syringe	**Fleximed® Easymix**
	
Image source: [b]	Image source: Neopac[c]

1.2. Description of innovation:

- Integrated reconstitution technologies such as dual-chamber delivery devices and dual-chamber vials pair dry vaccine with diluent in one technology to simplify the process of reconstitution. Vaccine components are stored in different compartments of the same device and then more easily mixed and administered at the time of use. Dual-chamber delivery devices are fully integrated reconstitution technologies that include the delivery device.
- The reconstitution of vaccines for immunization represents a public health challenge due to the potential for error during the transfer of diluent to the vial containing lyophilized (freeze-dried) vaccine using a reconstitution syringe. Errors in using traditional reconstitution systems include use of the incorrect volume of diluent; reuse of reconstitution syringes, causing contamination; use of improperly stored diluent that can render a vaccine ineffective; use of an incorrect diluent; or worse, using a potentially deadly liquid drug as a diluent by mistake. Adverse events as a result of reconstitution errors can include local abscesses, toxic shock syndrome, or even death (1).

* 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.

[b] https://www.pharmaceutical-networking.com/vetter-dual-chamber-delivery-systems/

[c] https://www.webpackaging.com/en/portals/webpac/assets/11138717/neopacs-fleximed-now-in-large-format/

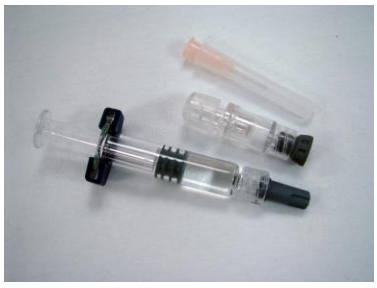
- Immunization programs could benefit from reconstitution and integrated delivery technologies that eliminate or reduce the risk of error, and are more convenient and safe when compared to the traditional, reconstitution method of diluent transfer using a needle and syringe.
- Dual-chamber delivery devices can be used for any vaccine that requires mixing of multiple components. This TN will focus on devices for injection that require mixing of a liquid (diluent) and dry (vaccine) component. Dual-chamber devices for oral delivery (or both oral and parenteral delivery) have also been included in Section 1.3 for completeness.
- There are several types of dual-chamber delivery devices: some are based on glass syringes or cartridges with valved stoppers actuated with plungers; others are based on tubes, pouches, or blister packs with frangible seals that burst upon mechanical pressure. No vaccines are licensed in dual-chamber delivery devices.
- The syringe- or cartridge-based devices consist of a prefilled syringe or cartridge containing both the dry and liquid components of the vaccine, separated by an elastomeric stopper. Mixing of the components occurs by means of a valve usually incorporated into the stopper and activated by mechanical pressure. Many—but not all—of these devices are based on standard glass syringes or cartridges, and often take advantage of commodity components and filling equipment.
- Frangible seals represent an alternative means of reconstituting the dry and liquid components of the vaccine at the point of use. Each of the dry and liquid components of the pharmaceutical are co-packaged in a tube, pouch/sachet, or blister, generally made from a foil, a polypropylene, polyester-based polymer, or a laminate that is amenable to heat sealing. The frangible seal separates the compartments and is engineered to open under a certain amount of applied pressure. Because these devices are generally based on foil or polymer materials (as opposed to glass), they can be formed into a wide variety of geometric shapes that incorporate functionality, such as a nozzle for oral delivery. However, unlike glass, they are unlikely to be able to allow lyophilisation to occur within the device itself and may require different drying/powder filling mechanisms.

1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Syringe- or cartridge-based dual-chamber delivery devices:		
Lyo-Ject® syringe  Image source : Vetter[d]	**Vetter** (Germany) https://www.vetter-pharma.com/	Available for market use. No data are publicly available about what drugs/vaccines have been evaluated for this device.
V-LK® reconstitution cartridge  Image source: Vetter[e]	**Vetter** https://www.vetter-pharma.com/	Cartridge-based version of the Lyo-Ject® syringe-based device currently in development.
LyoGo dual chamber pre-filled syringe  Image source: Provided by PATH	**LyoGo** http://www.lyogo.com/products/l-pfs/	Novel valve embedded in the chamber-separating stopper.

[d] https://www.pharmaceutical-networking.com/vetter-dual-chamber-delivery-systems/
[e] https://www.pharmaceutical-networking.com/vetter-dual-chamber-delivery-systems/

Product name; Image	**Developer (place); website**	**Brief description, notes**
EZMix 	**Unilife**	Incorporates the approach of a dual-chamber syringe coupled to a retractable needle feature, allowing for safer handling after delivery. Unilife entered bankruptcy in 2017, and the current status of the EZMix technology is unknown.
VaccJect (reconstitution version)  Image source: Duoject[f]	**Duoject** http://duoject.com/realisations/vaccject/	A concept for a reconstitution-capable version of the VaccJect was generated which would utilize two cartridges, and allow for transfer of the diluent from the cartridge containing diluent to the cartridge containing the dry vaccine.
LyoTip  Image source: Integrity Bio[g]	**Integrity Bio** http://integritybio.com/Innovation/LyoTip	Lyophilized pharmaceutical is in a chamber that screws onto a prefilled syringe containing the diluent, and a needle is attached. As the syringe plunger is pressed, the diluent flows through a spiral pathway within the chamber, reconstituting the product immediately before it is injected.

[f] http://duoject.com/realisations/vaccject/
[g] http://integritybio.com/Innovation/LyoTip

Product name; Image	**Developer (place); website**	**Brief description, notes**
Frangible seal-based dual-chamber delivery devices:		
Immunoject  Image source: Provided by PATH	**AktiVax** https://www.aktivax.com/	A dual-chamber device has been developed by AktiVax and is designated the Immunoject. In this design, AktiVax's ARCH (Aseptic Reconstitution Package Hybrid) two-compartment blister is attached to a needle and a folding plastic piece or card. The plastic piece shields the needle before use; compresses the blisters to rupture the frangible seal for reconstitution; allows for the subsequent parenteral delivery of the reconstituted pharmaceutical via the attached needle; and is then folded back in the opposite direction to disable and enclose the needle after use.
Fleximed® Easymix  Image source: Neopac[h]	**Neopac** https://www.neopac.com	Two-compartment, coextruded, polymer-based tube with a frangible seal separating two compartments either containing the dry and liquid or two liquid components for oral delivery. Currently available for market and research use.
IRAD  Image source: Provided by Hilleman Laboratories	**Hilleman Laboratories** https://www.hillemanlabs.org	Dual-chamber, frangible-seal reconstitution technology for oral delivery. Developed originally for delivery of heat-stable rotavirus vaccine with potential for CTC/outside cold chain use (9 months at 45°C). Human factors evaluation of IRAD design (India). Phase I/II (adults/infants): International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).

[h] https://www.webpackaging.com/en/portals/webpac/assets/11138717/neopacs-fleximed-now-in-large-format/

Product name; Image	**Developer (place); website**	**Brief description, notes**
Dualject *(concept phase, no images currently available)*	**PATH** www.path.org	PATH has developed a concept for a novel dual-chamber device, which seeks to extend the functionality of the Uniject injection system to liquid/dry presentations.
Dual Chamber Blister  Image source: Pharmapan[i]	**Pharmapan** https://www.pharmapan.com/portfolio/vaccine-delivery	Device contains two ultra-high barrier chambers designed for highly moisture-, light- and temperature-sensitive active pharmaceutical ingredients. Can be used for oral delivery or can be fitted with a needle for parenteral delivery.

[i] https://www.pharmapan.com/sites/default/files/downloads/2017-10/PHARMAPAN_Dual_Chamber_Blister_1.1.pdf

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- Dual-chamber delivery devices simplify and reduce the number of steps involved in reconstitution and delivery of lyophilized vaccines.
- The device is prefilled, which eliminates the risks of using the incorrect volume or type of diluent.
- It also eliminates the reconstitution syringe; reducing the number of sharps.
- The use of these technologies reduces mismatching and/or misallocation of vaccine components during distribution; potentially reducing vaccine and diluent wastage and simplifying inventory processes.

2.2 Key challenges:

- Autodisable features are not present on many dual chamber delivery devices, and would need to be developed.
  Dual-chamber delivery devices increase the packaging volume and lead to an increase in cold chain costs because the diluent is now stored in the cold chain with the vaccine as well as the delivery device.

2.3 Additional important information:

- Most dual-chamber technologies are at an early stage of development and there are significant technical hurdles that will need to be overcome related to the mechanism of the reconstitution feature, ensuring adequate mixing of the two components prior to delivery and ensuring that the moisture barrier between the liquid and dry components is sufficiently impermeable to ensure the stability of the lyophilised component.
- Dual-chamber delivery devices are likely to have an increased price per dose compared to existing technologies (a lyophilized vaccine in a single-dose vial, diluent, reuse prevention syringe & needle for reconstitution, and autodisable needle & syringe for delivery), which could be a barrier for adoption in low and middle income countries (LMICs).
- The costs of developing, installing and qualifying new filling equipment and obtaining regulatory approval of a vaccine in a novel container are also barriers to adoption of integrated reconstitution 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	Score	Assessment
	Does the innovation have features that may improve heat stability?	Neutral	Dual-chamber delivery devices are integrated primary containers and do not impact the heat stability of the vaccine.

	***No difference** to the comparator*

Indicator: Ability of the vaccine presentation to withstand freeze exposure

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

Table 3.

Ability of the vaccine presentation to withstand freeze exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve freeze resistance?	Neutral	Dual-chamber delivery devices are integrated primary containers for use with current lyophilised formulations of vaccines. As such, they do not impact the freeze resistance properties of the vaccine.

	***No difference** to the comparator*

3.2 Coverage and equity criteria

Indicator: Ease of use[j]

*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	Dual-chamber delivery devices do not avoid reconstitution, but simplify the process.
	Does the innovation require fewer vaccine product components?	Better	Dual-chamber delivery devices reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber delivery devices generally require one component (prefilled dual-chamber device alone), although some have a separate needle. The comparator requires four components (dry vaccine in a vial; diluent vial; reconstitution syringe; delivery syringe).
	[k]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	Dual-chamber devices simplify and reduce the number of steps involved in the reconstitution, delivery, and disposal. Depending on the device design and the formulation being reconstituted, additional time and agitation steps by the user might be needed to ensure complete reconstitution (2). A PATH user study among health care workers in India found this type of device

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

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)*			was generally acceptable and useful for overcoming reconstitution challenges. Preference varied between devices and was dependent on the number of steps involved (3).
	Does the innovation improve dose control?	Better	Dual-chamber delivery devices are prefilled and therefore offer better dose control than use of an AD N&S to withdraw and deliver vaccine from a vial. This assumes however, that the design of the device enables adequate and complete mixing of the two components prior to delivery.
	Does the innovation improve targeting the right route of administration?	Neutral	For an injectable vaccine, these innovations would likely not impact improving targeting the right route of administration. Oral vaccines requiring reconstitution can be delivered parenterally in error if a reconstitution syringe is required, resulting in serious adverse reactions (4). A dual chamber device intended for oral delivery could reduce this risk, providing a needle could not be fitted.

	Better *than the comparator*

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

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

Table 5.

Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • *Assessment of the potential to reduce stock outs based on the innovation's features*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Does the innovation require fewer components?	Better	Dual-chamber delivery devices reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber delivery devices generally require one (prefilled dual-chamber delivery device alone) or two (device plus separate needle) components. The comparator requires four components (dry vaccine in a vial; diluent; reconstitution syringe; delivery syringe).
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	The innovation has no impact on product labelling.

	Better *than the 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.*

VIPS is a Vaccine Alliance project from Gavi, World Health Organization, Bill & Melinda Gates Foundation, PATH and UNICEF

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	Dual-chamber delivery devices still require an injection if used for parenteral vaccines, and are not anticipated to impact pain associated with administration.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	Since dual-chamber delivery devices are not expected to impact the perception of ease of administration for caregivers/vaccines since they would not interact with the innovation and delivery would still be by the same method.
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	Better	Serious injuries and deaths from vaccine/diluent mismatches are rare, but when they occur they can be widely publicized and shake caregivers' confidence in vaccines and immunization programs. The innovation has the potential to reduce these errors and lead to increased acceptability of vaccination.

	Better *than the comparator*

3.3 Safety criteria

Indicator: Likelihood of contamination

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

Table 7.

Likelihood of contamination	Parameters to measure against a comparator	Score	Assessment
• *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?**	Better	Dual-chamber delivery devices reduce the risk of contamination while reconstituting since reconstitution takes place within the primary container which is a sterile environment.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Better	Dual-chamber delivery devices are ready to use and do not require filling a delivery device unlike the comparator.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	Dual-chamber delivery devices have fewer and simpler steps, which reduce preparation errors including mismatching dry vaccine and diluent (which are often shipped and stored separately with vaccine in the cold chain and diluent at ambient temperature), use of incorrect diluent, and reuse of reconstitution syringes. For instance, in 2014 in Syria, 15 children died after a muscle relaxant was accidentally administered instead of the proper diluent (5). Some of the devices involve a separate needle that would need to be assembled with the primary container.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	Dual-chamber delivery devices are expected to have an autodisable feature so the risk of reuse would be similar to an AD N&S.
	Does the innovation reduce the risk of use of nonsterile components?	Better	Since reconstitution is integrated into the device, dual-chamber delivery devices 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.

	Better *than 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	Parameters to measure against a comparator	Score	Assessment
• *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Does the innovation contain fewer sharps?**	Better	Delivery from a dual-chamber delivery device requires one fewer sharp as a needle is not required for reconstitution.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Better	Dual-chamber delivery devices only require a sharp for administering the vaccine and eliminate a reuse prevention (RUP) N&S for reconstitution. Some of the devices involve a separate needle that would need to be assembled with the primary container, which could have an impact on the risk of sharps injury, depending on the design.
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	Dual-chamber delivery devices are expected to have an autodisable feature similar to an AD N&S, though this has yet to be developed for many of the designs.
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Current dual-chamber delivery devices do not include sharps injury prevention features, similar to an AD N&S.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Dual-chamber delivery devices have no impact on the risk of injury.

	***Better** than the comparator*

3.4 Economic costs criteria

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

*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.

<table>
<tr><th>Total economic cost of storage and transportation of commodities per dose</th><th>Parameters to measure against a comparator</th><th>Score</th><th>Assessment</th></tr>
<tr><td rowspan="2"></td><td>Does the innovation reduce the volume per dose stored and transported in the cold chain?</td><td>Worse</td><td>A dual-chamber delivery device increases the volume per dose stored and transported in the cold chain since the reconstitution feature, diluent, and delivery device are now stored in the cold chain.

Estimated volumes based on current prototypes are summarized below (PATH internal communication). For the scoring, the mid-volume estimates were used and compared to the volume of an SDV for a lyophilized vaccine which can have volume stored in the cold chain ranging from 9.7 cm^3 (meningococcal conjugate vaccine) (6) and 21.09 cm^3 (measles containing vaccine) (7).
<table>
<tr><td rowspan="2">Innovation</td><td colspan="3">Volume estimate (cm^3)</td></tr>
<tr><td>Low</td><td>Mid</td><td>High</td></tr>
<tr><td>Dual-chamber delivery device</td><td>21</td><td>43</td><td>86</td></tr>
</table></td></tr>
<tr><td>Does the innovation reduce the volume per dose stored and transported out of the cold chain?</td><td>Better</td><td>A dual-chamber delivery device does not have any volume per dose stored and transported out of the cold chain since the diluent, reconstitution device and delivery device are integrated and all are stored in the cold chain.

Some of the devices require assembly of a separate needle or diluent component (Vaccject and LyoTip). These would be</td></tr>
</table>

[I] 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.

			stored and transported outside the cold-chain.

	Mixed *for the comparator*

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

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

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?	Better	It is expected that dual-chamber delivery devices would save time for the vaccinator in preparing and administering the vaccine because of simplifying and reducing the number of steps. However, data are not available comparing preparation and delivery time.
	[m]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	There are no attributes on dual-chamber delivery devices that would impact the time spent by staff involved in stock management.

	Better *than 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)

[m] 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.

*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**	**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. There are no upfront or recurrent costs for dual chamber delivery devices, other than training costs which would be required to introduce any innovation and are not included in this parameter.

	***No difference** to the comparator*

3.5 Secondary criteria on potential breadth of innovation use

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

Table 12.

Applicability of innovation to one or several types of vaccines • *What vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	This innovation could be applied to all dry vaccine presentations that require reconstitution with a diluent, or other two-component vaccines that require mixing. Versions for oral or injectable delivery are being developed. Examples of VIPS priority antigens that could be suitable include MR and yellow fever. Dual-chamber delivery devices are also well-suited for simplifying the preparation of vaccines with multiple components and complex preparation steps like ETEC to reduce preparation errors.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combination • *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	Integrated reconstitution devices do not impact the ability to combine vaccines relative to standard packaging for dry vaccine presentations requiring reconstitution with a diluent.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	**Assessment**
Type of study	The majority of the data has come from expert opinion. A small-scale in country feasibility study was conducted by PATH on prototype dual-chamber delivery devices in India (2008).
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*	*Most dual-chamber devices are at a very early stage of development and most available data are expert opinions. A small country-evaluation has been completed, but no recent studies have been completed.*

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 were conducted.

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
Collrane Frivold	PATH cfrivold@path.org	Developed and reviewed TN.
PATH Medical Devices and Health Technologies Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH Debra Kristensen dkristensen@path.org	Reviewed TN.
Fatema Kazi	Gavi, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Reviewed the TN.
Julian Hickling	Working in Tandem live.com#julian@workingintandem.co.uk	Reviewed the TN.

4.4 References:

Peer-reviewed publications of primary data, systematic reviews, other reports:

1. MODULE 3: Adverse event following immunization page. WHO website. Available at: http://vaccine-safety-training.org/immunization-error-related-reaction.html. Accessed April 4, 2019.

2. Werk T, Ludwig IS, Mahler HC, Luemkemann J, Huwyler J, Hafner M. The effect of formulation, process, and method variables on the reconstitution time in dual chamber syringes. PDA Journal of Pharmaceutical Science and Technology. 2016 11/12; 70(6):508-522.

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