

Prefilled dry-powder intranasal (DPIN) devices

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

Section 1: Summary of innovation

1.1 Example images:

Unidose^b Bepak



Image source: ^c

Bi-DirectionalTM nasal delivery technology, Optinose[®]



Image source: ^d

1.2. Description of innovation:

- There are a whole range of dry powder intranasal (DPIN) devices that are being developed or already on the market for delivering medicines.
- DPIN devices fall into two basic categories based on the activation method used. Most of the devices use (i) mechanical energy from fingers or thumb to generate pressure to disperse the powder, and others use (ii) passive or active breath flow to disperse the powder. Powders would likely reach only the nare(s) to which they are administered, and it is possible to administer doses to each nare. There may be some increased risk of pulmonary deposition of powders if the particle size range includes small particles (< 5 micron).
- **Powder sprayers** are devices that deliver IN dry powder sprays by creating an internal pressure on the compartment containing the formulation through an external mechanical force driving the release of powder particles into the nasal passageway, they use mechanical energy to create and internal pressure and these are known as passive devices. Examples include the UniDose, DriDoseTM, Fit-lizerTM.
- **Breath actuated powder inhalers** are active devices that allow the patients' breath to activate expulsion from the capsule or blister containing the dry powder formulation into the nasal passageway. An example is the Rhinocort[®] Turbuhaler[®]. The Rhinocort device uses nasal

* 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 A comparison against IN sprays will be required under Phase II if there is a vaccine (antigen) that is currently delivered as liquid spray in the scope of vaccines.

^b Universal Stabilization technologies. <https://www.vitrilife.com/>

^c Personal communication from Ian Anderson, Bepak, February 2015

^d <https://www.optinose.com/exhalation-delivery-systems/powder-delivery-device>

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inhalation flow to disperse the powder into the nares. **Nasal powder insufflators** are devices composed of 2 components (nosepiece and mouthpiece) that are connected. The user (patient) actively exhales through the mouthpiece allowing the airflow to carry the powder formulation through the nosepiece into the nasal passageway. Examples of this device are the OptiNose powder delivery device and Trivair™ nasal deposition system (section 1.1). By delivery of nasal powder during oral exhalation, pulmonary deposition is minimized to achieve better powder delivery in both the internal nasal airway passages (1). Because the nasal airway passages are connected in the nasopharynx, the larger volume of exhaled breath (compared to the dispersion volume of the mechanical devices) can also disperse the powder better into one nare, making a U-turn depositing powder in the opposite nare where the airflow exits that side^e.

- Dry powder vaccines for IN delivery require specialised drying methods to achieve a formulation that is aerosolizable and of appropriate particle size for efficient and sufficient delivery to the nasal cavity. Dry powder formulation methods are described in detail in the technical notes for “Heat stable dry formulations/CTC qualified vaccines”.
- Various studies have demonstrated the feasibility of preparing dry powder aerosolized vaccines using a variety of methods such as spray-drying, bubble drying (a gentle version of spray drying), spray-freeze drying or freeze-drying methods (2). The measles vaccine powder used in the non-human primate studies was produced by bubble drying (1,3), the powder used in the studies for the anthrax vaccine study (4,5) and measles vaccine (1) was produced by freeze drying or spray freeze followed by ball milling. For the studies with the measles rubella and live-attenuated influenza vaccine (LAIV), the vaccine was preserved using the Universal Stabilization technologies^f (UST) preservation by vaporization (PBV) method followed by ball milling. The PBV method demonstrated long term thermostability, with minimal loss of measles vaccine potency at 37°C for over 12 months (6).

^e <https://www.optinose.com/exhalation-delivery-systems/powder-delivery-device>

^f Universal Stabilization technologies. <https://www.vitrilife.com/>



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1.3 Examples of innovations and developers:

Table 1.

Product name; Image	Developer (place); website	Brief description, notes
Mechanically powered devices		
<p>UniDose^c</p>  <p>Image source: ^a</p>	<p>Bespak Drug Delivery Devices</p> <p>https://bespak.com/devices-technologies/</p>	<p>These devices are prefilled with a single-dose of the dry formulation, and require pressure applied to it for dispersion of the contents.</p> <p>It is available as a single-dose or multi-dose version using prefilled cartridges, which are disposed of once the contents have been delivered.</p> <p>This device is simple with a small storage footprint. The device was used to investigate intranasally delivered Norwalk Norovirus virus like particle (VLP) vaccine in a randomised controlled trial, which had demonstrated significant protection against norovirus gastroenteritis infection (7).</p>
<p>DriDose™, Indosys^d</p>  <p>Image source: ⁹</p>		<p>The device has a bellow that provides airflow following applied pressure, resulting in the dispersion of the dry powder formulation. The device employs a valve that ensures the proper pressure is applied, thus resulting in a high degree of dose reproducibility (<5% variability).</p> <p>It is available in 3 formats:</p> <ol style="list-style-type: none"> 1. A nosepiece with a luer fitting, prefilled with a single dose and compatible with a standard syringe or bellow (as in photo). 2. An integrated device consisting of the bellow and a nosepiece with prefilled single-dose. <p>A multi-dose device with reusable bellows attached to a replaceable single-dose cartridge.</p>




⁹ (personal communication from Paul Ballington and Nick Boyes, February 2015).

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<p>VRx2™ powder delivery systems</p>  <p>Image source: ^h</p>	<p>Mystic Pharmaceuticals®</p> <p>http://mysticpharmaceuticals.com/delivery-systems/intranasal-delivery-solutions/</p>	<p>A device that enables self-administration, pre-loaded with single-dose blister and available as multi-monodose which can be calibrated to a specified dose volume.</p>
<p>Fit-lizer™ Nasal delivery deviceⁱ</p> <p><i>Prefilled single-use device</i> <i>Capsule loading multiple-use</i></p>  <p>Image source: ^j Image source: ^k</p>	<p>Shin Nippon Biomedical Laboratories (SNBL)</p> <p>https://www.snbl-nds.com/technology/</p>	<p>Two self-administering and pre-filled devices exist for this type of innovation. A single-use device which is disposed of after use, or a device that is capsule loaded for multiple-use with up to 100 capsules (personal communication from Mic Iwashima, SNBL Nasal Delivery System Division, February 2015).</p> <p>The plastic chamber is compressed by hand, causing air to pass through a one-way valve and the capsule containing the dry powder formulation is expelled.</p> <p>It is lightweight and portable, delivering up to 100mg of dry powder per capsule.</p> <p>According to the manufacturer, it provides up to 100% delivery of the formulation.</p>
<p>Unit-Dose System (UDS)</p>  <p>Image source: ^l</p>	<p>Aptar pharma - Nasal inhaler</p> <p>https://pharma.aptar.com/en-us/dispensing-solutions/uds.html</p>	<p>Nasal inhalers available as single-dose, bi-dose and multi-dose, containing pre-loaded cartridges of dry powder formulation, currently used for drug delivery.</p>

^h <http://mysticpharmaceuticals.com/delivery-systems/intranasal-delivery-solutions/>

ⁱ A nasal delivery solution to the challenges in biotherapeutic delivery, SNBL.

^j <http://www.ondrugdelivery.com/publications/Biotherapeutics%202012/SNBL.pdf>

^k <http://www.ondrugdelivery.com/publications/Pulmonary%20Nasal%20November%202012/SNBL.pdf>


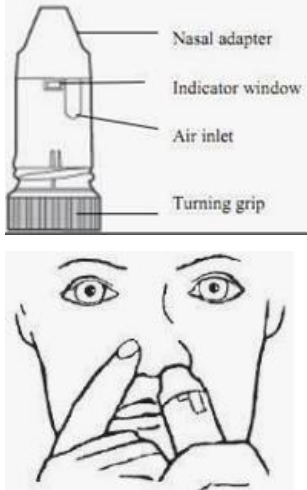
^l https://pharma.aptar.com/sites/default/files/products/marketing_sheet/files/pds_udsandbds_0.pdf

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<p>The BD Intranasal Dry Powder Delivery Device (Investigational Solvent)</p>  <p>Image source: ^m</p>	<p>Becton Dickinson and Co.</p> <p>dry powder inhaler prototypeⁿ (2).</p>	<p>Versions for both pulmonary delivery (via a mask) and direct intranasal delivery were developed. It is a small cylindrical plastic capsule open on both ends, with one end having a luer fitting for attachment to a standard syringe to provide airflow while the other end is used for the patient's interface. The capsule contains the powder formulation between two plastic membranes which ruptures when the airflow is provided by the syringe.</p> <p>The Solvent dry powder intranasal device has been used in multiple preclinical studies with anthrax and measles vaccines. The version for pulmonary delivery was also used in a phase I study with measles vaccine, which showed good safety and immunogenicity. ⁱ Device development seems to have been abandoned by BD.</p> <p>BD has discontinued development of the Solvent^o</p>
<p>Breath Actuated Devices</p>		
<p>Rhinocort® Turbuhaler®ⁱ</p>  <p>Image source: ^p</p>	<p>AstraZeneca Canada Inc.</p> <p>https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/rhinocort-turbuhaler-consumer-information-leaflet-en.pdf</p>	<p>The device is single-dose with the dry powder formulation contained in the blister/capsule that is emptied when inhaled through the nose.</p> <p>Currently, the device is used to deliver medication that is preloaded with a fixed number of doses. It has an indicator on the device to monitor the number of doses administered and is designed to release a single-dose at a time.</p>

^m Personal communication from Vince Sullivan, 2019, Becton Dickinson.

ⁿ https://books.google.co.uk/books?id=yUijDgAAQBAJ&pg=PA1348&lpg=PA1348&dq=becton+dickinson+solovent&source=bl&ots=Hs223egPhT&sig=ACfU3U1CF_9OMoZOanLJ1nF4qN9CKRkIQ&hl=en&sa=X&ved=2ahUKEwif3dHO8JXgAhVvYsBUIHWkYAKgQ6AEwBHoECAQQAQ#v=onepage&q=becton%20dickinson%20solovent&f=false

^o Personal communication (Vince Sullivan, Becton Dickinson)



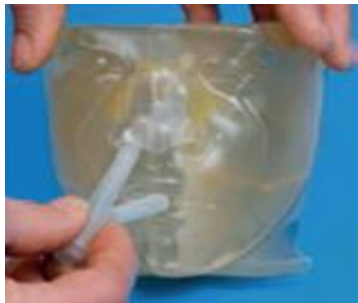
^p <https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/rhinocort-turbuhaler-consumer-information-leaflet-en.pdf>

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<p>Optinose - Bi-Directional™ nasal delivery technology</p>  <p>Image source: ^d</p>	<p>Optinose</p> <p>https://www.optinose.com/exhalation-delivery-systems/powder-delivery-device</p>	<p>The powder Exhalation Delivery System (EDS) has a disposable capsule prefilled with the dry powder formulation which is pierced into the device. The patient inserts the nasal piece and using the mouthpiece exhales into the device which delivers the product into the nasal passageway.</p> <p>This device has a spray and powder configuration, the spray device produced immunity to influenza in human subjects that were immunized with an inactivated whole-virus influenza vaccine(8).</p>
<p>Trivair™ nasal deposition system (1)</p>  <p>Image source: ^q</p>	<p>Trimel Pharmaceuticals, Toronto, Canada.</p>	<p>This device is simple and inexpensive. There does not seem to be way to prevent the mistake of a patient breathing in and taking the agent to the mouth, instead of blowing it into the nose.</p> <p>A cylindrical straw open at both ends, with the dry powder formulation located in the middle part of the chamber.</p> <p>The shorter end is placed in the mouth, while the longer end is placed in the nostrils, then the patients puffs/exhales to blow the powder into the nasal cavity.</p> <p>Each device is disposed after use.</p>
<p>Investigational Creare Intranasal powder delivery device</p>  <p>Image source: ^r</p>		<p>Patient exhalation through the mouth blows the powder into the nose while simultaneously generating air flow that limits entry to the lower respiratory tract. In three-dimensional plastic models, the device consistently delivered a significant fraction (>66%) of a fluorescein powder dose to the target IN airways.</p> <p>Preclinical studies (not yet published) show good rubella immune response following one dose of rubella vaccine and measles immune response following two doses of measles vaccine in non-human primates. Also studies in ferrets showed good immune responses to dry powder^m LAIV.</p>

^q Courtesy of Mark Papania, Centres for disease control and prevention.

^r Personal communication, Mark Papania

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SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- No need for reconstitution, thus removing a step in the process of vaccine preparation that increases the risk of errors.
- No need for filling of vaccine delivery devices for the DPIN devices that are pre-filled with a dry formulation and ready to administer (3).
- Dry powder formulations generally have better stability than conventional liquid formulations and can increase the product's shelf-life without refrigeration, thus cold chain requirements could be greatly reduced.
- Potential for self-administration or reducing the need for administration by medically trained personnel, as the prefilled DPIN devices do not require reconstitution or have sharps (9).
- A pain free form of vaccine administration, which can improve acceptability by recipients as well as eliminate the risk of needle-stick injuries during the handling of the device and preparation of the vaccine.

2.2 Key challenges:

- Few DPIN devices have been used with vaccines.
- Bells Palsy has been observed as a serious adverse event following IN delivery of some vaccines (13).
- Devices that require orally exhaled breath to disperse powder into the nares would need active patient cooperation; not likely be possible with children under 3-4 years of age (14).
- Each new DPIN vaccine would require preclinical testing and clinical studies, and regulatory approvals, which is time consuming and requires substantial financial investment. Furthermore, assessments of the various types of nasal devices would be necessary to identify the optimal delivery method that stimulates the most effective and protective immune response.
- A major challenge with DPIN inhalers is in achieving the balance between inhaler resistance and flow rate, for instance, high resistances would not be feasible for patients with asthma or chronic obstructive pulmonary disease (COPD) who already struggle to breathe (11).

2.3 Additional important information:

- The mechanical devices are designed so that they could be used to deliver powder to people of almost any age and require minimal passive cooperation. Powders would likely reach only the nares to which they are administered.
- Vaccination at the nasal mucosa can elicit better protective immunity and confer protection at other mucosal sites including the lungs, intestines and genital tract (4,10).
- The majority of vaccines are administered by parenteral injection, and reformulation into dry powders for intranasal delivery would require additional formulation work and new production methods. Multiple parameters need to be considered in order to optimise administration of an accurate and consistent dose including aerosol dynamics, particle physiochemical properties of the formulation and the respiratory impact on vaccination (11). Formulating the dry powders will require extensive changes to manufacturing methods (12). Finally, non-live vaccines are likely to require a

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mucosally-active adjuvant to be immunogenic after delivery to the nasal mucosae. No such adjuvants have been approved or licensed to date.

- Packaging of the DPIN vaccine would require automated and sophisticated filling technology (10).
- Less energy is required for dry powder dispersion compared to liquid droplet dispersion, so electromechanical devices are not necessary (12).
- DPIN formulations need to be protected from exposure to humidity during storage and transportation, so the composition and quality of the packaging system needs to be robust to prevent chemical and physical damage (11).

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SECTION 3: Evaluation criteria

3.1 Health impact criteria

Indicator: Ability of the vaccine presentation to withstand heat exposure

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

Table 2.

Ability of the vaccine presentation to withstand heat exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve heat stability?	Neutral	Since DPIN devices use dry powder formulations they are expected to be more stable at ambient temperatures outside the cold chain than conventional vaccine formulations (15,16) and are likely to have similar stability to the dry comparator. It is possible however, that development of the dry powder formulation will result in a product with better thermostability than current dry formulations. However, stability must be determined for each vaccine formulation on a case-by-case basis.

No difference to the comparator

Indicator: Ability of the vaccine presentation to withstand freeze exposure

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

Table 3.

Ability of the vaccine presentation to withstand freeze exposure	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have features that may improve freeze resistance?	Neutral	Since DPIN are a dry powder formulation they are anticipated to be freeze-resistant, similar to existing lyophilized vaccine formulations. However, stability must be determined for each vaccine formulation on a case-by-case basis.

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	<u>No difference</u> to the comparator
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3.2 Coverage and equity criteria

Indicator: Ease of use^s

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

Table 4.

Ease of use	Parameters to measure against a comparator	Score	Assessment
<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	DPIN devices directly deliver a dry powder formulation which does not require reconstitution.
	Does the innovation require fewer vaccine product components?	Better	The number of components involved in vaccine delivery with a DPIN device varies depending on the device design. However, in general fewer components are required. For example, DPIN device + disposable dry powder cartridge + disposable nosepiece (3 components) versus vaccine vial + diluent vial + reconstitution needle & syringe + delivery needle and syringe (4 components).
	[†] Does the innovation require additional components or equipment (such as scanners or label readers)?	N/A	

^s 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).

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

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Ease of use	Parameters to measure against a comparator	Score	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) 	<p>Does the innovation require fewer preparation steps and less complex preparation steps?</p>	<p>Better</p>	<p>The number of steps involved to prepare DPIN devices varies depending on device design. Some DPIN devices are prefilled and ready to use, while others require insertion of a unit dose dry powder vaccine cartridge. Some require other activation or assembly steps.</p> <p>In general, preparation is expected to be less complex than the comparator, which requires reconstitution and additional equipment (diluent and reconstitution needle & syringe) to prepare the vaccine.</p>
	<p>Does the innovation improve dose control?</p>	<p>Better</p>	<p>Both the innovation and comparator are single dose. The innovation has the added advantage of being prefilled with the correct dose and doesn't require drawing from a vial, reducing the error associated with filling the vaccine delivery device. However, intranasal devices can be more reliant on correct user technique and recipient compliance to ensure the full dose is delivered.</p>
	<p>Does the innovation improve targeting the right route of administration?</p>	<p>Worse</p>	<p>DPIN devices can be reliant on user technique and recipient compliance to ensure the dose is deposited correctly in the nares. The innovation could also be mistaken for an orally inhaled vaccine, resulting in reduced efficacy of the vaccine or even serious adverse events, which is not an issue with the comparator as it uses a traditional injectable device.</p> <p>Studies have shown that a common error with using inhalers intended via the mouth is to use it through the nose (17).</p> <p>Targeting the nasal mucosae, as opposed to mucosal surfaces lower down in the respiratory tract is very dependent on the particle size of the powder.</p>

Mixed for the comparator

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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	Score	Assessment
<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	<p>The innovation can vary in the number of components it is composed of as there are a variety of devices being designed and developed (refer to section 1.1) ranging from an all-in-one integrated device such as the UniDose, Bepak to having separate components such as the VRx2™ powder delivery systems.</p> <p>In general, most of the devices would have fewer separate components than the comparator.</p>
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	This innovation does not have any features that would facilitate labelling or product tracking.

	<u>Better</u> than the comparator
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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	Parameters to measure against a comparator	Score	Assessment
• Does the innovation include features that may improve acceptability of vaccinees and caregivers	Painful or not painful	Better	The DPIN devices are not painful, as they are needle-free.
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	Better	Some of the DPIN devices could be self-administered by adolescents and above, making it convenient for the patient or caregiver to use, as well as making it easier for less-trained workers to deliver the vaccine using this device. It is also a non-invasive form of administration which is presumed to be more acceptable by patients (10).
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	Worse	There are issues related to the lack of coordination between the device activation and inhalation due to lack of patient training (11), which could impact patient acceptability since the innovation could be perceived as more complex than the comparator.

 **Mixed** for the comparator

3.3 Safety criteria

Indicator: Likelihood of contamination

Legend: **Dark Green: Considerably better** than the comparator: Better for all applicable parameters; **Green: Better** than the comparator: Better for some of the applicable parameters AND no difference for the rest of the parameters; **White: Neutral**, no difference with the comparator; **Yellow: Mixed**: Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters; **Red: Worse** than the comparator: Worse for some of the applicable parameters AND

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no difference for the rest of the parameters; **Dark Red: Considerably worse** than the comparator: *Worse for all applicable parameters*, **N/A**: the indicator measured is **not applicable** for the innovation; **Grey: no data** available to measure the indicator.

Table 7.

Likelihood of contamination	Parameters to measure against a comparator	Score	Assessment
<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?	Better	As the innovation delivers vaccine as a dry powder, there is no need for reconstituting as there is with the comparator. Many of the devices come with blisters or cartridges preloaded with the dry formulation, so they are ready to use in this format.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Better	The innovation is a prefilled dry powder device and/or come with blisters or cartridges preloaded with the dry formulation, so there is no need to fill the delivery device as there is with the comparator.
	Does the innovation require fewer preparation steps and less complex preparation steps?	Better	The number and complexity of preparation steps varies between the different types of DPIN devices. In general, as the innovation is prefilled with the dry powder formulation, or the vaccine is preloaded into blisters/cartridges, there would be fewer preparation steps than with the comparator.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Worse	Reusable DPIN devices have replaceable pieces for the nose (and mouth, if breath-activated). The components of the delivery device are sealed and tamper-proof. Once the formulation has been administered from the device, it has to be replaced by a new blister/cartridge containing the formulation. As there is a danger that users could use the same nose and mouth piece, the risk of contamination due to reuse of the delivery device is greater than the comparator.
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	It is assumed that all the parts of the DPIN device are sterile packaged similar to the comparator.

Indicator: Likelihood of needle stick injury

Legend: **Dark Green: Considerably better** than the comparator: *Better for all applicable parameters*; **Green: Better** than the comparator: *Better for some of the applicable parameters AND no difference for the rest of the parameters*; **White: Neutral**, no difference with the comparator; **Yellow: Mixed**: *Better than the comparator for some of the applicable parameters AND worse than the comparator for the rest of the parameters*; **Red: Worse** than the comparator: *Worse for some of the applicable parameters AND*

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

no difference for the rest of the parameters; **Dark Red: Considerably worse** than the comparator: *Worse for all applicable parameters, N/A: the indicator measured is not applicable for the innovation; Grey: no data available to measure the indicator.*

Table 8.

Likelihood of needle stick injury	Parameters to measure against a comparator	Score	Assessment
<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	The DPIN devices are sharps free, thus removing any risk of needle stick injury. The comparator requires an RUP N&S for reconstitution and a standard N&S fitted with a nosepiece spray device.
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Better	The DPIN devices are sharps free, which means no sharps are used for preparing nor administering the vaccine, removing any risk of needle stick injury.
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	It is assumed that the innovation would be designed to have an AD feature to avoid re-using any component to reduce cross contamination, therefore no difference to the comparator. AD features are also about preventing the re-use of any part of the device that has the potential to result in cross contamination due to exchange of bodily fluids, which is possible with some of the DPIN devices as most of them are reusable – this is captured with the indicator in Table 7.
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	Better	The DPIN devices are sharps free, removing any risk of needle stick injury. Therefore, SIPs would not be required.
	Does the innovation reduce the risk of injury after vaccine administration?	Better	The DPIN devices are sharps free, which means there is no risk of needle stick injury after vaccine administration.

Better than the comparator.

Category: Integrated primary container and delivery technology

Innovation: Prefilled dry-powder intranasal devices

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

3.4 Economic costs criteria

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

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	Score	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Neutral	There is no publicly available data on the volume of the various DPIN devices. However, depending on the specific design of the DPIN device, the device could have a smaller or larger volume per dose stored and transported in the cold chain than the comparator. For example, the UniDose device is very compact while the Fit-lizer device is more similar to the size of a vial with an attached nose piece. Given this uncertainty about the cold chain volume per dose, we rank this innovation as neutral as some devices may be smaller or larger than the comparator.
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Better	If the DPIN is prefilled and does not require reconstitution, the volume of components stored out of cold chain is likely to be lower than for the comparator where the diluent, reconstitution syringe and AD N&S are all components stored out of the cold chain. However, even if a reusable delivery device is required like the VRx2 device that would likely be stored and transported out of the cold chain, the volume is shared across multiple uses and hence the volume per dose stored and transported out of the cold chain is likely to still be smaller than that of the comparator.

	<u>Better</u> than the comparator
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^u 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.


Category: Integrated primary container and delivery technology
 Innovation: Prefilled dry-powder intranasal devices
 Comparator: SDV (lyophilised) + diluent + RUP reconstitution N&S + 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 11.

Total economic cost of the time spent by staff per dose	Parameters to measure against a comparator	Score	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Better	Because of easier preparation of the vaccine compared to the comparator where the vaccine needs to be reconstituted, the time spent by vaccinators is potentially reduced.
	^v Does the innovation have attributes that save time for staff involved in stock management?	Neutral	The innovation does not have attributes that impact the time spent by staff on stock management.

 **Better** than the comparator

Indicator: Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)

Legend: **White:** **Neutral:** *NO* there are no one-time/upfront or recurrent costs and this is not different than the comparator; **Red:** **Worse** than the comparator: *YES,* there are one-time/upfront or recurrent costs.

^v 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: Prefilled dry-powder intranasal devices

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

Table 11.

Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)	Parameters to measure against a comparator	Score	Assessment
	Are there one-time upfront costs that will be incurred for use of this innovation or recurrent costs that will be incurred for use of this innovation?	Neutral	No. Similar to the comparator, there are no upfront or recurrent costs required with this innovation (other than training costs which would be required with any innovation). Note that the costs of the reusable delivery device for some types of DPIN devices would be captured under commodity costs in Phase 2 rather than here.

<u>No difference</u> to the comparator

3.5 Secondary criteria on potential breadth of innovation use

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

Table 12.

Applicability of innovation to one or several types of vaccines	Assessment
<ul style="list-style-type: none"> What vaccines/antigens does the innovation apply to, based on technical feasibility? 	<p>This innovation could be applied to vaccines that are intended for mucosal delivery and is particularly well suited for antigens that can be dried and that are immunogenic when delivered intranasally (i.e. respiratory pathogens) without an adjuvant. Live-vaccines are more likely to be suitable. Non-live vaccines are likely to require a mucosal adjuvant, and none are licensed at present.</p> <p>Live-attenuated influenza vaccine is not a VIPS priority antigen, but it could be well-suited for this innovation. The VSV-vectored Ebola and MR vaccines, which are on the VIPS priority list, might also benefit from this route of delivery. providing a dry formulation can be developed for the Ebola vaccine.</p>

Category: *Integrated primary container and delivery technology*
 Innovation: *Prefilled dry-powder intranasal devices*
 Comparator: *SDV (lyophilised) + diluent + RUP reconstitution N&S + AD N&S*

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combination	Assessment
<ul style="list-style-type: none"> Does the innovation facilitate novel combination vaccine products? 	Intranasal dry powder delivery devices could in theory allow combination of vaccines that cannot currently be combined because they are incompatible in liquid formulation. The innovation allows vaccines to be formulated separately, dried into a powder, and then mixed. However, it could be challenging to identify and develop combinations if some of the components require an adjuvant and some do not.

SECTION 4

4.1 Robustness of data:

Table 14.

Category	Assessment
Type of study	Data on the design and use of the innovation were taken from manufacturer websites and leaflets, expert opinion, testing studies, clinical trials and literature review. Vaccine specific data on the innovation is at the pre-clinical stage and clinical stage for one of the innovations (Solovent).
Inconsistency of results	
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 	Clinical studies (Phase I, II, III) available on use of the devices with various medicines. FDA has approved the use of some the devices referred to in this document for the delivery of medicines.

VIPS TECHNICAL NOTE

Category: Integrated primary container and delivery technology

Innovation: Prefilled dry-powder intranasal devices

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



Overall assessment:	<i>Low to moderate</i>	<i>In terms of vaccine specific data, it is mainly based on manufacturer information and pre-clinical studies.</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
Vincent Sullivan	Becton Dickenson Vince_Sullivan@bd.com	Contacted Vincent Sullivan for information on the Solvent device (section 1.1).

4.3 List of technical experts, manufacturers and/or technology developers that have reviewed and provided feedback/input to the technical notes (TN):

Table 16.

Reviewers	Organisation/contact details	Notes
Fatema Kazi	GAVI, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Developed and reviewed TN
Mark Papania Medical Epidemiologist at Centers for Disease Control and Prevention	CDC myp7@cdc.gov	Mark Papania reviewed the selection of DPIN devices in the TN, and provided evidence based information on various DPIN devices.
PATH Medical Devices & Health Technologies team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH Debra Kristensen dkristensen@path.org	Reviewed TN
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	Reviewed TN

Category: Integrated primary container and delivery technology

Innovation: Prefilled dry-powder intranasal devices

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

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Category: Integrated primary container and delivery technology

Innovation: Prefilled dry-powder intranasal devices

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



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