Dual chamber vials

Comparator* : Single dose vial (lyophilised) + diluent + reuse prevention (RUP) reconstitution needle and syringe (N&S)

Section 1: Summary of innovation

1.1 Examples images:

Dual-chamber vial:

Pfizer Injectable Act-O-Vial System.

Image source: provided by PATH.

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. Dual-chamber vials are integrated primary containers with a reconstitution feature, but require a separate delivery device. The separate vaccine components are stored in different compartments of the same device and then reconstituted and administered (with a separate delivery device) at the time of use.
- 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).
- Immunization programs may benefit from reconstitution 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 vials can be used for any vaccine that requires mixing of multiple components. This TN focuses on dual-chamber vials for vaccines for parenteral delivery that require mixing of a liquid

* 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.

(diluent) and dry (vaccine) component. Generally speaking, these devices are intended to emulate standard vials and a standard AD N&S can be used to withdraw the vaccine for injection

- There are several types of dual-chamber vials in development. No vaccine products are currently approved for use in dual-chamber vials, but some other pharmaceutical products are licensed in dual-chamber presentations. Although some of these dual-chamber technologies are available for market use, they would need to be approved with a specific antigen.

1.3 Examples of innovations and developers:

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Eulysis single vial system  Image source: Eulysis	**Eulysis**	Device stores a lyophilized active pharmaceutical ingredient (API) in a top compartment separated from the diluent located in the vial by a thin plastic cup. To combine the two components, a piston-shaped top compartment is pressed down to puncture the plastic cup containing the lyophilized pharmaceutical. The lyophilized product then falls from the piston into the vial containing the diluent. A needle and syringe can be used to draw a dose from the vial for delivery. This device is no longer in development and the company is no longer active.
Act-O-Vial  Image source: provided by PATH	**Pfizer** https://www.pfizerinjectables.com/ act-o-vial	In the Act-O-Vial, a rubber plug separates the diluent and dry lyophilized API compartments. By depressing the plastic cap, the plug is dislodged and forced into the lower compartment. Diluent from the upper compartment flows into the lyophilized API-filled lower compartment for mixing. Act-O-Vial is on the market for use with Solu-Cortef and Solu-Medrol (both glucocorticoids to treat allergic reactions and/or inflammation, also by Pfizer).

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- Dual-chamber vials simplify and reduce the number of steps involved in reconstitution of lyophilized vaccines.
- The vials are prefilled, which eliminates the risks of using the incorrect type or volume of diluent. They also remove the need for a reconstitution syringe, reducing the use 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:

- Dual-chamber vials 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.

2.3 Additional important information:

- Most dual-chamber technologies are at an early stage of development and there are technical hurdles that will need to be overcome related to the reconstitution feature and moisture barrier between the liquid and dry components.
- Dual-chamber vials are likely to have an increased price per dose compared to existing technologies (a lyophilized vaccine in a single-dose vial, diluent, and reuse prevention N&S for reconstitution), which could be a barrier for adoption in low and middle income countries (LMICs). Both would require an AD N&S for vaccine delivery.
- The costs of 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 vials 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 vials 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[a]

*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**	**Score**	**Assessment**
	Does the innovation avoid reconstitution and is that an improvement?	Neutral	Dual-chamber vials do not avoid reconstitution, but simplify the process.
	Does the innovation require fewer vaccine product components?	Better	Dual-chamber vials reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber vials typically require two components (vial, delivery syringe). The comparator requires four components (dry vaccine in a vial; diluent vial; reconstitution syringe; delivery syringe).
	[b]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 vials simplify and reduce the number of steps involved in the reconstitution, delivery, and disposal. Depending on the container design and vaccine formulation, additional time and agitation by the user may be needed to ensure complete reconstitution.

[a] 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).

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

Category: *Primary vaccine container (without delivery device)*

Innovation: *Dual-chamber vials*

Comparator: SDV (lyophilised) + diluent + RUP reconstitution N&S

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	An AD N&S is used with both dual-chamber and standard vials so dose control is similar to the comparator.
	Does the innovation improve targeting the right route of administration?	Neutral	Dual chamber vials are containers designed to facilitate reconstitution. As such they have no impact on the targeting the right route of administration.

	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.*

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

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 vials reduce the number of vaccine components by integrating a reconstitution feature. Dual-chamber vials typically require two components (vial, delivery syringe). 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 features that would facilitate labelling or product tracking, similar to the comparator.

	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.*

Table 6.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Painful or not painful	Neutral	Dual-chamber vials still require use of the 'standard' delivery device, and so will not impact pain associated with administration.

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

acceptability of vaccinees and caregivers	**Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)**	Neutral	Dual-chamber vials 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 • *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?	Better	Dual-chamber vials reduce the risk of contamination while reconstituting since the reconstitution takes place within the primary container which is a sterile environment.
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 filling the delivery device?	Neutral	Dual-chamber vials still require filling a delivery device and would have similar risk to the comparator.

	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	Dual-chamber vials 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 (2).
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	Dual-chamber vials are intended to be used with an AD N&S, so the risk of reuse of the delivery device is similar to the comparator.
	Does the innovation reduce the risk of use of nonsterile components?	Better	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.

	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 • *Risk assessment of the presence of sharps during the process of preparing*	**Parameters to measure against a comparator**	**Score**	**Assessment**
	Does the innovation contain fewer sharps?	Better	Delivery from an integrated reconstitution vial requires one fewer sharp as a needle is not required for reconstitution.

and administering the vaccine	**Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?**	Better	Dual-chamber vials only require a sharp for administering the vaccine and eliminates a reconstitution reuse prevention (RUP) N&S for reconstitution.
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	Dual-chamber vials are expected to be used with an AD N&S, similar to the comparator.
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Dual-chamber vials are a packaging technology and do not have sharps.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Dual-chamber technologies 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[c]

*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.

	Parameters to measure against a comparator	**Score**	**Assessment**
	Does the innovation reduce the volume per dose stored and	Worse	For the dual chamber vial, the reconstitution feature and diluent are now stored and transported in the cold

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

<table>
<tr><td rowspan="2">Total economic cost of storage and transportation of commodities per dose</td><td>transported in the cold chain?</td><td></td><td>chain together with the vial, which increases the volume.

Estimated volumes based on current prototypes are summarized below (PATH internal communication). For the scoring, the mid-volume estimates were used and compared these 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) (3) and 21.09 cm^3 (measles containing vaccine) (4).
<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 vial</td><td>20</td><td>41</td><td>81</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 vial still requires an AD N&S (43 cm^3 for the injection syringe per dose) and this is stored and transported out of the cold chain. However, the volume stored out of the cold chain is reduced compared to the comparator which requires a reconstitution syringe, diluent and AD N&S all stored and transported out of the cold chain.</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Mixed for the comparator</td></tr>
</table>

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	Better	It is expected that with dual chamber vials, time would be saved for the vaccinator in preparing and administering the vaccine because of simplifying and

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

	and administering the vaccine?		reducing the number of steps. However, data are not available comparing preparation and delivery time.
	[d]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	There are no attributes on dual-chamber vials 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)

*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 devices and vials, other than training costs which would be required to introduce any innovation and are not included in this parameter.
			No difference *to the comparator*

[d] 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.

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. Examples of VIPS priority antigens that could be suitable include MR and yellow fever.

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.
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*	With the exception of bench testing, all information is from non-vaccine applications.

Overall assessment:	*Low to moderate*	Most dual-chamber vials are at a very early stage of development and most available data are expert opinions. The Act-O-Vial device is one the market for a pharmaceutical product.

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 (TN):

Table 16.

Reviewers	Organisation/contact details	Notes
Collrane Frivold	PATH	Developed and reviewed TN

Reviewers	Organisation/contact details	Notes
	cjfrivold@path.org	
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. 18 September 2014. *Syrian children's deaths 'caused by vaccine mix-up.'* BBC News. Available at: http://www.bbc.com/news/world-middle-east-29251329.

3. WHO Prequalified Vaccines website. Meningococcal ACYW-135 (conjugate vaccine); Nimenrix page. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=301.

4. WHO Prequalified Vaccines website. Measles; Measles Vaccine, Live Attenuated page. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=145.