VIPS Phase I executive summary: Sublingual dosage forms

June 2019
Sublingual dosage forms

About Sublingual dosage forms

- Sublingual dosage forms are tablets and thin films that are placed under the tongue and rapidly dissolve to form a gel in a small amount of saliva.
- The gel is absorbed via the mucosal surfaces under the tongue inducing systemic immunity, similar to an injectable vaccine, and potentially inducing robust mucosal immunity.
- In contrast to oral ingestion vaccination, sublingual dosage forms are not intended to be swallowed or delivered to the intestinal tract.

Stage of development

- Sublingual dosage forms are in early-stage preclinical development for several vaccines including HIV Env protein and ETEC. The mucosal adjuvant dmLT is also being evaluated.
- Some have progressed to clinical trials including a seasonal influenza vaccine combined with a novel adjuvant in a sublingual tablet.
- Most studies of sublingual vaccines to date have not utilised optimised sublingual dosage forms that form a gel, which resulted in poor immune responses.
- Commercially available sublingual dosage forms are used to deliver allergy immunotherapies, low molecular weight drugs, and therapeutic vaccines.
Sublingual dosage forms scorecard
Comparators: Single dose vial (SDV) (liquid) and dropper or sprayer; SDV (lyophilised) + diluent + reuse prevention (RUP) reconstitution syringe and dropper sprayer; SDV(liquid) and autodisable (AD) needle and syringe (N&S); SDV (lyophilised) + diluent and RUP reconstitution syringe and AD N&S

Quality of evidence: Low to moderate

<table>
<thead>
<tr>
<th>VIPS Criteria</th>
<th>Indicators</th>
<th>Comparators</th>
<th></th>
<th></th>
<th></th>
<th>Priority indicators - Country consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oral/Intranasal</td>
<td>Injectable</td>
<td></td>
<td></td>
<td>RI* Facility</td>
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<tr>
<td></td>
<td></td>
<td>Dropper or sprayer + recon</td>
<td>Dropper or sprayer - recon</td>
<td>SDV AD N&amp;S + recon</td>
<td>SDV AD N&amp;S - recon</td>
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<tr>
<td></td>
<td>Ability of the vaccine presentation to withstand heat exposure</td>
<td>Neutral</td>
<td>Better</td>
<td>Neutral</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Ability of the vaccine presentation to withstand freeze exposure</td>
<td>Neutral</td>
<td>Better</td>
<td>Neutral</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td><strong>Health impact</strong></td>
<td>Ease of use&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td><strong>Coverage &amp; Equity impact</strong></td>
<td>Potential to reduce stock outs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Acceptability of the vaccine presentation to patients/caregivers</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Considerably better</td>
<td>Considerably better</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td><strong>Safety impact</strong></td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Likelihood of contamination</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Likelihood of needle stick injury</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Total economic cost of storage and transportation of commodities per dose</td>
<td>Considerably better</td>
<td>Considerably better</td>
<td>Considerably better</td>
<td>Considerably better</td>
<td>++</td>
</tr>
<tr>
<td><strong>Economic costs</strong></td>
<td>Total economic cost of the time spent by staff per dose</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>Better</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Total introduction and recurrent costs&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>+</td>
</tr>
<tr>
<td><strong>Secondary criteria</strong></td>
<td><strong>Potential breadth of innovation use</strong></td>
<td>All vaccines against mucosal pathogens that can be prepared in a dry format are potential candidates</td>
<td>No</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ease of use can prevent missed opportunities and impact ability for lesser trained personnel to administer the vaccine, including self-administration

<sup>b</sup> Based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities

<sup>c</sup> Total economic cost of one-time / upfront purchases or investments required to introduce the innovation and of recurrent costs associated with the innovation (not otherwise accounted for)
Sublingual dosage forms: Antigen applicability

- Sublingual dosage forms can potentially be applied to vaccines against mucosal pathogens that can be prepared in a dry format.
- Vaccines that are currently delivered parenterally are likely to be suitable for this innovation, but subunit and non-live vaccines are likely to require a mucosal adjuvant (such as dmLT), and none are approved at present.
- Live vaccines that are currently delivered intranasally may also be suitable.
- A sublingual dosage form is an attractive option for an HIV vaccine.
- Examples on the VIPS priority antigen list that might also be appropriate for sublingual delivery include HPV, IPV (both might require a mucosal adjuvant however) and the live VSV-vectored Ebola vaccine.
Sublingual dosage forms: Assessment outcomes

**KEY BENEFITS**

- May offer **improved heat stability and freeze resistance** over liquid vaccines given the **dried format**.

**Potential positively impact on coverage and equity:**
- Easy to use: simplify preparation and delivery and may **reduce errors and improve dose control**.
  - Could enable alternate delivery scenarios.
  - May be suitable for delivery by lesser-skilled health care workers.
- Potential to **increase acceptability**: likely to be more acceptable due to the reduced pain of delivery (compared to injectable presentations).
  - Potential to reduce stock-outs since the innovation has a single component to be procured, distributed, and tracked.

- May **improve safety** by reducing risk of contamination and needlestick injuries.

- Potential to **reduce overall delivery costs**:
  - May reduce storage and transportation costs since sublingual dosage forms are extremely compact and eliminate the need to store and transport any components out of the cold chain.
  - May save health care worker time, as easy to use.
- Have the potential to **increase immunogenicity** compared to a dropper/sprayer.

**KEY CHALLENGES**

- For infants and young children, the dry sublingual dosage forms **may need to be reconstituted** and then administered with a liquid dropper under the tongue to address the potential risk of choking which negates some of the benefits for this age group.
- Limited applicability for subunit and non-live vaccines unless combined with a mucosal adjuvant.

Important attribute for at least 2 settings or for the 3 settings based on the country consultation (see slide 3)

Important attribute for campaigns or routine facility-based immunisation based on country consultation (see slide 3)
Sublingual dosage forms: Rationale for prioritisation

- Based on the analysis, sublingual dosage forms are included in a ‘maybe’ category for prioritisation and the Steering Committee is requested to provide advice on whether this innovation should be prioritised or not for Phase II.

- While the technology may yield high public health benefits, its applicability to subunit and non-live vaccines is limited without the availability of a mucosal adjuvant and advancement of adjuvants is outside of the purview of VIPS.

Additional important information to be analysed in phase II (if prioritised for Phase II):

- Vaccine specific reviews of technical feasibility – especially for products requiring a mucosal adjuvant.

- Vaccine specific reviews of the public health value proposition – especially for products targeting younger age groups.