VIPS Phase I executive summary: Heat-stable/Controlled Temperature Chain (CTC) qualified dry formulations

June 2019
Heat-stable/controlled temperature chain (CTC) qualified dry formulations

About Heat-stable/CTC qualified dry formulations

- Dry formulations that are **heat-stable and CTC-qualified** have attributes enabling them to be exposed to ambient temperatures below a defined threshold without losing their potency.
- CTC-qualification allows vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions.
- CTC qualification involves **regulatory approval and prequalification by WHO**.
- Dry formulations vary in their sensitivity to heat and suitability for use in a CTC.
- Currently all dry vaccine formulations that are commercially available require reconstitution with a diluent and are delivered as a liquid (injectable and oral routes).
- **Common drying processes include:**
  - **Freeze-drying (lyophilisation)** is a complex multi-stage process used on an industrial scale, in particular for live-attenuated vaccines. The steps involve (i) freezing, (ii) primary drying and (ii) secondary drying, resulting in a dried cake in the final container.
  - **Foam-drying** is a desiccation process whereby a solution is transformed into a dried foam structure by boiling or foaming under reduced vapour pressure followed by rapid evaporation. Unlike lyophilisation, there is no freezing step, so it can be used with freeze-sensitive vaccines.
  - **Spray-drying**, spray-freeze drying, and supercritical fluid drying are processes that can be used to produce ‘free-flowing’ dry-powders with defined particle sizes.

Heat-stable/controlled temperature chain (CTC) qualified dry formulations

Stage of development

• The freeze drying process is commonly used for commercially available vaccines.
  • One freeze-dried vaccine (the meningococcal A conjugate vaccine, MenAfriVac) has received regulatory and WHO prequalification approvals for use in a CTC.
• Dry-powder formulations created by the other drying processes are not currently used for commercially available vaccines and are still at the early testing phases of R&D.
Heat-stable/controlled temperature chain (CTC) qualified dry formulations scorecard
Comparators: Current liquid and lyophilised formulations

**Quality of evidence**: Low to moderate

### VIPS Criteria

#### Primary criteria

<table>
<thead>
<tr>
<th>Health impact</th>
<th>Coverage &amp; Equity impact</th>
<th>Safety impact</th>
<th>Economic costs</th>
<th>Potential breadth of innovation use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability of the vaccine presentation to withstand heat exposure</td>
<td>Ability of the vaccine presentation to withstand freeze exposure</td>
<td>Ease of use</td>
<td>Total economic cost of storage and transportation of commodities per dose</td>
<td>Applicability of innovation to one or several types of vaccines</td>
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<tr>
<td>Ability of the vaccine presentation to withstand freeze exposure</td>
<td>Ease of use</td>
<td>Total economic cost of the time spent by staff per dose</td>
<td>Total introduction and recurrent costs</td>
<td>Ability of the technology to facilitate novel vaccine combination</td>
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<td>Acceptability of the vaccine presentation to patients/caregivers</td>
<td></td>
<td>Likelihood of contamination</td>
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<td></td>
<td></td>
<td>Likelihood of needle stick injury</td>
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#### Secondary criteria

- Risk of contamination
- Risk of needle stick injury
- Total economic cost of storage and transportation of commodities per dose
- Total economic cost of the time spent by staff per dose
- Total introduction and recurrent costs

### Indicators

- **Health impact**
  - Ability of the vaccine presentation to withstand heat exposure: Better
  - Ability of the vaccine presentation to withstand freeze exposure: Better

- **Coverage & Equity impact**
  - Ease of use: Worse
  - Potential to reduce stock outs: Worse
  - Acceptability of the vaccine presentation to patients/caregivers: Better

- **Safety impact**
  - Likelihood of contamination: Worse
  - Likelihood of needle stick injury: Worse

- **Economic costs**
  - Total economic cost of the time spent by staff per dose: Worse
  - Total introduction and recurrent costs: Neutral

- **Potential breadth of innovation use**
  - Applicability of innovation to one or several types of vaccines: Mixed
  - Ability of the technology to facilitate novel vaccine combination: No

### Comparators

<table>
<thead>
<tr>
<th>Comparators</th>
<th>Liquid formulations</th>
<th>Lyophilised formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI* Facility</td>
<td>RI* Community</td>
<td>Campaings</td>
</tr>
<tr>
<td>Health impact</td>
<td>Better</td>
<td>Better</td>
</tr>
<tr>
<td>Coverage &amp; Equity impact</td>
<td>Worse</td>
<td>Neutral</td>
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<td>Neutral</td>
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</tr>
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### Priority indicators - Country consultation

- **RI**: Routine immunisation
- **Country consultation**: Comparators:
  - Current liquid and lyophilised formulations

### Differences

- Ease of use can prevent missed opportunities and impact ability for lesser trained personnel to administer the vaccine, including self-administration
- Based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities
- 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)
Heat-stable/controlled temperature chain (CTC) qualified dry formulations: Antigen applicability

- Heat stable/CTC qualified dry formulations could be applied to any vaccine that is currently or can potentially be reformulated into a thermostable dry presentation.
- Developing heat-stable/CTC-qualified dry formulations will be technically challenging for some vaccines. No single formulation method will stabilise all vaccines; each vaccine requires a customised approach.
- Some drying process might not be compatible with aluminum-salt-based adjuvants.
- Vaccines that are currently liquid and adequately heat-stable would not be appropriate for this innovation since their current liquid format has benefits in terms of ease-of-use and lower costs (e.g., HPV vaccine).
- The benefits of CTC-qualification are greatest for vaccines that are used in campaigns or special strategies (e.g., meningococcal group A conjugate vaccine).
- Ebola and MR are other VIPS antigens that could be suitable for this innovation.
Heat-stable/controlled temperature chain (CTC) qualified dry formulations: Assessment outcomes

<table>
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<tr>
<th>KEY BENEFITS</th>
<th>KEY CHALLENGES</th>
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<tr>
<td>Improving the heat stability of vaccines can protect against damage caused by inadvertent heat-exposure. In some cases, a dry formulation will be more heat-stable and less freeze-sensitive than the same formulation as a liquid.</td>
<td>• Rated lower than liquid formulations comparator on some aspects of coverage and equity:</td>
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<tr>
<td>• Depending on the vaccine format, heat stability/CTC qualification can potentially increase coverage and equity by enabling alternative delivery scenarios where the vaccine is transported and stored outside of the cold chain – easing cold chain logistics for health care workers.</td>
<td>• <strong>May reduce ease of use:</strong> dry formulations that require reconstitution are more complex in terms of preparation.</td>
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<td>May increase acceptability among caregivers/vaccinees due to increased access to the vaccines.</td>
<td>• <strong>May increase stock-outs</strong> due to more components required for reconstitution (diluent and reconstitution syringe).</td>
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<td>Potentially reduce storage and transport volume in the cold chain and associated costs since both the diluent and dry formulation could be stored outside the cold chain during the last mile.</td>
<td>• <strong>May reduce safety compared to liquid formulations</strong> due to increased risk of contamination and needle-stick injuries during reconstitution.</td>
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<td>• Broad applicability to all vaccines that are currently dry and thermostable.</td>
<td>• Rated lower than liquid comparator for delivery costs:</td>
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<td>• Important attribute for at least 2 settings or for the 3 settings based on the country consultation (see slide 3)</td>
<td>• <strong>May increase out of the cold chain volume and associated storage and transport costs</strong> due to the greater space required for the reconstitution diluent and syringe.</td>
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<td>• Important attribute for campaigns or routine facility-based immunisation based on country consultation (see slide 3)</td>
<td>• <strong>May increase health care worker time</strong> to deliver the vaccine.</td>
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<td>• In multidose presentations, dry formulations without preservative increase vaccine wastage and missed opportunities as the reconstituted vaccine must be discarded at the end of the vaccination session. When used in a CTC, the drop in heat stability after reconstitution might also limit the length time the vaccine can be used in a session further increasing wastage.</td>
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Heat-stable/controlled temperature chain (CTC) qualified dry formulations: Rationale for prioritisation

- Based on the analysis, dry heat stable CTC formulations 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.

- Dry heat stable CTC formulations have advantages over existing dry formulations in terms of ability to withstand heat exposure and reduction in the need for cold chain during the last mile resulting in decreased logistics and storage/transport costs. However CTC use of dry formulations is likely most appropriate for vaccines that are in single dose formats.

- A number of innovations recommended for prioritisation in phase II are single dose dry formulations that could be CTC-qualified – microarray patches, solid dose implants, dual chamber devices – and have the advantage of not requiring reconstitution. Therefore it may not be necessary to advance dry heat stable CTC formulations as a separate VIPS innovation.

- Dry heat stable CTC formulations have clear coverage and equity, safety, and cost disadvantages in comparison to heat stable liquid formulations and it is important to not signal heat stability and CTC qualification as a standalone objective without taking into account these many negative tradeoffs.