Heat and Freeze Sensitivity of Vaccines

DCVMN Workshop
"Vaccine quality management systems for manufacturing excellence"

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Global Health Policy

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30 Good Distribution Practices World-Wide Regulations & Guidelines

- Initial focus – "cold chain"
  - Track-and –Trace/Serialization
- New terminology – Supply Chain Integrity
- Covers entire process: GLP, GCP, GDP
- Expanded to include
  - Supply chain temperature management
  - Import/export compliance/security

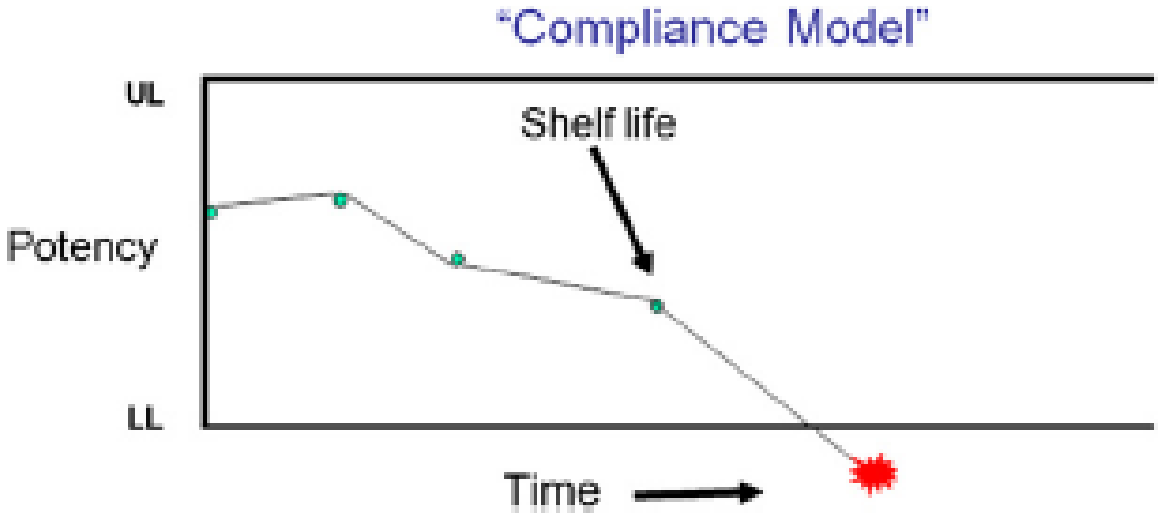
Studies Supporting Product Licensure [1]

- 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]

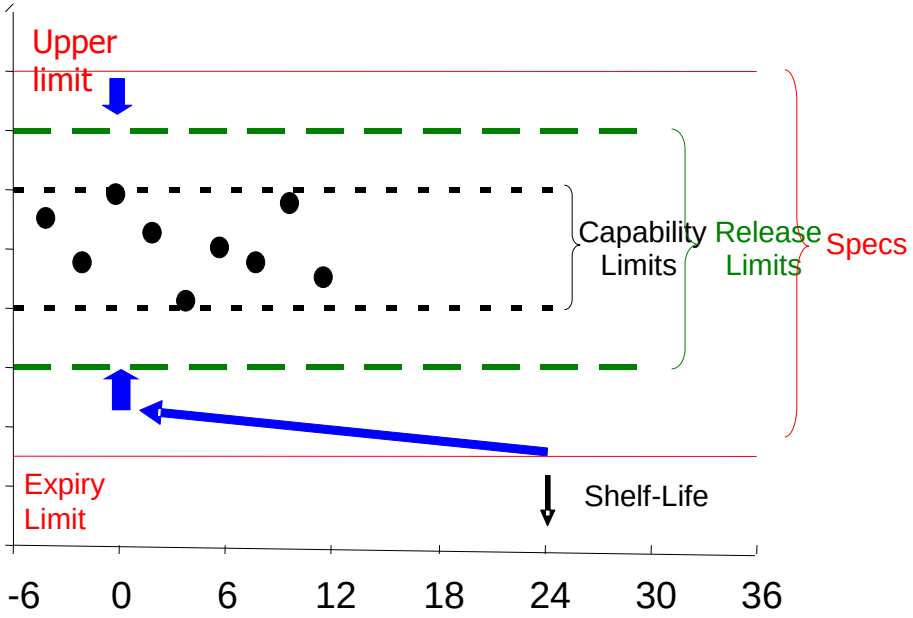
- Currently stability data are usually analyzed using a "single point" model, wherein any individual data point on a stability study must meet end expiry specifications
  - This has also been called the "compliance model"



[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

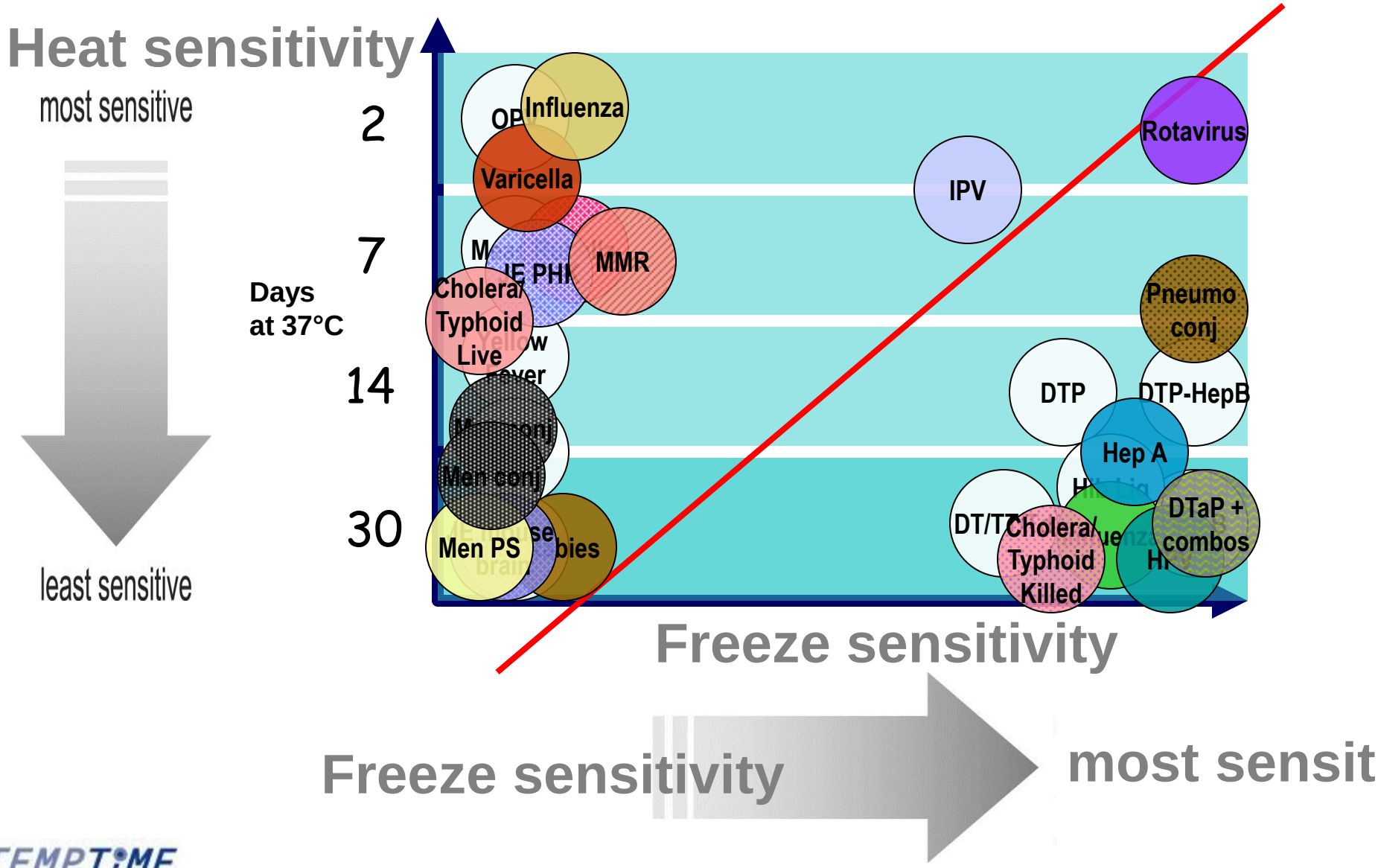
Vaccine categories and characteristics

- Viral vaccines
  - Live attenuated
    - Generally heat sensitive
    - Usually can be frozen
    - (Protect from light)
  - Killed or purified protein
    - Normally very stable at 37 ºC
    - If adjuvanted may be sensitive to freezing

Vaccine categories and characteristics

- Bacterial vaccines
  - Live attenuated
    - Usually sensitive to heat
    - Generally lyophilized, so can be frozen
  - Killed or purified protein
    - Normally very stable
    - If adjuvanted, will be freeze-sensitive
  - Polysaccharide
    - Fairly stable and if lyophilized, can be frozen
  - Polysaccharide conjugate
    - Stability depends on possibility of hydrolysis of conjugate
    - Lyophilized products can be frozen; if liquid, probably not

Vaccine Temperature Sensitivity



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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/99.114), Getting started with vaccine vial monitors (WHO/V&B/02.35), 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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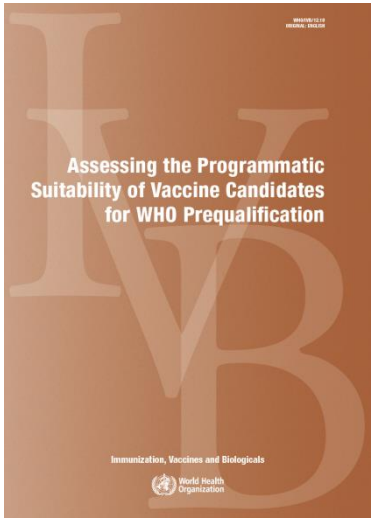
Protecting Patients - Reducing Risk™

2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification



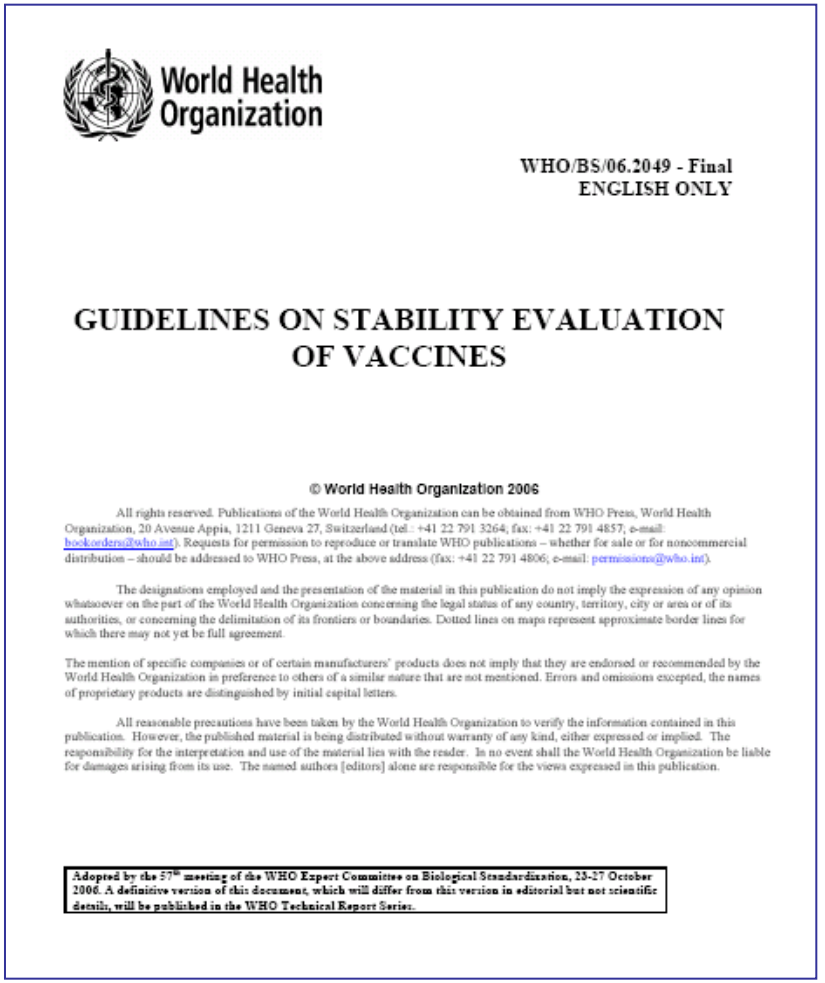
Vaccine vial monitor (VVM)	All vaccines	Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type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

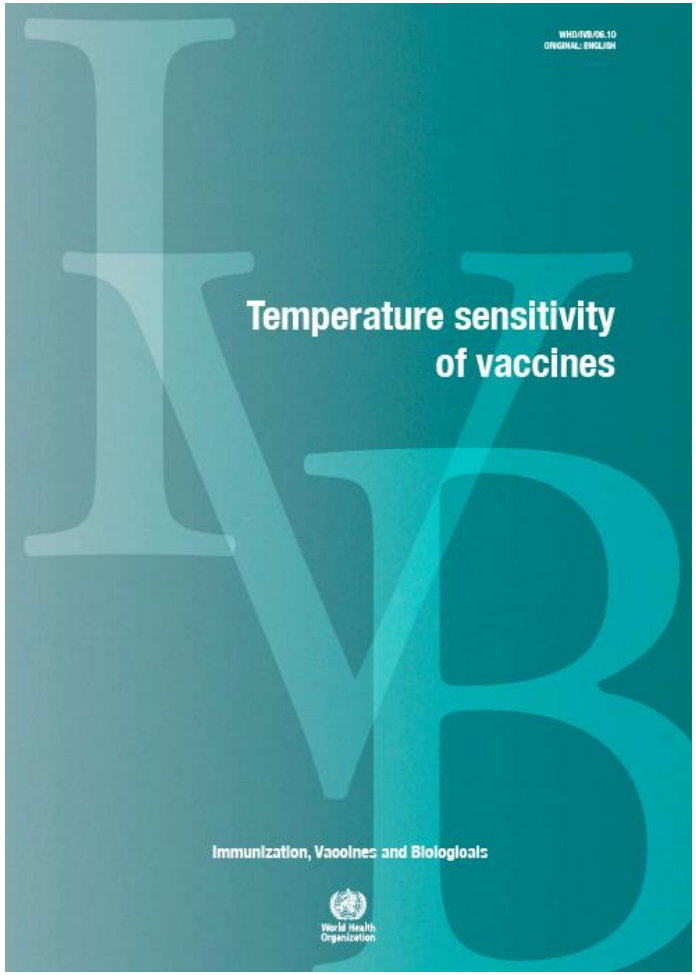
Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

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]

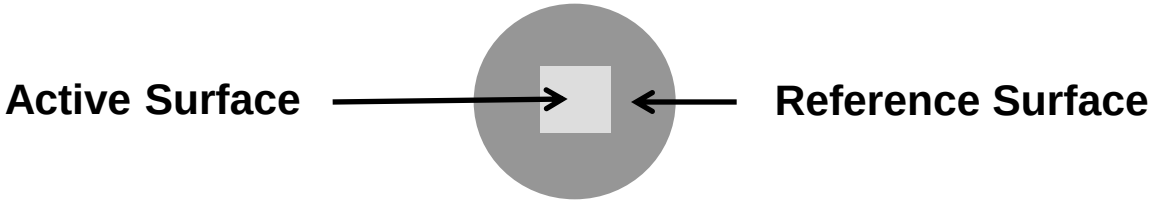
- The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).
- In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation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



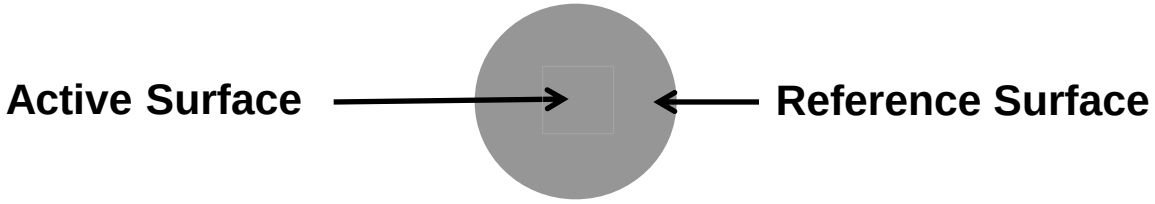
[3] http://www.who.int/vaccines-documents/DocsPDF06/847.pdf

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

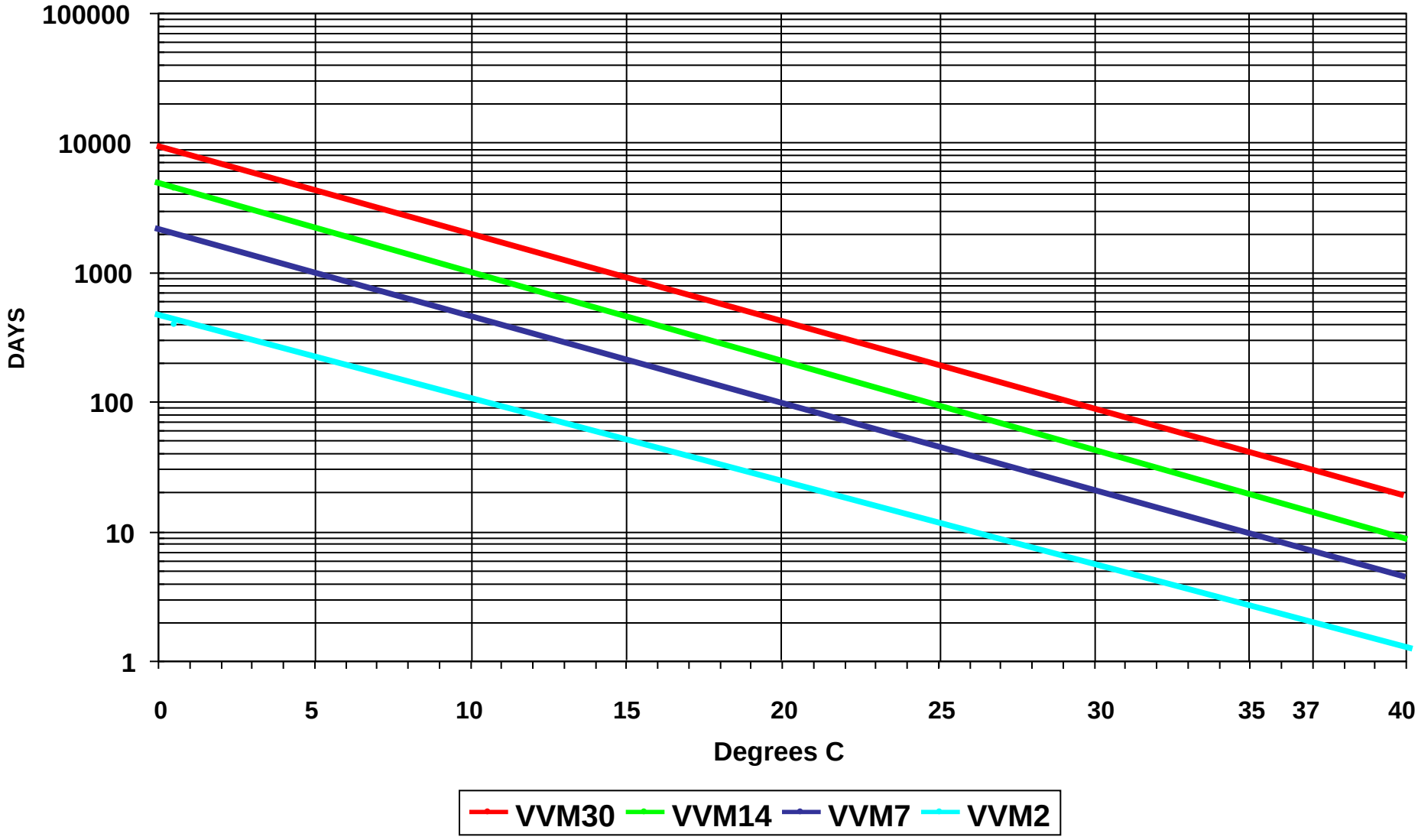
Category (Vaccines)	No. of days to end point at +37°C	No. of days to end point at +25°C	Time to end point at +5°C
VVM 30: High Stability	30	193	> 4 years
VVM 14: Medium Stability	14	90	> 3 years
VVM 7: Moderate Stability	7	45	> 2 years
VVM 2: Least Stable	2	N/A*	225 days

- 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

Arrhenius Graph of VVM Categories

Based on Upper Limits at 25°C and 37°C



Selection of VVM Category
Example: Product A

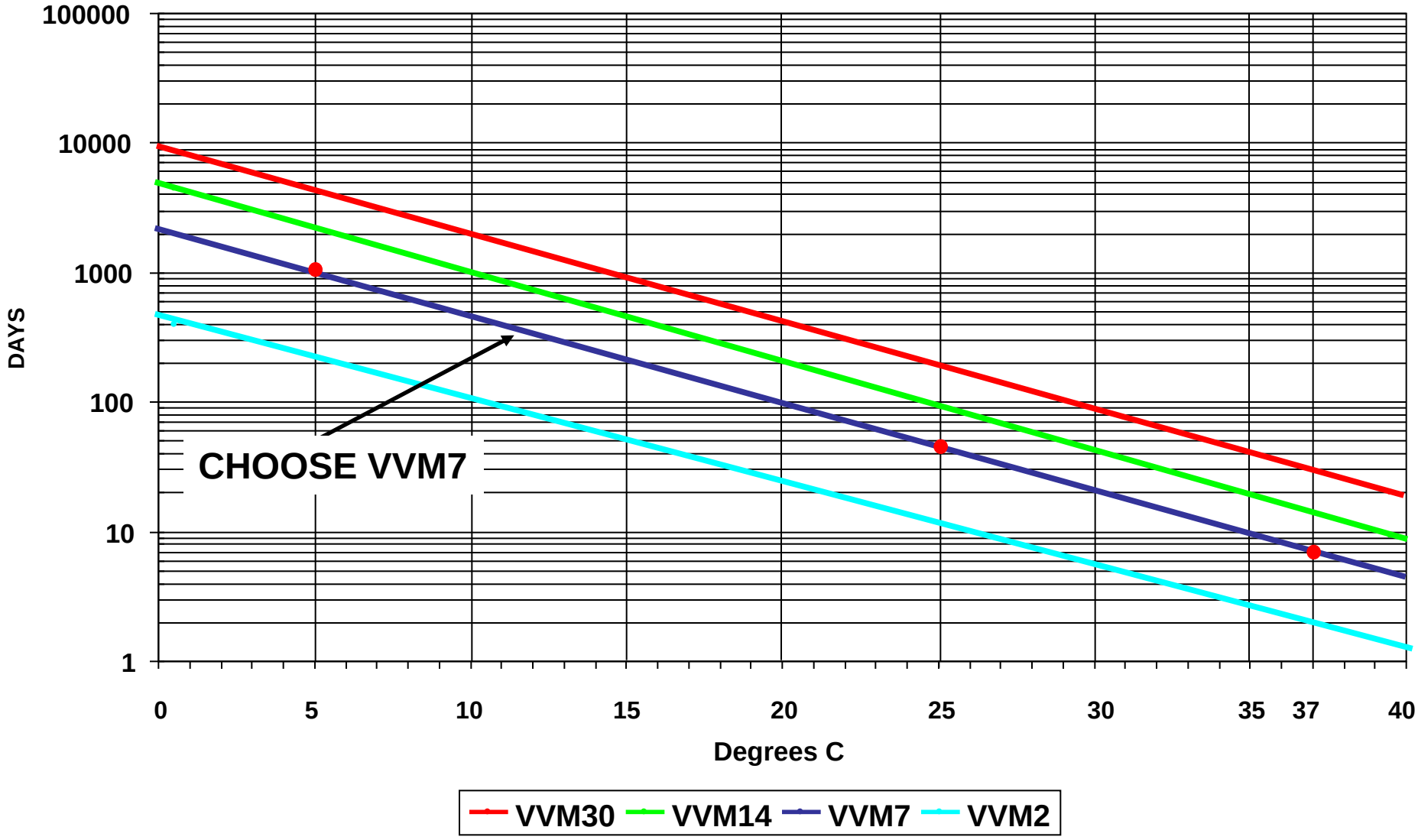
Step 1: Summarize stability data

- 2 to 8ºC[1]: 3 years (1095 days)
- 25ºC: 45 days
- 37ºC: 7 days
- Expiry Date: 2 years

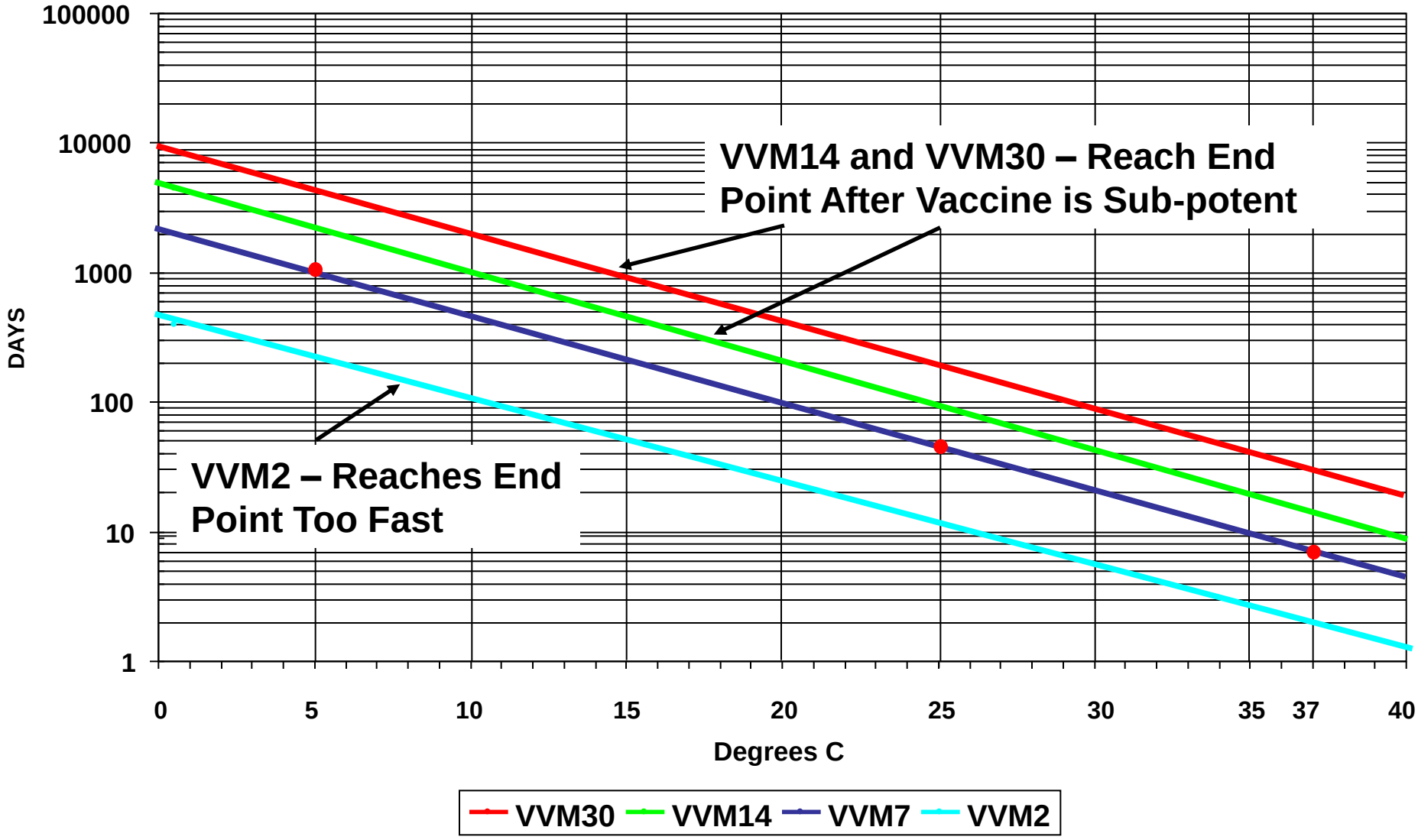
Step 2: Compare Stability Data with VVM Categories

[1]2 to 8ºC is treated as 5ºC

Product A Stability Data and VVM Categories



Product A - VVM Choice and Rationale



Selection of VVM Category
Example: Product B

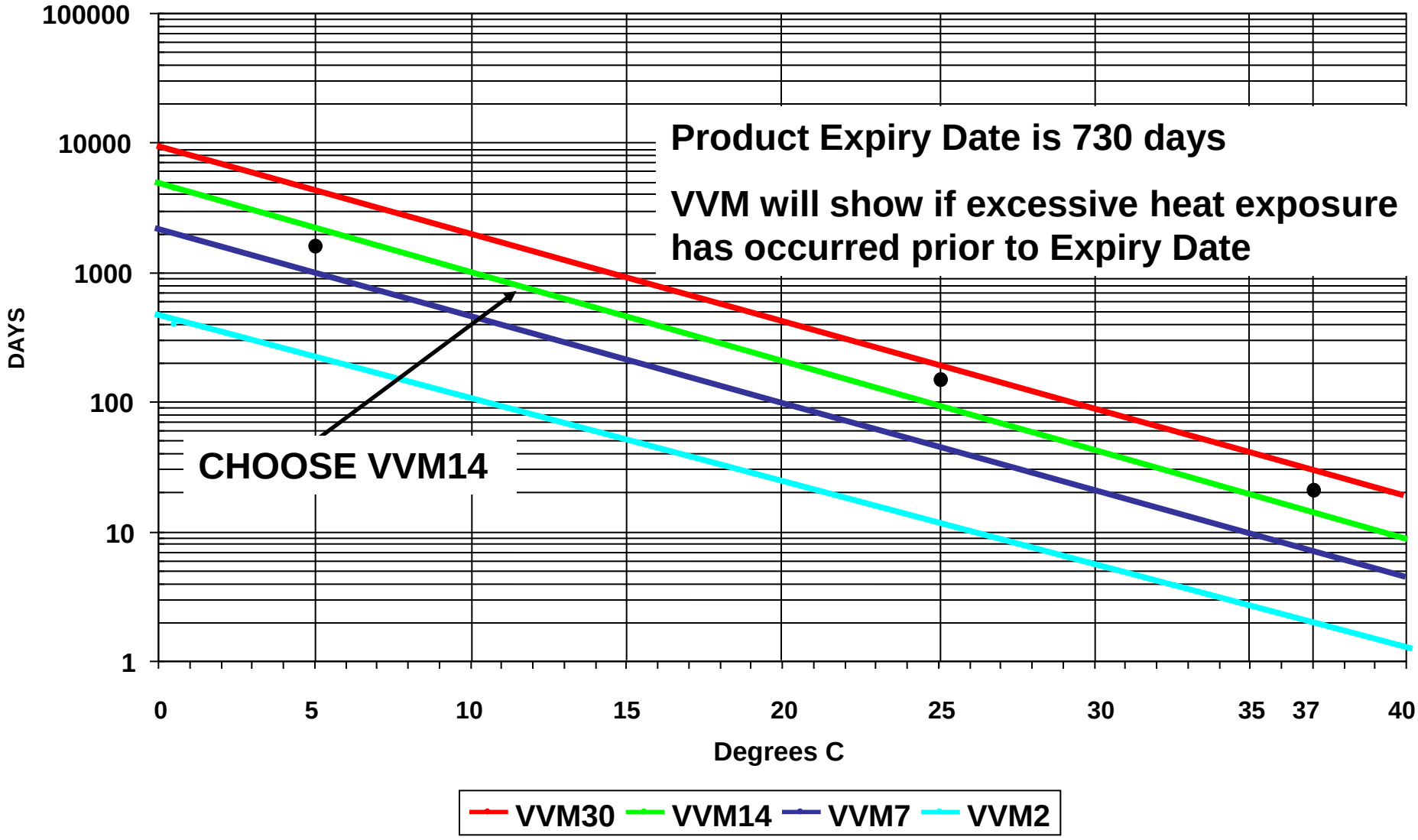
Step 1: Summarize stability data

- 2 to 8ºC[1]: 1600 days
- 25ºC: 150 days
- 37ºC: 21 days
- Expiry Date: 2 years

Step 2: Compare Stability Data with VVM Categories

[1]2 to 8ºC is treated as 5ºC

Product B Stability Data and VVM Categories



Obrigado
Gracias

Thank You

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