

Sublingual dosage forms

Comparators*:

- Single dose vial (liquid) and dropper or sprayer^a;
 - Single dose vial (lyophilised) + diluent + reuse prevention (RUP) reconstitution syringe and dropper sprayer;
 - Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 - Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.
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Section 1: Summary of innovation

1.1 Examples images:



Photo source: Provided by PATH



Photo source: LTS Lohmann

1.2. Description of innovation (1,2):

- Sublingual (under the tongue) administration allows direct absorption into the systemic circulation.
- The sublingual region under the tongue is highly vascularized, rich in blood supply, allowing for direct absorption of the active into systemic circulation. It also contains numerous subsets of antigen presenting cells (APCs) and plays a critical role in induction of immune responses offering a non-invasive route for vaccine administration.
- The sublingual dosage forms reported in this TN have been developed to contain penetration enhancers and mucoadhesive agents to assist with antigen uptake by the underlying APCs similar to an injectable formulation (IM/SC/ID routes). Sublingual delivery is a needle-free and simplified alternative presentation to a parenteral vaccine.
- In addition to systemic immunity, sublingual delivery also has the potential to induce robust mucosal immunity.
- Oral mucosal vaccination (i.e. sublingual and buccal routes) is distinct from oral ingestion vaccination because the dosage form is not intended to be swallowed or delivered to the intestines.
- The sublingual route has the potential to induce mucosal immune responses in a broad range of tissues at more distance sites compared to other mucosal routes (i.e. the respiratory, gastrointestinal, or reproductive tract) (1).
- Sublingual dosage forms can be produced via different manufacturing processes such as direct compression, melt extrusion, liquid blending or freeze drying.

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

^a The dropper or sprayer comparator is expected to be delivered by the oral or intranasal route.

Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

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- Most commercially available sublingual products (i.e. pharmaceuticals, immunotherapies) are delivered as sublingual tablets. Some spray and thin film products are also commercially available.
- Despite the potential benefits of sublingual immunization, several challenges have delayed development progress including immune tolerance, as demonstrated by the successful delivery of immunotherapy products through the sublingual route designed to induce tolerance. To induce a protective immune response for vaccines, manipulation of the antigen formulation and dose may be required including the use of a mucosal adjuvant.
- The rapid flow of saliva also limits the residence time of antigen in the mouth and opportunity for contact with APCs, which reduces effectiveness. To enhance the residence time on the oral mucosa, optimized dosage forms are being explored for sublingual vaccine delivery to improve performance. Sublingual dosage forms can be formulated as rapid (fast dissolving) or extended (slow) release formulations where the gel remains in the sublingual region for an extended period of time (1):
 - *Gel-forming sublingual tablets* (also known as sublingual fast dissolving tablets and orally disintegrating tablets): These rapidly dissolving tablets are placed under the tongue and form a gel upon contact with the oral mucosa. Sublingual tablets are the most well-characterized sublingual dosage form and are used for several allergy immunotherapies (see Table 1 for examples).
 - *Gel-forming thin films*: Thin films are prepared using hydrophilic polymers that rapidly form a gel upon contact with the oral mucosa. The technology is similar in size and shape to a postage stamp.
 - *Thermoresponsive gels*: These liquid formulations are kept at room temperature and delivered with a dropper that forms a gel upon contact with the oral mucosa (development discontinued due to technical challenges).
 - *Sprays*: Sprayers are used to deliver product under the tongue, but are less likely to be appropriate for vaccines given the need for accurate dosing and disadvantages of the liquid format in terms of lower heat stability and the added requirement of a delivery device. The sprays also remain in a liquid formulation and do not form a gel.

This Technical Note will focus predominately on gel-forming sublingual tablets and thin films as sublingual dosage forms since thermoresponsive gel (TRG) development has been discontinued and given the disadvantages of the spray format described above. The scoring was completed for vaccines meant for older children and adults given the difficulties in delivering these formats to infants because of the risk of choking. While reconstitution and delivery by an oral dropper is a possibility for infant populations (children under 2 years of age), many of the advantages of these formats are lost in this scenario of use.

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Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.*

1.3 Examples of innovations and developers:

Most sublingual vaccine candidates are in early-stage preclinical development. Some have progressed to clinical trials including a seasonal influenza vaccine combined with a novel adjuvant in a sublingual tablet (Phase 1 completed) (3,4) Several other Phase 1 clinical trials have explored sublingual delivery including for influenza (LAIV) (5), cholera (subunit) (6), human papillomavirus (HPV) (7), and tuberculosis (8) vaccines as well as for dmLT (9). However, these studies have not utilized optimized sublingual dosage forms that form a gel and deliver a precise dose, with a sufficient residence time, on the oral mucosa to induce a robust immune response; e.g. in the trial with HPV vaccine, the injectable vaccine formulation was administered as drops without reformulation to optimize the vaccine for sublingual administration and was significantly less immunogenic than SC (7). Sublingual tablet delivery is currently used for low-molecular weight drugs such as nitroglycerin and allergy immunotherapies. Spray sublingual dosage forms, not covered in the assessment portion of this TN, are also marketed for therapeutic vaccines to prevent recurrent urinary tract infections including Uromune and Pulmigen. Although these products are not intended for prophylactic vaccine delivery, learnings could be applied. Dosage forms suitable for sublingual administration include tablets, thin films, thermoresponsive gels, and sprays are summarized in Table 1 (thermoresponsive gels and sprays are not covered in the assessment portion of this TN).

Table 1.

Product name; Image	Developer (place); website	Brief description, notes
Sublingual tablet:		
Tablet-type influenza vaccine	Nitto Denko Corporation; Research Foundation for Microbial Diseases of Osaka University Japan https://www.nitto.com	Phase 1 clinical study completed for a quadrivalent seasonal influenza vaccine sublingual tablet. This formulation includes the novel adjuvant ND002. https://www.nitto.com/us/en/press/2016/1102.jsp
Ragwitek	Merck Sharp & Dohme Corp (USA)	Allergy immunotherapy; sublingual tablet; commercially available. https://www.fda.gov/downloads/BiologicsBloodVaccines/Allergens/UCM393600.pdf

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SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;

Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);

Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.


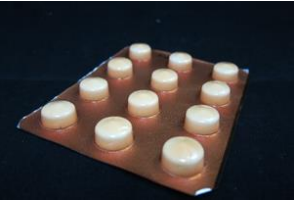


Product name; Image	Developer (place); website	Brief description, notes
 <ul style="list-style-type: none"> • Place under tongue until dissolved and wait at least 1 minute before swallowing • Avoid food or beverage for least 5 minutes after dissolution of the table • * First dose administered in healthcare setting observed for 30 mins <p>Image source: American Osteopathic Association</p>		
<p>Abstral</p>  <p>Image source: Top Supply Chemicals</p>	<p>ProStrakan Inc (Scotland)</p> <p>http://www.prostrakana.com/</p>	<p>Narcotic; sublingual tablet; commercially available.</p> <p>https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022510s015lbl.pdf</p>
<p>Pulmigen</p>	<p>CiplaMed (India)</p> <p>https://ciplamed.com/content/pulmigen-tablets</p>	<p>Prevention of acute, sub-acute, recurrent or chronic infections of the upper and lower airways and of the bronchopulmonary tree; sublingual tablet; commercially available.</p> <p>https://ciplamed.com/content/pulmigen-tablets</p>

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Product name; Image	Developer (place); website	Brief description, notes
 <p>Image source: CiplaMed</p>		
<p>Sublingual fast dissolving tablet</p>   <p>Photos source: provided by PATH</p>	<p>PATH</p>	<p>PATH is developing sublingual fast dissolving tablets (resembling oral fast dissolving tablets described in the respective TN, but different in composition and route of administration) for several applications including oxytocin for prevention of postpartum haemorrhage (10); FDTs containing dmLT mucosal adjuvant which can potentially be co-administered with non-injectable mucosal vaccines; and HIV Env protein.</p> <p>Previously PATH has evaluated sublingual FDTs for vaccines against Newcastle disease (11) (for poultry) and ETEC (12).</p>
<p>Striant™</p>  <p>Photo source: Rxlist</p>	<p>Endo Pharmaceuticals, Inc (USA)</p> <p>http://www.endo.com/</p>	<p>Commercially available mucoadhesive buccal tablet (forming a gel on the cheek) for testosterone therapy, which have been developed to stay in place for several hours at the administration site. Learnings could be applied to sublingual tablets.</p>

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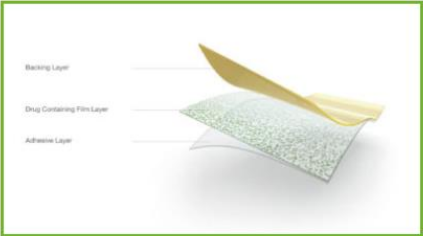

Product name; Image	Developer (place); website	Brief description, notes
<p>Buccastem® M buccal tablets</p>  <p>Photo source: Alliance Pharmaceuticals</p>	<p>Alliance Pharmaceuticals Limited (UK)</p> <p>https://www.alliancepharmaceuticals.com/</p>	<p>Commercially available mucoadhesive buccal tablet (forming a gel on the cheek) to treat nausea and vomiting associated with migraines, which have been developed to stay in place for several hours at the administration site. Learnings could be applied to sublingual tablets.</p>
Thin film:		
<p>Nanofibrous mucoadhesive film (used for pig and mice experiments)</p>  <p>Photo source: Veterinary Research Institute</p>	<p>Veterinary Research Institute (Czech Republic)</p> <p>https://www.vri.cz/</p>	<p>A research group at the Veterinary Research Institute is exploring multi-layered nanofibrous thin films for sublingual administration of drug and vaccine nanoparticles in an animal model (13).</p>

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Product name; Image	Developer (place); website	Brief description, notes
 <p>Fast Disintegrating Buccal Film</p>  <p>Non-Disintegrating Buccal Film</p> <p>Images source: LTS Lohmann</p>	<p>LTS Lohmann (Germany)</p> <p>https://ltslohmann.de/en/technology/oral-thin-films/</p>	<p>LTS Lohmann is developing a thin film dosage form for buccal delivery, which could be applied to sublingual delivery. Thin films can be formulated for fast or sustained release.</p>
<p>Suboxone® (buprenorphine and naloxone) Subutex® (buprenorphine)</p>  <p>Photo source: Shutterstock</p>	<p>Indivior (USA)</p> <p>http://www.indivior.com/</p> <p>https://www.suboxone.com/</p>	<p>Indivior has two commercially available sublingual thin film drug products for the treatment of opioid dependence. The thin films are placed under the tongue until they completely dissolve. Patients are instructed not to cut, chew, or swallow the sublingual film.</p>



Other sublingual dosage forms that are not the focus of this Technical Note:

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Product name; Image	Developer (place); website	Brief description, notes
Thermoresponsive gel:		
 <p>Photo source: provided by PATH</p>	<p>PATH (USA) https://www.path.org/</p>	<p>PATH previously evaluated thermoresponsive gels (TRGs) to enhance residence time on the oral mucosa. This technology is formulated as a liquid, which can be delivered using an oral dropper to the sublingual region, and changes to a viscous gel upon contact with the mucosa at body temperature. Previous preclinical studies evaluated sublingual immunization with a TRG for IPV (14) and tetanus toxoid (15), both adjuvanted with dmLT. Influenza was also evaluated. PATH has discontinued development of TRG due to challenges with gel formation. The transition from liquid to gel, could be triggered by warmer ambient temperatures (~39°C), which could be a challenge in tropical regions.</p>
Spray:		
<p>Uromune</p>  <p>UROMUNE</p> <p>Photo source: Inmunotek</p>	<p>Inmunotek (Spain) https://www.inmunotek.com/en/122016-uro-mune-mechanisms/</p>	<p>Therapeutic vaccine for the prevention of recurrent urinary tract infections. The vaccine is sprayed daily under the tongue, maintained under the tongue for 1-2 minutes, and then swallowed; commercially available.</p>

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SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits

- Sublingual (SL) delivery can induce both systemic and mucosal immunity.
- Compared to other mucosal routes, the sublingual route has the potential to induce mucosal immune responses in a broad range of more distant tissues (i.e. the respiratory tract or reproductive tract) (1,16,17).
- The innovation represents an optimized sublingual dosage form compared to a dropper/sprayer since it increases permeability and uptake of antigen at the mucosal site by forming a gel that remains under the tongue and increases the oral residence time and minimizes losses due to swallowing. The innovation also improves dose control and ensures consistency in administration compared to a dropper/sprayer.
- Sublingual dosage forms are easy to administer and do not require delivery by a skilled health worker, which could facilitate alternative delivery scenarios.
- Eliminates the use of sharps in comparison to injectable formulations or those that require reconstitution.
- May offer improved heat stability over liquid vaccines given the dried format.
- Sublingual dosage forms are compact with a decreased storage and transport volume compared to a single-dose vial.

2.2 Key challenges:

- Some training will be required to ensure proper handling and administration of the sublingual dosage forms. Since the sublingual route is quite novel and only used for a limited number of pharmaceutical products, sublingual vaccines could easily be mistaken for an oral ingestion product and swallowed, which could decrease effectiveness.
- For infants and young children, the dry sublingual dosage forms need to be reconstituted and then administered with a liquid dropper/oral syringe under the tongue to address the potential risk of choking, which increases complexity and negates many of the benefits so the applicability of the

2.3 Additional important information:

- The SL route has been historically used to induce tolerance (immune non-responsiveness) to antigens. Mucosal adjuvants are likely to be needed to enhance immunogenicity and induce protective responses.
 - The only published results from a clinical trial found SL delivery to be significantly less immunogenic than SC injection, although in this case the vaccine was administered as drops (7).
- Development is hindered by the fact that animal models have extremely small oral cavities which makes it difficult to test the dry sublingual formats (fast dissolving tablets (FDTs) and thin films) and limits the amount of liquid that can be delivered using liquid formulations.

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 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

- format is likely limited to older populations. Alternatively, the SL formulations could be used with a more limited range of vaccines for adults, adolescents and older children.

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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
	Does the innovation have features that may improve heat stability?	Neutral (+recon system) Better (-recon system)	Neutral (+recon system) Better (-recon system)	The dry sublingual dosage forms are likely to have improved heat stability in comparison to liquid formulations and to have similar heat stability to the dry comparators (i.e. dropper/sprayer + 'recon system'; SDV AD N&S + 'recon system').

Dropper or sprayer + recon	SDV AD N&S + recon	No difference with comparator (dropper or sprayer+ 'recon system'; SDV AD N&S + 'recon system')
Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV AD N&S)

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 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe 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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
	Does the innovation have features that may improve freeze resistance?	Neutral (+recon system) Better (-recon system)	Neutral (+recon system) Better (-recon system)	The sublingual dosage forms are dried and therefore not freeze sensitive, similar to the dropper or sprayer + 'recon system' comparator, SDV AD N&S + 'recon system' comparator. Whether or not the sublingual dosage form is more freeze-resistant than a liquid vaccine (i.e. no recon system) will be vaccine dependent, as not all liquid vaccines are freeze sensitive. It is probably reasonable to assume however that for most vaccines the sublingual version will be more freeze resistant.

Dropper or sprayer + recon	SDV AD N&S + recon	No difference with comparator (dropper or sprayer + 'recon system'; SDV AD N&S + 'recon system')
Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV AD N&S)

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3.2 Coverage and equity criteria

Indicator: Ease of use^b

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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
<ul style="list-style-type: none"> 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 (+recon system) Neutral (-recon system)	Better (+recon system) Neutral (-recon system)	The +‘recon system’ comparators require reconstitution while the others do not. The innovation does not require reconstitution as it is placed directly on the mucosal surface and is dissolved by saliva to form a gel.

^b 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).

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Ease of use	Parameters to measure against a comparator	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
<ul style="list-style-type: none"> 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 require fewer vaccine product components?	Better	Better	Sublingual dosage forms have a single component (thin film/sublingual FDT). The comparators have multiple components: <ul style="list-style-type: none"> Dropper or sprayer: vaccine + dropper/sprayer device (2 components) Dropper or sprayer + 'recon system': vaccine, diluent, reconstitution syringe, + dropper/sprayer device (4 components) SDV AD N&S: SDV, AD N&S (2 components) SDV AD N&S + 'recon system': vaccine, diluent, reconstitution syringe, AD N&S (4 components)
	Does the innovation require additional components or equipment (such as scanners or label readers)?	N/A	N/A	
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	Better	Sublingual dosage forms can be administered directly into the patient's mouth, eliminating reconstitution and vaccine preparation steps, requiring fewer steps than all the comparators.

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

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 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

Ease of use	Parameters to measure against a comparator	Comparators:	Comparators:	Assessment
<ul style="list-style-type: none"> 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 improve dose control?	Oral/ intranasal: Dropper or sprayer +/- reconstitution	Injectable: SDV AD N&S +/- reconstitution	<p>Better</p> <p>Better</p> <p>A sublingual dosage form is a fixed dose and some formats are designed to stay in place after administration, which improves the ability to deliver a correct dose under the tongue. Striant™ and Buccastem® M are examples of buccal mucoadhesive tablets (forming a gel on the cheek) on the market similar to sublingual tablets, which have been developed to stay in place for several hours at the administration site.</p> <p>However, some tablets require the recipient to wait 1 minute before swallowing (see table 1), so there is a risk that poor compliance could result in an incomplete dose being given.</p>
	Does the innovation improve targeting the right route of administration?	Neutral	Neutral	<p>Neutral</p> <p>Neutral</p> <p>This innovation has been optimized for sublingual delivery to remain under the tongue as a gel and prevent antigen loss due to swallowing and salivary washout.</p> <p>There is a potential that the sublingual FDT could be mistaken for an oral tablet and swallowed, which could reduce the oral residence time and contact with APCs in the mouth, which could impact effectiveness.</p>

Total score for the indicator:	Dropper or sprayer + recon	SDV AD N&S + recon	Better (dropper or sprayer + 'recon system'; SDV AD N&S + 'recon system')
	Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV AD N&S)

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 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe 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	Parameters to measure against a comparator	Comparators:	Comparators:	Assessment
		Oral/ intranasal: Dropper or sprayer +/- reconstitution	Injectable: SDV AD N&S +/- reconstitution	
<ul style="list-style-type: none"> Assessment of the potential to reduce stock outs based on the innovation's features 	Does the innovation require fewer components?	Better	Better	Sublingual dosage forms have a single component (thin film/sublingual FDT). The comparators have multiple components: <ul style="list-style-type: none"> Dropper or sprayer: vaccine, dropper/sprayer device (2 components) Dropper or sprayer + 'recon system': vaccine, diluent, reconstitution syringe, dropper/sprayer device (4 components) SDV AD N&S: SDV, AD N&S (2 components) SDV AD N&S + 'recon system': vaccine, diluent, reconstitution syringe, AD N&S (4 components)
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neutral	A sublingual dosage form does not impact product labelling.

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Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

Total score for the indicator:	Dropper or sprayer + recon	SDV AD N&S + recon	Better (dropper or sprayer + 'recon system'; SDV N&S + 'recon system')
	Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV 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 <ul style="list-style-type: none"> Does the innovation include features that may improve acceptability of vaccinees and caregivers 	Parameters to measure against a comparator	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
	Painful or not painful	Neutral	Better	The sublingual dosage form is likely to be less painful than an injectable vaccine and similar to a dropper/sprayer.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Neutral	Better	It is expected that caregivers and vaccinees would find sublingual dosage forms similar to a dropper or sprayer since they are all needle-free, but sublingual dosage forms would likely improve the vaccinees/caregivers vaccination experience compared to an injectable formulation.

Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	N/A	N/A	

Total score for the indicator:	Dropper or sprayer + recon	SDV AD N&S + recon	<u>No difference with comparator</u> (dropper or sprayer + 'recon system') <u>Considerably better</u> (SDV AD N&S + 'recon system')
	Dropper or sprayer - recon	SDV AD N&S - recon	<u>No difference with comparator</u> (dropper or sprayer) <u>Considerably better</u> (SDV 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.

Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

Table 7.

Likelihood of contamination	Parameters to measure against a comparator	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
<ul style="list-style-type: none"> 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?	Neutral (+recon system) Neutral (-recon system)	Better (+recon system) Neutral (-recon system)	The sublingual dosage form, dropper/sprayer comparator, and SDV AD N&S comparator do not require reconstitution, while the dropper or sprayer + 'recon system' and SDV AD N&S + 'recon system' comparators require reconstitution. However, the risk to the vaccine recipient is less than for an injectable vaccine because SL delivery devices are not required to be sterile.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Neutral	Better	The innovation is ready to use which eliminates the need for a separate delivery device, reducing the risk of contamination occurring when assembling a dropper or sprayer to a vial or filling a delivery device. However, the risk to the vaccine recipient is less than for an injectable vaccine because SL delivery devices are not required to be sterile.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	Better	Sublingual dosage forms can be administered directly into the patient's mouth, eliminating reconstitution and vaccine preparation steps, requiring fewer steps.

VIPS TECHNICAL NOTE



Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

Likelihood of contamination	Parameters to measure against a comparator	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
<ul style="list-style-type: none"> Risk assessment of potential for contamination based on design of innovation and on usability data from field studies 	Does the innovation reduce the potential risk of reuse of delivery technology?	Better	Neutral	No delivery device is required for sublingual dosage forms eliminating the risk of reuse. An AD N&S cannot be reused so the rating is neutral in comparison. A dropper/sprayer is not required to be AD. Therefore, the innovation reduces the risk of reuse that might occur with a dropper/sprayer.
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Neutral	No components are required for the sublingual dosage form, though there is a risk of contamination of the tablet/thin film itself when handled during administration. Since sublingual dosage forms are placed under the tongue the likelihood of the tablet/film being non-sterile may be higher, however, the risk to the vaccine recipient is less than for an injectable vaccine. Oral delivery devices are not required to be sterile.

Total score for the indicator:	Dropper or sprayer + recon	SDV AD N&S + recon	Better (dropper or sprayer + 'recon system'; SDV AD N&S + 'recon system')
	Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV AD N&S)

Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
<ul style="list-style-type: none"> Risk assessment of the presence of sharps during the process of preparing and administering the vaccine 	Does the innovation contain fewer sharps?	Better (+recon system) Neutral (-recon system)	Better	Sublingual dosage forms and the dropper or sprayer comparator without the recon system are both sharps-free. The comparators contain the following quantities of sharps: <ul style="list-style-type: none"> Dropper or sprayer – ‘recon system’: (0 sharps) Dropper or sprayer + ‘recon system’: reconstitution syringe (1 sharp) SDV AD N&S: AD N&S (1 sharp) SDV AD N&S + ‘recon system’: reconstitution syringe, AD N&S (2 sharp)
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Better (+recon system) Neutral (-recon system)	Better	Sublingual dosage forms and the dropper or sprayer comparator do not require sharps for preparing/ administering the vaccine. An AD N&S is required for delivering the AD N&S +/- ‘recon system’ comparators and a reconstitution N&S is required for reconstituting the dropper or sprayer + ‘recon system’ and AD N&S + ‘recon system’ comparators.

VIPS TECHNICAL NOTE



Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

Likelihood of needle stick injury	Parameters to measure against a comparator	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
<ul style="list-style-type: none"> Risk assessment of the presence of sharps during the process of preparing and administering the vaccine 	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	Neutral	A sublingual dosage form would dissolve after contact with a small amount of saliva and could not be reused. A dropper or sprayer are not required to be AD. The 'recon system' AD N&S comparator includes an AD feature.
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Neutral	Better	Sublingual dosage forms are sharps-free and a SIP feature would not be included. The AD N&S comparator does not include a SIP feature.
	Does the innovation reduce the risk of injury after vaccine administration?	Neutral	Better	There are fewer risks of injury when administering sublingual vaccines in comparison to injectable vaccines. The risks are similar compared to a dropper/sprayer.

Total score for the indicator:	Dropper or sprayer + recon	SDV AD N&S + recon	Better (dropper or sprayer + 'recon system'; SDV N&S + 'recon system')
	Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV N&S)

Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

3.4 Economic costs criteria

Indicator: Total economic cost of storage and transportation of commodities per dose^d

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.

Total economic cost of storage and transportation of commodities per dose	Parameters to measure against a comparator	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Better	Better	<p>Sublingual dosage forms are compact compared to single-dose glass vials, which are used for the comparators. Measurements by PATH of a sublingual FDT prototype estimated the volume per dose to be 2 cm³ 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 cm³ (Quinvaxem) (18) and 14.53 cm³ (Euvax, hepatitis B) (19).</p> <p>Since dry sublingual dosage technologies can improve heat stability, there is a possibility a dry sublingual dosage form 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 and presentation (FDT and thin films).</p>

^d 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.

VIPS TECHNICAL NOTE



Category: *Integrated primary container and delivery technology*

Innovation: *Sublingual dosage forms*

Comparators: *SDV (liquid) and dropper or sprayer;*
SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

Total economic cost of storage and transportation of commodities per dose				No volume data are available for thin films. They are expected to have similar or smaller volume per dose compared to sublingual FDTs.
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Better	Better	The sublingual dosage form eliminates the need to store and transport any components out of the cold chain unlike the comparators which require dropper/sprayer, or AD N&S for administration. The dropper or sprayer + 'recon system' and SDV AD N&S + 'recon system' comparators also require diluent and a reconstitution syringe.

Total score for the indicator:	<i>Dropper or sprayer + recon</i>	<i>SDV AD N&S + recon</i>	<u>Considerably better</u> (dropper or sprayer + 'recon system'; SDV N&S + 'recon system')
	<i>Dropper or sprayer - recon</i>	<i>SDV AD N&S - recon</i>	<u>Considerably better</u> (dropper or sprayer; SDV N&S)

VIPS TECHNICAL NOTE



Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe 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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Better	Better	Sublingual dosage forms may require no to minimal preparation prior to administration while the comparators require steps for preparing the dropper/sprayer or drawing doses. Some comparators also require reconstitution.
	^e 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.
Total score for the indicator:		<i>Dropper or sprayer + recon</i>	<i>SDV AD N&S + recon</i>	Better (dropper or sprayer + 'recon system'; SDV N&S + 'recon system')

^e 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.

VIPS TECHNICAL NOTE



Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

	Dropper or sprayer - recon	SDV AD N&S - recon	Better (dropper or sprayer; SDV N&S)
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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	Comparators: Oral/ intranasal: Dropper or sprayer +/- reconstitution	Comparators: Injectable: SDV AD N&S +/- reconstitution	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 sublingual dosage forms. However, as with any innovation, vaccinators will need to be trained on the innovation. Using a sublingual dosage form will require training of vaccinators to ensure that the dose is properly removed from the packaging and administered under the tongue/not swallowed. We are not including training costs as part of the assessment in this phase.

Dropper or sprayer + recon	SDV AD N&S + recon	No difference with comparator (dropper or sprayer + 'recon system'; SDV AD N&S + 'recon system')
Dropper or sprayer - recon	SDV AD N&S - recon	No difference with comparator (dropper or sprayer; SDV AD N&S)

Category: *Integrated primary container and delivery technology*

Innovation: *Sublingual dosage forms*

Comparators: *SDV (liquid) and dropper or sprayer;*
SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

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	Assessment
<ul style="list-style-type: none"> What vaccines/antigens does the innovation apply to, based on technical feasibility? 	<p>This innovation can potentially be applied to vaccines against mucosal pathogens that can be prepared in a dry format. Vaccines that are currently delivered parenterally are likely to be suitable for this innovation, but non-live vaccines are likely to require a mucosal adjuvant (such as dmLT), and none are approved at present. Live vaccines that are delivered intranasally may also be suitable.</p> <p>A sublingual dosage form is an attractive option for an HIV vaccine since it is a mucosal pathogen and sublingual delivery can induce mucosal immune responses in the reproductive tract. Several candidate HIV vaccines including live vectors and recombinant proteins have been evaluated in preclinical studies. Examples on the VIPS priority antigen list that might also be appropriate for sublingual delivery include HPV, IPV (both might require a mucosal adjuvant however) and the live VSV-vectored Ebola vaccine.</p>

Indicator: Ability of the technology to facilitate vaccine combination

Legend: **Green**: The innovation **improves** the ability to combine vaccines; **White**: **Neutral**, no difference with the comparator; **Red**: The innovation **reduces** the ability to combine vaccines.

Table 13.

Ability of the technology to facilitate vaccine combination	Assessment
<ul style="list-style-type: none"> Does the innovation facilitate novel combination vaccine products? 	<p>A sublingual dosage form is not expected to facilitate combination vaccine products any differently than the comparators as all these products begin as liquid formulations that are either filled into vials or dried into their final formats. If the injectable vaccine is currently a combination vaccine, then the sublingual formulation would also be a combination.</p>

Category: *Integrated primary container and delivery technology*

Innovation: *Sublingual dosage forms*

Comparators: *SDV (liquid) and dropper or sprayer;*
SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

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 <ul style="list-style-type: none"> 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. Additional data are available for allergy immunotherapy and drug applications but were not used in this evaluation.

Overall assessment:	<i>Low to moderate</i>	<i>Sublingual dosage forms for vaccine delivery are at a very early stage of development and most data available comes from expert opinion or manufacturers. Most vaccine candidates are in preclinical development.</i>
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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.

VIPS TECHNICAL NOTE



Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

*Comparators: SDV (liquid) and dropper or sprayer;
SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.*

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 TN
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	Reviewed TN

4.4 References:

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

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Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

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Category: Integrated primary container and delivery technology

Innovation: Sublingual dosage forms

Comparators: SDV (liquid) and dropper or sprayer;
 SDV (lyophilised) + diluent + RUP reconstitution syringe and dropper sprayer;
 Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S);
 Single dose vial (lyophilised) + diluent and RUP reconstitution syringe and AD N&S.

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