Vaccine Stability and Global Policy Requirements

DCVMN
Rio Workshop

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Executive Director - Global Health Policy

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Goals of stability studies in product development

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

*Slide Courtesy of Prof. David Volkin, Univ of Kansas*
### Examples of Commercial Vaccine Dosage Forms

<table>
<thead>
<tr>
<th>Recombinant or Inactivated Viral Vaccines</th>
<th>Adjuvant</th>
<th>Formulation</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV, Hepatitis B, Hepatitis A, Polio, Influenza</td>
<td>Aluminum</td>
<td>Liquid</td>
<td>Injection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactivated, Purified or Conjugated Bacterial Vaccines</th>
<th>Adjuvant</th>
<th>Formulation</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis, Anthrax, Diphtheria, Tetanus, Anthrax, Haemophilus B, Pneumonia, Meningitis (many linked to protein carriers)</td>
<td>Aluminum</td>
<td>Liquid</td>
<td>Injection</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Live, Attenuated Viral Vaccines</th>
<th>Adjuvant</th>
<th>Formulation</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles, Mumps, Rubella, Varicella, Yellow Fever, Vaccinia, Rotavirus, Polio, Influenza, Adenovirus</td>
<td>None</td>
<td>Lyophilized</td>
<td>Injection</td>
</tr>
<tr>
<td>Liquid</td>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid</td>
<td>Nasal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyo/Tablet</td>
<td>Oral</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Live, Attenuated Bacterial Vaccines</th>
<th>Adjuvant</th>
<th>Formulation</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG (tuberculosis), Typhoid Fever</td>
<td>None</td>
<td>Lyophilized</td>
<td>Injection, Oral</td>
</tr>
</tbody>
</table>

## Vaccine Distribution World-Wide: Stability Issues in the “Vaccine Cold Chain”


<table>
<thead>
<tr>
<th>Type</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 Bacterial Vaccines</strong></td>
<td>+++</td>
<td>- / +</td>
</tr>
</tbody>
</table>
Vaccine Temperature Sensitivity (2006)

Heat sensitivity

most sensitive

2

7

14

30

Days at 37°C

most sensitive

least sensitive

Freeze sensitivity

least sensitive

most sensitive

J. Milstien
TechNet Mexico
2006
Diverging temperature sensitivity (2013)

S. Kone
TechNet Dakar
2013
Temperature sensitivity of vaccines (2015)

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

**Heat sensitivity**
- Most sensitive
- Least sensitive

**Freeze sensitivity**
- Not sensitive
- Least sensitive
- Most sensitive

- Freeze dried
- Liquid, no adjuvant
- Liquid, with alum adjuvant

*The diluent for MenA PS-PCV contains alum adjuvant and is freeze sensitive.*
Studies Supporting Product Licensure

Studies supporting product licensure include:

- Long term stability of bulk intermediate
- Long term stability of final container product
- Accelerated stability at conditions of handling, excursion, and use
- Release and manufacturing models
- Clinical support of specifications

\(^1\)T.L. Schofield, *Biologicals* 37 (2009) 387-396
Approaches to Stability Assessment$^2$

- Currently stability data are usually analyzed using a “single point” model, wherein any individual data point on a stability study must meet end expiry specifications
  - This has also been called the “compliance model”

Approaches to Stability Assessment (cont.)

- Use of statistical models is scientifically correct, is recognized by the WHO Guidance, and represents the future of stability analysis
  - This has also been called the “comprehensive model”, or the “estimation model” or the “statistical model”

Adapted from T.L. Schofield, *Biologica*ls 37 (2009) 387-396
Accelerated Stability Studies for WHO Prequalification

● GOAL
  - Accelerated stability data must be generated that allows the choice of the highest stability VVM category possible.

● RATIONALE
  - At elevated temperatures, the highest category VVM which reaches its end point before the vaccine stored at the same temperature becomes sub-potent should be chosen. This ensures that the product is still suitable to use while minimizes wastage through premature discard of vaccine that is still potent.
## Characteristics that Define Vaccine Suitability

<table>
<thead>
<tr>
<th>Type of characteristic</th>
<th>Compliance</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory</td>
<td>Pre-qualification process proceeds</td>
<td>Rejection of application for prequalification evaluation.</td>
</tr>
<tr>
<td>Critical</td>
<td>Pre-qualification process proceeds</td>
<td>Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for pre-qualification evaluation.</td>
</tr>
<tr>
<td>Unique and innovative</td>
<td>Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for pre-qualification evaluation.</td>
<td>Pre-qualification evaluation proceeds.</td>
</tr>
<tr>
<td>Preferred</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UNICEF/WHO Policies on Criticality of VVMs

2007 UNICEF/WHO Joint Policy Statement Urging Member States, Donor Agencies and NGOs to Include VVMs As Minimum Requirement for Purchase of Vaccine

2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification

Vaccine vial monitor (VVM) | All vaccines
--- | ---
Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 or VVM30) or a future VVM type approved by WHO (WHO/V&B/99.187, WHO/IVB/07.048).

Signed declaration, as part of the cover letter submitted along with the file for prequalification confirming that the manufacturer will apply a VVM to the vaccine, and has the technical capacity to do so if requested by the purchasing specifications.
The temperature sensitivity of vaccine characteristics, particularly potency, has a major impact on the success of global immunization programmes. WHO has acknowledged the importance of clearly defining the stability characteristics of a vaccine.

Chapter 10. Labeling states:

“If Vaccine Vial Monitors (VVM) are to be used, adequate stability data should be generated to support selection of appropriate VVM for a vaccine in question. Further details on the use of VVM for different types of products are available elsewhere.”


2 WHO Temperature Sensitivity of Vaccines (WHO/IVB/06.10)
WHO Temperature Sensitivity of Vaccines

- The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).

- In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation occurs is measured and analyzed in accordance with the Arrhenius equation.

- Vaccines should be tested to failure at these accelerated temperatures.

- Vaccines do not need to follow the Arrhenius equation exactly to have a suitable VVM applied.

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http://www.who.int/vaccines-documents/DocsPDF06/847.pdf
VVM Characteristics

• VVM is a WHO prequalified device

VVM BEFORE end point: Active Surface lighter than Reference Surface

VVM AT end point: Active Surface matches Reference Surface
VVM Reaction Rates

<table>
<thead>
<tr>
<th>Category (Vaccines)</th>
<th>No. of days to end point at +37°C</th>
<th>No. of days to end point at +25°C</th>
<th>Time to end point at +5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM 30: High Stability</td>
<td>30</td>
<td>193</td>
<td>&gt; 4 years</td>
</tr>
<tr>
<td>VVM 14: Medium Stability</td>
<td>14</td>
<td>90</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>VVM 7: Moderate Stability</td>
<td>7</td>
<td>45</td>
<td>&gt; 2 years</td>
</tr>
<tr>
<td>VVM 2: Least Stable</td>
<td>2</td>
<td>N/A*</td>
<td>225 days</td>
</tr>
</tbody>
</table>

- The four categories of VVM are VVM2, VVM7, VVM14 and VVM30.
- The number following “VVM” corresponds to the upper limit in days at 37°C for at least 95% of VVMs to reach the end point.
- This Table lists the upper limit in days at 25°C for 95% of each VVM category to reach the end point, except for VVM2.
- The critical temperatures for VVM2 are 37°C and 5°C. VVM2 is only used for Oral Polio Vaccine and is not included in further discussion.

5 [http://www.who.int/immunization_standards/vaccine_quality/who_pqs_e06_in05_1.pdf](http://www.who.int/immunization_standards/vaccine_quality/who_pqs_e06_in05_1.pdf)
The innovation of the Controlled Temperature Chain (CTC) – where do we go from here?
Programmatic incentive of CTC

- **CHALLENGE:** The logistics for campaigns— from surge cold chain capacity to ice pack freezing are extremely complex and time consuming.

- **BENEFITS:** Allowing more cost-effective & efficient immunisation programmes, particularly in the last mile of outreach efforts.
Last Mile Challenges at 2-8°C

- Carrying vaccines, cold water packs and supplies
- Conditioning ice packs to avoid freezing
- Navigating rough roads and trails (and maintaining a vehicle)
- Getting out and back in one day
- Reaching an active population
- Refreshing cooling supplies mid-day
- Estimating the correct quantity of vaccine required
Programmatic definition of a Controlled Temperature Chain (CTC)

- a specific set of conditions allowing for a vaccine to be stored and transported outside of the traditional 2° to 8°C cold chain
  - One excursion, just prior to administration
  - Ambient temperatures up to 40° or more
  - Specifically limited duration/at least 3 days

- Current EPI priorities for CTC:
  - Campaigns & special settings
  - Appropriate tools: VVM, PTTI, Monitoring
  - Tested (for safety & stability), Licensed & Prequalified

CTC | 15 May 2015
The CTC Agenda: UPSTREAM

• Development and licensure of more CTC-compatible vaccines
  o Clarify definition and programmatic priorities
  o Regular dialogue with manufacturers and regulators
    ✓ Promoting awareness and interest in CTC
    ✓ Exploring thermostability of existing vaccines
    ✓ Encouraging CTC consideration in new product development
      – Generic Preferred Product Profiles (VPPAG)
    ✓ Clarifying barriers and challenges / identifying solutions
  o Development of WHO Guidelines on the Regulatory pathway for CTC licensure
CTC licensure to date

- December 2012 – Meningitis A Vaccine (MenAfriVac) licensed, prequalified and pilot tested for CTC
  - 4 days / 40°C

- May 2015 – Pneumococcal Conjugate Vaccine 13-valent (Prevnar13) licensed and prequalified for CTC, guidance to be developed
  - 3 days / 40°C

- End of 2015 – Oral Cholera vaccine (Shanchol) expected to be licensed and prequalified for CTC

- 8 manufacturers working on generating data in support of CTC for at least 10 different vaccines.
CTC Demand/Implementation Momentum
Impact of CTC on Vaccine Stability Studies

- Manufacturers will need to provide additional stability data to support CTC on-label approval.
Guidelines on the stability evaluation of vaccines for use in a controlled temperature chain

• Drafting group and consultation meetings were held at Health Canada (2012), Paul-Ehrlich-Institute (2013) and WHO HQ (2015)
• Draft was published for public comment (comment period over)
• Intention is to submit to the Executive Committee on Biological Standards in October 2015
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

- Trehalose in the 1980s
- Deuterium Oxide in the 1990s
- Polyethylene glycol in the 2000s

### Formulation and Rationale

- Lyophilized for heat stability
- Liquid for heat stability
- Liquid for freeze stability of alum vaccines

### Examples from Today

<table>
<thead>
<tr>
<th>Additive</th>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silk protein</td>
<td>Vaxess</td>
<td><a href="http://www.vaxess.com">http://www.vaxess.com</a></td>
</tr>
<tr>
<td>Buffer mixtures</td>
<td>Arecor</td>
<td><a href="http://www.arecor.com">http://www.arecor.com</a></td>
</tr>
<tr>
<td>Sucrose and raffinose</td>
<td>Stabilitech</td>
<td><a href="http://www.stabilitech.co.uk">http://www.stabilitech.co.uk</a></td>
</tr>
<tr>
<td>Lipid mixtures</td>
<td>VBI Vaccines</td>
<td><a href="http://www.vbivaccines.com">http://www.vbivaccines.com</a></td>
</tr>
</tbody>
</table>

### Overall

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

SlideCourtesy of Prof. David Volkin, Univ of Kansas
### General Examples

- **Freeze-drying**
  - Lyophilized formulations of aluminum vaccines
- **Spray-drying**
  - Lyophilized for heat stability
- **Foam-drying**
  - Lyophilized for heat stability
- **Microneedles**
  - Novel delivery technology

### Specific Examples:

- **PATH**
- **Sologenix**
  - [http://www.soligenix.com](http://www.soligenix.com)
- **Aridis**
  - [http://www.aridispharma.com](http://www.aridispharma.com)
- **Aktiv-dry**
  - [http://www.aktiv-dry.com](http://www.aktiv-dry.com)
- **Nova Labs**
  - [http://www.novalabs.co.uk](http://www.novalabs.co.uk)
Novel Antigens with Improved Stability

1. Molecular design to improve stability of antigens
   - Many research papers and programs to improve antigen stability at molecular level
   - Long term research programs…

2. 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
   - Moderna  http://modernatx.com/
   - Novartis Vaccines (now GSK…)
**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 to proceed</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 vaccines 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</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>

Agenda

- Global Policy Requirements
Global Vaccine Policy Requirements – Global Health Organizations

- WHO, UNICEF, & GAVI

  - WHO/UNICEF – procurement policies requiring VVM use since 1996
  - GAVI – procurement policies requiring VVM use since 2003
  - These and other Global Health Organizations, including the Bill & Melinda Gates Foundation are considering expanded policies to account for CTC; VVM+ being considered for use by global vaccine manufacturers – as the “standard” for vaccine procurement and delivery
  - BMGF Challenge grant provided to Temptime to develop combination VVM + Peak Threshold Temperature Indicator
Global Vaccine Policy Requirements – Developing World countries

- Indonesia – national VVM requirement
- Pakistan – national VVM requirement
- Gulf Cooperation Council countries (Bahrain, Kuwait, Qatar, Saudi Arabia, UAE)
  - Arabio (GSK/tech transfer of all childhood vaccines) leading implementation of GCC VVM policy
- India – national requirement
Global Vaccine Policy Requirements – India

- **Indian MoH** requested that the National Cold Chain Training Center (NCCTC) prepare a field trial protocol to evaluate the FREEZEmarker L technology in vaccine carrier and on multi-pack boxes.
  - The study will take 4-6 months from commencing until submission of the final report/recommendation.

- The **IAP** (Indian Academy of Pediatrics) committee on vaccine safety proposing rule for use of VVMs to expand beyond public sector vaccines to use on all private sector vaccines.
  - MoH and DCGI (Drug Controller General of India) meeting first week of August with all vaccine manufacturers re expanded VVM use requirement on all private sector vaccines (as well as sera and insulin).
Global Vaccine Policy Requirements – Developed World countries

- China – expanding provincial requirements
VVM Requirement in Chinese provinces
Beijing CDC Launches HEATmarker® VVM for Type II Vaccines

- N.CDC launched a study covering 5 vaccines in three provinces
- Beijing CDC requiring VVM on all private sector vaccines
Vaccine Policy Requirements - China

Beijing CDC Policy:
- The Beijing CDC has informed all multi-national company vaccine manufacturers and local Chinese vaccine manufacturers supplying Type 2 vaccines (private market) of the requirement to use the HEATmarker VVM on all vaccines supplied.
- HEATmarker VVM orders for the first requirements (> 3.6 million units) have been placed by Kyuan (distributor) with deliveries scheduled to begin last April and early May 2015.
- On-going HEATmarker training of local Chinese and international manufacturers is being coordinated between Temptime, the Beijing CDC, and Kyuan.

National CDC Field Study
- N.CDC Vaccine Study initiated and is running in Shandong, Hubei and Xinjiang provinces with Type 1 vaccines and Type 2 vaccines from local manufacturers - Chengda and Walvax.
- Study to run for one year from October 2014 to October 2015.
- Study supported by grant to UNICEF, which is providing technical assistance.

Additional Targeted Provincial CDCs
- Kyuan already working with other provincial CDCs (Shanghai, Tianjin and Shandong) for the 2015 flu season; Shanghai City using VVMs on 3 vaccines.
Global Vaccine Policy Requirements – Developed World countries

- USA – evaluating new national Vaccine Storage & Handling requirements
# Cold Chain Problems are Global

## Vaccines – US San Francisco Bay Area 10 County Region (2006)

<table>
<thead>
<tr>
<th>Category</th>
<th># of Incidences</th>
<th>Loss (dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigeration Problems</td>
<td>16</td>
<td>$42,958</td>
</tr>
<tr>
<td>Shipping/Receiving</td>
<td>4</td>
<td>$34,772</td>
</tr>
<tr>
<td>Improper Storage</td>
<td>6</td>
<td>$187,133</td>
</tr>
<tr>
<td>Expired Vaccines</td>
<td>51</td>
<td>$127,289</td>
</tr>
<tr>
<td><strong>Total Losses</strong></td>
<td><strong>77</strong></td>
<td><strong>$392,717</strong></td>
</tr>
</tbody>
</table>

**Extrapolation to state**

$2,352,426

Source: California Department of Public Health
Global Vaccine Policy Requirements – Developed World countries

- United States – evaluating vaccine (and other temperature-sensitive biologics) storage & handling policies, including potential VVM use
  - **2012 study** identifying potential heat and freeze damage to CDC-purchased vaccines in 76% of pediatric offices studied in 5 large US states over 2 weeks; as much as $1 million USD of vaccines potentially wasted.

- **US Vax Storage & Handling Best Practices Forum** being planned for Oct/Nov 2015
  - Will include American Academy of Pediatrics, Association of Immunization Managers, CDC and national vaccine stakeholder leadership and input

- **AAP Leadership Forum national policy resolution** vote. 2 TTI resolutions passed: 1) national TTI requirement for use by mail-order pharmacies sending temp-sensitive meds to pediatric patients; and 2) national TTI use on all vaccines (passed 99-1); now assigned to ped committees for further advocacy/lobbying action;

- **US State laws/regulations requiring TTI use:**
  - Georgia state legislators (pharmacist, dentist, geriatric doc) introduced and passed 2013 law requiring pharmacy TTI-use for shipments; invitation to work with GA legislative pharmacy caucus and GA Pharmacy Assoc to create cold-chain task force & highlight TTI solutions;
  - Colorado state board of pharmacy evaluating GA pharmacy TTI “model legislation;” Colorado, Florida, Texas, and Utah state pharmacy boards, pharmacy associations & state legislators evaluating vaccine storage & handling laws and possible use of heat (VVM) and freeze indicators
Thank You, Obrigado, y Gracias!