Thermostability of Vaccines
Why are all vaccines sensitive to heat and some to freezing?

Why is thermostability of vaccine important?

What can be done to improve the thermostability of vaccines?
Goals of stability studies in product development

- Establish product stability characteristics:
  - Understand factors that influence stability \(\rightarrow\) strategies to minimize product decay during storage
  - Generate real time and real condition stability data \(\rightarrow\) support proposed shelf life for licensure
  - Establish forced degradation characteristics \(\rightarrow\) support post-licensure manufacturing changes
  - Generate data at temperatures relevant to CTC

From: WHO Informal Consultation on Scientific and Regulatory Considerations on Stability of Vaccines under a Controlled Temperature Chain

Dean Smith & Tong Wu, Ph.D., Health Canada
4 June 2013, PEI, Langen, Germany
General considerations for stability studies

• Adequate testing points → rates of product decay may differ at different intervals over the shelf-life
• Potency assessment using a battery of tests → note that all tests have limitations
• Data analysis:
  • Note trends, not just compliance with specifications
  • Determine the rate of product decay using appropriate statistical methods: \textit{explore alternate approaches}

From: WHO Informal Consultation on Scientific and Regulatory Considerations on Stability of Vaccines under a Controlled Temperature Chain

Dean Smith & Tong Wu, Ph.D., Health Canada
4 June 2013, PEI, Langen, Germany
Stability-indicating parameters

- Potency: most critical for vaccines
- Safety
  - Residual toxin / reversibility of toxoid
  - Toxicity of degradation products
- Additional parameters
  - Moisture content for lyophilized vaccines:
  - pH
  - Adsorption to alum or other adjuvant characteristics

From: WHO Informal Consultation on Scientific and Regulatory Considerations on Stability of Vaccines under a Controlled Temperature Chain

Dean Smith & Tong Wu, Ph.D., Health Canada
4 June 2013, PEI, Langen, Germany
Vaccine Antigens: Complex Macromolecular Structures


**Live, Attenuated Virus:**
- Measles, Mumps, Rubella, Varicella, Yellow Fever,
- Vaccinia, Rotavirus, Polio, Adenovirus

**Inactivated Virus:**
- Hepatitis A, Polio, Influenza

**Recombinant Virus-like Particles:**
- Human Papillomavirus, Hepatitis B

**Live, Attenuated Bacteria:**
- BCG (tuberculosis), Typhoid Fever

**Inactivated Bacteria:**
- Anthrax, wPertussis

**Bacterial (proteins):**
- aPertussis, Diphtheria, Tetanus

**Bacterial (polysaccharides):**
- Haemophilus B, Pneumonia, Meningitis
  (often linked to protein carriers)
Examples of Commercial Vaccine Dosage Forms


<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Formulation</th>
<th>Delivery</th>
</tr>
</thead>
</table>

**Recombinant or Inactivated Viral Vaccines**
- HPV, Hepatitis B
- Hepatitis A, Polio, Influenza

- Alum
- Liquid
- Injection

**Inactivated, Purified or Conjugated Bacterial Vaccines**
- wPertussis, Anthrax
- aPertussis, Diphtheria, Tetanus, Anthrax
- Haemophilus B, Pneumonia, Meningitis
  (many linked to protein carriers)

- Alum
- Liquid
- Injection

**Live, Attenuated Viral Vaccines**
- Measles, Mumps, Rubella, Varicella,
- Yellow Fever, Vaccinia
- Rotavirus, Polio,
- Influenza
- Adenovirus

- None
- Lyophilized
- Injection

<table>
<thead>
<tr>
<th>None</th>
<th>Liquid</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liquid</td>
<td>Nasal</td>
</tr>
<tr>
<td></td>
<td>Lyo/Tablet</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Live, Attenuated Bacterial Vaccines**
- BCG (tuberculosis), Typhoid Fever

- None
- Lyophilized
- Injection, Oral

Slide Courtesy of Prof. David Volkin, Univ of Kansas
## Vaccine Distribution World-Wide: Stability Issues in the “Vaccine Cold Chain”


<table>
<thead>
<tr>
<th></th>
<th>Freeze Sensitive?</th>
<th>Heat Sensitive?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Viral Vaccines</strong></td>
<td>- / +</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Live Bacterial Vaccines</strong></td>
<td>- / +</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Recombinant or Inactive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral Vaccines</strong></td>
<td>+++</td>
<td>- / +</td>
</tr>
<tr>
<td><strong>Inactivated, Purified or Conjugate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial Vaccines</strong></td>
<td>+++</td>
<td>- / +</td>
</tr>
</tbody>
</table>

Slide Courtesy of Prof. David Volkin, Univ of Kansas
Temperature sensitivity of vaccines

Vaccines to the left of the line are not damaged by freezing.

*The diluent for MenA PS-PCV contains alum adjuvant and is freeze sensitive.
The innovation of the Controlled Temperature Chain (CTC) – where do we go from here?
Controlled Temperature Chain: No Ice packs for days

WHAT IS A CONTROLLED TEMPERATURE CHAIN (CTC)?

A controlled temperature chain is an optional method of transporting and storing vaccines in carriers without ice packs up to a specific number of days before the vaccines are administered.

It is only recommended for vaccines officially labeled for this use where a pronounced need is apparent and training and supervision are provided.

Vaccines carried in a CTC must be monitored using a vaccine vial monitor (VVM) and peak temperature threshold indicator (PTTI) to indicate exposure to heat.

Challenge for vaccine stability, safety and efficacy
Overview of Novel Approaches to Stabilize Vaccines

Formulation Composition
- New additives
- New approaches to identify combinations of additives

Formulation Processing Technologies
- Novel drying or delivery technologies

Novel Antigens with Improved Stability
- Molecular design of current antigens
- New macromolecules: e.g., DNA/RNA vaccines
# Analysis of Some Interesting Approaches Formulation Composition

## Past Examples

<table>
<thead>
<tr>
<th>Formulation and Rationale</th>
<th>Past Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilized for heat stability</td>
<td>Trehalose in the 1980s</td>
</tr>
<tr>
<td>Liquid for heat stability</td>
<td>Deuterium Oxide in the 1990s</td>
</tr>
<tr>
<td>Liquid for freeze stability of alum vaccines</td>
<td>Polyethylene glycol in the 2000s</td>
</tr>
</tbody>
</table>

## Examples from Today

<table>
<thead>
<tr>
<th>Formulation and Rationale</th>
<th>Examples from Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silk protein Vaxess <a href="http://www.vaxess.com">http://www.vaxess.com</a></td>
<td>Silk protein</td>
</tr>
<tr>
<td>Buffer mixtures Arecor <a href="http://www_arecor.com">http://www_arecor.com</a></td>
<td>Buffer mixtures</td>
</tr>
<tr>
<td>Sucrose and raffinose Stabilitech <a href="http://www.stabilitech.co.uk">http://www.stabilitech.co.uk</a></td>
<td>Sucrose and raffinose</td>
</tr>
<tr>
<td>Lipid mixtures VBI Vaccines <a href="http://www.vbivaccines.com">http://www.vbivaccines.com</a></td>
<td>Lipid mixtures</td>
</tr>
</tbody>
</table>

*Overall, novel additives have had a limited impact to date...*

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Slide Courtesy of Prof. David Volkin, Univ of Kansas
Novel approaches to identify stabilizers

Increasing number of research papers on the use of high throughput screening technologies:

- Empirically identify unique combinations of common excipients
- Empirically focus on specific vaccine and specific stress
- Most likely will become useful tool in future, but more from point of view of resources, time, and potentially patents

Slide Courtesy of Prof. David Volkin, Univ of Kansas
Novel drying and delivery technologies

General Examples
• Freeze-drying
• Spray-drying
• Foam-drying
• Microneedles

Formulation and Rationale
Lyophilized formulations of aluminum vaccines
Lyophilized for heat stability
Lyophilized for heat stability
Novel delivery technology

Specific Examples:
PATH  http://sites.path.org/vpfst/product-stability/heat-stability
Sologenix  http://www.soligenix.com
Aridis  http://www.aridispharma.com
Aktiv-dry  http://www.aktiv-dry.com
Nova Labs  http://www.novalabs.co.uk

Slide Courtesy of Prof. David Volkin, Univ of Kansas
Novel Antigens with Improved Stability

• Molecular design to improve stability of antigens
  • Many research papers and programs to improve antigen stability at molecular level
  • Long term research programs...
• New classes of macromolecular antigens with potential of improved stability
  • e.g., commercial polysaccharide and protein VLP vaccines are more stable than viral vaccines
  • e.g., peptide and nucleic vaccine candidates. RNA as vaccine candidates include:
    • Curevac  [http://www.curevac.com](http://www.curevac.com)
    • Moderna  [http://modernatx.com/](http://modernatx.com/)
    • Novartis Vaccines (now GSK...)

Slide Courtesy of Prof. David Volkin, Univ of Kansas
Stability of heat stable, live attenuated Rotavirus vaccine (ROTASII®)

Sameer P. Naik, Jagdish K. Zade *, Rajendra N. Sahale, Sambhaji S. Pisal, Ravi Menon, Subhash G. Bankar, Sunil Gairola, Rajeev M. Dhere

Serum Institute of India Pvt LTD, 213/2, Mahape, Pune 411021, India

A up to six hours as, at higher temperatures, any microorganism introduced during the reconstitution process could multiply.

The thermo-stability of ROTASII®, ironically, has thrown up a new challenge in terms of vaccine vial monitors (VVM). The presently available VVM portfolio (Max VVM30: 30 days at 37 °C) does not begin to cover the extreme thermo stability of ROTASII which is 18 months- (540 days) at 37 °C. Efforts to develop a more appropriate VVM are on-going.

It has been already noted that there is remarkable reduction in mortality from diarrheal disease after vaccine introduction in
Requirements to Implement

From a Published Review from PATH...

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**Table 3. Challenges involved in developing thermostable vaccines.**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Challenges</th>
<th>Consequences and solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addition of novel stabilizers, adjuvants or excipients</td>
<td>Novel components might be unproven in terms of safety, immunogenicity or quality of raw ingredients</td>
<td>Additional regulatory scrutiny might be applied; use excipients of proven safety whenever possible</td>
</tr>
<tr>
<td>Introduction of novel production processes or novel equipment</td>
<td>Production facilities need to comply with good manufacturing practices in order to produce material for clinical trials</td>
<td>Additional regulatory scrutiny might be applied</td>
</tr>
<tr>
<td>Healthy infants are the target population</td>
<td>The tolerance of serious adverse events in healthy infants is extremely low</td>
<td>Use excipients of proven safety if possible; new formulations might not be adopted</td>
</tr>
<tr>
<td>Convincing demonstration of safety will be required</td>
<td>Very rare, serious adverse events can be detected only in very large clinical trials</td>
<td>Postmarketing surveillance will be required</td>
</tr>
<tr>
<td><strong>Technical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation development might be complex</td>
<td>There is no predictive rapid potency assay; many diseases/vaccines do not have good predictive preclinical models</td>
<td>Lack of preclinical models might increase amount of clinical testing needed for approval</td>
</tr>
<tr>
<td>Demonstrating clinical efficacy of reformulated product</td>
<td>There is still a lack of validated clinical end points and biomarkers (including assays of immune function) for many diseases</td>
<td>Longer, larger clinical trials with clinical end points might be needed; noninferiority trials comparing immunogenicity with existing vaccine might be possible</td>
</tr>
<tr>
<td>Reformulation of vaccines that are used in combinations</td>
<td>The components of combination vaccines can interact differently with each other and also with excipients</td>
<td>Extensive development and testing can be required, including noninferiority clinical studies with excipients</td>
</tr>
<tr>
<td><strong>Commercial &amp; intellectual property</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs associated with developing and obtaining registration for reformulated vaccines are large and are not compatible with the low prices paid for vaccines for public-sector markets</td>
<td>Lack of commercial incentive for manufacturers to produce improved formulations</td>
<td>Procurement incentives might be required to convince vaccine manufacturers to invest</td>
</tr>
<tr>
<td>It is often difficult to quantify the problem (e.g., health and economic impact of vaccine instability) and the potential benefits of the stable vaccines</td>
<td>Improvements such as thermostability might not lead to a sufficient price premium to cover the development costs</td>
<td>Economic analyses of the impact of the stability improvement upon the whole immunization system could be useful; advocacy might be needed around both the problem and solution to proceed</td>
</tr>
<tr>
<td>Vaccine producer IP</td>
<td>The need to protect IP means that manufacturers are often reluctant or unable to share critical information (e.g., formulations, production methods and assays) necessary to develop improvements to vaccines outside of individual vaccine-manufacturing facilities</td>
<td>R&amp;D might be limited to individual manufacturers and the pace of development driven by their interests</td>
</tr>
<tr>
<td>Technology IP</td>
<td>The owners of stabilization technologies must be convinced of public-sector health priorities to ensure that such technologies are made broadly available and do not adversely impact the affordability of public-sector vaccines</td>
<td>Organizations acting on behalf of public-sector interests can create contract mechanisms to protect IP on behalf of the public sector; advocacy might be needed around both the problem and solution to proceed</td>
</tr>
</tbody>
</table>

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Chen D, Kristensen D, Expert Rev Vaccines. 2009 May;8(5):547-57. Opportunities and challenges of developing thermostable vaccines
Links to Pertinent Publications
Thank you!!!