Compact prefilled auto-disable devices (CPADs)

Comparator* : Single dose vial (liquid) and autodisable (AD) needle and syringe (N&S)

Section 1: Summary of innovation

CPADs fall into two main subtypes based on their manufacturing method: (1) preformed CPADs and (2) Blow-Fill-Seal (BFS) CPADs. Devices that do not fall into one of these categories were considered under a third subtype: (3) other types of CPADs (as described in detail below). CPADs are by definition small in size (compact), prefilled with the vaccine by the manufacturer, and contain an auto-disable mechanism. However, as described in this technical note, there are differences between the types such as with their vaccine filling process, number of components and assembly requirements.

The following devices were selected as examples to evaluate the three CPAD subtypes for this assessment.

- Preformed CPAD: UNIJECT™ (commercially available and licensed to deliver Hepatitis B vaccine).
- BFS CPAD: Apiject prototype (in development).
  - Pre-assembled (with integrated needle hub).
  - User-assembled (with separate needle hub).
- Other types of CPADs: INJECTO™ easyject (in development).

1.1 Example images:

Preformed CPAD

Image source: (1)

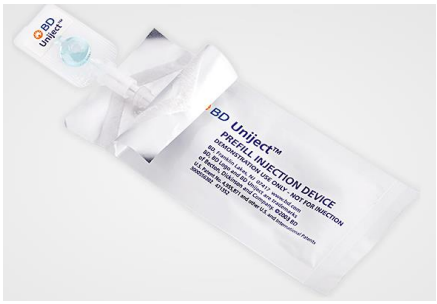


Image source: [a]

* 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] https://drugdeliverysystems.bd.com/products/prefillable-syringe-systems/vaccine-syringes/uniject-auto-disable-pre-fillable-injection-system

Category: *Integrated primary container and delivery technology*
Innovation: *Compact prefilled auto-disable devices (CPADs)*
Comparator: *Single dose vial (liquid) and autodisable needle and syringe*

Blow fill seal (BFS-CPAD)

Apiject

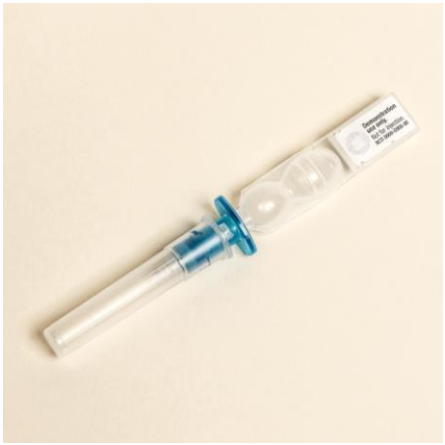


Photo source: [b]

Other type of CPAD (easyject): Polymer or glass

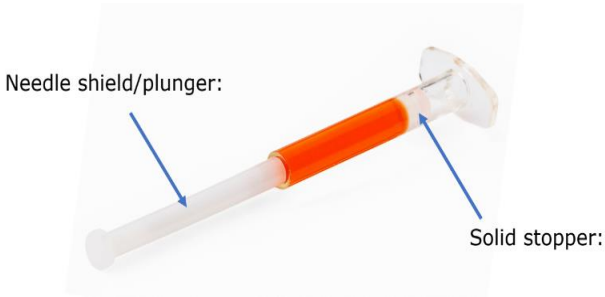


Image source: [c]

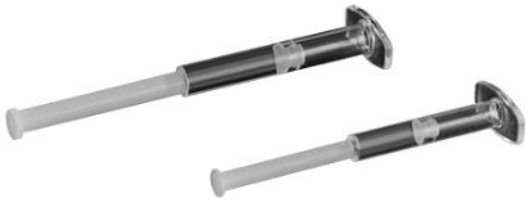


Image source: [c]

[b] Source: PATH
[c] Source: INJECTO. http://injecto.eu/easyject/

1.2. Description of innovation:

Preformed CPAD:

- One preformed CPAD is currently available on the market from Becton Dickinson (BD; Uniject™.)
- The vaccine containers are manufactured 'open' and supplied sterile, clean and ready to fill (SCF™), followed by a heat-sealing step for closure.
- Uniject™ was developed by PATH Seattle, WA, USA based on a concept licensed to PATH from Merck. PATH then worked with a private medical device packaging company called Horizon Medical, Inc. for piloting production and development of automated filling systems (2). Later, the technology was transferred and licensed to BD, which currently manufactures and supplies the device to vaccine and pharmaceutical companies.
- Uniject™ is an integrated primary container and delivery device and also a simplified injection-delivery system. It is available with different needle lengths and gauges (for intramuscular or subcutaneous injections) and for different fill volumes.
- It is composed of a polymer blister containing a single dose of the vaccine with a needle hub permanently attached and a removable needle shield. An activation step is necessary to prepare the device for use.
- The one-way valve prevents re-filling and use so it is AD.
- It has a label on the unit and can be packaged in an individual sealed foil pouch or a resealable tray containing multiple units.

BFS CPAD:

- A BFS CPAD is composed of a blister containing a single dose of vaccine and a needle hub with a removable needle shield (the needle hub can be pre-assembled or assembled at the point of use).
- It is intended to be compatible with different lengths of needles for different depths of injection.
- The user-assembled version could be co-packaged with the needle hub, or the cold chain footprint could be reduced by storing the needle hub out of the cold chain in dry storage. For a pre-assembled CPAD, the needle hub is assembled to the container during manufacturing, requiring an activation step before use.
- It is manufactured using BFS automated technology whereby the container is produced and filled in a continuous process.
- The innovation is currently in the feasibility development phase where several container designs are being explored through rapid design iteration and bench testing (3). Current prototype designs do not include an AD feature.

Other types of CPAD[d]:

- INJECTO's easyject is an integrated compact, pre-filled injection unit with a solid stopper. Among the CPAD devices, this device is most similar to the traditional prefilled syringes commonly used for vaccines in high income countries, but is designed to be more compact and to incorporate an AD feature.
- The device introduces a dual-functionality component, where the needle shield also includes plunger rod functionality, which is the basis of its innovative AD mechanism.

[d] Source: INJECTO. http://injecto.eu/easyject/

- The device is manufactured open and the solid stopper is placed after filling to prevent contamination of the pre-filled device.
- Prior to administration, the needle shield/plunger is removed from the container tip and inserted into the container pushing against the solid stopper to release the contents.
- After injection, the stopper is trapped at the bottom of the syringe barrel and the device cannot be refilled/reused.
- The device is available in different volumes, diameters and needle lengths. The container is composed of cyclic olefin copolymer (COC) material allowing for greater design flexibility and to minimize interaction with the product.

1.3 Examples of innovations and developers:

Table 1.

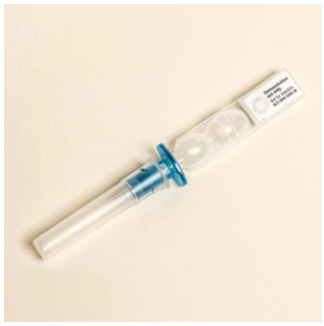
Product name; Image	Developer (place); website	Brief description, notes
Preformed CPAD		
Quinvaxem[e] DTwP-HepB-Hib vaccine ('Pentavalent')	**Janssen** (including Berna Biotech Korea Corporation, a Crucell Company). https://www.janssen.com/infectious-diseases-and-vaccines/crucell	WHO prequalified (PQ), but discontinued
Hepatitis B Vaccine Recombinant [f]	**BioFarma**, Indonesia; http://www.biofarma.co.id	WHO PQ. Primarily used in Indonesia and small quantities are exported.
TT vaccine[g]	**BioFarma**, Indonesia	WHO PQ, but discontinued
Sayana Press  Image source: [h]	**Inject Sayana Press** http://www.injectsayanapress.org/	Licensed to deliver medroxyprogesterone acetate (MPA) – a hormonal therapy commercially known as Depo-Provera.

[e] http://www.who.int/immunization_standards/vaccine_quality/pq_283_dtphepbhib_1dose_uniject_Crucell_Korea/en/

[f] http://www.who.int/immunization_standards/vaccine_quality/10_hepb/en/

[g] http://www.who.int/immunization_standards/vaccine_quality/17_tet/en/

[h] http://encomium.ng/wp-content/uploads/2015/09/sayana-650x400.jpg

BFS CPAD		
Apiject 	**Apiject** https://www.apiject.com/	This device is in early stage development. A preliminary user evaluation was conducted on a previous prototype design by PATH. PATH is planning technical performance testing of the current generation of prototypes. This device does not have an AD feature, but one could potentially be developed in the future.
Other types of CPAD		
Easyject - INJECTO™ 	Injecto A/S Pharmaceutical Packaging Strandvejen 60, 5. 2900 Hellerup Denmark Phone: +45 2785 1000 Email: info@injecto.eu http://injecto.eu/easyject/#	In development

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- CPADs in general have several useful features including being prefilled, ready-to-use and auto-disable (AD).
- They are intended to be simpler to use in terms of preparation and administration of the vaccine compared to using vials with needles and syringes (N&S) and are therefore potentially suitable for use by lesser trained vaccinators to enable alternative delivery scenarios.
- Because they are prefilled with a single dose of vaccine, CPADs avoid reconstitution and measuring of vaccine doses thereby ensuring there is a reliable dose administration.
- CPADs that are fully assembled and all-in-one integrated devices have less components and therefore can reduce the risk of stock-outs.
- Preformed CPADs have demonstrated acceptability by vaccines and caregivers in terms of reducing pain and anxiety. This is also expected to be the same for BFS CPADs.

2.2 Key challenges:

- CPADs are only suitable for liquid vaccines.
- As with all novel vaccine delivery devices, training will be needed to introduce CPADs in immunization programs.
- CPADs typically require specialized filling equipment that will need to be purchased and validated by vaccine manufacturers requiring time and investment/resources as well as regulatory and WHO prequalification for each vaccine packaged in a CPAD.

2.3 Additional important information:

Preformed CPAD:

- Uniject™ is suitable for many liquid vaccines for injection subcutaneously (SC) or intramuscularly (IM), with a range of needle sizes (18–30G, 10–38 mm) and different dose volumes (0.25–2.0 ml). There are considerable data about its properties and use.
- Vaccine manufacturers need to establish a new filling line to use Uniject™ but there are precedents for this being successful.
- The cost of goods sold (COGS) is higher for Uniject™ compared to vaccines in standard vial formats (5).

BFS-CPAD:

- This CPAD type is manufactured using blow-fill-seal (BFS) –a continuous, automated and aseptic process which means the filling and finishing process is completed in one production line as opposed to separate manufacturing stages which can be complex and more costly.
- BFS-CPADs have the potential to be used for SC, IM or possibly intradermal (ID) administration of liquid vaccines.
- They have the potential to lower total cost of delivery (TCOD) compared to the currently available preformed CPAD (5). However, the actual cost of goods sold (COGS) and TCOD are unknown, and

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

might not be lower than preformed CPAD costs, as designs have changed since the previous analysis was conducted.
- Feasibility of a BFS CPAD design has yet to be demonstrated. Further design work and evaluation is needed to address issues previously identified with Apiject prototypes including incorporation of an AD feature, fluid path leakage, and container squeezeability. The earlier Apiject prototypes evaluated were also not intuitive to users and required instruction to deliver the vaccine (3).
- The device is still in the design phase and has not received regulatory approval/WHO PQ for delivery with any antigen.
- Concerns have been raised with exposure to heat during the vaccine filling process of BFS containers. However, several vaccines have been demonstrated to be stable when filled in BFS, including live attenuated rotavirus (6), live attenuated influenza (7), and respiratory syncytial virus vaccines (3).
- For the user-assembled device, additional training may be required, and it may not be suitable for use in all scenarios, such as delivery by lesser-trained health care workers.

Other types of CPAD:

- INJECTO's easyject is available in 2 materials – polymer (COP/COC) or glass, which provide good chemical resistance.
- The device most closely resembles a traditional N&S and therefore it has the potential to align with current prefilled syringe manufacturing facilities.
- Using the needle shield as the plunger rod may require additional training and skill for successful vaccine delivery.
- The device is still in the design phase and has not received regulatory approval/WHO PQ for delivery with any antigen.

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	Assessment for sub-types			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation have features that may improve heat stability?	**Neutral** The preformed CPAD primary container has no impact on the ability of the vaccine to withstand heat exposure which is similar to the comparator.	**Neutral** The BFS pre-assembled CPAD primary container has no impact on the ability of the vaccine to withstand heat exposure, which is similar to the comparator.	**Neutral** The BFS field-assembled CPAD primary container has no impact on the ability of the vaccine to withstand heat exposure, which is similar to the comparator.	**Neutral** The CPAD device is a primary container and has no impact on the ability of the vaccine to withstand heat exposure, which is similar to the comparator.
		Neutral	***Neutral***	***Neutral***	***Neutral***

Category: *Integrated primary container and delivery technology*

Innovation: *Compact prefilled auto-disable devices (CPADs)*

Comparator: *Single dose vial (liquid) and autodisable needle and syringe*

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	Assessment for sub-types			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation have features that may improve freeze resistance?	**Neutral** The preformed CPAD primary container has no impact on the ability of the vaccine to withstand freeze exposure, which is similar to the comparator.	**Neutral** The BFS pre-assembled CPAD primary container has no impact on the ability of the vaccine to withstand freeze exposure, which is similar to the comparator. PATH completed an evaluation of the shake test (used to identify whether vaccine has been freeze damaged) on BFS container prototypes which demonstrated that the shake test is accurate despite the reduced transparency of BFS containers.	**Neutral** The BFS field-assembled CPAD primary container has no impact on the ability of the vaccine to withstand freeze exposure, which is similar to the comparator. PATH has completed an evaluation of the shake test (used to identify whether vaccine has been frozen) on BFS container prototypes which demonstrated that the shake test is accurate despite the reduced transparency of BFS containers.	**Neutral** The other type of CPAD primary container has no impact on the ability of the vaccine to withstand freeze exposure, which is similar to the comparator.
		Neutral	***Neutral***	***Neutral***	***Neutral***

3.2 Coverage and equity criteria

Indicator: Ease of use[i]

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

Table 4.

Ease of use • *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation avoid reconstitution and is that an improvement?	**Neutral** All CPAD devices are prefilled with liquid vaccine product and cannot be used with lyophilised vaccines. Therefore, there is no reconstitution and thus there is no difference with the comparator			
	Does the innovation require fewer vaccine product components?	**Better** Uniject™ is a fully assembled all-in-one integrated device, consisting of needle and vaccine dose. Thus it requires fewer vaccine product components than the comparator.	**Better** Is an all-in-one integrated device, consisting of a custom needle hub, needle, and blister containing the vaccine dose. Thus it requires fewer vaccine product components than the comparator.	**Neutral** It has a separate custom needle hub/needle which must be assembled to the blister by the vaccinator to administer the vaccine. The needle hub/needle can be stored separately in dry storage. The user-assembled BFS CPAD would have the same number of components as the AD N&S comparator, thus it has been ranked neutral.	**Better** The easyject is an integrated device with all the components for delivery packaged together.

[i] 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).

Ease of use • *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	[j]**Does the innovation require additional components or equipment (such as scanners or label readers)?**	N/A	N/A	N/A	N/A
	Does the innovation require fewer preparation steps and less complex preparation steps?	**Better** Uniject™ is a fully assembled all-in-one integrated device, consisting of needle and vaccine dose. Therefore, it has fewer preparation steps than the comparator, so it is better. In general, Health-Care workers have found the device to be easy and quick to use (8). Lay healthcare workers (LHWs) in the field demonstrated the ability to effectively manage Uniject™ supplies and administer Uniject™ with technical ease following training and supervision. LHWs described Uniject™ as having the potential to reduce work load, increase coverage and demonstrate the ability of LHWs to conduct vaccinations (6) .	**Better** Would have fewer steps to prepare the vaccine than the comparator as it comes already prefilled with the vaccine. This makes it less complex.	**Neutral** The user-assembled BFS CPAD requires assembly of the needle hub with needle and container, which is the same number of steps as the comparator.	**Better** Although there is no test/field study data to directly support the scoring, technically the easyject device would be easier to handle as there are fewer and less complex steps, and no filling is required, whereas the comparator needs to withdraw the vaccine.

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

Ease of use • *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation improve dose control?	**Better** The Uniject™ device is pre-filled by the manufacturer, therefore preparation errors are minimised (5)·(9).Whereas, the comparator requires withdrawing of the vaccine from the vial. Feedback from HCWs in Vietnam was that dosing preparation was more accurate and safer due to preparation by the manufacturer thus minimizing human error (10). Vaccinators in the field were concerned about the appropriate dose not being delivered using this CPAD due to residual vaccine remaining in the reservoir and whether this would have an impact on its effectiveness (10). Some HCWs felt that the residual amount left in the CPAD reservoir was needed for injecting into the recipient. Despite the perceived risks in the field, the Uniject™ device is designed with	**Better** It is prefilled with the vaccine whereas the comparator (SDV AD N&S) requires the vaccinator to draw the dosage from the vial. Hence, it has the ability to improve dose control. The squeeze force should be optimized to ensure successful expulsion of the entire dose volume. The appropriate overfill will need to be determined based on the required squeeze force to ensure that a sufficient dose control can be reliably delivered.	**Better** Refer to the same rationale provided for BFS pre-assembled.	**Better** It is prefilled with the vaccine whereas the comparator (SDV AD N&S) requires the vaccinator to draw the dosage from the vial. Hence, it has the ability to improve dose control. This device also uses a plunger which offers more control to successfully expel the full dose compared to the squeezing mechanism of the other CPAD subtypes.

Ease of use • *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*		sufficient overfill to account for this, thus reducing the likelihood of delivering an ineffective dose.			
	Does the innovation improve targeting the right route of administration?	**Neutral** The route of administration for this innovation is similar to the comparator, therefore the risks would be the same. It has similar risks to the comparator for targeting the right route for vaccine administration.	**Neutral** Same rationale as preformed CPAD.	**Worse** There is a potential risk that the blister could be mistaken for oral administration, which could impact effectiveness of the vaccine. This risk could be mitigated with training and visual cues on the device.	**Neutral** Same rationale as preformed CPAD.
		Better	***Better***	***Mixed***	***Better***

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

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

Table 5.

Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • *Assessment of the potential to reduce stock outs based on the innovation's features*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation require fewer components?	**Better** Compared to AD single dose vial (SDV) with needle and syringe (N&S) it will be better because the Uniject™ preformed CPAD is a fully assembled, all-in-one integrated device. HCWs in Senegal and Vietnam reported that the use of CPADs could reduce stock-outs, reduce risk of glass vials breaking and eliminating shortage of either the vaccine or syringe as CPAD is an all in one device[iv].	**Better** It is an all-in-one integrated device consisting of the needle hub, needle, and blister with vaccine dose.	**Neutral** It has a separate needle hub with needle that is transported and stored separated, which must be assembled with the blister at the point of use to administer the vaccine, so it has the same number of components as the comparator.	**Better** The easyject is an integrated device with all the components for delivery packaged together.
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	**Neutral** All CPADs are expected to have the same labelling as the comparator.			
		Better	***Better***	***Neutral***	***Better***

Indicator: Acceptability of the vaccine presentation and schedule to patients/caregivers

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

Table 6.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Painful or not painful	**Better** In a study of mothers whose infants had been injected using Uniject, mothers expressed a strong preference for the Uniject device over a standard needle and syringe and considered Uniject less painful. Their perceptions of reduced pain may have been due to the sharpness of the single-use needle, although, the speed of injection may also have played a role in reducing anxiety and perceived pain (11). A study in Bolivia found that of women who received TT UNIJECT™ at antenatal home visits, 50% of women interviewed stated it was less painful that traditional injections (12).	**Better** The assumption is that it would be no different to UNIJECT™, thus would be better than the N&S. However, there is no data available on this from the perspective of the recipient. Score is based on expert opinion.	**Better** The assumption is it would be no different to UNIJECT™ , thus would be better than the N&S. However, there is no data available on this from the perspective of the recipient. Score is based on expert opinion.	**Neutral** The assumption is as the device is more similar to the traditional AD N&S (comparator), it would be no different. However, there is no data available on this from the perspective of the recipient. Score is based on expert opinion.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*		Similar feedback was obtained in different country settings (Indonesia and Brazil), whereby vaccinees had perceived less pain with administration of vaccine using UNIJECT™ compared to standard N&S (13)(14).			
	Perception of ease of administration (i.e. convenience for the vaccinees/caregivers)	**Better** Uniject™ prefilled with TT vaccine was successfully used in an outreach immunization program in Bolivia, the performance of the device and its acceptability by the vaccinators and recipients was high (12). Various studies have reported the acceptability of recipients in receiving TT and HepB- Uniject™ vaccine, due to better convenience and access, as the vaccine can be delivered by lay healthcare workers (LHW) and at home (8). Since Uniject is considered very easy to administer, it is also used for self-administration. Uniject has also been approved for	**Better** Although there is no data, as the BFS CPAD is a pre-assembled device it is assumed to be no different than preformed CPAD.	**No data**	**No data**

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*		self-administration of DMPA-SC [k].			
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers	**Better** Uniject™ has also been used for storing and transporting vaccines out of the cold chain with heat stable TT and hepatitis B vaccine in many countries. The single dose and easy to use format facilitated the out of cold chain use for outreach immunization.	**N/A**	**N/A**	**N/A**
		Considerably Better	***Better***	***Better***	***Neutral***

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.*

[k] http://www.injectsayanapress.org/

Category: *Integrated primary container and delivery technology*

Innovation: *Compact prefilled auto-disable devices (CPADs)*

Comparator: *Single dose vial (liquid) and autodisable needle and syringe*

Table 7.

Likelihood of contamination • *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?	**Neutral** All CPADs are prefilled with a liquid vaccine, which is no different to the comparator. They cannot be used with lyophilized vaccines.			
	Does the innovation reduce the risk of contamination while filling the delivery device?	**Better** Device is prefilled reducing the risk of contamination in comparison to the comparator which requires that the AD syringe be filled from a vial.	**Better** Device is prefilled reducing the risk of contamination in comparison to the comparator which requires that the syringe be filled from a vial.	**Better** Device is prefilled reducing the risk of contamination in comparison to the comparator which requires that the syringe be filled from a vial.	**Better** Device is prefilled reducing the risk of contamination in comparison to the comparator which requires that the syringe be filled from a vial.
	Does the innovation require fewer preparation steps and less complex preparation steps?	**Better** Since the innovation is prefilled it would have fewer preparation steps than the comparator.	**Better** Since the innovation is prefilled it would have fewer preparation steps than the comparator.	**Worse** The user-assembled BFS CPAD requires assembly of the needle hub and container, which is the same number of steps as the comparator. However, the steps are more complex from a contamination perspective because the user has to take care not to touch the orifice while assembling the device.	**Better** Although there is no test/field study data to directly support the scoring, technically the easyject device would have fewer and less complex steps, and no filling is required, whereas the comparator needs to withdraw the vaccine.

Likelihood of contamination • *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation reduce the potential risk of reuse of delivery technology?	**Neutral** The innovation has an AD feature and it is expected to have the same risk of reuse as the comparator.	**Neutral** The innovation does not have an AD feature, however it could be feasible given the design and would need to be incorporated in the future, thus it would be expected to have the same risk of reuse as the comparator.	**Neutral** The innovation does not have an AD feature, however it could be feasible given the design and would need to be incorporated in the future, thus it would be expected to have the same risk of reuse as the comparator.	**Neutral** The innovation is expected to have an autodisable feature and it is expected to have the same risk of reuse as the comparator.
	Does the innovation reduce the risk of use of nonsterile components?	**Neutral** No difference, as all the equipment is manufactured and packaged under sterile conditions.	**Neutral** No difference, as all the equipment is manufactured and packaged under sterile conditions.	**Neutral** No difference, as all the equipment is manufactured and packaged under sterile conditions.	**Neutral** No difference, as all the equipment is manufactured and packaged under sterile conditions. The stopper is solid, which prevents contamination when inserting the plunger.
		Better	***Better***	***Mixed***	***Better***

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.*

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

Table 8.

Likelihood of needle stick injury • *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation contain fewer sharps?	**Neutral** All CPADs have the same number of sharps as the comparator.			
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	**Better** Delivery of vaccine using the CPAD device requires one sharp. There is a slight reduction in needlestick injury risk compared to standard needle and syringe technique because vaccine withdrawal from a vial is not needed. A study based in Vietnam had identified a perceived risk by HCWs using CPAD (UNIJECT™) was that the needle could break in the arm or leg of restless children or that the needle could potentially "break bone" of children, due to its length(10).	**Better** Delivery of vaccine using the CPAD device requires one sharp. There is a slight reduction in needlestick injury risk compared to standard needle and syringe technique because vaccine withdrawal from a vial is not needed.	**Better** Delivery of vaccine using the CPAD device requires one sharp. There is a slight reduction in needlestick injury risk compared to standard needle and syringe technique because vaccine withdrawal from a vial is not needed.	**Better** Delivery of vaccine using the CPAD device requires one sharp. There is a slight reduction in needlestick injury risk compared to standard needle and syringe technique because vaccine withdrawal from a vial is not needed.
	Does the innovation include an auto disable feature and is that better than the comparator?	**Neutral** All CPADs are expected to have an AD feature, which prevents re-use of contaminated needles. It is not different than the comparator**.** For the BFS CPAD devices, an AD feature is considered feasible given the design, but still needs to be incorporated into the device.			

Likelihood of needle stick injury • *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?	**Neutral** CPADs do not currently include a SIP feature, which is the same as the comparator (AD N&S). Injury after vaccination could be reduced if a sharps injury protection (SIP) feature is incorporated into the device.			
	Does the innovation reduce the risk of injury after vaccine administration?	**Neutral** Similar risk as the comparator. It is not known whether or not it will be possible to add a SIP feature to the CPAD device. The needle length and gauge for Unject is the same as for an AD needle and syringe, and risks are similar.	**Neutral** Similar risk as the comparator. It is not known whether or not it will be possible to add a SIP feature to the CPAD device.	**Neutral** Similar risk as the comparator. It is not known whether or not it will be possible to add a SIP feature to the CPAD device.	**Neutral** Similar risk as the comparator. It is not known whether or not it will be possible to add a SIP feature to the CPAD device.
		Better	***Better***	***Better***	***Better***

3.4 Economic costs criteria

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

*Legend: Dark Green: **Considerably better** than the comparator: Reduces the volume per dose for applicable parameters; Green: **Better** than the comparator: Reduces the volume per dose for either of the applicable parameter, and there is no difference for the other; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the volume for one of the parameter, and increases the volume for the other parameter compared to the comparator; Red: **Worse** than the comparator: Increases the volume per dose for either of the applicable parameters, and there is no difference for the other; Dark Red: **Considerably worse***

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

*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	Assessment for sub-types			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	**Neutral** Uniject™ is expected to have a similar volume per dose stored in the cold chain as the single dose vial comparator (typically 12-18 cm^3).[m] HepB Uniject™ (**12cm^3**) versus SDV Euvax B (14.53cm^3), Shanvac-B (16.8cm^3). TT vaccine Uniject™ (**12cm^3**) versus TT vaccine SDV (14.7cm^3). Crucell's Quinvaxem in Uniject at 15.2 cm^3/dose in secondary carton of 12 trays of 20 Uniject devices per tray (this product was discontinued).	**Neutral** The final cold chain volume per dose is unknown. However, the pre-assembled BFS CPAD is expected to have a similar volume per dose stored in the cold chain as the single-dose vial comparator (typically 12-18 cm^3). The target cold chain packaged volume per dose is less than or equal to 15 cm^3. Another prototype has a volume per dose of approximately17 cm^3. This design is the most compact nesting of 5 cards of 5 units resulting in ~ 17 cm^3 per dose (roughly including overwrap). Current prototypes measured by PATH fall within this range (PATH personal communication).	**Better** The final volume per dose stored in the cold chain is unknown but the measurements of the BFS user-assembled prototypes by PATH showed a much smaller volume per dose compared to SDVs. The volumes presented here are estimates of Apiject prototypes: Blister, 5.5 cm^3 (assumes nesting)	**Worse** The final volume per dose stored in the cold chain is unknown, but it is expected that this device would be larger than the comparator based on the design of current easyject prototypes. Volumes for current prototypes were not available.

[m] WHO Access to Technologies Team. *Guidelines on the International Packaging and Shipping of Vaccines*. WHO/IVB/05.23. Geneva: WHO; 2005. Available at https://apps.who.int/iris/bitstream/handle/10665/69368/WHO_IVB_05.23_eng.pdf?sequence=1.

Total economic cost of storage and transportation of commodities per dose	**Parameters to measure against a comparator**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	**Better** Uniject™ is fully assembled and all-in-one integrated device, consisting of needle and vaccine dose. There is no volume stored out of the cold chain.	**Better** A pre-assembled BFS is an all-in-one integrated device, consisting of needle and vaccine dose. There is no volume stored out of the cold chain.	**Better** The field-assembled BFS has a separate needle hub. The final packaged volume of the needle hub is unknown but measurements of Apiject prototypes by PATH showed a much smaller volume per dose compared to AD N&S. Needle hub, 6.6 cm^3 AD N&S[n]: 42cm^3	**Better** A pre-assembled CPAD is an all-in-one integrated device, consisting of needle and vaccine dose. There is no volume stored out of the cold chain.
		Better	***Better***	***Considerably better***	***Mixed***

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.*

[n] WHO PQS Catalogue. Prequalified Devices and Equipment. http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=37

Table 11.

Total economic cost of the time spent by staff per dose	Parameters to measure against a comparator	Assessment for sub-types			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	**Better** Vaccine is pre-filled in Uniject™, thus no need for preparation. A time and motion study conducted by PATH showed it took 7.3 seconds for a provider to deliver a dose when using Uniject compared to 19.3 seconds for a liquid vaccine in a SDV[o]. Program officers, medical officers, nurses, HCWs and vaccinators expressed how simple it is to prepare a CPAD–it is time saving(10). There is some indication that time to immunise using CPAD is reduced: In Senegal, CPAD reduced administration time by 27-35%, while in Vietnam it was reduced by 40-61% compared to AD syringes. The timing included all the steps starting from the child being present to the disposal of the device(4).	**Better** Given that this would be a similar mechanism and activation procedure as the Uniject, this is ranked better than the comparator. Further time and motion studies should be conducted to verify this assumption.	**Better** Since this is a prefilled device, the only required step for administration is assembly of the needle. With the SDV the vaccinator has to take time to draw and calibrate the dose which is not required for prefilled container[p]. Further time and motion studies should be conducted to verify this assumption.	**Better** Since this is a prefilled device, the only required step for administration is to place the needle shield/plunger rod into the barrel of the device. With the SDV the vaccinator has to take time to draw and calibrate the dose which is not required for prefilled container[q]. Further time and motion studies should be conducted to verify this assumption.

[o] PATH. Time and motion study. https://path.azureedge.net/media/documents/TS_pentavalent_vac.pdf

[p] Discussion with Ben Creelman

[q] Discussion with Ben Creelman

Total economic cost of the time spent by staff per dose		The average time for HCWs to deliver one dose was fastest using the Uniject™ device (7.6 seconds) compared to SDV and AD needle/syringe (19.3 seconds)(8).			
	[r]Does the innovation have attributes that save time for staff involved in stock management?	**Neutral** None of the CPADs have attributes that save time for staff involved in stock management similar to the comparator.			
		Better	***Better***	***Better***	***Better***

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.*

[r] 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.

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**	**Assessment for sub-types**			
		Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	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?	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).	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).	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).	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).
		Neutral	***Neutral***	***Neutral***	***Neutral***

3.5 Secondary criteria on potential breadth of innovation use

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

Table 12.

Applicability of innovation to one or several types of vaccines • *What vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment for sub-types**			
	Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	This innovation could be applied to any liquid parenteral vaccine. The innovation may be most useful with vaccines that would benefit from a compact single-dose presentation, for instance, for outreach settings. In the case of BFS CPADs, compatibility of a vaccine with the BFS filling process and material would have to be assessed on a case-by-case basis. Hepatitis B vaccine (a VIPS priority antigen) is currently WHO prequalified for use in Uniject and used for birth dose delivery in Indonesia. Pandemic influenza is another example of a potentially suitable vaccine for packaging in a CPAD.			

Indicator: Ability of the technology to facilitate novel vaccine combination

Table 13.

Ability of the technology to facilitate novel vaccine combination • *Does the innovation facilitate novel combination vaccine products?*	**Assessment for sub-types**			
	Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
	CPADs do not have features that facilitate novel combination products. For existing combinations, studies would be required to show that each component in the combination formulation was compatible with, and stable in the non-glass CPAD			

SECTION 4

4.1 Robustness of data:

Table 14.

Category	**Assessment**			
	Preformed CPAD	**BFS Pre-assembled**	**BFS User-assembled**	**Other type**
Type of study	There are 10 clinical trials registered of which 1 (no results available) is only for a vaccine (Quinvaxem), the others are for drug delivery by UNIJECT™. A range of technical reports and papers. 1 systematic review. A number of primary field studies available.	Most of the device specific data is from the manufacturer/developers and expert opinion.	Most of the device specific data is from the manufacturer/developers and expert opinion.	All data captured from manufacturer brochures on the easyject device INJECTO™
Inconsistency of results				
Indirectness of comparison • *Indicate the setting in which the study was conducted*			*There has been a pilot feasibility*	*Information was only available from*

(low, middle or high income setting); • *Comment if the data is on non-vaccine application of the innovation*			*study in LIC on an earlier prototype.*	*manufacturer brochures/website.*

Overall assessment:	**Preformed CPAD***:* *Moderate-High* *Based on the availability of field studies, RCTs and data on comparing preformed CPAD with the comparator, the robustness of the data used for the assessment is moderate to high. However, it should be noted a lot of the indicators were assessed using device specific features.*	**BFS Pre-assembled***:* *Low-moderate*	**BFS Field-assembled***:* *Low-moderate*	**Other types:** *Low*

4.2 List of technical experts, manufacturers and/or technology developers interviewed for input:

Table 15.

Expert/type	Organisation/contact details	Notes
N/A	N/A	No interviews conducted.

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

Table 16.

Reviewers	Organisation/contact details	Notes
Fatema Kazi	GAVI, the Vaccine Alliance fkazi-external-consultant@Gavi.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
Julian Hickling	Working in Tandem Ltd julian@workingintandem.co.uk	Reviewed TN

4.4 References:

1. Uniject B. Auto-disable Prefi llable Injection System. 2016;1–5.
2. HealthTech. HealthTech Historical Profile: The Uniject Device [Internet]. 2005. Available from: http://rih.stanford.edu/elias/resources/Uniject.pdf
3. Yen-Huei Lin1, Roe Hau1, Eduard Orvisky1, Sarathi Boddapati1, Kalpen Patel1, Eugene Wu1, Stephan Gschwind3, Yves Schwander3, Tim Kram2 TH, 1Novavax Inc, Gaithersburg, MD, USA; 2Rommelag USA Inc, Evergreen, CO, USA; 3Maropack AG, Zell S. Feasibility Evaluation of Blow Fill Seal Process and Compatibility with Aluminum Phosphate Adjuvanted Recombinant RSV F Vaccine. 2017;
4. Apiject brochure. It ' s Time to Replace Syringes and Glass Vials An easy new way to inject vaccines and medicines.
5. Sedita J, Perrella S, Morio M, Berbari M, Hsu J-S, Saxon E, et al. Cost of goods sold and total cost of delivery for oral and parenteral vaccine packaging formats. Vaccine. 2018;36(12):1700–9.
6. Lal M, Jarrahian C, Zhu C, Hosken NA, McClurkan CL, Koelle DM, et al. Stability of live attenuated rotavirus vaccine with selected preservatives and primary containers. Vaccine. 2016;34(22):2483–9.
7. Sheldon EA, Jeanfreau R, Sliman JA, Charenkavanich S, Rousculp MD, Dubovsky F, et al. Immunogenicity of a quadrivalent Ann Arbor strain live attenuated influenza vaccine delivered using

a blow-fill-seal device in adults: a randomized, active-controlled study. Influenza Other Respi Viruses. 2013;7(6):1142–50.

8. Glenton C, Khanna R, Morgan C, Nilsen ES. The effects, safety and acceptability of compact, pre-filled, autodisable injection devices when delivered by lay health workers. Trop Med Int Heal. 2013;18(8):1002–16.
9. World Health Organization. DTwP-HepB-Hib vaccine available in a compact, pre-filled auto-disable injection technology (cPAD) [Internet]. 2015. Available from: http://www.who.int/immunization/programmes_systems/service_delivery/InfoBulletin_Uniject_March2015_FINAL_ENG.pdf
10. Guillermet E, Dicko HM, N'Diaye M, Hane F, Ba SO, Gomis K, et al. Acceptability and feasibility of delivering pentavalent vaccines in a compact, prefilled, autodisable device in Vietnam and Senegal. PLoS One. 2015;10(7):e0132292.
11. Morgan C, Bisibisera L, Bauze A, Winjong H, Coppola A, Lagani W. integrating Birth-dose Vaccination With Early Post-natal Care In A Remote Setting In Papua New Guinea: o32. J Paediatr Child Health. 2011;47:10.
12. Quiroga R, Halkyer P, Gil F, Nelson C, Kristensen D. A prefilled injection device for outreach tetanus immunization by Bolivian traditional birth attendants. Rev Panam Salud Pública. 1998;4:20–5.
13. Creati M, Saleh A, Ruff TA, Stewart T, Otto B, Sutanto A, et al. Implementing the birth dose of hepatitis B vaccine in rural Indonesia. Vaccine. 2007;25(32):5985–93.
14. Bahamondes L, Marchi NM, Nakagava HM, de Melo MLR, Cristofoletti M de L, Pellini E, et al. Self-administration with UniJect® of the once-a-month injectable contraceptive Cyclofem®. Contraception [Internet]. 1997;56(5):301–4. Available from: http://www.sciencedirect.com/science/article/pii/S0010782497001625
15. PATH. Pentavalent vaccine in the Uniject injection system - A time and motion study [Internet]. 2014. Available from: https://path.azureedge.net/media/documents/TS_pentavalent_vac.pdf