Stability Studies and Choice of VVM Category

Overview

- These slides are focused mainly on vaccines
- The principles involved in choice of a vaccine vial monitor (VVM) or more generically a time-temperature indicator (TTI) are the same
- The principle is fashioned from WHO guidelines and their established methodologies
- This process has been applied to monoclonal antibodies, hormones, small molecules, diagnostic test kits and other pharma products
- The final choice of TTI category (sensitivity) is up to the manufacturer

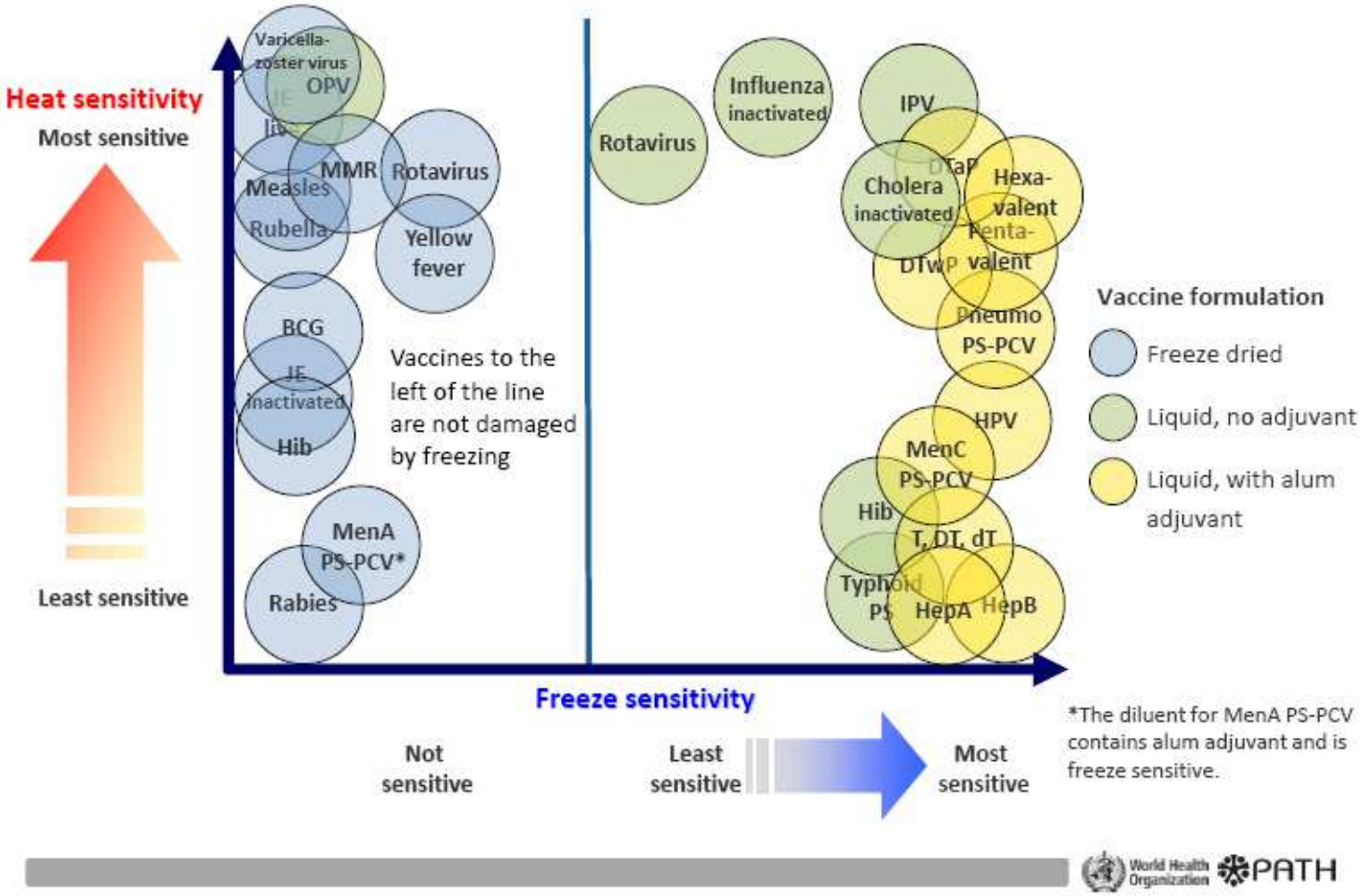
Goals of Stability Studies in Product Development

- Establish product stability characteristics:
  - The principles involved in choice of a vaccine vial monitor (VVM) or more generically a time-temperature indicator (TTI) are the same
  - The principle is fashioned from WHO guidelines and their established methodologies
  - This process has been applied to monoclonal antibodies, hormones, small molecules, diagnostic test kits and other pharma products
  - The final choice of VVM category (sensitivity) for WHO/UNICEF is decided by WHO
  - The final choice of VVM/TTI category for other uses is up to the manufacturer

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

Temperature Sensitivity of Vaccines (2015)



B. Schreiber, D. Chang Blanc, *TechNet* Bangkok 2015

Studies Supporting Product Licensure[1]

Studies supporting product licensure include:

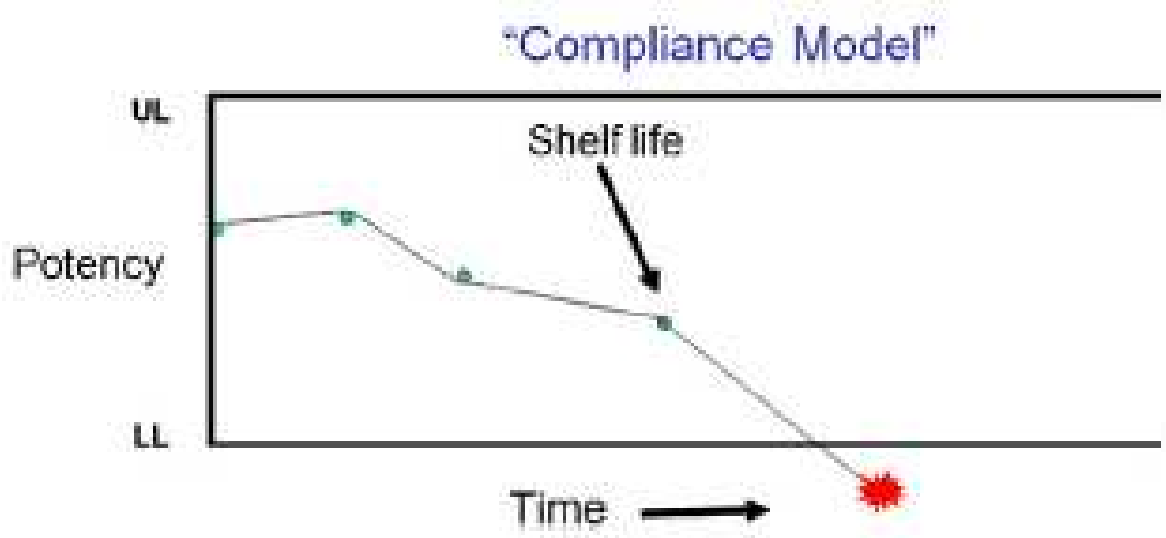
- Long term stability of bulk intermediate
- Long term stability of final container product
- Accelerated stability at conditions of handling, excursion, and use
- Release and manufacturing models
- Clinical support of specifications

[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”

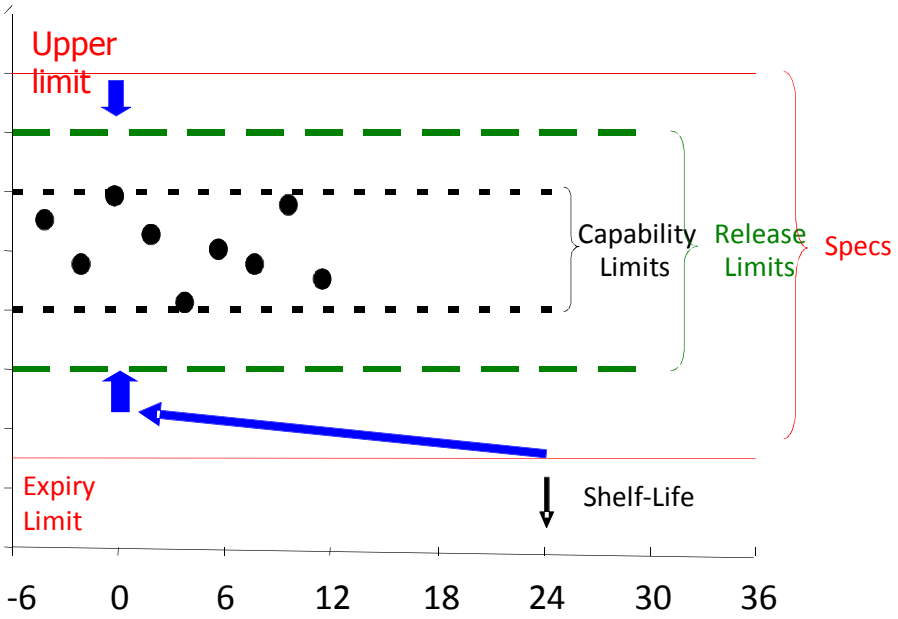


[2]W. Egan, T. Schofield, Biologicals 37 (2009) 379-386

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

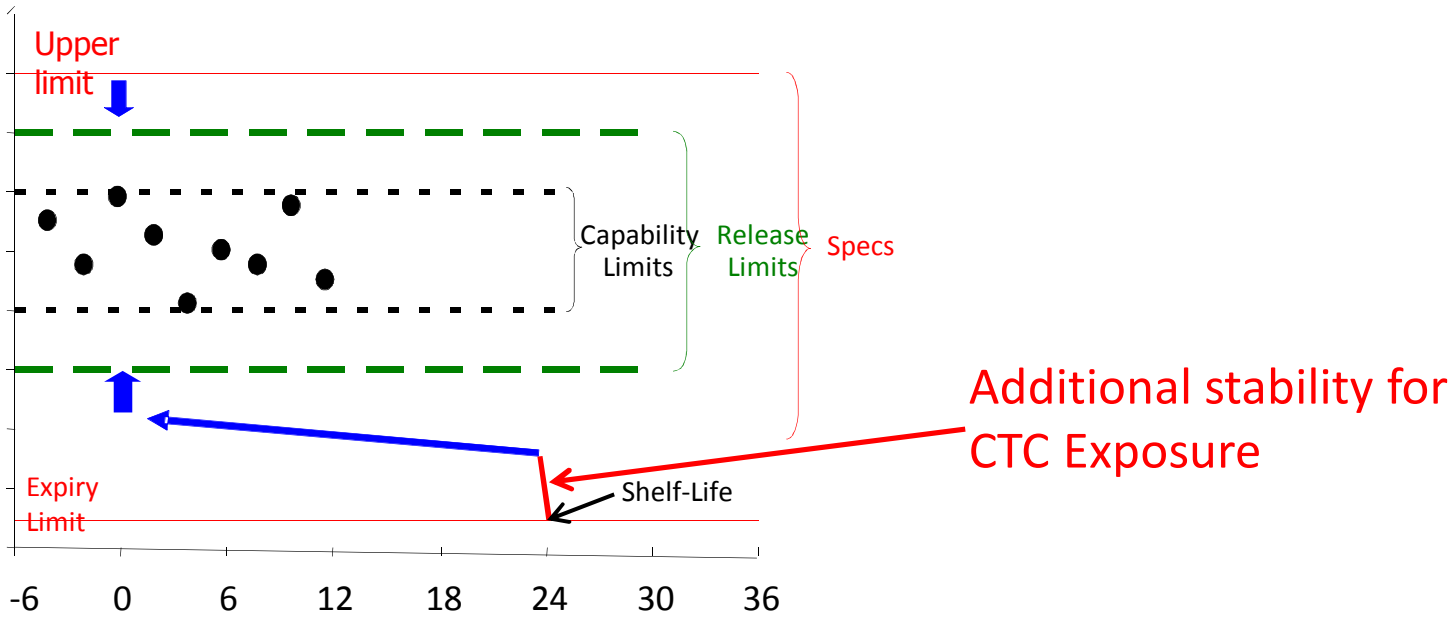
- This has also been called the “comprehensive model”, or the “estimation model” or the “statistical model”



Adapted from T.L. Schofield, Biologicals 37 (2009) 387-396

Impact of CTC on Vaccine Stability Studies

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



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.	

*VVM is a critical characteristic for vaccine prequalification

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/98.10), Making use of vaccine vial monitors (WHO/V&B/00.14), 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;

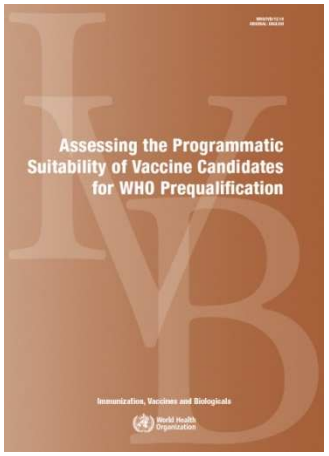
Appreciating the evidence produced by many field studies on the positive impact of the VVM on field operations, both routine and supplemental;

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;

2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification



Vaccine Vial Monitor (VVM)

Vaccines

Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below.

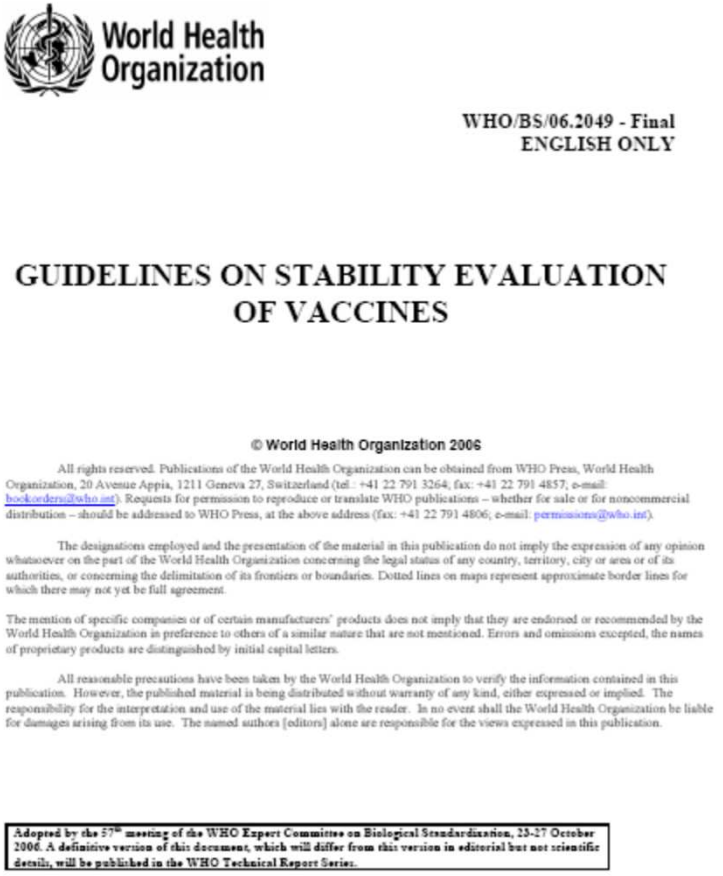
- The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 orVVM30) or a future VVM type approved by WHO(WHO/V&B/99.187, WHO/IVB/07.048).
- Signed declaration, as part 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

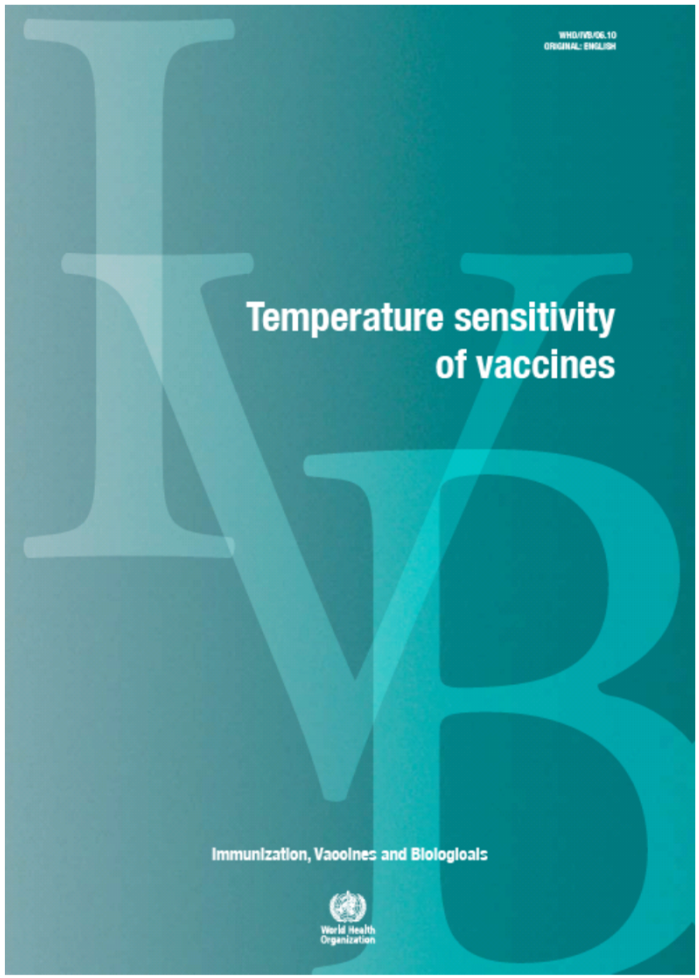
Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

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]

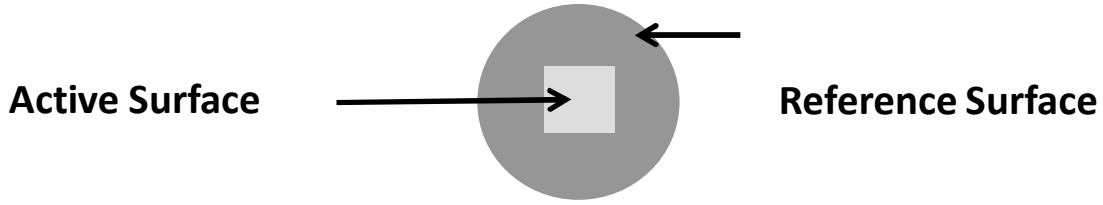
- The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).
- In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation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



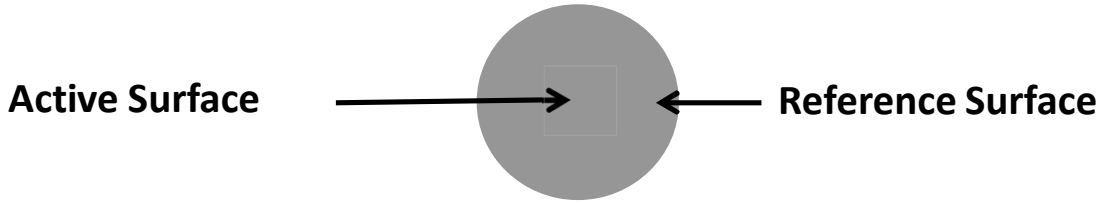
[3]http://www.who.int/vaccines-documents/DocsPDF06/847.pdf

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

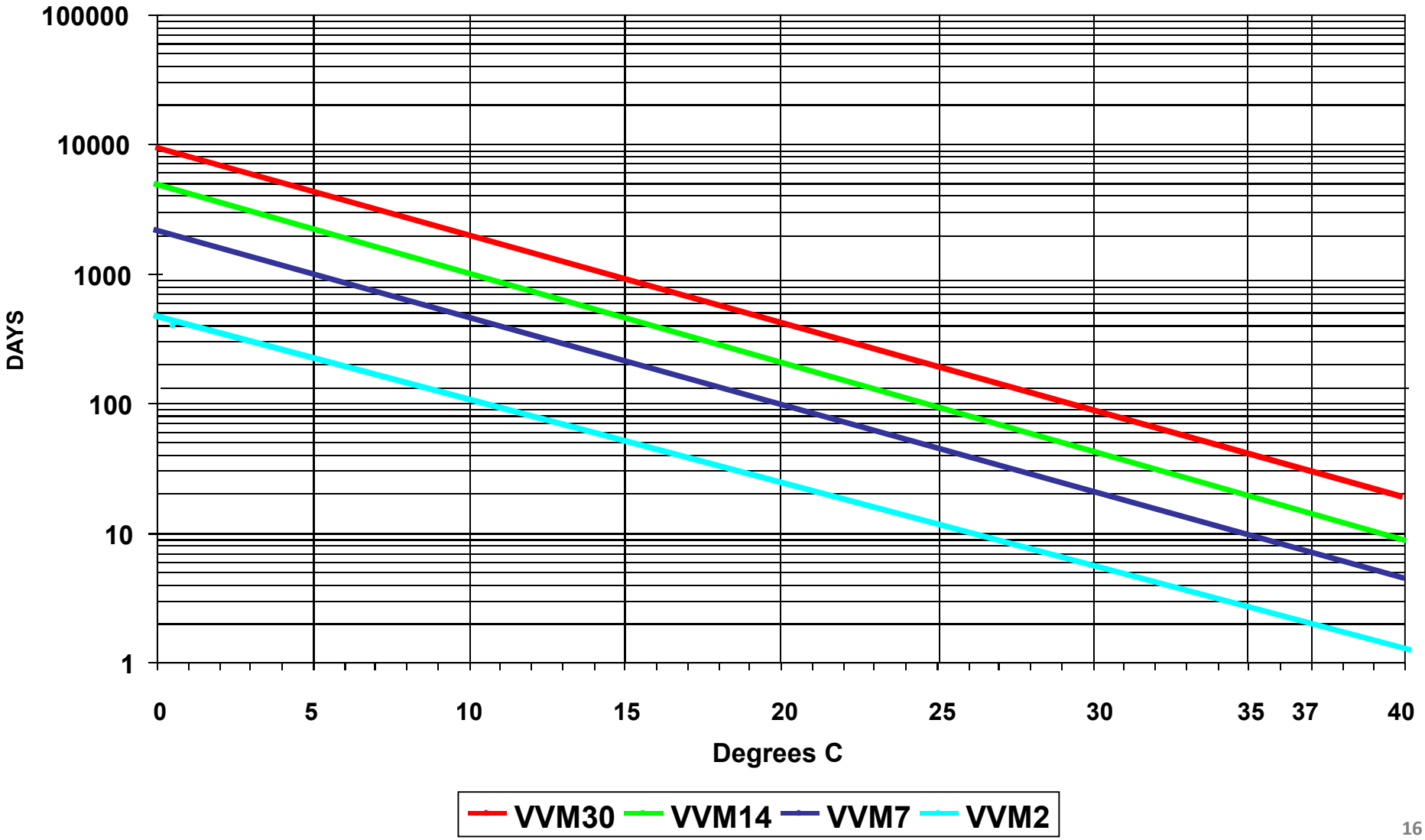
(new categories to be added: VVM11 and VVM250)

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 30: Least Stable	2	N/A*	225 days

The four categories of VVM are VVM2, VVM7, VVM14 and VVM30

[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

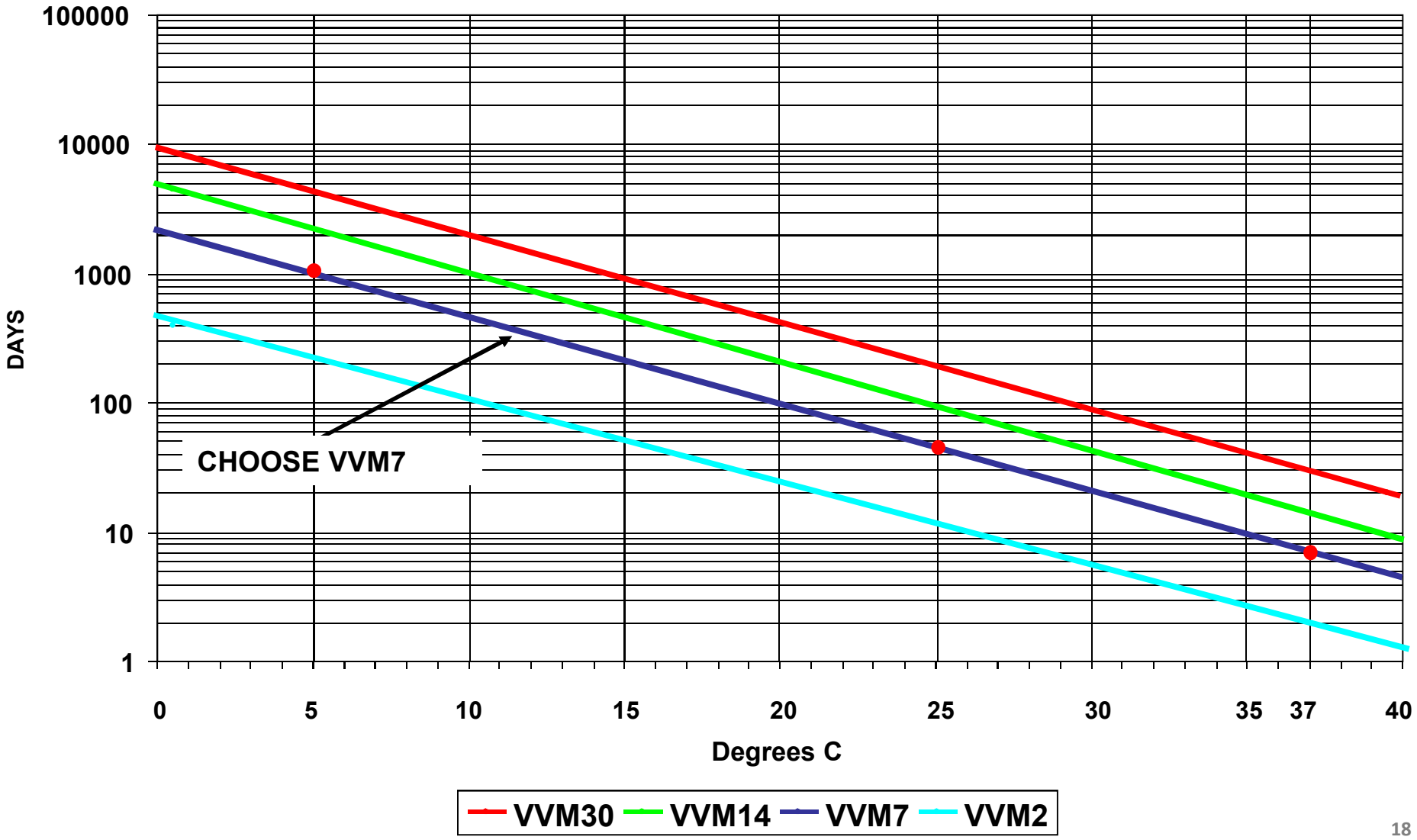
Step 1: Summarize stability data

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

[1]2 to 8°C is treated as 5°C

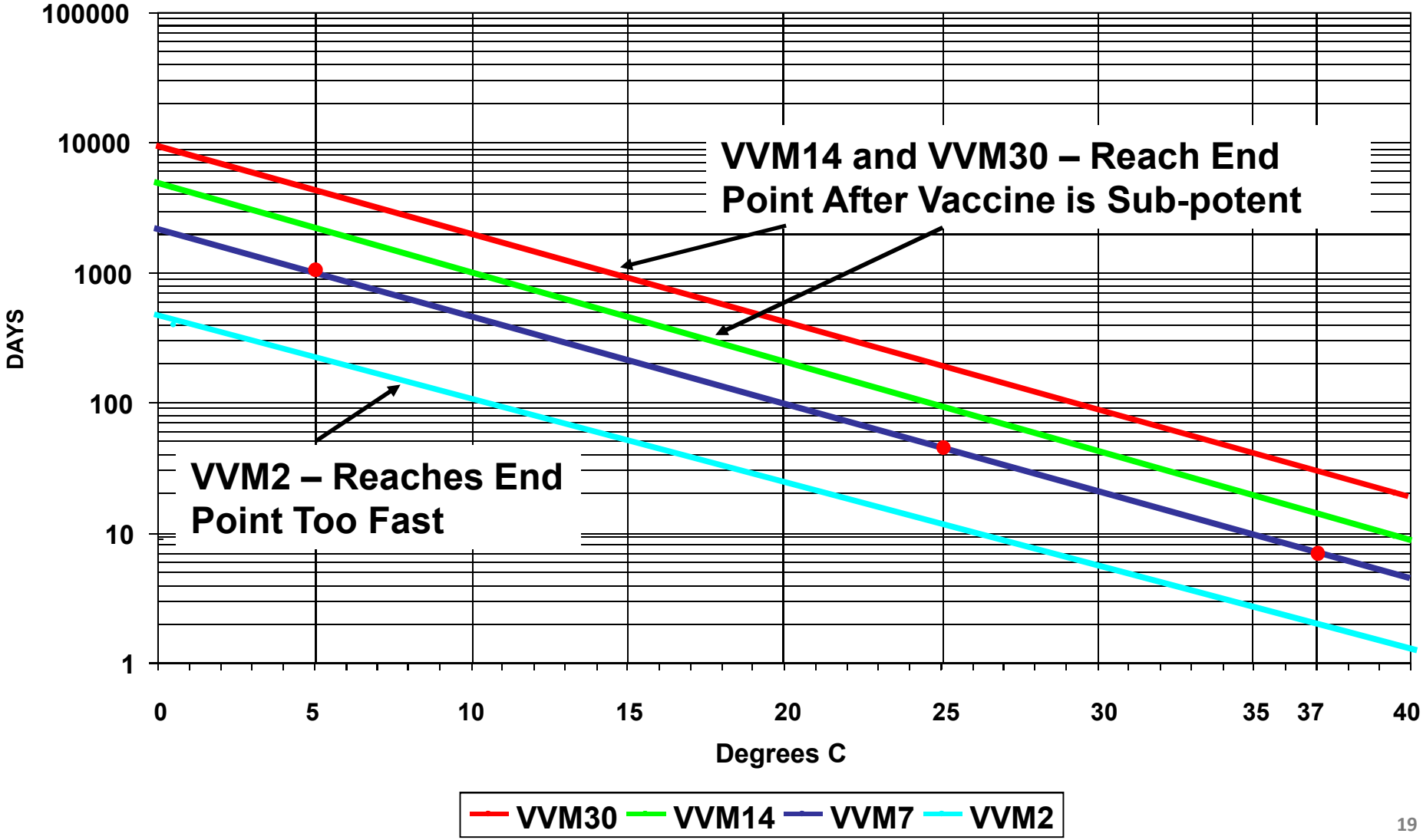
Product A Stability Data and VVM Categories

Step 2: Compare stability data with VVM categories



Product A VVM Choice and Rationale

Step 2: Compare stability data with VVM categories



Selection of VVM Category
Example: Product B

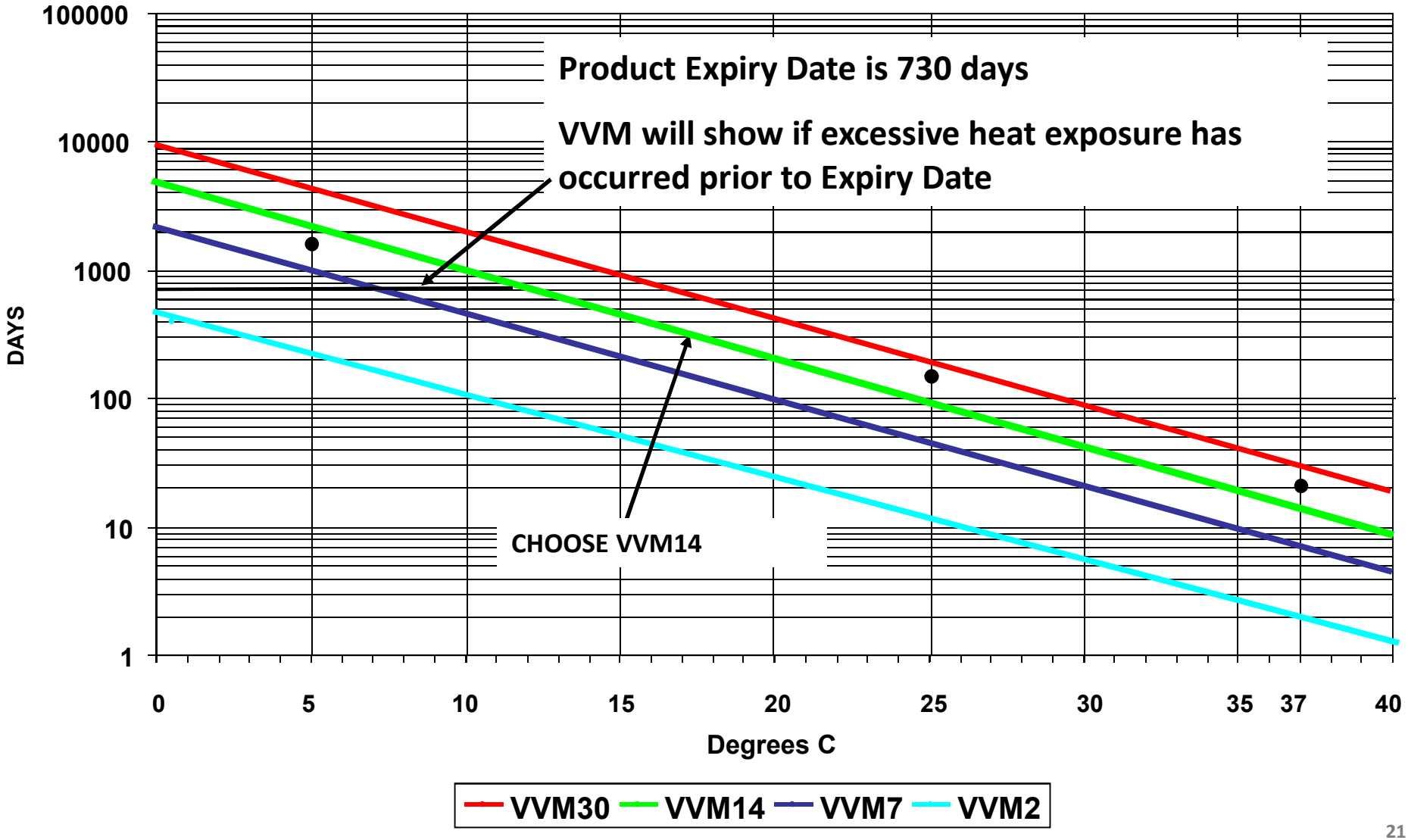
Step 1: Summarize stability data

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

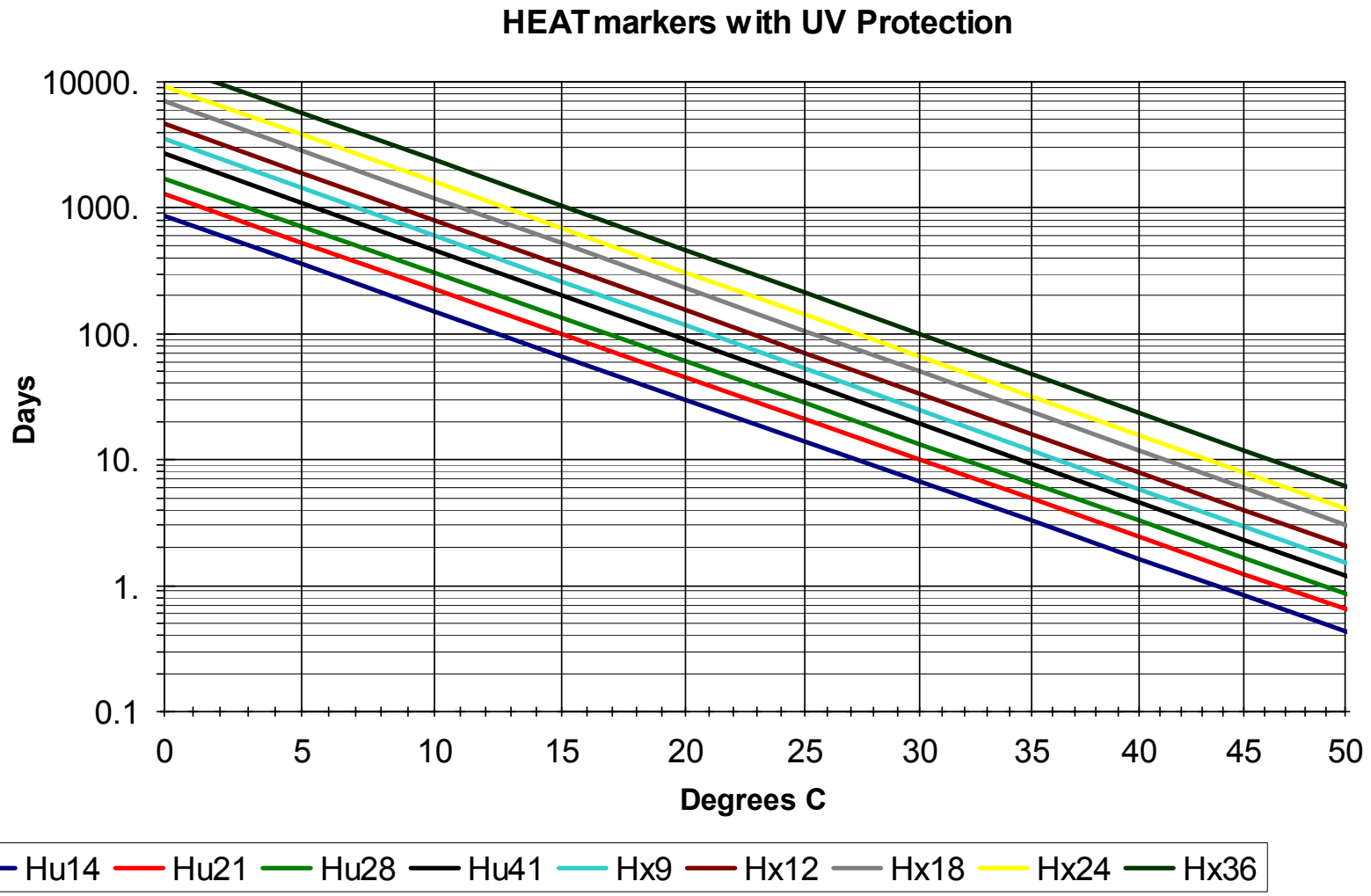
[1]2 to 8°C is treated as 5°C

Product B Stability Data and VVM Categories

Step 2: Compare stability data with VVM categories



Other HEATmarker TTI Categories



Thank you!!!