Oral fast dissolving tablets

Comparators* :

- **Single dose vial (lyophilised) + diluent + reuse prevention (RUP) reconstitution syringe and dropper;**
- **Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S)**

Section 1: Summary of innovation

1.1 Examples images:

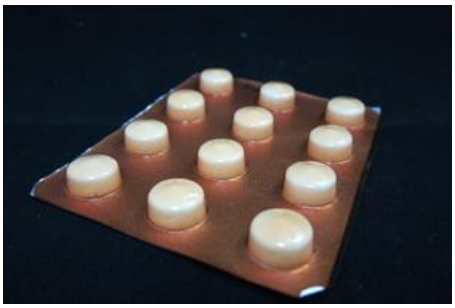

Photo source: provided by PATH

1.2. Description of innovation:

- Fast dissolving tablets (FDTs) are freeze dried vaccine tablets that disintegrate rapidly in saliva, requiring no/minimal fluid for oral administration. This feature allows the FDTs to be dispersed *in situ* for adults or dispersed in minimal volume for administration to infants, thus eliminating any hazards associated with choking.
- Oral FDTs are swallowed and rapidly disintegrate (not forming a gel under the tongue like sublingual dosage forms described in the Sublingual Dosage Form TN). This innovation is thus delivered to the intestines and not absorbed in the mouth. This is particularly relevant for vaccines against enteric pathogens that replicate in the gut.
- FDTs can be delivered through several routes of administration including oral, sublingual, buccal, vaginal, or rectal. This TN will focus on FDTs for oral delivery. Referred to as oral FDTs in this document. Sublingual FDTs, which are placed under the tongue and form a gel upon contact with saliva, will be discussed in the Sublingual Dosage Form TN.
- The small tablets are packaged in unit-dose blisters made from foil or other pharmaceutical grade material, offering an inexpensive, scalable, and easy-to-use product presentation for live attenuated vaccines.
- Some new oral enteric vaccines in development are complex vaccines with multiple components (e.g., multiple strains, mucosal adjuvant, and antacid buffer) that often must be packaged separately due to cross-reactivity during testing or formulation incompatibility (1,2). With traditional lyophilization being carried out in glass vials, this results in multiple vials and large footprint in

*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.

packaging and storage. A freeze dried oral FDT vaccine can enable multivalent vaccine strains to be combined in a single blister sheet as separate unit dose tablets which can be taken orally. The requirement for co-administering multiple oral FDTs is antigen-specific and will be evaluated in more detail in Phase 2.

- It might also be possible to develop oral FDTs for vaccines that are currently delivered by injection, including vaccines currently in a liquid format (hence inclusion as a second comparator). However, non-live vaccines are likely to require a mucosal adjuvant, and currently no adjuvants of this type are used in any approved vaccines. Development of oral FDTs for this type of vaccine therefore has significantly more development challenges than for live oral vaccines.

The scoring for this Technical Note was completed for vaccines meant for older children and adults. Administration of FDTs to infants under 2 years of age is problematic because of the risk of choking. This can be overcome by reconstitution and delivery by an oral dropper, however many of the advantages of these formats are lost in this scenario of use.

1.3 Examples of innovations and developers:

There are several pharmaceutical companies with drug products on the market using a similar technology for developing oral FDTs.

Table 1.

Product name; Image	**Developer (place); website**	**Brief description, notes**
Loperamide-Lyoc® Paralyoc® Proxalyoc® Spasfon-lyoc®  Photo source: CIMA	**CIMA** http://www.cimalabs.com/technology/lyoc.aspx	CIMA labs is a US based pharmaceutical company focusing on oral drug delivery technologies
Zyprexa Zydis®	**Catalent**	Catalent's Zydis® orally disintegrating tablet (ODT) fast-dissolve formulation, is

Product name; Image	**Developer (place); website**	**Brief description, notes**
 Image source: Catalent	http://www.catalent.com/index.php	a freeze-dried oral dosage form that disperses instantly in the mouth, requiring no water
Fast dissolving tablet  Photo source: PATH	**PATH** http://www.path.org	PATH is evaluating FDTs in preclinical studies for several indications, both drugs and vaccines. Oral enterotoxigenic E.coli (ETEC) tablet: Freeze dried fast dissolving oral tablet containing trivalent ACE-527 strains (3). Oral combination anti-retrovirals (LPV/r) tablet: Flexible pediatric friendly dosage form containing Lopinavir and Ritonavir Oral/Ocular Newcastle disease vaccine tablet: Freeze dried fast dissolving tablet containing Newcastle disease vaccine. The tablet can be reconstituted for ocular (eye-drop) or oral (mixed with feed) administration (4). Oxytocin: Heat stable freeze dried fast dissolving tablet contain oxytocin to prevent postpartum haemorrhage (5).

Category:	*Integrated primary container and delivery technology*
Innovation:	*Oral fast dissolving tablets*
Comparators:	*SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- Oral FDTs are easy to administer since they only have one component, fewer and less complex preparation steps, and improved dose control. They should not require a skilled healthcare worker (HCW).
- Orals FDTs have an improved safety profile since they are needle-free and reduce the likelihood of contamination.
- Compared to injectable presentations, oral FDTs are likely to be more acceptable due to the reduced pain of delivery, and to reduce the risk of needle-stick injuries.
- Oral FDTs reduce the number of vaccine components (1 component versus 4 for dry oral comparator and 2 for liquid injectable comparator) and storage volumes, reducing delivery costs, health care worker time, and the risk of stockouts.
- Oral FDTs rapidly disintegrate in a small amount of saliva, reducing the risk of choking and making them suitable for individuals with difficulty swallowing.
- May offer improved heat and freeze stability over liquid vaccines.
- FDTs can simplify administration and preparation of complex vaccines (particularly oral vaccines) with incompatible components (i.e. vaccine, adjuvant, and buffer for ETEC vaccine) by formulating as several different FDTs (see Table 13 below).
-

2.2 Key challenges:

- For infants and young children, the innovation needs to be reconstituted and then administered with a liquid dropper/oral syringe to address the potential risk of choking, which increases complexity and negates many of the benefits so the applicability of the format is likely limited to older populations.
- Some training of HCWs on removal of vaccine FDTs will be required to ensure that vaccine FDTs are removed by peeling the blister lid and not by a push-through mechanism.

2.3 Additional important information:

- The manufacturing/packaging processes for FDTs are widely used in the pharmaceutical industry and equipment is broadly available. Vaccine manufacturers should be able to adapt their existing freeze-drying processes to produce FDTs.
- Developing freeze drying processes to form FDTs is challenging as additional excipients are needed to form robust FDTs, which can otherwise be brittle or fragile and might require specific packaging.
- Since FDTs are formed in blisters, the process for ensuring the sterility of the blister prior to vaccine filling must be in place.
- Since FDTs are formed inside the freeze drier and blister sealing is performed outside, maintaining low humidity is of critical importance.

- Each oral vaccine FDT will require an individual development process to identify appropriate excipients which are suitable and compatible with vaccine antigen(s).
- Addition of excipients in the formulation to form tablets may add to the cost of final product.
- Process for maintaining dry environment outside of freeze-drying equipment may add to the cost of manufacturing.
- Since FDTs can improve heat stability compared to a liquid formulation, there is a possibility a oral FDTs could be stored in a controlled temperature chain, which could further reduce the cold chain volume compared to the comparators.

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	Dried oral comparator	Liquid injectable comparator	Assessment
	Does the innovation have features that may improve heat stability?	Neutral	Better	Both the dried oral vaccine comparator and the FDT are produced using freeze drying processes and are likely to have similar stability. However, the dried FDT is likely to have improved heat stability in comparison to a liquid injectable vaccine.

		No difference *to the dry oral comparator* ***Better*** *than the liquid injectable comparator*

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Category: *Integrated primary container and delivery technology*
Innovation: *Oral fast dissolving tablets*
Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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	Dried oral comparator	Liquid injectable comparator	Assessment
	Does the innovation have features that may improve freeze resistance?	Neutral	Better	Both the dried oral vaccine comparator and the FDT are produced using freeze drying processes and therefore are similarly not freeze sensitive. Liquid injectable vaccines that are freeze-sensitive and are reformulated into FDTs must be made freeze-resistant (e.g., through the removal of aluminium adjuvant) to withstand the freeze-drying process.

		No difference *to the dry oral comparator* ***Better*** *than the liquid injectable 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	Parameters to measure against a comparator	Dried oral comparator	Liquid injectable comparator	Assessment
• *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Does the innovation avoid reconstitution and is that an improvement?**	Better	Neutral	The dried oral vaccine comparator requires reconstitution and the liquid injectable vaccine does not. The FDT does not require reconstitution as it is placed directly on the mucosal surface and is dissolved by saliva.
	Does the innovation require fewer vaccine product components?	Better	Better	The FDT has a single component (i.e. a single blister sheet, although this might contain several different FDTs which all need to be taken depending on the antigen), while the comparators have multiple components (dry oral comparator: vaccine, diluent, mixing and delivery devices; liquid injectable comparator: vaccine and AD N&S.).
	[b]Does the innovation require additional components or equipment (such as scanners or label readers)?	N/A	N/A	

[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: *Integrated primary container and delivery technology*

Innovation: *Oral fast dissolving tablets*

Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD 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**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	Better	Steps for reconstitution, vaccine preparation and injection are eliminated with the FDT technology. It can be administered directly into the patient's mouth requiring little training of the health worker. If multiple vaccine components (i.e. vaccine, adjuvant, buffer) or antigens are incompatible and cannot be co-formulated, then several different FDTs might need to be given to the recipient to ensure all components are administered, which simplifies vaccine administration compared to combining and delivering multiple vials at the time of use. This will be antigen-specific and assessed further in phase 2.
	Does the innovation improve dose control?	Better	Better	A FDT is a fixed dose which can improve dose control compared to delivery with an oral dropper or AD N&S.
	Does the innovation improve targeting the right route of administration?	Neutral	Neutral	Tablets are widely used and it is unlikely that they would be administered incorrectly. The comparators also are unlikely to be administered to the wrong site assuming that the oral vaccine will be accompanied by an appropriate oral delivery device and injectable vaccines are widely in use.

		Better *than both dry oral and liquid injectable comparators*

Category: *Integrated primary container and delivery technology*
Innovation: *Oral fast dissolving tablets*
Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	Does the innovation require fewer components?	Better	Better	The FDT has a single component while the comparators have multiple components. (dry oral comparator: vaccine, diluent, mixing and delivery devices; liquid injectable comparator: vaccine and AD N&S.) If the FDT has been developed to avoid formulation problems with dried oral vaccines, then several co-packaged FDTs may need to be given to the recipient to ensure all components are administered.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neutral	A FDT does not impact product labelling.

		***Better** than both dry oral and liquid injectable comparators*

Category: *Integrated primary container and delivery technology*

Innovation: *Oral fast dissolving tablets*

Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	Painful or not painful	Neutral	Better	Both oral vaccine presentations are given via the oral route and are not painful. The FDT is likely to be less painful than an injectable vaccine.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	Better	It is expected that caregivers and vaccinees would find FDTs easy to use since they are needle-free, do not require preparation, are easy to administer, and can potentially be self-administered.
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	N/A	N/A	

		No difference *to the dry oral comparator* ***Considerably better*** *than the liquid injectable comparator*

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Innovation: *Oral fast dissolving tablets*

Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?	Better	Neutral	The FDT technology and liquid injectable vaccine do not require reconstitution, while the dried oral vaccine does require reconstitution.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	Better	FDTs are ready to use and do not require filling a delivery device unlike the comparators. However, oral vaccine devices are not required to be sterile, so overall risk to the patient is unchanged.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	Better	FDTs do not require preparation (other than opening the package) unlike the comparators which require reconstitution, withdrawal of liquid, and use of an oral delivery device or AD needle/syringe. Some FDTs require careful handling however, as they can be fragile. If multiple vaccine components or antigens are incompatible and cannot be co-formulated, which is the case for some novel enteric vaccines, several FDTs could be co-packaged and administered together, which simplifies vaccine administration compared to combining multiple vials at the time of use.

Category: *Integrated primary container and delivery technology*

Innovation: *Oral fast dissolving tablets*

Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	Does the innovation reduce the potential risk of reuse of delivery technology?	Better	Neutral	No delivery device is required for FDT technology eliminating the risk of reuse. An oral vaccine delivery device can be reused, so the FDT is an improvement. An AD needle and syringe cannot be reused so the FDT rating is neutral in comparison for liquid injectable comparator.
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Neutral	No components are required for the FDT, though there is a risk of contamination of the tablet itself when handled during administration. Because the FDT is given orally, though the likelihood of the tablet being non-sterile may be higher, the risk to the vaccine recipient is less than for an injectable vaccine.
				Better *than both dry oral and liquid injectable comparators*

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.*

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Innovation: *Oral fast dissolving tablets*

Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

Table 8.

Likelihood of needle stick injury	Parameters to measure against a comparator	Dried oral comparator	Liquid injectable comparator	Assessment
• *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Does the innovation contain fewer sharps?**	Better	Better	A oral FDT and the dried oral vaccine comparator are both sharps-free, assuming a device other than a needle and syringe (such as a vial adapter) is used for reconstitution of the dried oral vaccine. The lyophilized oral comparator could use one sharp to reconstitute the vaccine and therefore the innovation would be an improvement. The liquid injectable vaccine requires an AD needle and syringe for administration.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Better	Better	A FDT does not require sharps for preparing/administering the vaccine. One sharp could be used to reconstitute the vaccine if a needle-free device such as a vial adapter is not used. An AD needle and syringe is required for the injectable liquid vaccine.
	Does the innovation include an auto disable feature and is that better than the comparator?	Better	Neutral	A FDT would dissolve after contact with a small amount of saliva and could not be reused. The dried oral vaccine comparators includes mixing and a delivery device – both could potentially be reused. However, as oral FDTs do not require an AD feature it would be better than the comparator. The injectable vaccine comparator uses an AD syringe that also cannot be reused.

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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**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Better	A FDT does not require sharps for preparing/administering the vaccine and therefore a SIP would not be indicated, which is similar to the dried oral vaccine comparator. A standard AD N&S does not include a SIP feature.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Better	There are fewer risks of injuries when administering oral vaccines in comparison to injectable vaccines.
				Better *than both dry oral and liquid injectable comparators*

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.*

[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.

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Category: *Integrated primary container and delivery technology*

Innovation: *Oral fast dissolving tablets*

Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

Table 9.

Total economic cost of storage and transportation of commodities per dose	**Parameters to measure against a comparator**	**Dried oral comparator**	**Liquid injectable comparator**	**Assessment**
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Better	Better	The FDT technology is compact compared to a glass vial containing either a lyophilized oral vaccine and diluent or liquid injectable vaccine. Measurements by PATH of an oral FDT prototype estimated the volume per dose to be 2 cm^3 per dose (packaged in a 12-dose blister packet, no secondary packaging) compared with a SDV where this varies by vaccine type and manufacturer but examples of the volume per dose are of 10.3 cm^3 (Quinvaxem) (6). If multiple FDTs are required, the potential benefits related to a reduced cold chain volume would be even greater compared to multiple SDVs. Since FDTs can improve heat stability compared to a liquid formulation, there is a possibility a oral FDTs could be stored in a controlled temperature chain, which could further reduce the cold chain volume compared to the comparators. However, this would need to be evaluated for each antigen.
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Better	Better	The FDT eliminates the need to store any components out of the cold chain unlike the comparators which require syringes / droppers for preparation and/or administration.
				Considerably better *than both dry oral and liquid injectable comparators*

Category: *Integrated primary container and delivery technology*
Innovation: *Oral fast dissolving tablets*
Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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	Dried oral comparator	Liquid injectable comparator	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Better	Better	FDT technology may require no to minimal preparation prior to administration while the comparators may require steps for reconstitution and drawing doses.
	[d]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	Neutral	The innovation does not impact the time spent by staff for stock management.
				***Better** than both dry oral and liquid injectable comparators*

[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.

Category: *Integrated primary container and delivery technology*
Innovation: *Oral fast dissolving tablets*
Comparators: *SDV (lyophilised) + diluent + RUP syringe and dropper; SDV (liquid) and AD N&S*

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	Dried oral comparator	Liquid injectable comparator	Assessment
	Are there one-time upfront costs that will be incurred for use of this innovation or recurrent costs that will be incurred for use of this innovation?	Neutral	Neutral	There are no upfront and recurrent costs associated with using FDT. However, as with any innovation, vaccinators will need to be trained on the innovation. Using FDT will require training of vaccinators to ensure that vaccine FDTs are removed by peeling the blister lid and not by a push-through mechanism, on careful handling to avoid breakage, and on how to administer a vaccine in this new presentation. We are not including training costs as part of the assessment in this phase.
				No difference *to the dry oral and liquid injectable comparators*

3.5 Secondary criteria on potential breadth of innovation use

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

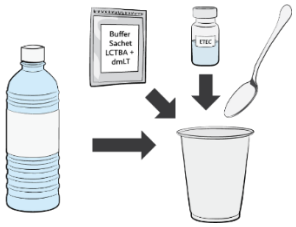
Table 12.

Applicability of innovation to one or several types of vaccines • *What vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	This innovation could be applied to vaccines that are intended for oral ingestion delivery and is particularly well suited for enteric pathogens. All vaccines against mucosal pathogens that can be lyophilized are potential candidates. Live vaccines against enteric pathogens are likely to be most suitable. Non-live vaccines are likely to require a mucosal adjuvant, and none are approved at present. An oral FDT would be particularly useful for ETEC vaccine since the current presentation requires mixing of multiple components at the point of use. The innovation could also be applied to oral live-attenuated rotavirus vaccine.

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**
	Novel vaccines for enteric pathogens often have incompatible components and can be combined only after individual reconstitution of vials at the point of use. A FDT presentation could simplify this method by combining multiple tablets into a single diluent vial or directly taking the tablets orally. Example of a candidate ETEC vaccine that has a complex, three-component presentation: vial containing cellular suspension; foil sachet containing recombinant protein, buffer, and adjuvant; and water, mixing cup, and spoon supplied on-site. With the oral FDT innovation, this vaccine presentation could be simplified to three FDTs for the vaccine, buffer, and adjuvant:

Current presentation	**Oral FDT presentation**
	 Images provided by PATH.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	Assessment
Type of study	The majority of the data has come from expert opinion. There are several published articles on the formulation studies. No usability/in-country data are available.
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*	*FDTs are at a very early stage of development and most data available comes from expert opinion or manufacturers. Most candidates are in preclinical development. The results from phase 1 clinical trial of a* norovirus FDT were recently reported.

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
Manjari Lal, Jessica White	PATH, Formulation Technologies Portfolio mlal@path.org; jwhite@path.org	Developed and reviewed TN
PATH Medical Device and Health Technology Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH Debra Kristensen dkristensen@path.org	Reviewed TN
Fatema Kazi	Gavi, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Reviewed the TN
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	Reviewed the TN

4.4 References:

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

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5. Zhu C, Estrada M, White J, Lal M. Heat-stable sublingual oxytocin tablets as a potential needle-free approach for preventing postpartum hemorrhage in low-resource settings. Drug Deliv Transl Res. 2018 Jun;8(3):853-856. doi: 10.1007/s13346-017-0471-7.

6. WHO prequalified vaccines website. Diphtheria-tetanus-pertussis (whole cell)-hepatitis B-*Haemophilus influenzae* type b: Quinvaxem page. https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=6. Accessed April 12, 2019.