Solid-dose implants (with applicator)[a]

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

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

Section 1: Summary of innovation

1.1 Examples of innovation types:

Separate, compressed gas-powered applicator: Bioneedle

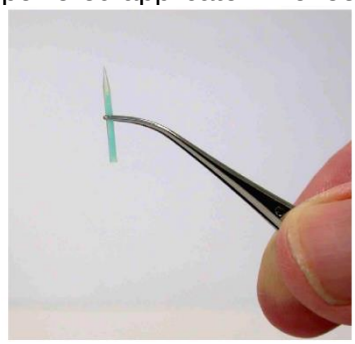


Image source: (1)

Separate, spring-powered applicator: Implavax®

Image source: [b]

Optional, separate applicator: Micropatch™

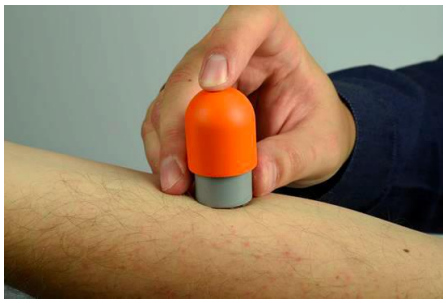


Image source: [c]

1.2. Description of innovation:

Solid-dose implants (SDIs) consist of vaccines (including antigens, adjuvants and excipients) that have been reformulated into a solid single-dose format, typically needle-shaped, that is sharp and strong enough to be implanted below the skin. After injection, the dose either dissolves immediately or is released slowly depending on the formulation. SDIs are also described as bioneedles (one of the SDI developers is also called Bioneedles), pellets, bars, bio-degradable mini-implants, or mini-projectiles.

SDI devices have two or three components:

- **The vaccine dose**: This is in a solid format. Some SDIs have a central cavity of known volume filled with liquid vaccine that is then dried. In other SDIs the vaccine and excipients are distributed uniformly throughout the implant. Ideally the dose would be sufficiently thermostable to allow storage and distribution outside the cold chain for a defined period of time.
- **Vaccine dose container or cassette**: In some cases, the solid vaccine dose is contained in a cartridge or cassette for easy handling. This is expected to have a relatively small volume, possibly similar to a single dose vial.
- **An applicator or actuator**: is used to propel the implant into the skin, using a spring or compressed-gas. The applicator might be separate and re-usable, or integrated and single use. In one device (Micropatch), manual pressure is used to deliver the implant.

[a] All SDIs require an applicator including separate gas- or spring-powered, or integrated applicators

[*] 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.

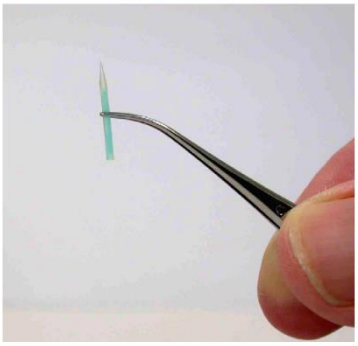
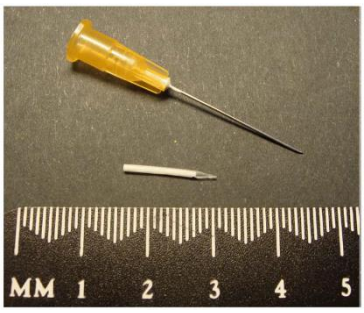
[b] https://www.enesipharma.com/technologies/platform/

[c] Nemaura presentation. Teriparatide microneedle patch for osteoporosis, December 2018. Presented during telecon 12 February 2019.

Category: *Integrated primary container and delivery technology*
Innovation: *Solid-dose implants (with applicator)*
Comparators: *SDV (liquid) and AD N&S;*
SDV (lyophilised)+ diluent +RUP reconstitution N&S and AD N&S

1.3 Examples of innovations and developers:

Table 1.

Product name; Image	Developer (place); website	Brief description, notes
 Image source: (1)  Image source: (2)	**Intravacc**[d] is now developing Bioneedles.[e] The technology was originally developed by Gijsbert van de Wijdeven, from Bioneedle Technologies Group (bioneedle.com)[f] **Partnerships:** Serum Institute of India Ltd and Intravacc will jointly develop Bioneedles for vaccines against measles and rubella (MR) vaccine. Intravacc will optimize vaccine formulation, preparation of the Bioneedles and the freeze-drying process; Serum Institute of India will supply MR vaccine. [g]	Bioneedles are small (approx. 1–1.6 cm long)(1,3–5) biodegradable implants, composed of a starch-like polymer that degrades after injection, releasing freeze-dried vaccine contained within the implant (1–3,6,7) Preclinical testing has been carried out with several vaccines (see below). In all cases, Bioneedles induced systemic humoral immune responses. **Preclinical studies, vaccines:** • Tetanus toxoid (mice) (1) • HepB (mice) (6) • Candidate TB vaccine (Ag85B-ESAT-6, adjuvated with CAF01) (mice) (2) • Influenza (mice) (7) • Trivalent IPV (3) Unpublished results with bovine herpes virus, streptococcus, BCG.[h] **Clinical trials:** Phase 1 (18 adults) with 'empty' bioneedles: SC (5).

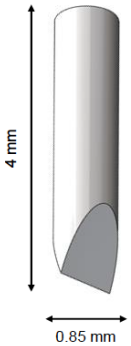
[d] https://www.intravacc.nl/
[e] https://www.utrechtsciencepark.nl/nl/over-het-park/nieuws/serum-institute-of-india-and-intravacc-to-develop-bioneedles
[f] https://www.launch.org/innovators/gijsbert-van-de-wijdeven/
[g] https://www.utrechtsciencepark.nl/nl/over-het-park/nieuws/serum-institute-of-india-and-intravacc-to-develop-bioneedles (also on Intravacc website – news).
[h] Blend corporate finance: Business case Intravacc-Bioneedle. 2 November 2015

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

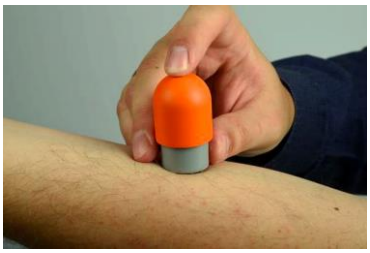
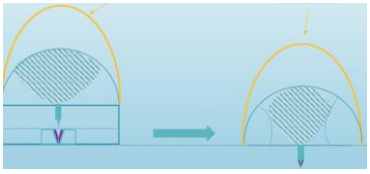
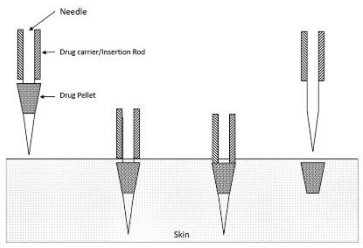
Comparators: *SDV (liquid) and AD N&S;*

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

Product name; Image	**Developer (place); website**	**Brief description, notes**
ImplaVax®   Image source: [i]	**Enesi Pharma** (Abingdon, UK; founded October 2017). Enesi; purchased assets from Glide Pharmaceutical Technologies.[j],[k] **Partnerships**: 2 January 2019: GeoVax (Atlanta, GA, USA). Using virus-like particles (VLP) produced by a live-recombinant virus vector for multiple human vaccine applications (all of global-health interest)[l]. 5 November 2018: Sementis[m] (Melbourne, Australia): dual chikungunya & Zika vaccine and peanut allergy immunotherapy; [n] uses Sementis Copenhagen Vector (SCV) live-virus vector. 1 October 2018: Public Health England: Anthrax recombinant Protective Antigen (rPA) and Crimean-Congo Haemorrhagic Fever (Public Health England).[o] 24 September 2018: CRADA with Walter Reed Army Institute: Invaplex Shigella (preclinical). [p]	**Use**: The pre-loaded unit dose cassette is inserted into the actuator. Priming and skin tensioning is achieved by pressing the loaded cassette gently against the skin. Further downward pressure actuates the internal mechanism to deliver the implant through the skin into the subcutaneous tissue where it dissolves releasing the active ingredient over time.[u],[j] **Actuator:** spring-loaded, activated by downward pressure; audible click confirms delivery; re-useable for 1,000 cycles.[j] **Single use, unit-dose cassette**: contains solid implant; needle-free; viewing window confirms delivery; lock-out mechanism prevents re-use; eliminates cross-contamination. **Preclinical studies, vaccines** using Enesi or Glide SDIs: • Diphtheria (guinea pigs).[v] • HiB (guinea pigs).[v] • fluenza (ferrets).[v] • Anthrax (rPA) (rabbits).[v]

[i] https://www.enesipharma.com/technologies/platform/ and https://www.enesipharma.com/wp-content/uploads/2018/11/Enesi-flyer-Nov-2018.pdf
[j] https://www.enesipharma.com/
[k] https://www.linkedin.com/company/glide-pharmacetitical-technologies
[l] https://www.enesipharma.com/enesi-pharma-and-geovax-to-collaborate-on-development-of-multiple-vaccines-administered-by-implavax-a-novel-needle-free-vaccine-delivery-platform/
[m] http://www.sementis.com.au/
[n] https://www.enesipharma.com/enesi-pharma-and-sementis-sign-rd-collaboration-focused-on-needle-free-solid-dose-vaccines-for-peanut-allergy-and-chikungunya-zika-infection/
[o] https://www.enesipharma.com/enesi-pharma-and-public-health-england-enter-rd-collaboration-for-novel-needle-free-solid-dose-vaccine-for-emergent-threat-pathogens/
[p] https://www.enesipharma.com/enesi-pharma-and-walter-reed-army-institute-of-research-wrair-sign-cooperative-rd-agreement-crada-for-needle-free-solid-dose-vaccine-for-shigella-infection/
[u] Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019.
[v] ImplaVax™ Unique needle free solid dose vaccine platform delivering enhanced immunogenicity with ultimate convenience and no cold chain. Enesi Pharma. 4 April 2018: (via PATH)

Category: *Integrated primary container and delivery technology*
Innovation: *Solid-dose implants (with applicator)*
Comparators: *SDV (liquid) and AD N&S;*
SDV (lyophilised)+ diluent +RUP reconstitution N&S and AD N&S

Product name; Image	**Developer (place); website**	**Brief description, notes**
	22 September 2015: Glide with Cilian[q] (Munster, Germany; CiFlu) for influenza.[r] 29 April 2013: Glide and Pfenex [s] for anthrax vaccine (US government support) [t]	**Clinical studies, non-vaccine:** • 'Fentanyl, Octreotide, Sumatriptan' [v] **Clinical studies, other:** • Human factors studies. [v]
Micropatch™ (Various device formats)  Image source : [w]  Image source : [w]  Image source: [x]	**Nemaura Pharma** (Loughborough, UK; since 2005); In clinical development with one vaccine (plus 10 other drugs).[y] **Partnerships**: 2014: '[UK] government-funded project to convert the Boostrix® vaccine from a liquid form to a micro-solid dose' (8)	The implant consists of a releasable, solid drug collar, held in a cassette. Pressure on the actuator pushes a sharp metal needle into the collar and then into the skin where the collar is released. After use, the needle retracts into the device. Additional, separate applicators can be used to improve ease-of-use for subjects with poor dexterity.[z] **Claims**: 'precise, easy to use and minimally invasive skin-based drug delivery technologies, Fast with minimal pain, designed to enhance the delivery of almost any drug. **Preclinical studies, vaccines:** • Tetanus toxoid (mice) and DTaP (Infanrix) (mice) [x] Size (without optional applicator): 2cm tall x 1.5 cm diameter. [z]

[q] http://www.cilian.com/
[r] https://www.manufacturingchemist.com/news/article_page/Glide_Technologies_collaborates_with_Cilian_to_develop_flu_vaccine/112074
[s] https://www.pfenex.com/
[t] https://www.in-pharmatechnologist.com/Article/2013/04/30/Injex-Gets-China-Approval-Glide-to-Make-Solid-Dose-Anthrax-for-Pfenex
[w] Nemaura presentation. Teriparatide microneedle patch for osteoporosis, December 2018. Presented during telecon 12 February 2019.
[x] http://www.microneedles2016.org/uploads/2/4/9/7/24973350/fazchowdhury.pdf
[y] http://www.nemaura.co.uk/pipeline/
[z] Teleconference with Nemaura Pharma (and JH), 12 February 2019

SECTION 2: Summary of assessment for prioritisation

2.1 Key benefits:

- **Avoidance of reconstitution** of lyophilized vaccines, **reducing the risk of errors or contamination**.
- Some SDI systems allow **needle/sharps-free** administration, thereby **improving safety**.
- Potentially **suitable for use by minimally-trained healthcare workers** (HCWs) or self-administration.
- SDIs could **enable novel vaccine combinations** depending on the manufacturing process.
- SDIs **might be able to be used in a controlled temperature chain if sufficiently thermostable thereby facilitating outreach and potentially improving coverage**. This will be vaccine-specific.

2.2 Key challenges:

- Some SDIs will have **small payloads** and **might be incompatible with adjuvanted vaccines.**
- Possible need to demonstrate no risk of **transfer of infectious substances** by re-usable actuators.
- Most or all SDI systems require a **separate applicator**; in the case of Bioneedles this needs a compressed gas source.

2.3 Additional important information:

- **Slow-release of vaccine** might improve immunogenicity, resulting in **fewer doses per regimen**.[aa]
- All vaccines used will **need to be reformulated** into the solid-dose form.
- The **manufacturing processes** for SDIs will be novel and specific for each SDI format.
- Vaccine and excipients **will remain at the injection site** longer than a liquid vaccine. Studies will need to confirm this doesn't have short- or long-term safety issues.
- SDIs are **combination products** and will need regulatory approval for use with a specific vaccine.
- SDIs are **very early in** development. No clinical studies with vaccines have been published.
- Relatively **few developers** (possibly only three) are developing SDIs.
- SDIs are likely to **cost more per unit** than SDV + AD N&S when introduced and possibly when manufactured at scale

[aa] Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019

Category: *Integrated primary container and delivery technology*
Innovation: *Solid-dose implants (with applicator)*
Comparators: *SDV (liquid) and AD N&S;*
SDV (lyophilised)+ diluent +RUP reconstitution N&S and AD N&S

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	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation have features that may improve heat stability?	Better	Neutral	SDIs require vaccines to be reformulated into a dry state. For liquid vaccines, this is likely to improve heat stability. If the residual moisture content is sufficiently low, and appropriate stabilising excipients are used, the solid formulation might have improved thermostability compared with current lyophilised formulations. Whether or not this is achieved will be vaccine specific. Encouraging thermostability results have been obtained with Bioneedles with sIPV (3) and an anthrax vaccine.[bb]

Liquid	*Lyophilised*	***Better** than the liquid comparator* ***No difference** to the lyophilised 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.*

[bb] Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019.

Category: *Integrated primary container and delivery technology*
Innovation: *Solid-dose implants (with applicator)*
Comparators: *SDV (liquid) and AD N&S;*
SDV (lyophilised)+ diluent +RUP reconstitution N&S and AD N&S

Table 3.

Ability of the vaccine presentation to withstand freeze exposure	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation have features that may improve freeze resistance?	Better	Neutral	It is possible that vaccines in a dry SDI format will be more resistant to freeze-damage than liquid vaccines, because of their low moisture content. Vaccines that are currently lyophilized will not necessarily be more freeze-resistant when formulated as SDIs however. All SDIs incorporate stabilizing excipients such as sugar-glasses to preserve vaccine potency during fabrication[cc],[dd] (1,3,6). These excipients should protect against further exposure to freezing temperatures. No data on the freeze-resistance of SDIs could be found however.

Liquid	*Lyophilised*	***Better*** *than the liquid comparator* ***No difference*** *to the lyophilised comparator*

[cc] Teleconferences with Enesi Pharma (and JH), 12 February 2019
[dd] Teleconference with Nemaura Pharma (and JH), 12 February 2019

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

3.2 Coverage and equity criteria

Indicator: Ease of use[ee]

*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	Liquid comparator	Lyophilised comparator	Assessment
• *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Does the innovation avoid reconstitution and is that an improvement?**	Neutral	Better	SDIs avoid the need for reconstitution of lyophilized vaccines (but score neutral for liquid vaccines).
	Does the innovation require fewer vaccine product components?	Neutral	Better	SDIs are likely to have the same number of components (relative to the comparator used with liquid vaccines), or fewer components (compared with lyophilised vaccines). SDIs will typically consist of the applicator and dose cassette compared with: Vaccine vial and AD N&S for liquid vaccines– hence neutral. Vaccine vial, AD N&S, diluent, reconstitution syringe for lyophilised vaccines – hence better
	[ff] **Does the innovation require additional components or equipment (such as scanners or label readers)?**	N/A	N/A	

[ee] 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).

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

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

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

Ease of use	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
• *Assessment of the potential for incorrect preparation based on usability data from field studies (or based on design of innovation if field studies not available)* • *Assessment of the potential for incorrect administration based on usability data from field studies (or based on design of innovation if field studies not available)*	**Does the innovation require fewer preparation steps and less complex preparation steps?**	Neutral	Better	SDIs are likely to require the same (or possibly fewer) number of steps as used for N&S injection of liquid vaccines: unpack and insert the pre-loaded cassette into the applicator, inject, discard. Compared with unpack syringe, unpack vial, draw-up dose, inject and discard. SDIs will require fewer steps compared with reconstitution and injection of lyophilised vaccines, as none of the steps involved in reconstitution will be needed. Implavax® and the Nemaura device are claimed to be suitable for self-administration,[gg],[hh] including by subjects with poor dexterity (Nemaura). [hh]
	Does the innovation improve dose control?	Better	Better	The dose is formulated as a single solid implant. There is no need to manually draw-up the correct dose, so the chance of a dosing error is reduced.
	Does the innovation improve targeting the right route of administration?	Neutral	Neutral	Depth of administration will be dependent on the size of the implant and the actuator settings. Implavax® delivers the dose 2–3 mm below the surface of the skin; [gg] for a 4 mm implant, the 'point' is 6–7 mm below the skin surface. There are currently no data on the accuracy or reproducibility of SDI delivery.

[gg] Teleconference with Enesi Pharma (and JH), 12 February 2019
[hh] Teleconference with Nemaura Pharma (and JH), 12 February 2019

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

Liquid	*Lyophilised*	***Better*** *than both the liquid and lyophilised comparator*

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**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Does the innovation require fewer components?	Neutral	Better	SDIs are likely to have the same number of components (relative to the comparator used with liquid vaccines), or fewer components (compared with lyophilised vaccines). SDIs will typically consist of the applicator and dose cassette compared with: Vaccine vial and AD N&S for liquid vaccines– hence neutral. Vaccine vial, AD N&S, diluent, reconstitution syringe for lyophilised vaccines – hence better
	Or does the innovation include labelling that facilitates product tracking and is it better than the comparator?	Neutral	Neutral	SDI do not have labelling features that facilitate product tracking.

Liquid	*Lyophilised*	***No difference*** *to the liquid comparator* ***Better*** *than the lyophilised comparator*

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

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

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

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

Table 6.

Acceptability of the vaccine presentation to patients/ caregivers • *Does the innovation include features that may improve acceptability of vaccinees and caregivers*	**Parameters to measure against a comparator**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Painful or not painful	Neutral	Neutral	There are very few data on this subject. In one study with Bioneedles, some subjects reported a mild burning sensation (but not pain) at the time of injection. Some subjects reported moderate pain several hours after injection however (5). In a human factors study with Implavax®, at least one participant commented that the process was pain-free.[ii]
	Perception of ease of administration (i.e. convenience for the vaccinees/ caregivers)	Better	Better	There are few data on this subject. In one unpublished human factors study with Implavax®, subjects commented favourably on the speed of the injection process.[jj] In addition, adults, parents of infants and parents of children expressed a strong preference for Implavax® compared with N&S.[jj]
	Any other tangible benefit to improve/impact acceptability to vaccinees/caregivers			

[ii] Teleconferences with Enesi Pharma (and JH), 12 February 2019

[jj] ImplaVax™ Unique needle free solid dose vaccine platform delivering enhanced immunogenicity with ultimate convenience and no cold chain. Enesi Pharma, 4 April 2018. (via PATH)

Category: *Integrated primary container and delivery technology*
Innovation: *Solid-dose implants (with applicator)*
Comparators: *SDV (liquid) and AD N&S;*
SDV (lyophilised)+ diluent +RUP reconstitution N&S and AD N&S

Liquid	*Lyophilised*	***Better*** *than both the liquid and lyophilised 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 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	Liquid comparator	Lyophilised comparator	Assessment
• *Risk assessment of potential for contamination based on design of innovation and on usability data from field studies*	**Does the innovation reduce the risk of contamination while reconstituting the dry vaccine?**	Neutral	Better	There is no need to reconstitute vaccines.
	Does the innovation reduce the risk of contamination while filling the delivery device?	Better	Better	There is no need to fill SDIs. For at least two of the systems, the implant is provided in a pre-loaded cassette.[kk],[ll]
	Does the innovation require fewer preparation steps and less complex preparation steps?	Neutral	Better	SDIs are likely to require a similar number of steps compared with N&S injection of liquid vaccines, and fewer steps than for lyophilised vaccines.
	Does the innovation reduce the potential risk of reuse of delivery technology?	Neutral	Neutral	Some SDI devices have mechanisms to prevent re-use.[kk,ll]
	Does the innovation reduce the risk of use of nonsterile components?	Neutral	Neutral	Some SDIs have a re-usable applicator or actuator.[kk,ll] In at least one case, the implant cassette is designed to prevent

[kk] Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019.
[ll] Nemaura presentation. Teriparatide microneedle patch for osteoporosis, December 2018. Presented during telecon 12 February 2019.

				contact of the actuator with the skin or body fluids.[mm]

Liquid	*Lyophilised*	***Better*** *than both the liquid and lyophilised 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 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	Liquid comparator	Lyophilised comparator	Assessment
• *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**Does the innovation contain fewer sharps?**	Better	Better	Bioneedles (6) and ImplaVax® are claimed to be sharps-free.[mm] The Nemaura SDI has a concealed needle within the device that delivers a 'collar' of vaccine to the tissue.[nn]
	Does the innovation use sharps for preparing and/or administering the vaccine and is that better than the comparator?	Better	Better	
	Does the innovation include an auto disable feature and is that better than the comparator?	Neutral	Neutral	Some SDI devices have autodisable mechanisms to prevent re-use. [mm,nn] It is not clear whether the Bioneedle device is auto-disabling.

[mm] Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019
[nn] Nemaura presentation. Teriparatide microneedle patch for osteoporosis, December 2018. Presented during telecon 12 February 2019

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
Likelihood of needle stick injury • *Risk assessment of the presence of sharps during the process of preparing and administering the vaccine*	**If the innovation uses sharps, does it include a sharps injury prevention feature and is that better than the comparator?**	Better	Better	Two SDIs are sharps free(6).[oo] The needle in the Nemaura device retracts after use.[pp]
	Does the innovation reduce the risk of injury after vaccine administration?	Better	Better	

Liquid	*Lyophilised*	***Better*** *than both the liquid and lyophilised comparator*

3.4 Economic costs criteria

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

*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.*

[oo] Enesi Pharma, Summary Presentation, February 2019. Presented during telecon, 12 February 2019

[pp] Nemaura presentation. Teriparatide microneedle patch for osteoporosis, December 2018. Presented during telecon 12 February 2019

[qq] 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: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

Table 9.

Total economic cost of storage and transportation of commodities per dose	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation reduce the volume per dose stored and transported in the cold chain?	Worse	Worse	No data on the size of SDIs in primary or secondary packaging found in the public domain. In general, the volume will vary by type of SDI. PATH VTIA used volumes of 20, 35 and 50 cm^3 for analysis of the Implavax cassette based on information provided by Enesi. For the Nemaura Micropatch, the volume is estimated at 2cm tall x 1.5 cm diameter[z] but does not include the applicator and does not account for packaging. For some vaccines, a SDI may be more thermostable and enable storage in a CTC. Thermostability, and therefore dependence on the cold-chain, is likely to be vaccine specific. We base the indicator on the Implavax data since this includes packaging. We compare this to the volume of a SDV for Quivaxem vaccine of $10cm^3$ per dose or measles vaccine of $21.09cm^3$ per dose. The cassette volume of the Implavax stored in the cold chain is likely larger than a SDV.

Total economic cost of storage and transportation of commodities per dose	**Parameters to measure against a comparator**	**Liquid comparator**	**Lyophilised comparator**	**Assessment**
	Does the innovation reduce the volume per dose stored and transported out of the cold chain?	Better	Better	There are no data in the public domain on the volume of the actuators or applicators used with SDI. We have assumed the Implavax actuator is packaged separately from the vaccine cassettes. This is a 'best case' assumption; Implavax have indicated that they would pack actuators with vaccine.[rr] PATH's VTIA model used a volume of 90cm^3 for the Implavax actuator which is used for 1,000 cycles and hence a volume of 0.09 cm^3 per dose. This is also based on information provided by Enesi. There is no data available on the volume of the applicator used with the Nemaura Micropatch. So we base the indicator on the Implavax data. SDVs require a syringe for delivery and the AD syringe has volume of about 30cm^3. For lyophilized vaccines in SDVs, they require a reconstitution syringe. In addition, they require a diluent which is typically stored out of the cold chain except at the service delivery level. So the volume stored out of the cold chain will likely be reduced for SDI compared to the SDVs, assuming a reusable actuator as for the Implavax.

Liquid	*Lyophilised*	***Mixed*** *for both the liquid and lyophilised comparator*

[rr] Enesi Pharma, Personal communication during telecon, 12 February 2019

Category: *Integrated primary container and delivery technology*

Innovation: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

Indicator: Total economic cost of the time spent by staff per dose

*Legend: Dark Green: **Considerably better** than the comparator: Reduces time for all applicable parameters; Green: **Better** than the comparator: Reduces time for either, and there is no difference for the other one; White: **Neutral**, no difference with the comparator; Yellow: **Mixed**: Reduces the time for one of the parameters, and increases the time for the other parameter; Red: **Worse** than the comparator: Increases the time for either of the applicable parameters; and there is no difference for the other one; Dark Red: **Considerably worse** than the comparator: Increases time for all applicable parameters, N/A: the indicator measured is **not applicable** for the innovation; Grey: **no data** available to measure the indicator.*

Table 10.

Total economic cost of the time spent by staff per dose	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
	Does the innovation have attributes that can save time for the vaccinator in preparing and administering the vaccine?	Neutral	Better	Comments from unpublished ImplaVax® human factors studies suggest that use is at least as fast as the comparator.[ss] There are no other data on this indicator. It is anticipated the time to administer a SDI would likely be the same when administering a liquid vaccine from a SDV and better than when administering a lyophilized vaccine from a SDV.
	[tt]Does the innovation have attributes that save time for staff involved in stock management?	Neutral	Neutral	SDIs do not have attributes that save time for staff involved in stock management.

Liquid	*Lyophilised*	***No difference** to the liquid comparator* ***Better** than the lyophilised comparator*

[ss] ImplaVax™ Unique needle free solid dose vaccine platform delivering enhanced immunogenicity with ultimate convenience and no cold chain. Enesi Pharma, 4 April 2018. (via PATH)

[tt] 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: *Solid-dose implants (with applicator)*

Comparators: *SDV (liquid) and AD N&S;*

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

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

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

Table 11.

Total economic cost of one-time/upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)	Parameters to measure against a comparator	Liquid comparator	Lyophilised comparator	Assessment
	Are there one-time upfront costs that will be incurred for use of this innovation or recurrent costs that will be incurred for use of this innovation?	Neutral	Neutral	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).

Liquid	*Lyophilised*	***No difference** to both the comparators*

3.5 Secondary criteria on potential breadth of innovation use

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

Table 12.

Applicability of innovation to one or several types of vaccines • *To what types of vaccines/antigens does the innovation apply to, based on technical feasibility?*	**Assessment**
	This innovation could theoretically be applied to all vaccines that are currently delivered by injection. The need to dry the antigen (which might preclude vaccines with alumunium-salt-based adjuvants) and available payload volume could potentially limit the number and types of vaccine that can be incorporated into a solid dose implant. Examples on the VIPS priority antigen list that might be suitable include MR, IPV, and rabies vaccines.

Indicator: Ability of the technology to facilitate vaccine combination

Table 13.

Ability of the technology to facilitate vaccine combination • *Does the innovation facilitate novel combination vaccine products?*	**Assessment**
	Yes / Possibly. All SDI approaches involve reformulation and drying of vaccines. If vaccines need to be combined in the liquid phase before drying, it is unlikely that novel combinations will be possible. Implavax® implants might allow combination of different, previously lyophilised antigens[uu]. which might overcome this drawback. However: • The limited payload of some SDIs might preclude some existing as well as novel combinations. • In cases where vaccines have to be blended and then dried, it is possible that different antigens might require different, incompatible stabilisers that are not compatible with one another, thereby reducing the ability to combine vaccines. • More data on the feasibility of combining vaccines in SDIs is needed.

[uu] ImplaVax™ Unique needle free solid dose vaccine platform delivering enhanced immunogenicity with ultimate convenience and no cold chain. Enesi Pharma. 4 April 2018: (via PATH)

SECTION 4

4.1 Robustness of data:

Table 14.

Category	Assessment
Type of study	The majority of the data has come from manufacturers' websites, presentations or interviews (Enesi Pharma, Nemaura Pharma), or from a small number of peer-reviewed publications of preclinical studies (Bioneedles). This has been combined with expert opinion.
Inconsistency of results	There are too few comparable studies to assess inconsistency of results.
Indirectness of comparison • *Indicate the setting in which the study was conducted (low, middle or high income setting);* • *Comment if the data is on non-vaccine application of the innovation*	All the data assessed has been for vaccine applications

Overall assessment:	*Low*	*SDIs are at a very early stage of development. Most of the data can be categorised as manufacturers claims or is from non-peer-reviewed studies.*

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

Table 15.

Expert/type	Organisation/contact details	Notes
David Hipkiss, CEO Ludovic Bonnet, VP Product Development	Enesi Pharma Ltd, Milton Park, Abingdon, Oxfordshire, OX14 4SA, UK www.enesipharma.com David.hipkiss@enesipharma.com	Webex conference with JH, 12 February 2019

Expert/type	Organisation/contact details	Notes
Faz Chowdhury, CEO	Nemaura Pharma Ltd, Loughborough, Leicestershire, LE11 3QF, UK www.nemaura.co.uk fazc@nemaura.co.uk	Telephone conference with JH, 12 February 2019
Ivo Ploemen, Business Development Manager	Intravacc, Bilthoven, The Netherlands www.intravacc.nl ivo.ploemen@intravacc.nl	E-mail exchange with JH. No updates since information provided to PATH in 2016 and 2017, therefore no need for an interview.

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
Julian Hickling Rebecca Jones	Working in Tandem Ltd julian@workingintandem.co.uk	Developed and reviewed the TN
PATH Medical Device and Health Technology Team Debra Kristensen Courtney Jarrahian Mercy Mvundura Collrane Frivold	PATH cjarrahian@path.org dkristensen@path.org	Reviewed the TN
Fatema Kazi	GAVI, the Vaccine Alliance fkazi-external-consultant@Gavi.org	Reviewed the TN

4.4 References:

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8. Chowdhury F. Interview with Faz Chowdhury. Ther Deliv. 2014 Jun 1;5(6):631–3.