

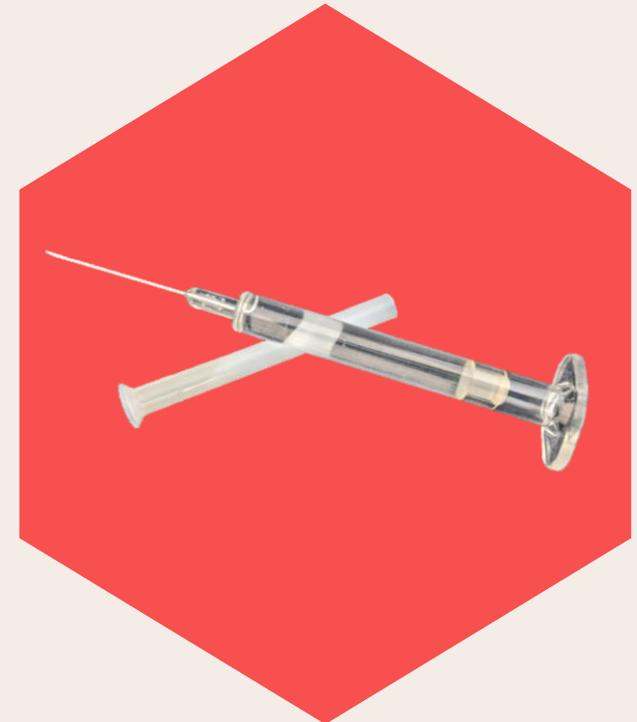
Prefilled injection devices: Updates on CPADs and dual-chamber devices

DCVMN New Packaging Technologies Workshop

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Medical Devices and Health Technologies



VIPS technologies

Goal: Prioritise innovations in vaccine delivery attributes to provide greater clarity to manufacturers and immunisation partners to make investment decisions

VIPS has prioritised **3 innovations with the broadest public health benefits and broad applicability** that can help to **better meet country needs** and **contribute to coverage & equity goals**.

Microarray patches



Heat-stable and CTC qualified vaccines



Barcodes on primary packaging



While VIPS has the capacity to focus on only a few innovations in the coming years, the **6 shortlisted innovations** that were not prioritised have **strengths and merit** and **remain of high interest to VIPS**.



AD SIP syringe



Dual-chamber delivery device



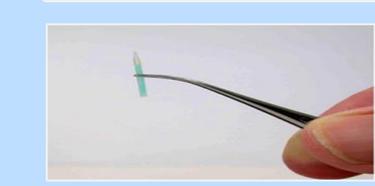
Combined VVM and threshold indicator



Freeze damage resistant liquid formulation



CPAD



Solid dose implant

<https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy>

Outline

Compact, prefilled autodisable devices (CPADs)

- VIPS assessment
- Device types and status
 - Preformed CPAD: BD Uniject
 - Blow-fill-seal: ApiJect and Brevetti Angela
 - Prefilled syringe CPAD: Injecto easyject
- User evaluation

Dual-chamber devices

- VIPS assessment
- Device types and status
 - Glass dual-chamber prefilled syringes
 - Frangible-seal dual-chamber device: Dualject

CPADs



Compact prefilled auto-disable devices (CPADs)



About CPADs

- CPADs are **integrated primary containers and injection devices prefilled with liquid vaccines**. They have features to **prevent reuse** and **minimize the space required for storage and shipping**.

Three CPAD subtypes have been assessed:

- **Preformed CPADs:** Squeezable polymer device, manufactured 'open' and supplied sterile and ready to fill/seal by the vaccine manufacturer.
- **Blow-fill-seal (BFS) CPADs:** produced, filled, and sealed in a continuous BFS process.
 - **Pre-assembled** (with needle attached) and **user-assembled** configurations are possible¹.
- **Other CPAD types:** Designs are in development leveraging prefilled syringe components.

Stage of development

- One preformed CPAD, **Uniject™**, is **commercially available**.
- Uniject™ presentations of **Penta**, **HepB** and **TT vaccines were WHO prequalified** in 2006, 2004 and 2003 respectively. The pentavalent and tetanus toxoid products have been discontinued. Medroxyprogesterone acetate (similar to Depo-Provera) is also commercially available in Uniject™.
- **BFS and other CPAD types are in design phases.**



Preformed CPAD (Uniject™)



BFS device (Apiject)



Other CPAD (Easyject)

¹ During the Phase I VIPS review, the Steering Committee suggested de-prioritising user-assembled BFS CPAD configurations because they have fewer potential benefits than all other CPAD types, due to the greater number of components and preparation steps, and risk of preparation and delivery errors and contamination.

Summary of key VIPS insights

Potential public health impact of innovation



Applicability to vaccines

- **CPADs should be applicable to most or all liquid vaccines that are injected.**
 - Vaccine compatibility with the materials in the CPAD and stability in the device will need to be demonstrated.



Public health benefits

- **Public health benefits** across vaccines may include:
 - **Easier to prepare/use**, allowing **lesser trained staff** to administer the vaccines and with a **reduced risk of needle-stick injury**;
 - Single-dose presentation, potentially **reducing missed opportunities** and **contamination risks** associated with multi-dose vials;
 - **Improved acceptability** to caregivers/parents;
 - Fewer components **reducing stock-outs**, and a smaller **size simplifying waste disposal**.



Vaccine problem statements

- **CPADs could potentially address several of the top 5 problem statements** for Penta, HepB, HPV, IPV and TCV, particularly those related to:
 - **Ease of use and acceptability:**
 - **Difficult preparation.**

Summary of key VIPS insights

Barriers to realise the innovation's potential impact



Costs

- The **commodity costs for preformed CPADs** are **larger** than for vaccines in single- or multi-dose vials (SDV and MDV). Reduced costs for delivery and needle and syringe probably offset this increase for SDV (cost neutral), but not for MDV (net increase of ~\$0.30 per dose).
- The costs for **BFS CPADs and other CPAD types are not known.**



Technology Readiness

- Preformed CPADs have been **commercially available for at least 20 years.**
- **BFS and other CPAD types are early in development** and have manufacturing and technical challenges. However these devices utilise some existing manufacturing processes, so should be less complex than innovations with completely novel processes (such as MAPs or SDIs).



Commercial feasibility

- Uptake of preformed **CPADs has been limited.** This is assumed to be due to purchasers being **unwilling to pay a higher cost**, and therefore **lack of incentives for manufacturers** to adopt the technology.

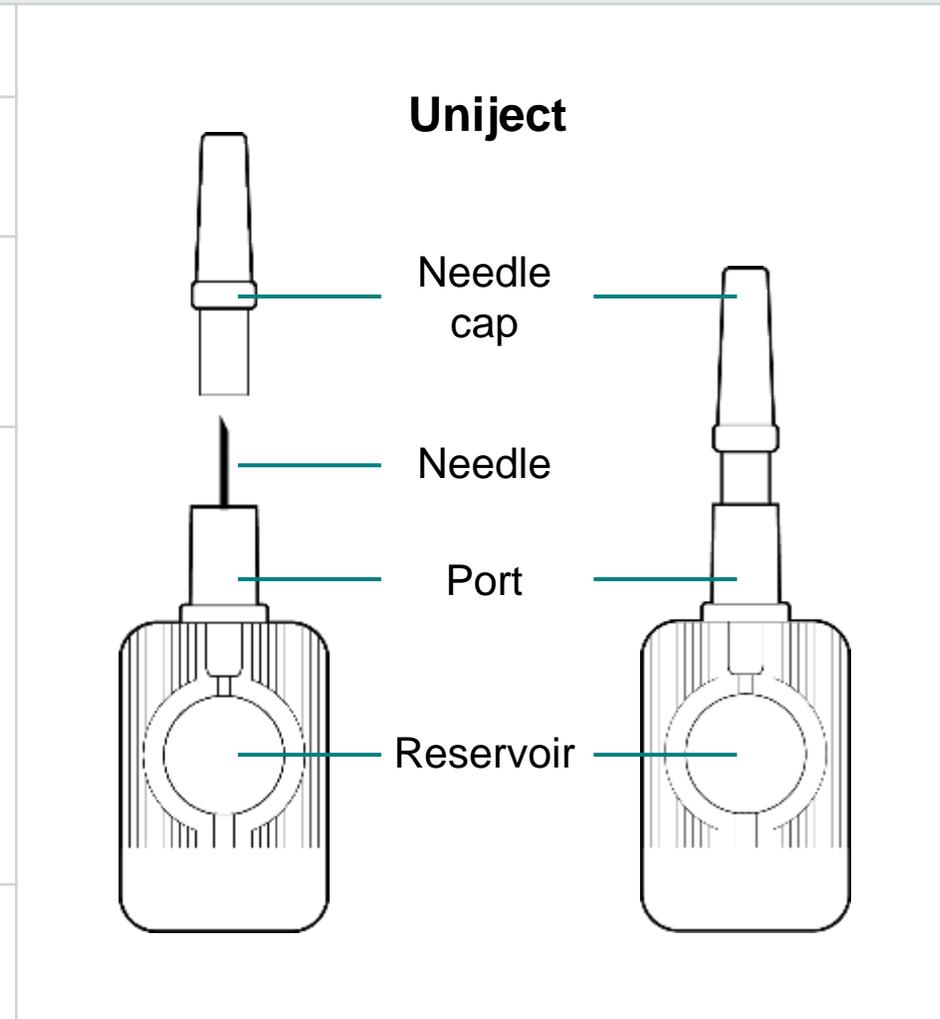


Countries interest

- **Country interest** based on VIPS country interviews in CPADs appears to be **moderate** at this point, with an overall ranking of number 5 amongst the 9 tested.

Preformed CPAD: Uniject™

Developer	BD
Device status	Commercialized for products including HepB vaccine (BioFarma) and DMPA-SC (Pfizer).
Filling process	Sterile, preformed containers on a reel are fed into a custom aseptic filling machine and then heat sealed and separated.
Device configurations	<ul style="list-style-type: none"> • Reservoir sizes of 0.25 mL, 0.5 mL, 1.0 mL, and 2.0 mL. • Reservoir is made of a low-extractable, linear, low-density polyethylene. • Standard needle gauges and lengths (18 G to 26 G, 3/8" to 1 1/2"). • Oral dropper configuration also available. • Needle shields are supplied in two lengths.
Compatibility data	Stability data for multiple vaccines and pharmaceuticals.



<https://drugdeliversystems.bd.com/products/prefillable-syringe-systems/vaccine-syringes/uniject-auto-disable-pre-fillable-injection-system>

Blow-fill-seal prefilled devices

Developer	ApiJect, Brevetti Angela
Device status	<ul style="list-style-type: none"> • Manufacturing capacity exists for non-autodisable devices. • Design concepts with autodisable feature are in development.
Filling process	<ul style="list-style-type: none"> • Container formed, filled, and sealed in one process on BFS equipment. Needle assembly could either be insert molded during the BFS process or aseptically assembled to the container in a secondary process. • Although filled on standard BFS machinery, custom inline assembly machinery is required for CPAD configuration.
Device configurations	<ul style="list-style-type: none"> • Configurations for autodisable devices unknown. • Typically constructed from polyethylene or polypropylene material.
Compatibility data	Stability data for multiple vaccines and pharmaceuticals in the BFS process.



Photo: Brevetti Angela

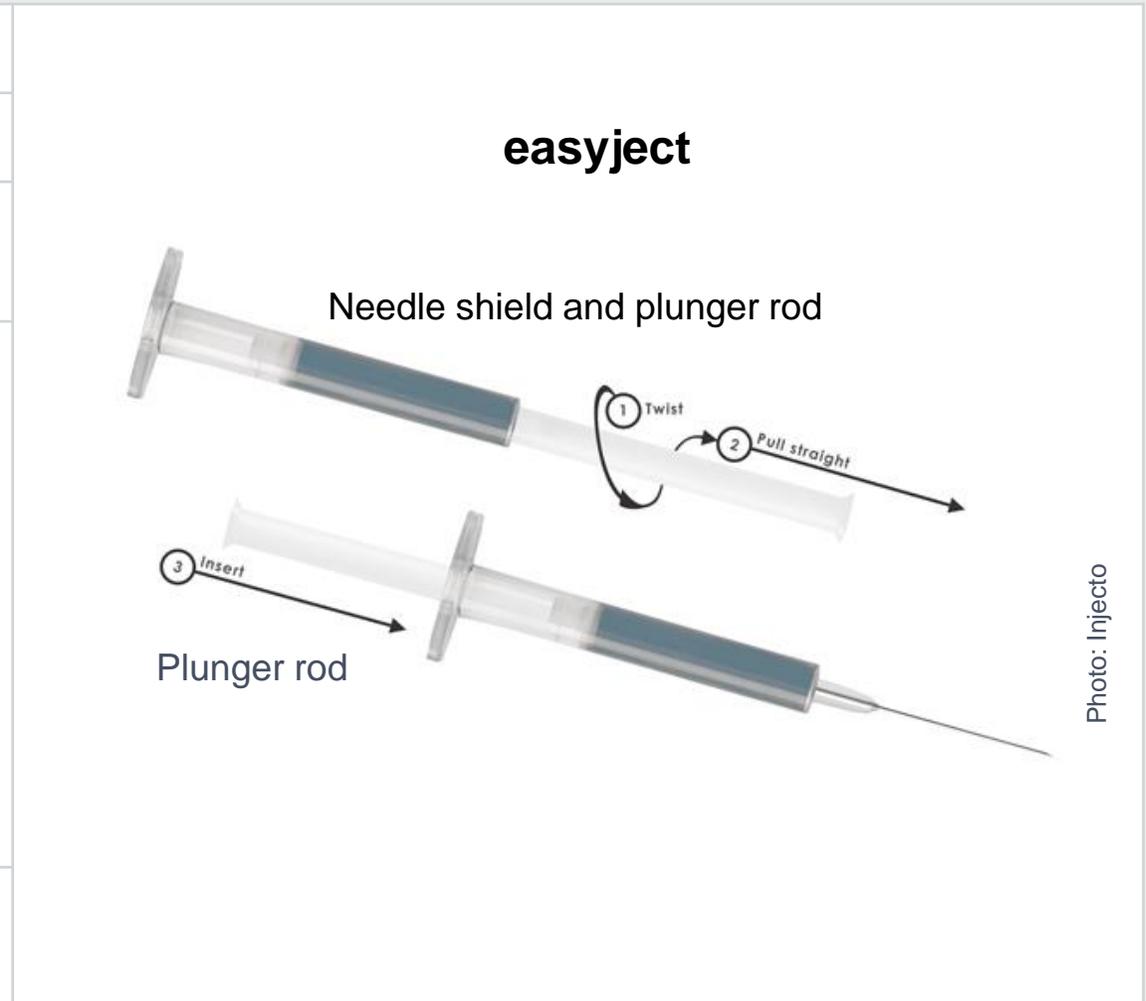
ApiJect™ prefilled injector



Photo: ApiJect

Prefilled syringe CPAD: easyject

Developer	Injecto A/S
Device status	Verification/validation testing.
Filling process	<ul style="list-style-type: none"> Compatible with standard prefilled syringe fill/finish lines.
Device configurations	<ul style="list-style-type: none"> Dose volumes from 0.1 mL–0.5 mL (up to 1 mL with potential design change). Made of COC plastic with a silicone-free barrel (not coated like most syringes due to proprietary plunger stopper design). Standard needle gauges and lengths (22 G–24 G, 3/8" to 1")* Needle shield acts as plunger rod.
Compatibility data	Preliminary stability data for IPV vaccine.



*With design change could enable 21 G–27 G and longer needles.

<http://injecto.eu/easyject/>

Injecto easyject—user study

easyject evaluation

PATH aimed to **evaluate the usability, acceptability, and programmatic feasibility of the easyject** in comparison to the Uniject for contraceptive and vaccine delivery.

Use cases

Contraceptive delivery: To understand if the easyject device is acceptable and can be used correctly by family planning clients who may decide to self-inject in the future and by providers who administer DMPA-SC.

Vaccine delivery: To understand if the easyject device is acceptable and can be used correctly by immunization providers and fit into immunization systems.



Immunization provider in Zambia practices a simulated injection with the easyject device.

Study procedures

Evaluation focus

- **Usability:** How challenging is the easyject device to use? What features of the easyject device make it easy or difficult to use?
- **Acceptability:** Does the easyject simulated use experience meet user needs and expectations? Is the easyject system comparable to Uniject among providers, clients, and other stakeholders?

Simulated use (procedure for both devices):

- Participants were **randomly assigned** which device to use first—easyject or Uniject.
- Participants were **trained on the selected device**—using the job aid along with a live demonstration.
- Participants were then asked to **deliver a simulated injection**—*no coaching* was done during simulated use.

Data collection:

- Observation checklists (simulated injections).
- Semi-structured surveys.
- Stakeholder interviews.





easyject usability for vaccine delivery

Immunization providers liked the easyject, saying that they found it to be **simple, easy to use, and familiar.**

What were your initial impressions?

- Easy to use
- Prefilled
- Saves time (no need to draw from vial)
- Easier to transport and store (all-in-one, no need to transport separate needles, syringes, and vials)
- Low risk of contamination

If you could change something about the easyject device, what would it be?*

- Make delivery smoother (avoid pain or impression of painful injection)
- Improve cap design
 - Make it easier to twist and remove
 - Slippery, requires dry hands
 - Chance of contamination
- Have the plunger already be attached

¹³ * Participants also noted the need for labeling and a vaccine vial monitor, which would be required on a device containing an actual vaccine.

easyject—Usability of the device

Vaccine use case in Zambia

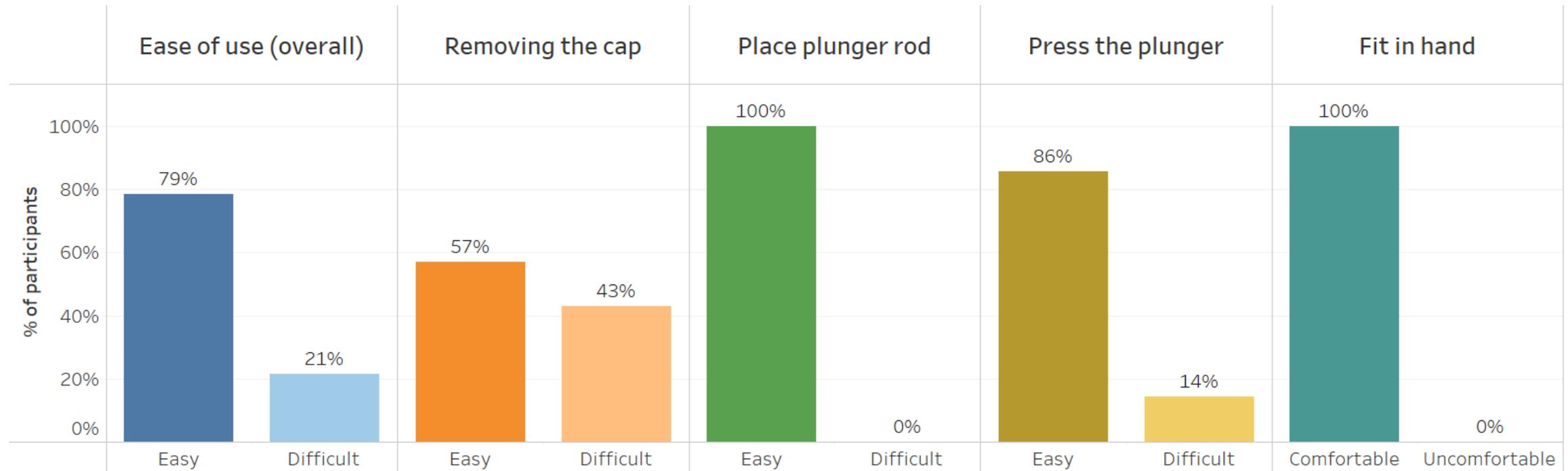
“I was able to learn how to use the device from the initial demonstration.”



“The procedure is not difficult to follow.”

Overall, participants found the easyject **easy to use**.

The **most difficult step was removing the cap**, which impacted feedback on overall ease of use.



14 * Response categories were collapsed for figure: Easy = very easy, easy, or somewhat easy; Difficult = very difficult, difficult, or somewhat difficult; Comfortable = very comfortably, comfortably, or somewhat comfortably; Uncomfortable = very uncomfortably, uncomfortably, or somewhat uncomfortably

Vaccine delivery

Overall impressions of easyject were positive.

Providers liked the easyject, saying they found it simple, easy to use, and familiar.

Most providers were “very confident” or “confident” in their ability to deliver vaccines using the easyject.

Providers expressed a preference for Uniject.

However, providers also indicated their willingness to use either device.



Indicator		Provider (n = 14)	
		easyject	Uniject
Ease of use (overall)	Very to somewhat easy	79%	86%
	Very to somewhat difficult	21%	14%
Confidence with delivery	Very confident	50%	93%
	Confident	29%	7%
	Fairly confident	21%	-
	A little bit confident	-	-
Device preference (if any preference)		14%	86%
Willingness to use either device		100%	100%
Average # of injection steps done satisfactorily (out of 7)		6.5	7
% of respondents completing all 7 injection steps satisfactorily		57%	93%
Time for injection (mm:ss, median)		01:10	00:57

Programmatic fit

Participants thought the easyject would **fit well into current immunization scenarios**, particularly for outreach, mass vaccination campaigns, under-fives, and congested clinics.

Specific advantages identified included the following:

- **Less time-consuming**—Prefilled, no recapping, can offer services faster.
- **Reduces vaccine wastage and potential shortages** associated with multidose vials.
- **Reduces errors**—A lot of potential for mistakes in busy clinics.
- **Easier to transport**—Fewer supplies to carry.
- **Acceptable to clients**—Looks like a normal syringe.



Immunization providers in Zambia.

***"Easy to carry when going for outreach as one does not need to carry syringes, needles, and vials."
– Registered nurse***

Summary of findings—Acceptability, usability, and preference



Acceptability:

- Participants in both countries liked the advantages of a prefilled device and were willing to use the easyject.
- In both countries, **participants highlighted that the device was easy to learn and use, easy to transport, and time saving.**
- Across both countries, 100% of providers said the device fit comfortably in the hand, and over 80% of all respondents said the device was easy to use.

Usability:

- Some challenges with using the easyject were noted.
- **Removing the cap and pressing down the plunger rod were challenging steps for several participants.**
- Though clients found the easyject more challenging to use than did providers, they were slightly more successful than providers with their simulated injections.

Device preference:

- Device preference was mixed between countries and cadres.
- Providers in Zambia and clients in Uganda stated an overall preference for the Uniject, while providers in Uganda had a higher preference for the easyject.
- However, **the majority of respondents in both countries were willing to use either device:** 100% of providers in Zambia; 95% of providers and 86% of clients in Uganda.

Summary of findings

Design and training recommendations

Device-related:

- **Improve cap design:** Make sure cap on final design is easy to twist and remove with either dry or wet hands.
- **Plunger mechanism:** Minimize resistance when delivering the dose (pressing the plunger) to make delivery smoother and support acceptability.

Non-device related—training suggestions:

- **Address perceptions around risk of contamination** (even if the plunger drops on the floor, the vaccine dose remains sterile, and a new device would not be needed).
- Focus training for clients on **how to manipulate the plunger** (transform the cap into a plunger).



Design modifications in process to address user feedback.

CPAD technology summary

Preformed CPADs:

- More than **155 million Uniject devices** have been supplied for delivery of vaccines and essential medicines.
- Uniject is **acceptable** to health providers and patients, can be **used in non-clinic settings and for self-administration** to deliver selected medicines, and presents **potential cost savings in training and waste management.**



Photo: BD

Blow-fill-seal CPADs:

- Technology holds promise, but a **device with a WHO PQ-compliant autodisable feature must be developed**, validated, and assessed for usability, cost, and cold chain volume.



Photo: Brevetti
Angela

Photo: ApiJect

Other (prefilled syringe) CPADs:

- Injecto easyject device has an autodisable feature, is acceptable to users, and is **compatible with standard prefilled syringe filling equipment.**



Photo: Injecto

Dual-chamber delivery devices



Dual-chamber delivery devices

About dual-chamber delivery devices

- Dual chamber delivery devices are **prefilled with liquid and dry vaccine components**, which are mixed within the device and administered.
- They could be regarded as **alternative innovations to microarray patches (MAPs) or solid dose implants (SDIs)**, and they should not have the payload restrictions of these innovations. However, they offer fewer potential benefits than MAPs or SDIs.

Stage of development

- Technologies are at various stages of development, **from early design stage through to commercial availability**, however most dual-chamber device formats are still early in development.
- **No liquid/dry vaccines are licensed** in dual-chamber delivery devices. Two liquid/liquid vaccine products are licensed: (ViATIM [Sanofi] & hepatyrix [GSK], both are hepatitis A plus typhoid polysaccharide vaccines).

www.pharmaceutical-networking.com^a



Dual chamber syringe
(Vetter Lyoject)

PharmaPan^b



Dual chamber blister with
frangible seal

Neopac^c



Dual chamber blister with
frangible seal

^a https://www.pharmaceutical-networking.com/vetter-dual-chamber-delivery-systems/10/PHARMAPAN_Dual_Chamber_Blister_1.1.pdf

^b <https://www.pharmapan.com/sites/default/files/downloads/2017->

^c <https://www.webpackaging.com/en/portals/webpac/assets/11138717/neopacs-fleximed-now-in-large-format/>

Potential public health impact of innovation



Applicability to vaccines

- Dual chamber delivery devices could be **applicable to most or all vaccines that are currently lyophilised** and require reconstitution with diluent before administration.



Public health benefits

- Public health benefits from use of dual chamber devices may include:
 - **Easier to prepare/use** allowing **lesser trained staff** to administer the vaccines, as the innovation removes the need for a separate reconstitution process;
 - **Avoidance of vaccine wastage and missed opportunities** for vaccines in multi-dose vials (MDVs);
 - The devices are single component, so should **reduce risk of stock-outs**;
 - **Removing the risk of errors and contamination during reconstitution**;
 - **Reducing the risk of needle-stick injuries.**



Vaccine problem statements

- Dual chamber delivery devices could potentially address several of the top 5 problem statements identified for **MR, MenA, rabies and yellow fever vaccines**, particularly those related to:
 - **Vaccine wastage or missed opportunities** due to MDV presentations;
 - **Reconstitution-related safety issues**;
 - **Difficult preparation**;
 - **Needle-stick injuries.**
- Dual-chamber devices do not improve the heat-stability of the vaccine, unless a formulation with improved stability is used; then, **damage due to heat exposure**, and **cold-chain requirements during outreach** might also be addressed.

Summary of key VIPS insights

Barriers to realise the innovation's potential impact



Costs

- The **commodity costs** for dual chamber devices are **unknown** but are very **likely to be higher than for vials and N&S**.
- Delivery and distribution costs are also unknown, although are likely to increase because the devices are single-dose and will occupy more space in the cold-chain.



Technology Readiness

- Most dual chamber device formats are **early in development** and face **significant technical and manufacturing challenges** that include ensuring complete mixing within the device and identifying materials with the necessary barrier properties to prevent ingress of moisture.
- In addition, **new formulations and novel drying processes** (e.g. to produce powders) might be needed for **some vaccine/device combinations**.
- **Devices that can be filled with the current lyophilised formulation face fewer challenges** and might be faster to commercialise than technologies such as MAPs or SDIs.



Commercial feasibility

- The **commercial feasibility of dual chamber delivery devices is uncertain**. A dual market in high income countries (HICs) that might incentivise vaccine manufacturers is less likely for dual chamber devices compared with other innovations (such as MAPs or SDIs), as they offer fewer potential benefits for HIC settings than these alternative innovations.



Countries interest

- There appears to be **strong country-interest in dual chamber devices**, which rank 2nd amongst the 9 tested innovations in the VIPS country interviews.

Glass dual-chamber prefilled syringes

Developers	Credence MedSystems, Vetter, etc.
Device status	Commercially available.
Filling process	Glass prefilled syringe equipment, with additional steps for powder filling and stopper insertion.
Device configurations	<ul style="list-style-type: none">• Standard diameter glass prefilled syringe and components.• Various needle and dose volumes possible.• Retractable needle version prevents reuse (Credence Companion).
Compatibility data	Licensed liquid/liquid vaccines in glass dual-chamber syringes, but not liquid/dry.

Credence Companion®

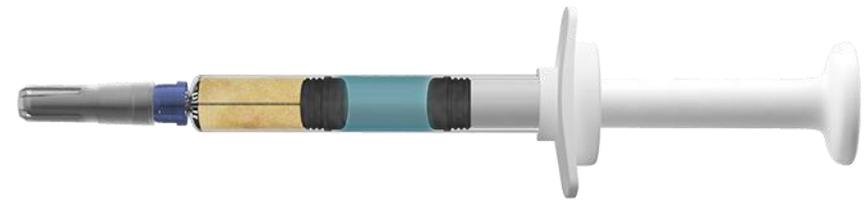


Image: Credence MedSystems

Frangible-seal dual-chamber device: Dualject

Developer	PATH	<p style="text-align: center;">Dualject</p>
Device status	Design in development.	
Filling process	<ul style="list-style-type: none"> • Sterile, preformed devices could be filled on custom, aseptic machine via liquid and powder filling as for Uniject. • Continuous form-and-fill process also possible. 	
Device configurations	<ul style="list-style-type: none"> • 0.5-mL reservoirs, additional reservoir volumes may be developed. • Films being investigated are LDPE, LDPE-Aclar-LDPE laminate, and COC-Aclar-PP laminate. • Configurations with partial or complete foil overwrap and with desiccant are being investigated. • Same needle gauges and lengths as Uniject should be possible, and an oral dropper configuration. 	
Compatibility data	None.	

Dual-chamber device technology summary

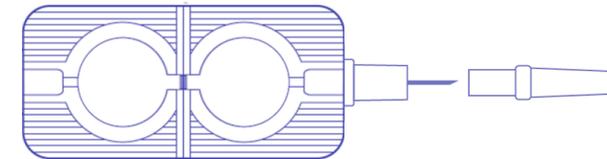
Glass dual-chamber prefilled syringe:

- Glass devices are currently available, but **cold chain volume and cost** may put them out of reach for low- and middle-income country vaccine markets.



Frangible-seal dual-chamber delivery devices:

- Technology for injectable vaccines is in early-stage development, with key technical challenges to overcome, including identification of **materials with sufficient water vapor barrier** properties.



For more
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Abbreviations

BD, Becton, Dickinson and Company

BFS, blow-fill-seal

COC, cyclic olefin copolymer

CPAD, compact prefilled autodisable

DPMA-SC, subcutaneous depot medroxyprogesterone acetate

HepB, hepatitis B

HPV, human papillomavirus

IM, intramuscular

IPV, inactivated polio vaccine

LDPE, low-density polyethylene

MAP, microarray patch

MenA, meningococcal serogroup A

MR, measles-rubella

N&S, needle and syringe

Penta, pentavalent vaccine (diphtheria, tetanus, pertussis hepatitis B, and *Haemophilus influenzae* type b)

SC, subcutaneous

SDI, solid-dose implants

SIP, sharps injury prevention

TT, tetanus toxoid

ViATIM [Sanofi] hepatyrix [GSK]

VIPS, Vaccine Innovation Prioritisation Strategy

VVM, Vaccine vial monitor

Steps to administer an injection

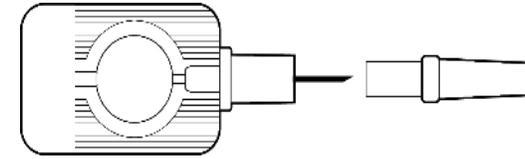
easyject



Photo: Injecto

1. Mix solution and check device.
2. Twist cap and pull straight off.
3. Insert plunger into syringe back.
4. Pinch skin to form a “tent” and insert needle (SC).
Or, hold arm and insert needle (IM).
5. Press plunger.
6. Remove needle (then release skin tent, if SC).
7. Discard device.

Uniject



1. Mix solution and check device.
2. Activate device (close gap).
3. Remove needle cap.
4. Pinch skin to form a “tent” and insert needle (SC).
Or, hold arm and insert needle (IM).
5. Press reservoir slowly to inject.
6. Remove needle (then release skin tent, if SC).
7. Discard device.

easyject—Usability



Contraceptive use case in Uganda

Most providers and clients liked the easyject, saying it was **simple and easy to use**. However, some were less positive.

What were your initial impressions?

Provider

- Self-contained
- Easy to use
- Easy to store and transport
- Not “tricky” like Uniject/fewer steps
- Small and nonthreatening

Client

- Easy to learn
- Not fear inducing
- Plunger requires a lot of force
- Cap is difficult to remove

If you could change something about the easyject, what would it be?

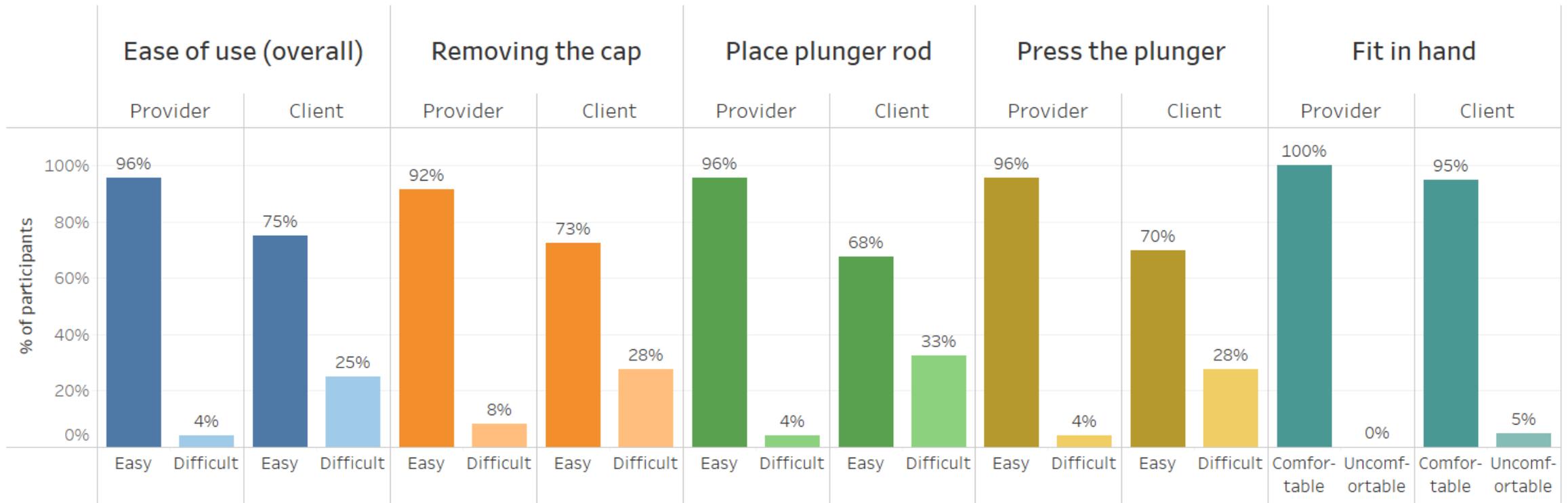
- Add a stopper at the back to reduce leakage
- Include a preassembled plunger rod that is separate from the cap
- Reduce the resistance of the plunger
- Make the seal airtight (clients concerned about air mixing with the drug)
- Prefer pressing (squeezing) over pushing
- Make it easier to remove the cap

easyject—Ease of use



Contraceptive use case in Uganda

Overall, participants found the device easy to use. **Clients were more likely to express difficulties** than providers, particularly with respect to removing the cap and placing and pressing the plunger rod.



* Response categories were collapsed for figure: Easy = very easy, easy, or somewhat easy; Difficult = very difficult, difficult, or somewhat difficult; Comfortable = very comfortably, comfortably, or somewhat comfortably; Uncomfortable = very uncomfortably, uncomfortably, or somewhat uncomfortably

Contraceptive delivery

Overall impressions of easyject were positive.

Providers tended to view easyject more favorably than clients, with 96% reporting it was easy to use (compared with 74% of clients).

A majority of providers were “very confident” in their ability to give contraceptive injections with easyject vs. just under half of clients.

A majority of providers prefer easyject over Uniject vs. just over one-third of clients.



Indicator		Provider (n = 24)		Client (n = 40)	
		easyject	Uniject	easyject	Uniject
Ease of use (overall)	Very to somewhat easy	96%	88%	74%	91%
	Very to somewhat difficult	4%	13%	25%	9%
Confidence with delivery	Very confident	58%	71%	45%	38%
	Confident	42%	25%	30%	32%
	Fairly confident	0%	4%	20%	28%
	A little bit confident	0%	0%	5%	3%
Device preference (if any preference)		58%	21%	35%	57%
Willingness to use either device		95%		86%	
Average # of injection steps done satisfactorily (out of 7)		6.3	-	6.5	6.3
% of respondents completing all 7 injection steps satisfactorily		50%	-	60%	55%
Time for injection (mm:ss, median)		02:43	-	02:05	02:00

Summary of findings



Programmatic fit

Vaccine use case:

- Participants recognized several benefits associated with the easyject compared with a needle and syringe, allowing them to provide services faster and reducing vaccine wastage and potential errors.
- The prefilled easyject would be easier to transport, since they would not have to carry vaccine vials, syringes, and needles.
- Also, the similarity to currently used delivery technologies was perceived as an advantage for clients.

Contraceptive use case:

- Participants in Uganda thought users would be receptive because it is easy to learn.
- A senior Ministry of Health stakeholder liked easyject and saw advantages to Uniject. He cautioned that having two DMPA-SC devices may be confusing.
- An additional caution was that there must be a firm commitment to maintain supply (by government, donors, and manufacturers), prior to introducing any new device.