Vaccine Stability and Global Policy Requirements

DCVMN
Rio Workshop

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Executive Director - Global Health Policy

08 July 2015

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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

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

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***

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

Stability-indicating parameters

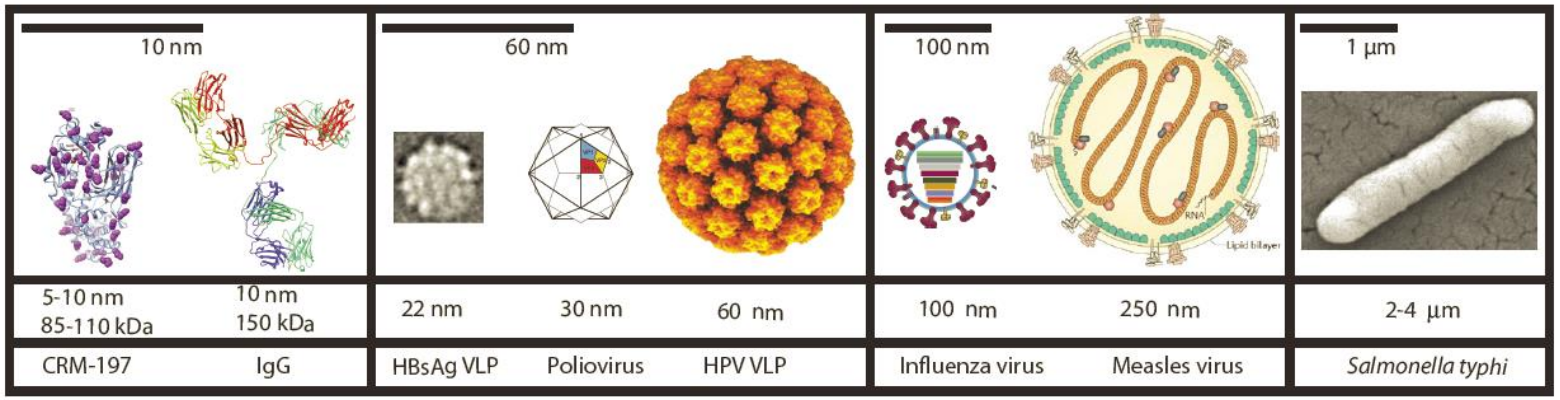
- Potency: most critical for vaccines
- Safety
  - Residual toxin / reversibility of toxoid
  - Toxicity of degradation products
- Additional parameters
  - Moisture content for lyophilized vaccines:
  - pH
  - Adsorption to alum *or* other adjuvant characteristics

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

Vaccine Antigens: Complex Macromolecular Structures

Review: Kumru O et al, *Biologicals* 42: 237 (2014)

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

Kumru O et al, *Biologicals* 42: 237 (2014)

	Adjuvant	Formulation	Delivery
Recombinant or Inactived Viral Vaccines			
HPV, Hepatitis B	**Aluminum**	Liquid	Injection
Hepatitis A, Polio, Influenza	**(some with new adjuvants)**		
Inactived, Purified or Conjugated Bacterial Vaccines			
wPertussis, Anthrax			
aPertussis, Diphtheria, Tetanus, Anthrax	**Aluminum**	Liquid	Injection
Haemophilus B, Pneumonia, Meningitis			
(many linked to protein carriers)			
Live, Attenuated Viral Vaccines			
Measles, Mumps, Rubella, Varicella,	None	**Lyophilized**	Injection
Yellow Fever, Vaccinia			
Rotavirus, Polio,		Liquid	Oral
Influenza		Liquid	Nasal
Adenovirus		**Lyo/Tablet**	Oral
Live, Attenuated Bacterial Vaccines			
BCG (tuberculosis), Typhoid Fever	None	**Lyophilized**	Injection, Oral

Slide Courtesy of Prof. David Volkin, Univ of Kansas

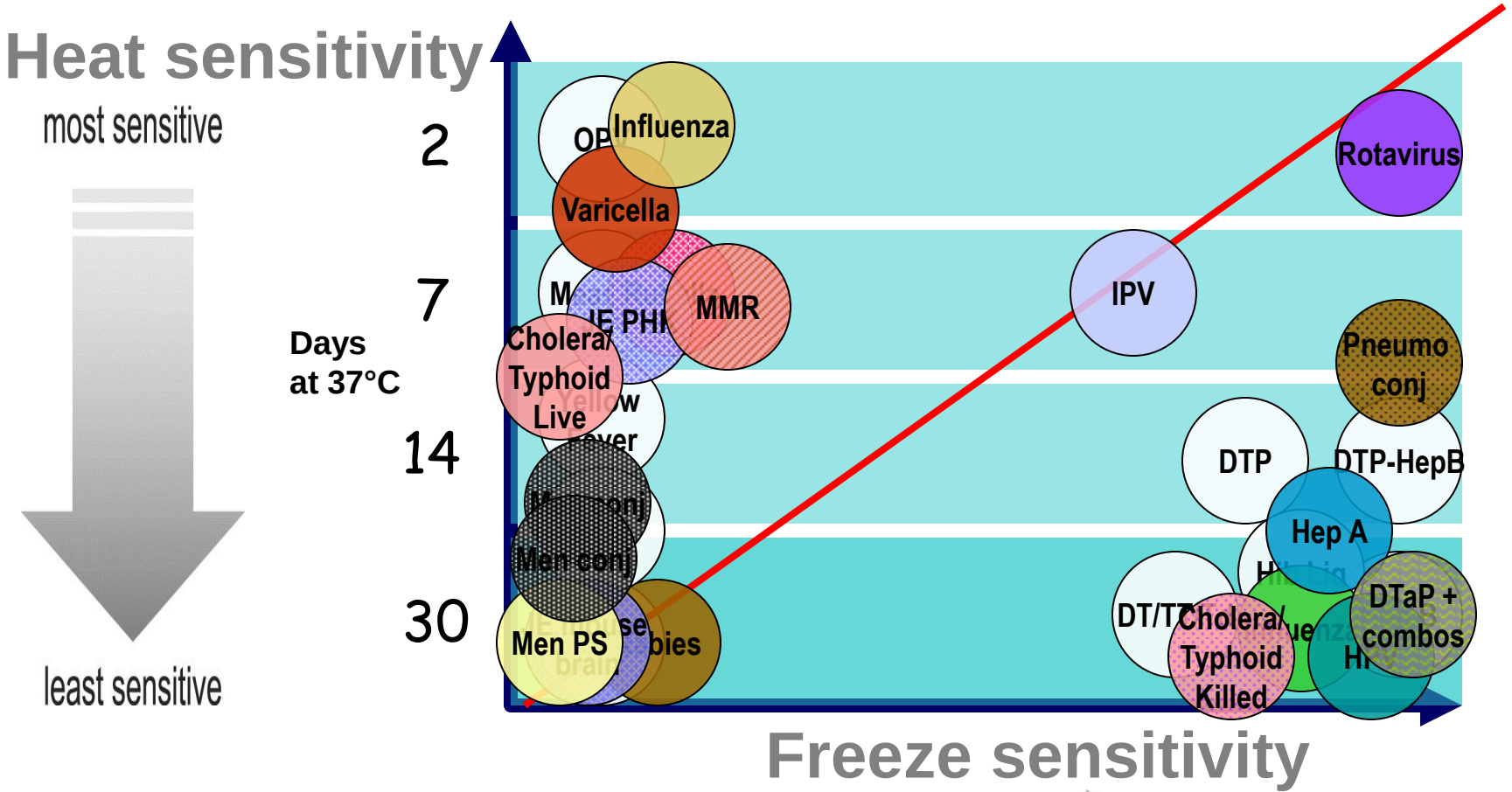
Vaccine Distribution World-Wide: Stability Issues in the "Vaccine Cold Chain"

Kumru O et al, *Biologicals* 42: 237 (2014)

	Freeze Sensitive?	*Heat Sensitive?*
Live Viral Vaccines	- / +	+++
Live Bacterial Vaccines	- / +	+++
Recombinant or Inactive Viral Vaccines	+++	- / +
Inactived, Purified or Conjugate Bacterial Vaccines	+++	- / +

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Vaccine Temperature Sensitivity (2006)



J. Milstien
TechNet Mexico
2006

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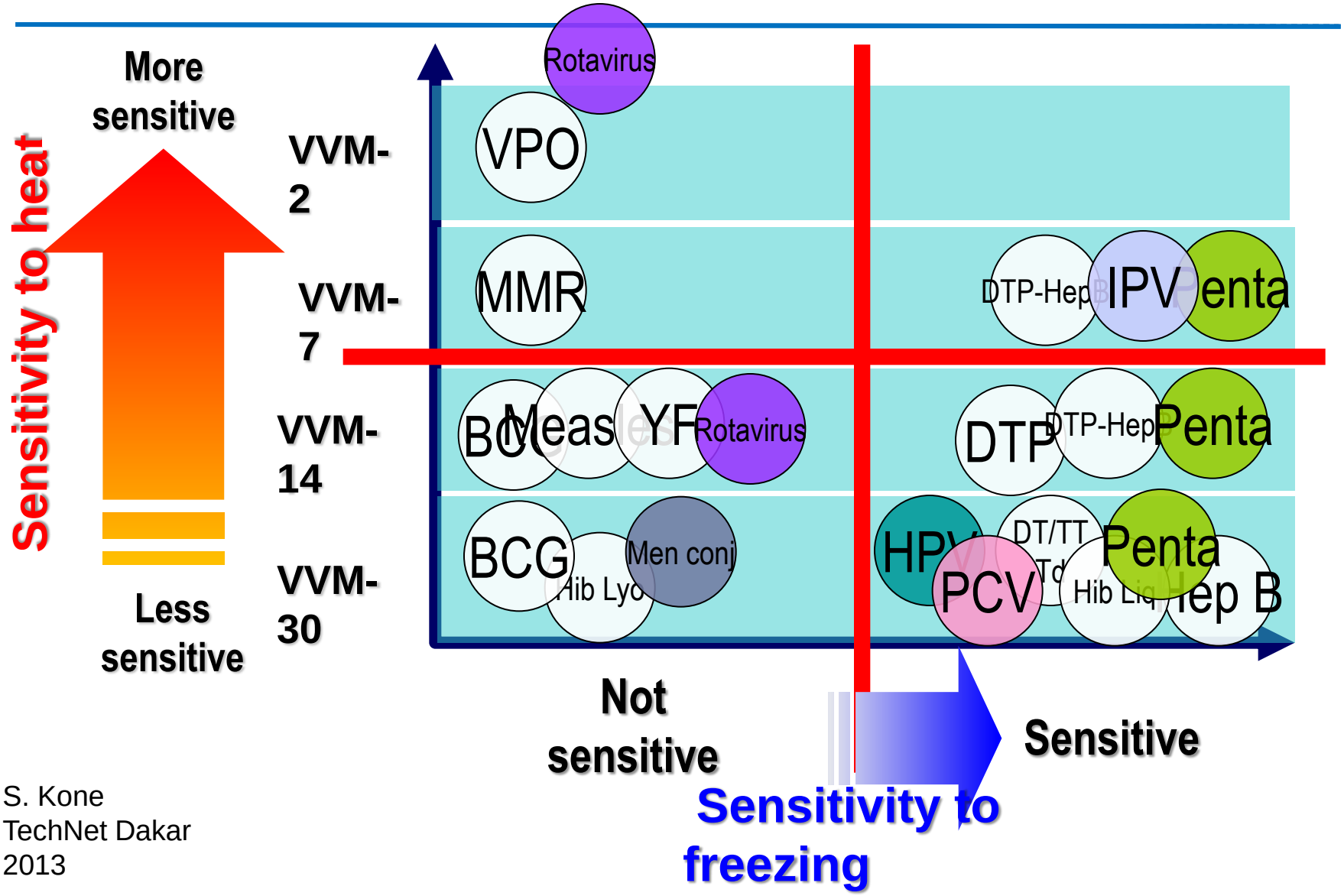
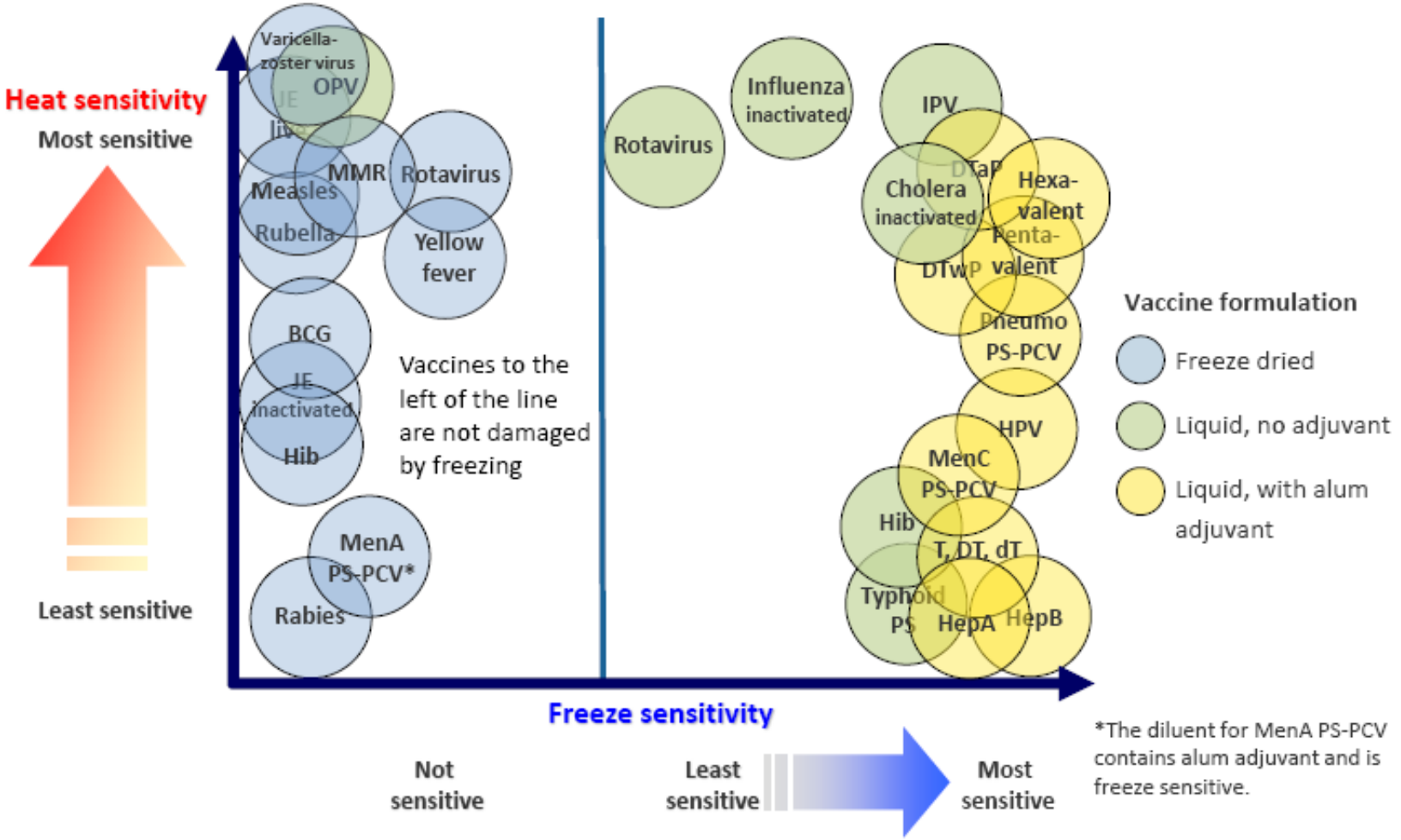
Diverging temperature sensitivity (2013)



S. Kone
TechNet Dakar
2013

Temperature sensitivity of vaccines (2015)



B. Schreiber
D. Chang Blanc
TechNet Bangkok 2015

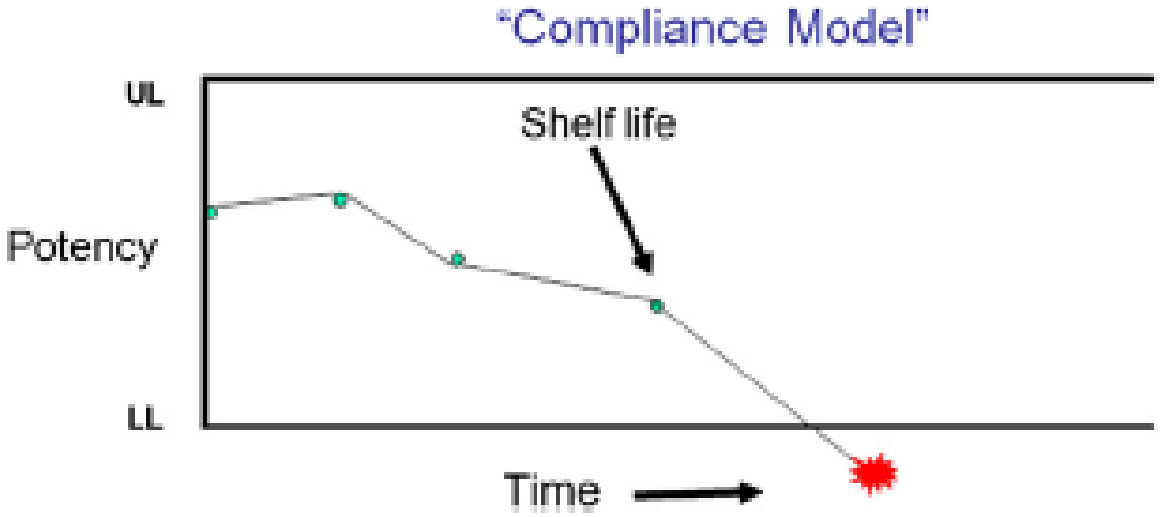
Studies Supporting Product Licensure [1]

- 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]

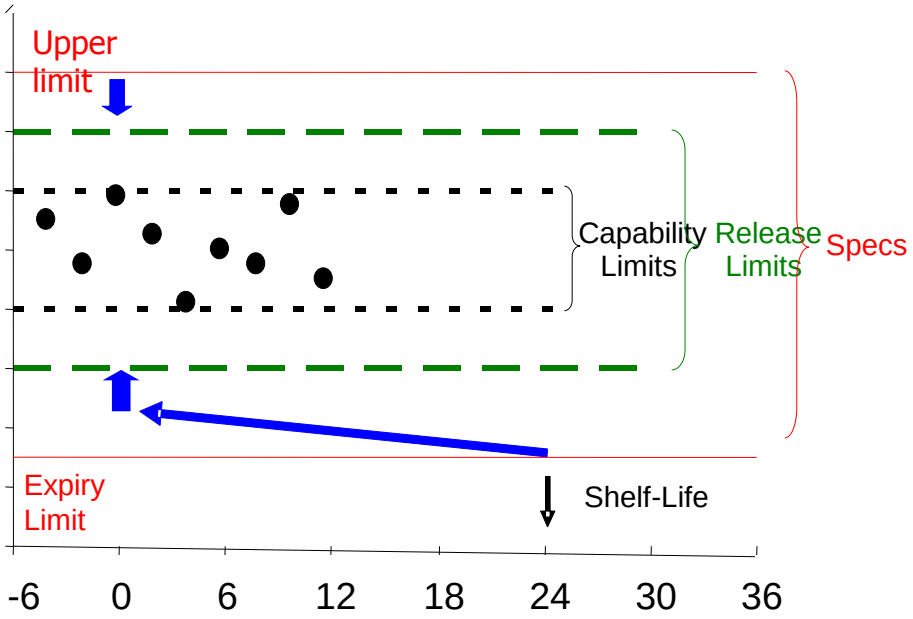
- Currently stability data are usually analyzed using a "single point" model, wherein any individual data point on a stability study must meet end expiry specifications
  - This has also been called the "compliance model"



[2] W. Egan, T. Schofield, *Biologicals* 37 (2009) 379-386

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, *Biologicals* 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

Type of characteristic	Compliance	Deviation
Mandatory	- Pre-qualification process proceeds	- Rejection of application for prequalification evaluation.
Critical	- Pre-qualification process proceeds	- 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.
Unique and innovative	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.	
Preferred	Pre-qualification evaluation proceeds.	

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

WHO/IVB/07.04
ORIGINAL: ENGLISH

WHO-UNICEF policy statement on the implementation of vaccine vial monitors:

The role of vaccine vial monitors in improving access to immunization

World Health Organization (WHO) and United Nations Children's Fund (UNICEF),

Marking the 10 years of successful implementation of vaccine vial monitors (VVMs);

Referring to the WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services (WHO/V&B/98.18, Making use of vaccine vial monitors (WHO/V&B/00.14), Getting started with vaccine vial monitors (WHO/V&B/02.26), WHO-UNICEF joint statement on effective vaccine store management (WHO/IVB/03.14), and Monitoring vaccine wastage at country level (WHO/IVB/03.18/Rev.1);

Emphasizing the Global Immunization Vision and Strategy aiming to protect more people against more diseases by expanding the reach of immunization to every eligible person, including those in age groups beyond infancy, within a context in which immunization is high on every health agenda;

Determined to reach every mother and child for vaccination against vaccine preventable diseases;

Noting the challenges in immunization service delivery especially in areas with weak or no cold chain infrastructure;

Acknowledging with appreciation the dedication of health workers throughout the world to overcome challenges in reaching all mothers and children with life saving vaccines;

Recognizing the cooperation of vaccine manufacturers in applying vaccine vial monitors on WHO prequalified vaccine products;

Acknowledging that the VVM is the only tool among all time and temperature indicators that is available at all times – in the process of storage, distribution and at the time the vaccine is administered – indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged;

Further noting that since its introduction in 1996 with oral polio vaccine, the VVM has contributed to the success of national immunization days as well as to overcoming access problems in areas with weak or no cold-chain infrastructure and reduction of vaccine wastage;

Appreciating the evidence produced by many field studies on the positive impact of the VVM on field operations, both routine and supplemental;

Recognizing that the benefits of VVM in overcoming the cold chain challenges and reaching the hard-to-reach populations will not be realized if they are not available;

Noting the use of VVMs to support policies for storage and administration of vaccines outside the cold chain to reach infants in rural and remote areas, such as for the hepatitis B vaccine birth dose for newborns;

Stressing the need that health workers require a consistent supply of vaccine with VVMs in order to be able to rely upon them as a tool.

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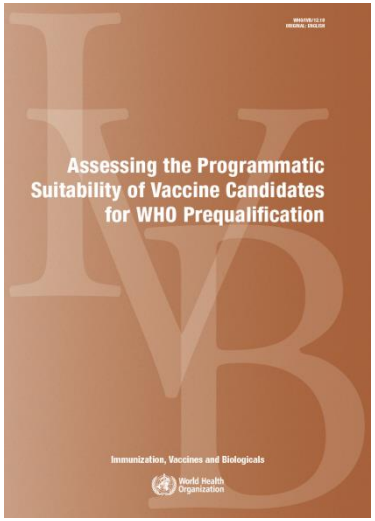
2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification



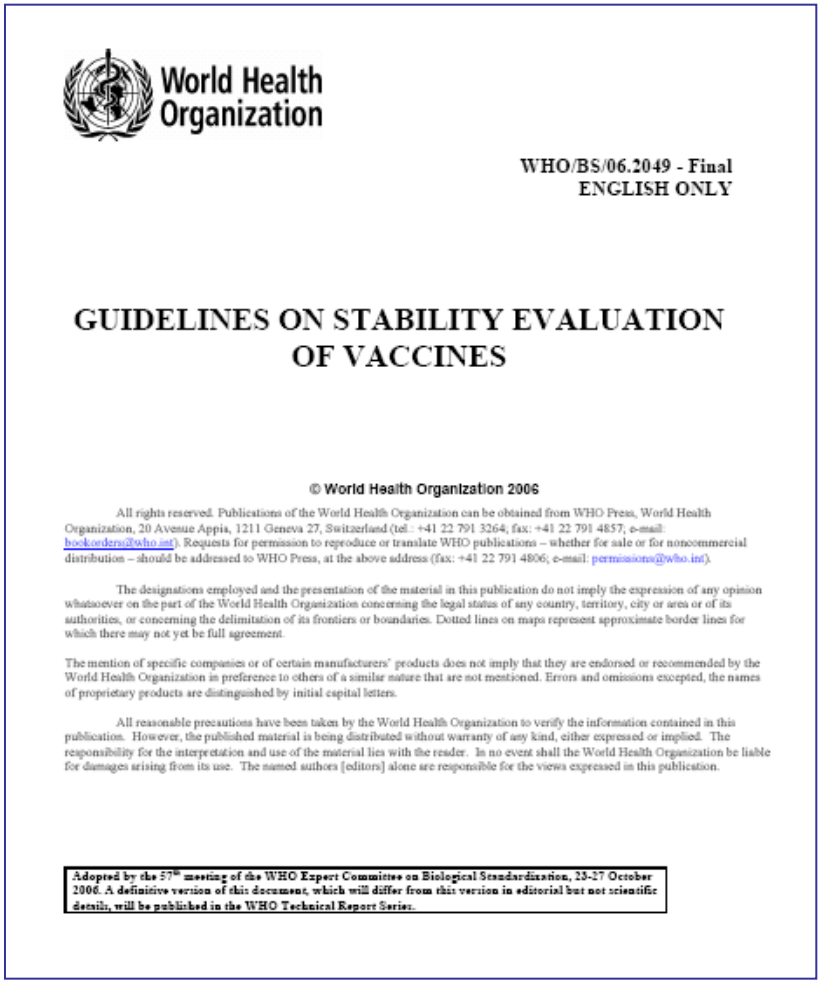
Vaccine vial monitor (VVM)	All vaccines	Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 orVVM30) 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.

WHO Guidelines on Stability Evaluation of Vaccines[1]

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]



World Health Organization

WHO/BS/06.2049 - Final
ENGLISH ONLY

GUIDELINES ON STABILITY EVALUATION OF VACCINES

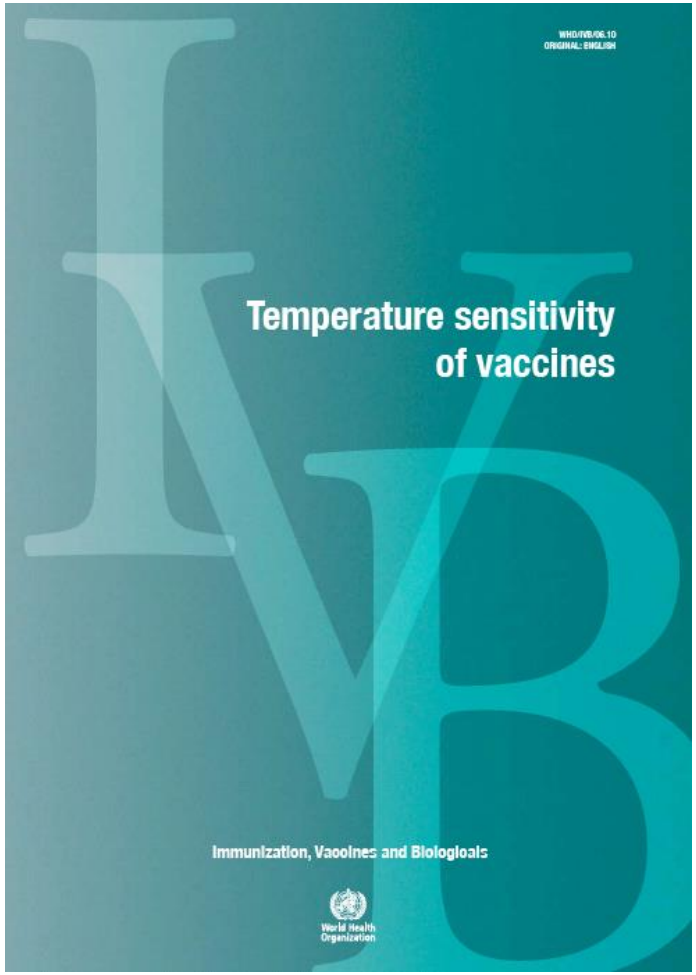
Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

1 http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%20BS%202049.Stability.final.09_Nov_06.pdf

[2]WHO *Temperature Sensitivity of Vaccines (WHO/IVB/06.10)*

WHO Temperature Sensitivity of Vaccines[3]

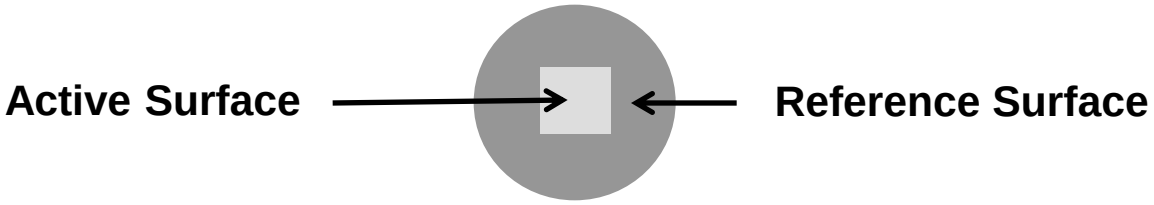
- The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).
- In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation 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.



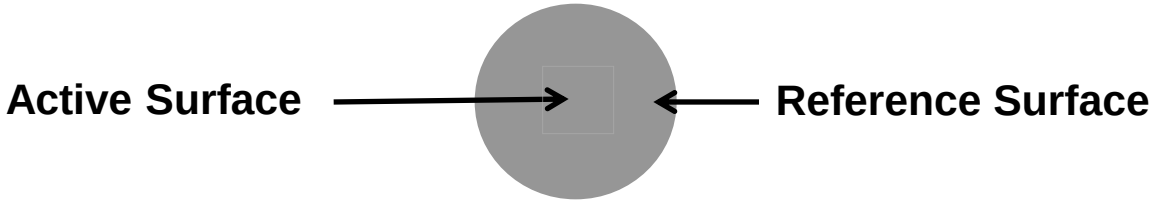
[3] http://www.who.int/vaccines-documents/DocsPDF06/847.pdf

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

WHO PQS Performance Specification – Vaccine Vial Monitor (WHO/PQS/E06/IN05)[5]

VVM Reaction Rates

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

- 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

World Health Organization

Anna-Lea Kahn - WHO-HQ/ EPI

14th TechNet Conference - Bangkok, Thailand

13 May 2015

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

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**

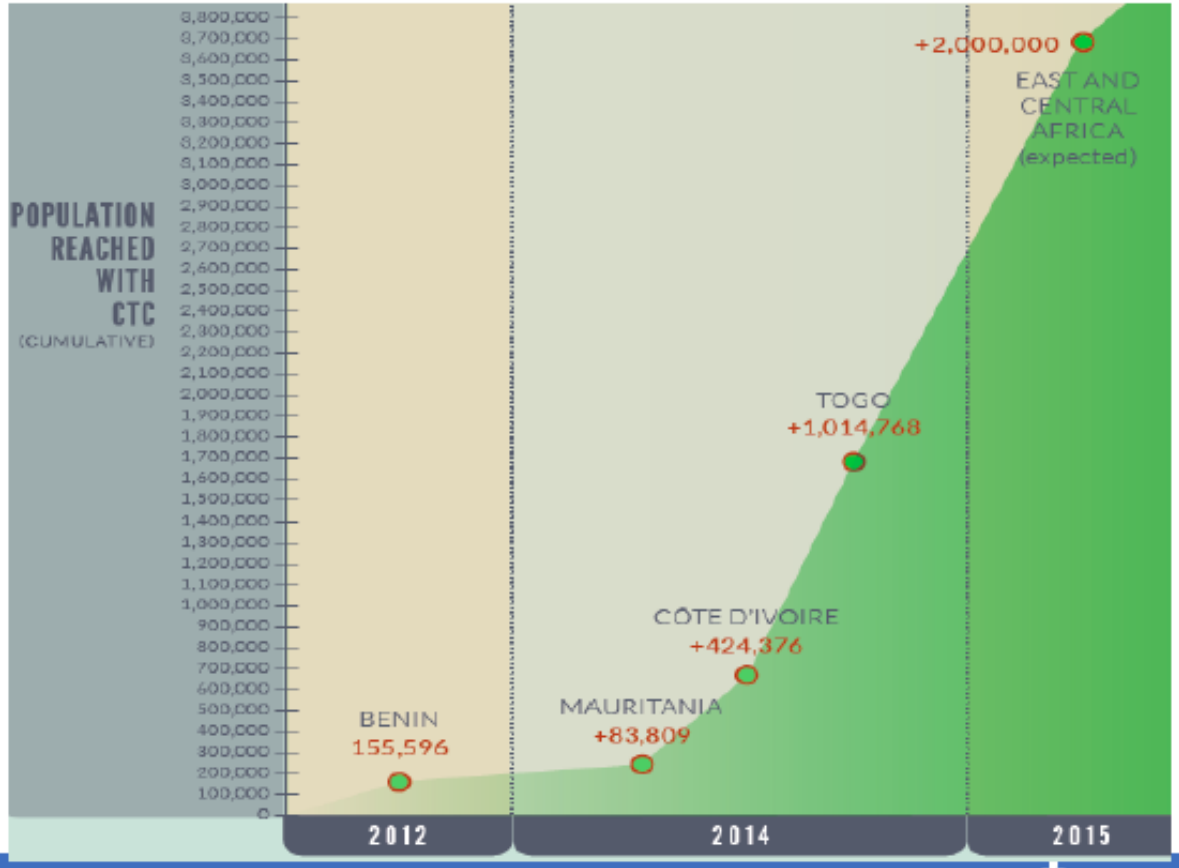
The CTC Agenda : UPSTREAM

- Development and licensure of more CTC-compatible vaccines
  - Clarify definition and programmatic priorities
  - 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
  - Development of WHO Guidelines on the Regulatory pathway for CTC licensure

CTC licensure to date

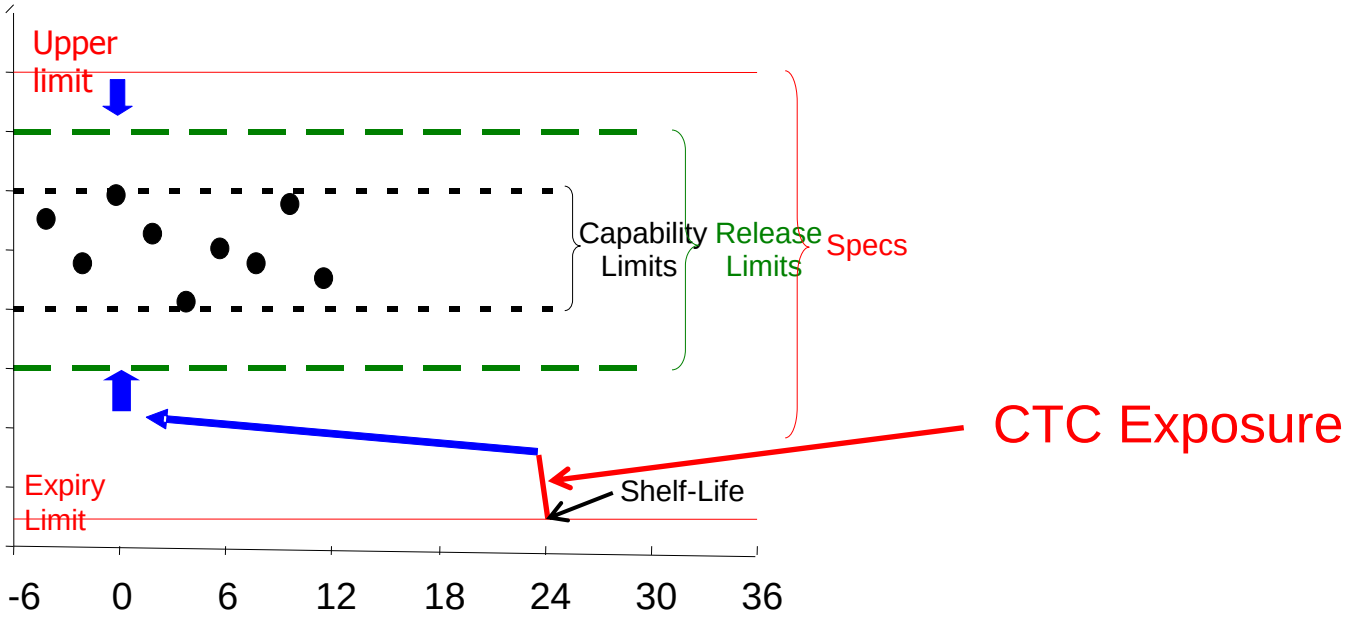
- December 2012 – **Meningitis A Vaccine** (MenAfriVac) licensed, prequalified and pilot tested for CTC
  - 4 days / 40°C
- May 2015 – **Pneumococcal Conjugate Vaccine** 13-valent (Prevnar13) licensed and prequalified for CTC, guidance to be developed
  - 3 days / 40°C
- End of 2015 – **Oral Cholera 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

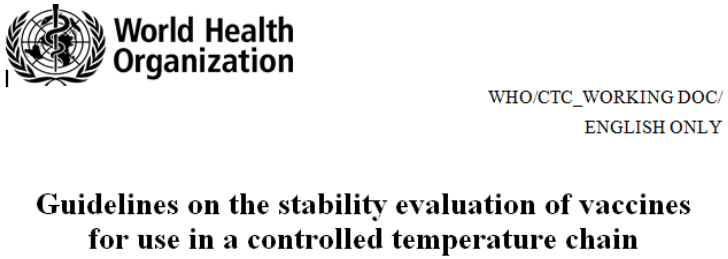


Impact of CTC on Vaccine Stability Studies

- Manufacturers will need to provide additional stability data to support CTC on-label approval



WHO DRAFTING Guidelines on *Stability Evaluation of Vaccines for use in a Controlled Temperature Chain*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WHO/CTC_WORKING DOC/
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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

WHO/Paul-Ehrlich-Institut Informal Consultation on Scientific and Regulatory Considerations on the Stability Evaluation of Vaccines under Controlled Temperature Chain (CTC), Langen, Germany, 4-6 June 2013
pdf, 197kb

WHO/Health Canada Drafting Group Meeting on Scientific and Regulatory Considerations on the Stability Evaluation of Vaccines under Controlled Temperature Chain, Ottawa, Canada, 4-6 December 2012
pdf, 266kb

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

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Analysis of Some Interesting Approaches
Formulation Composition

Past Examples	Formulation and Rationale
• Trehalose in the 1980s	Lyophilized for heat stability
• Deuterium Oxide in the 1990s	Liquid for heat stability
• Polyethylene glycol in the 2000s	Liquid for freeze stability of alum vaccines

Examples from Today

• Silk protein	Vaxess	http://www.vaxess.com
• Buffer mxitures	Arecor	http://www.arecor.com
• Sucrose and raffinose	Stabilitech	http://www.stabilitech.co.uk
• Lipid mixtures	VBI Vaccines	http://www.vbivaccines.com

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

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	Formulation and Rationale
• Freeze-drying vaccines	Lyophilized formulations of aluminum
• Spray-drying	Lyophilized for heat stability
• Foam-drying	Lyophilized for heat stability
• Microneedles	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

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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…)

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Requirements to Implement

From a Published Review from PATH…

Table 3. Challenges involved in developing thermostable vaccines.

Issue	Challenges	Consequences and solutions
Regulatory		
Addition of novel stabilizers, adjuvants or excipients	Novel components might be unproven in terms of safety, immunogenicity or quality of raw ingredients	Additional regulatory scrutiny might be applied; use excipients of proven safety whenever possible
Introduction of novel production processes or novel equipment	Production facilities need to comply with good manufacturing practices in order to produce material for clinical trials	Additional regulatory scrutiny might be applied
Healthy infants are the target population	The tolerance of serious adverse events in healthy infants is extremely low	Use excipients of proven safety if possible; new formulations might not be adopted
Convincing demonstration of safety will be required	Very rare, serious adverse events can be detected only in very large clinical trials	Postmarketing surveillance will be required
Technical		
Formulation development might be complex	There is no predictive rapid potency assay; many diseases/vaccines do not have good predictive preclinical models	Lack of preclinical models might increase amount of clinical testing needed for approval
Demonstrating clinical efficacy of reformulated product	There is still a lack of validated clinical end points and biomarkers (including assays of immune function) for many diseases	Longer, larger clinical trials with clinical end points might be needed; noninferiority trials comparing immunogenicity with existing vaccine might be possible
Reformulation of vaccines that are used in combinations	The components of combination vaccines can interact differently with each other and also with excipients	Extensive development and testing can be required, including noninferiority clinical studies
Commercial & intellectual property		
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	Lack of commercial incentive for manufacturers to produce improved formulations	Procurement incentives might be required to convince vaccine manufacturers to invest
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	Improvements such as thermostability might not lead to a sufficient price premium to cover the development costs	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
Vaccine producer IP	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	R&D might be limited to individual manufacturers and the pace of development driven by their interests
Technology IP	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	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

IP: Intellectual property.

Chen D, Kristensen D, Expert Rev Vaccines. 2009 May;8(5):547-57.

Opportunities and challenges of developing thermostable vaccines

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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

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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)

Category	# of Incidences	Loss (dollars)
Refrigeration Problems	16	**$42,958**
Shipping/ Receiving	4	**$34,772**
Improper Storage	6	**$187,133**
Expired Vaccines	51	$127,289
Total Losses	77	$392,717
Extrapolation to state		**$2,352,426**

Source: California Department of Public Health[44]

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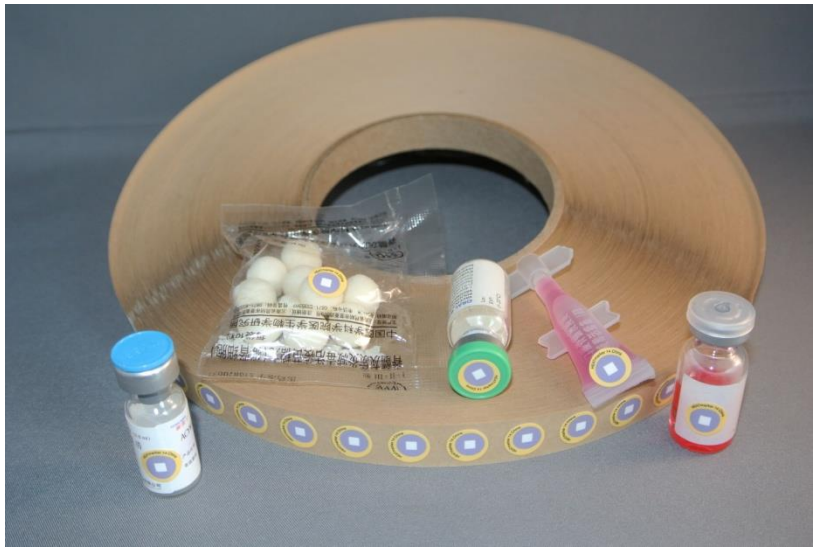
Global Vaccine Policy Requirements – Developed World countries

- 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!

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