

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

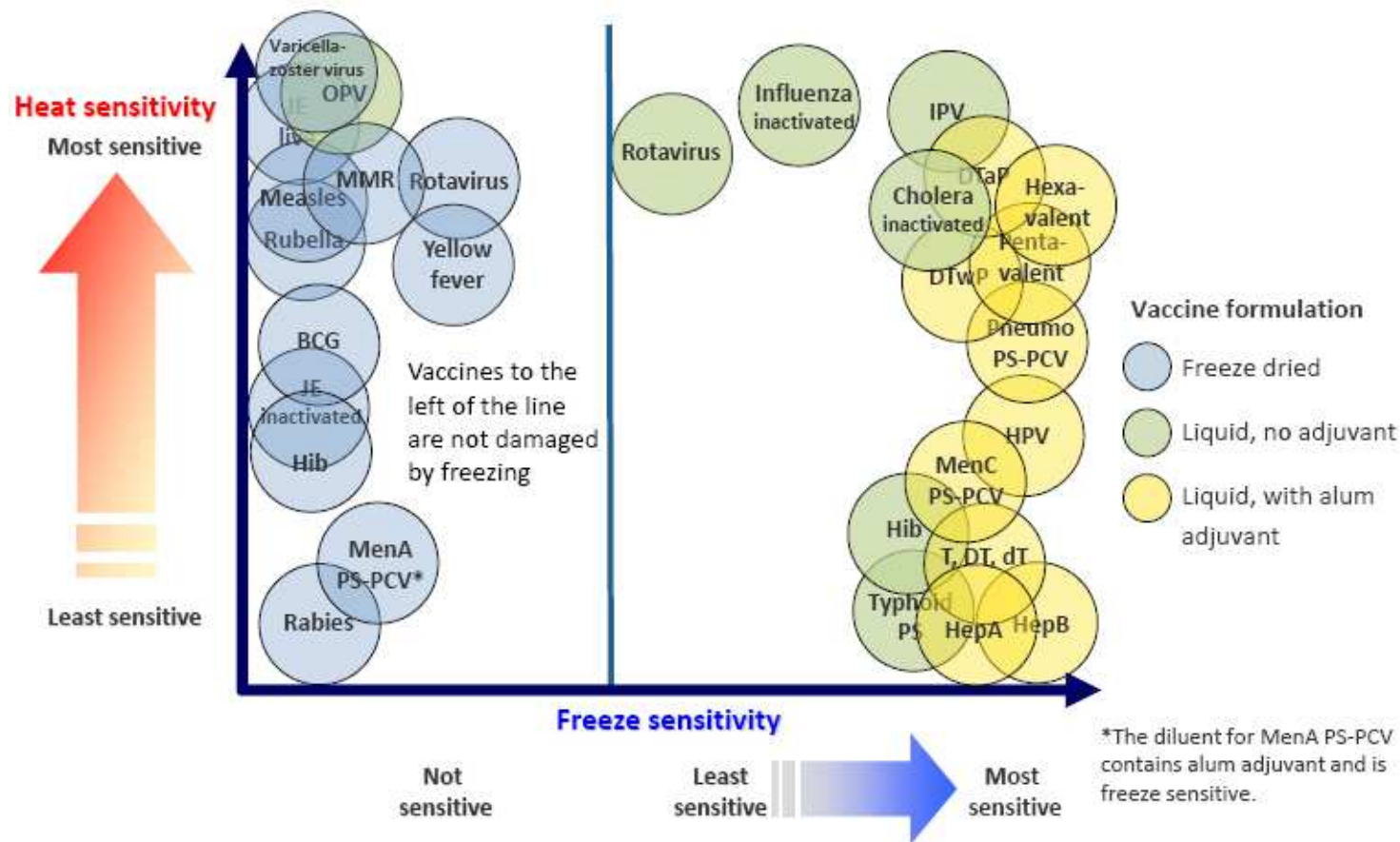
Goals of Stability Studies in Product Development

- 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)



Studies Supporting Product Licensure¹

Studies supporting product licensure include:

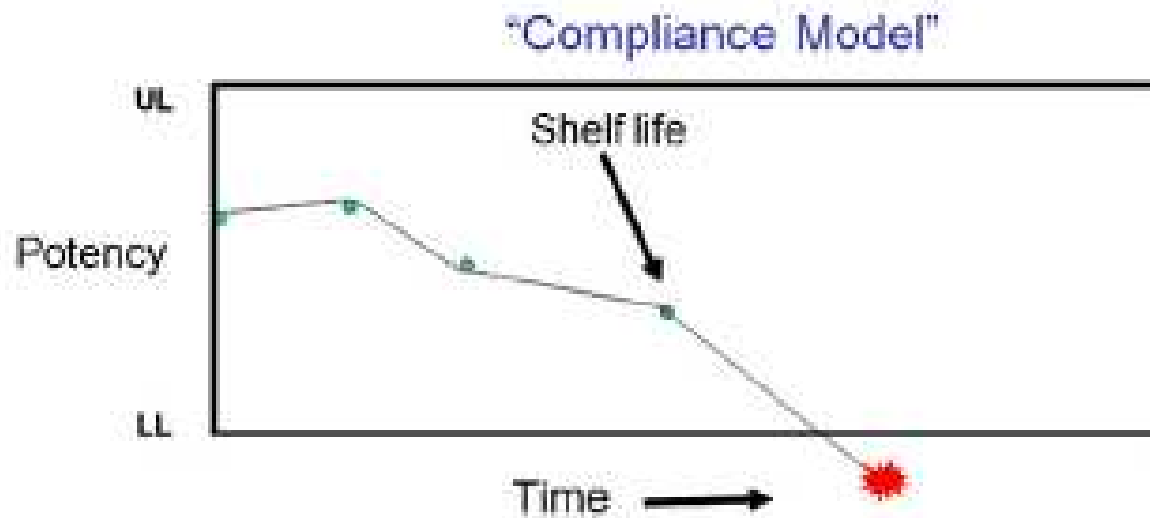
- Long term stability of bulk intermediate
- Long term stability of final container product
- Accelerated stability at conditions of handling, excursion, and use
- Release and manufacturing models
- Clinical support of specifications

¹T.L. Schofield, *Biologicals* 37 (2009) 387-396

Approaches to Stability Assessment²

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”

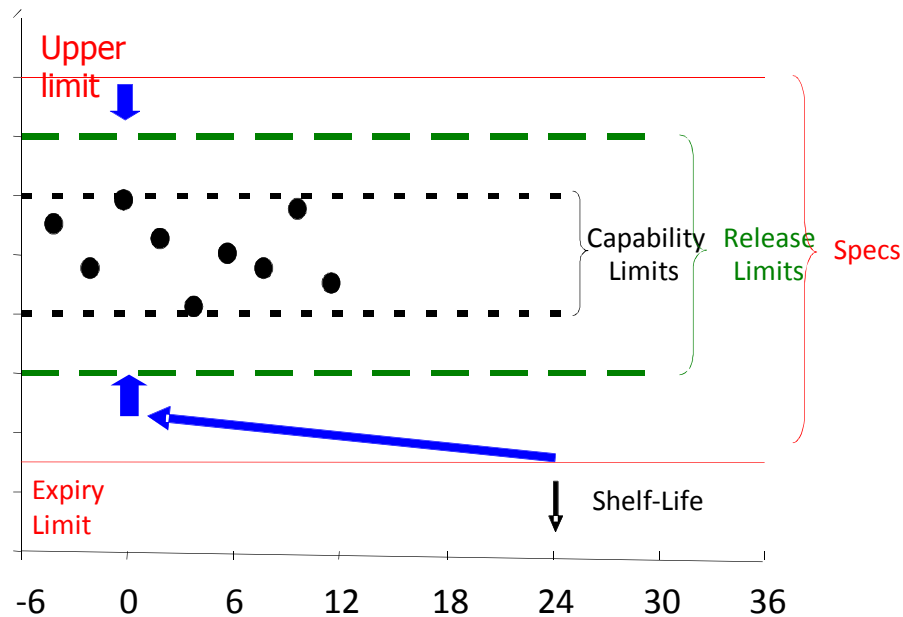


²W. Egan, T. Schofield, *Biologicals* 37 (2009) 379-386

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

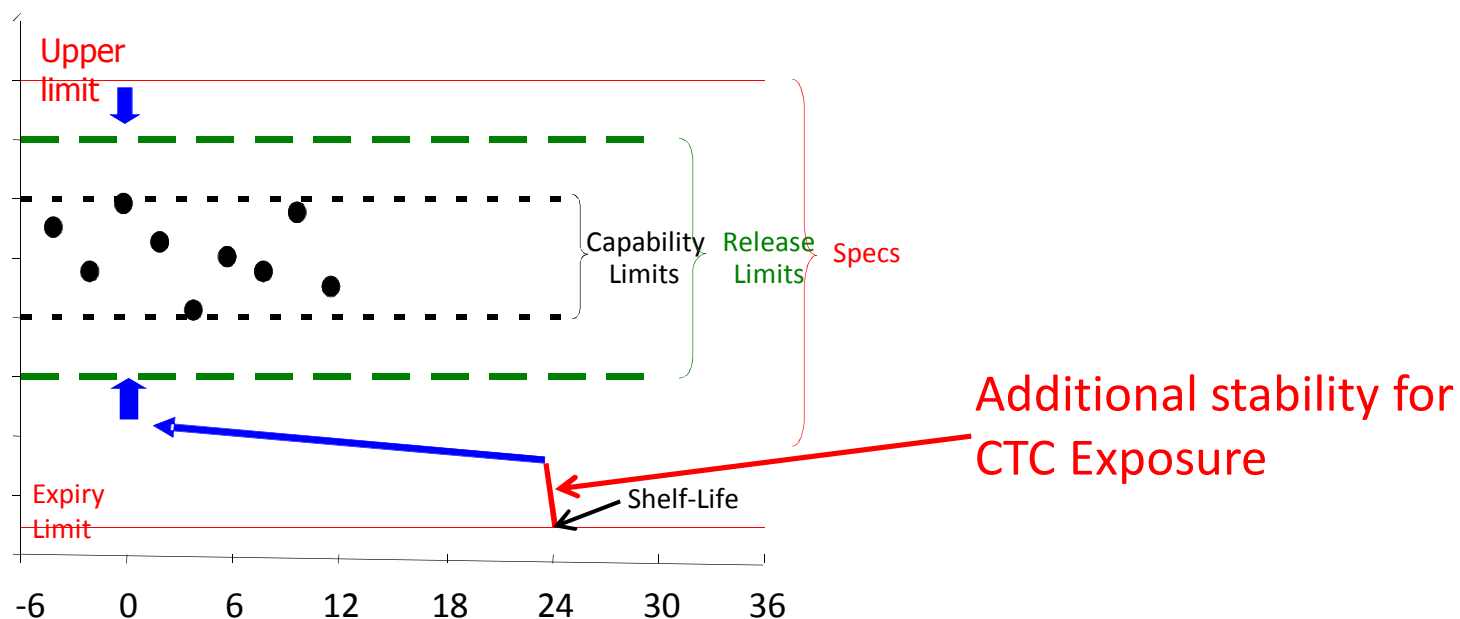
- This has also been called the “comprehensive model”, or the “estimation model” or the “statistical model”



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.

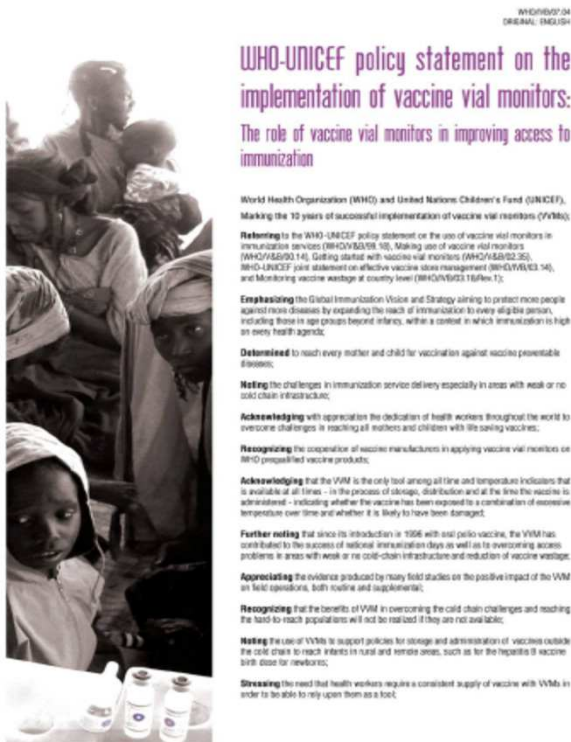
Characteristics That Define Vaccine Suitability

| 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. | |

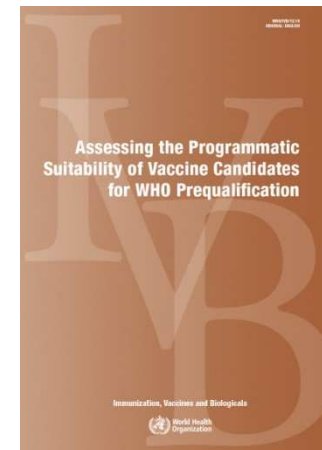
*VVM is a critical characteristic for vaccine prequalification

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



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 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.

WHO Guidelines on Stability Evaluation of Vaccines¹

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



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GUIDELINES ON STABILITY EVALUATION OF VACCINES

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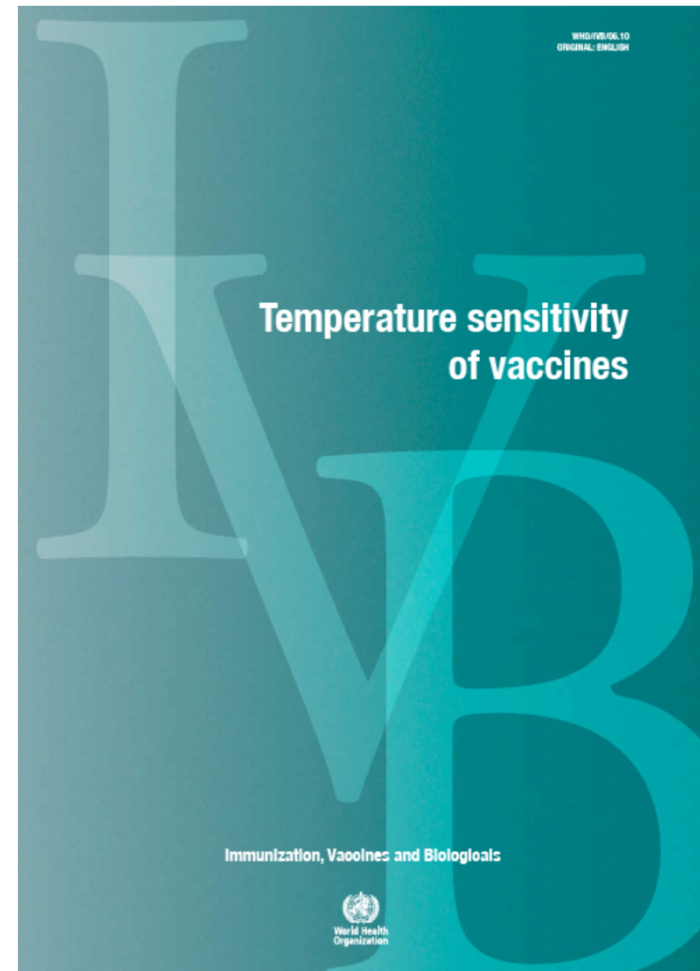
Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

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 Vaccines³

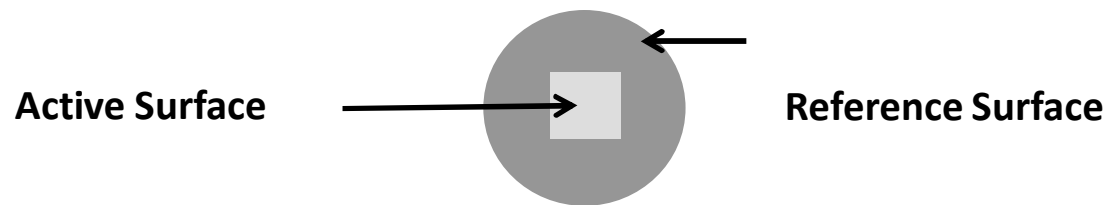
- The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).
- In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation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



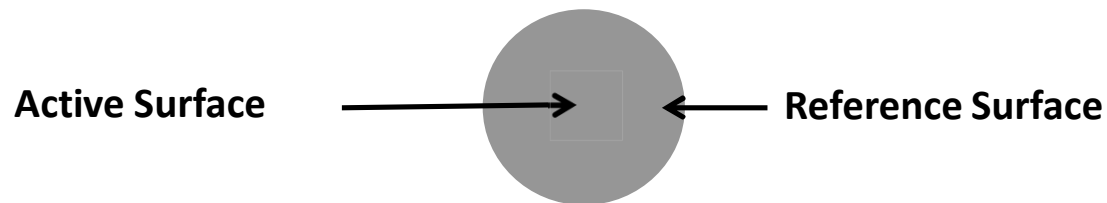
³<http://www.who.int/vaccines-documents/DocsPDF06/847.pdf>

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

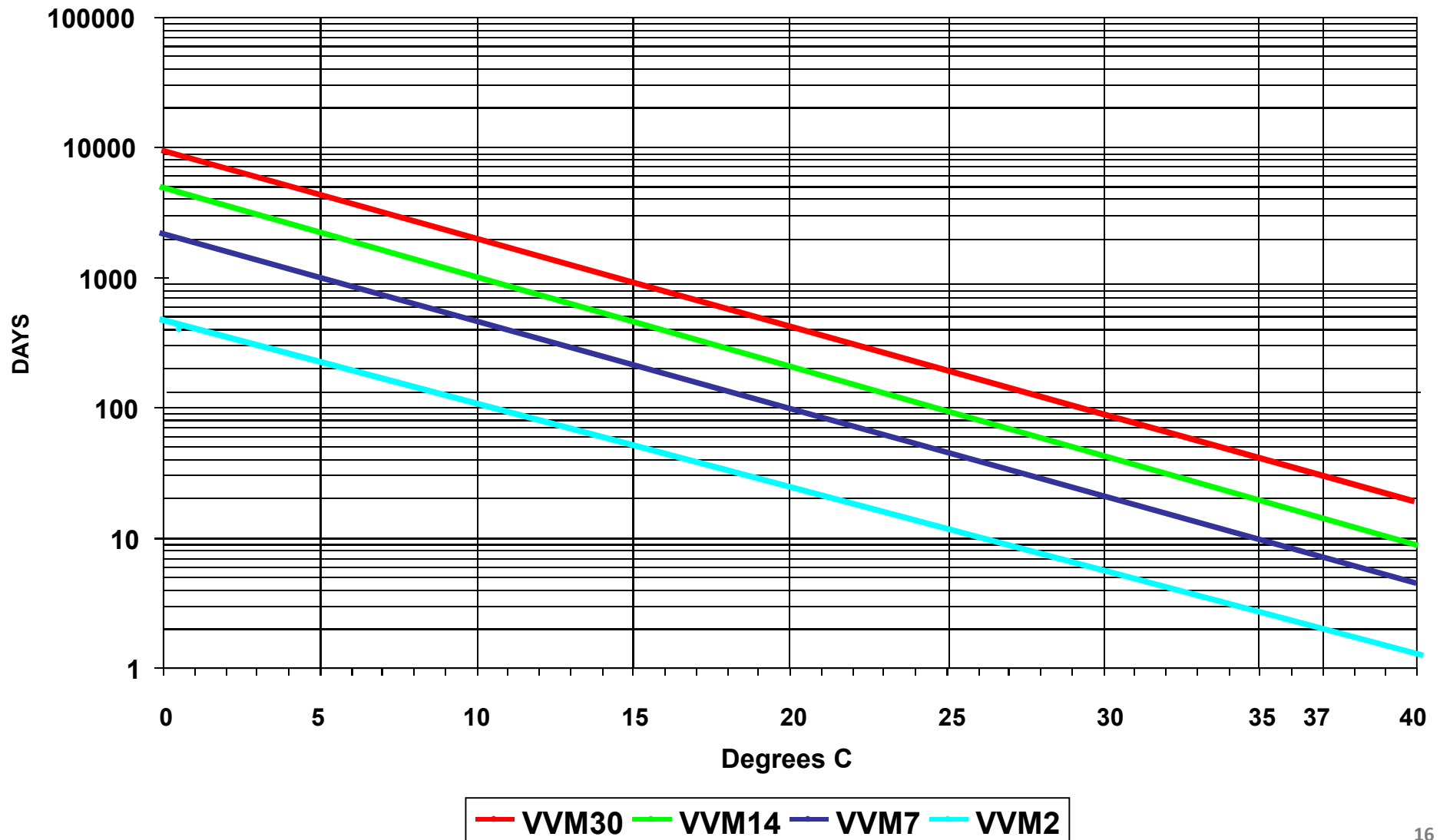
(new categories to be added: VVM11 and VVM250)

| 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

⁵http://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

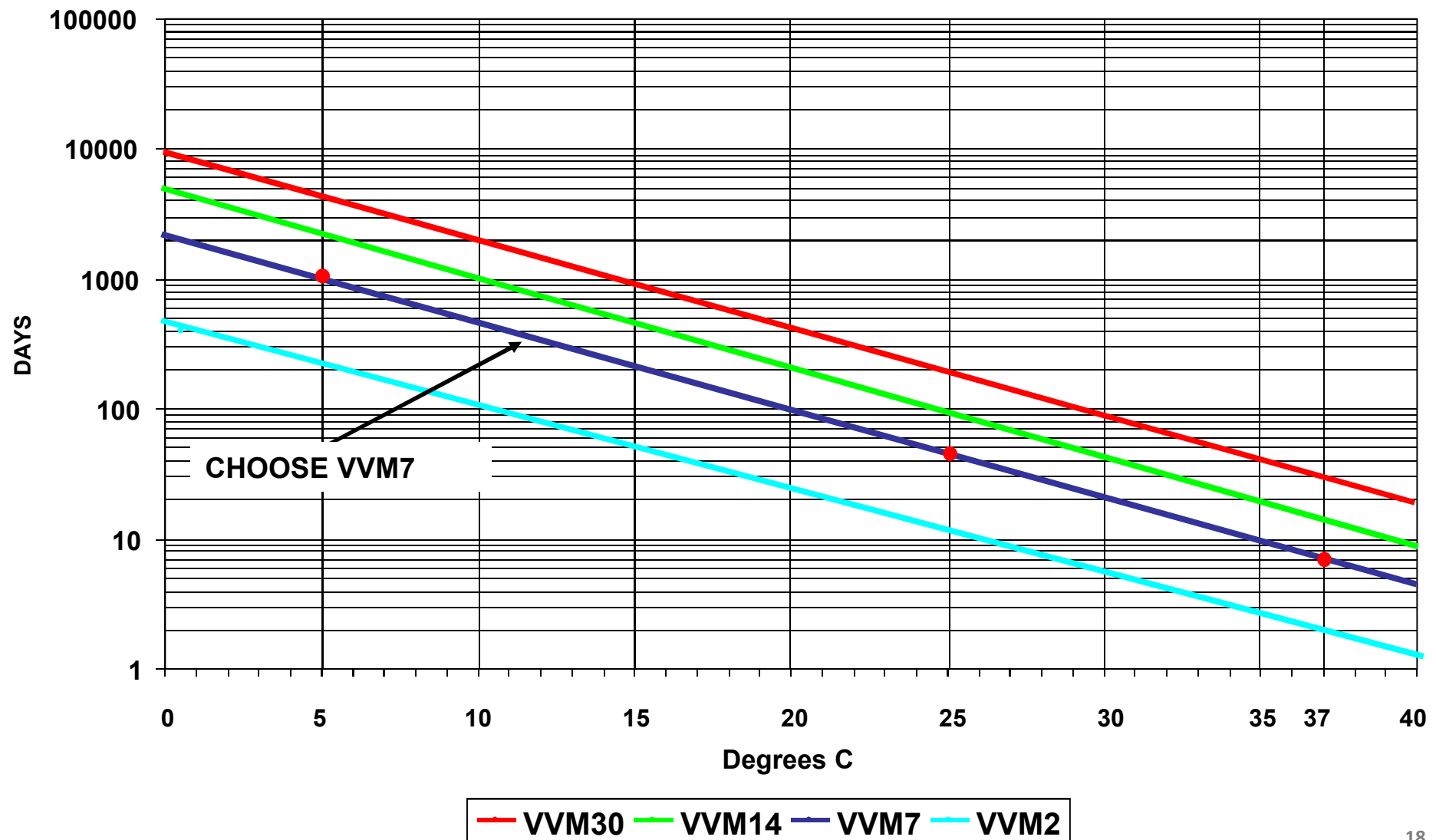
Step 1: Summarize stability data

- 2 to 8°C¹: 3 years (1095 days)
- 25°C: 45 days
- 37°C: 7 days
- Expiry Date: 2 years

¹2 to 8°C is treated as 5°C

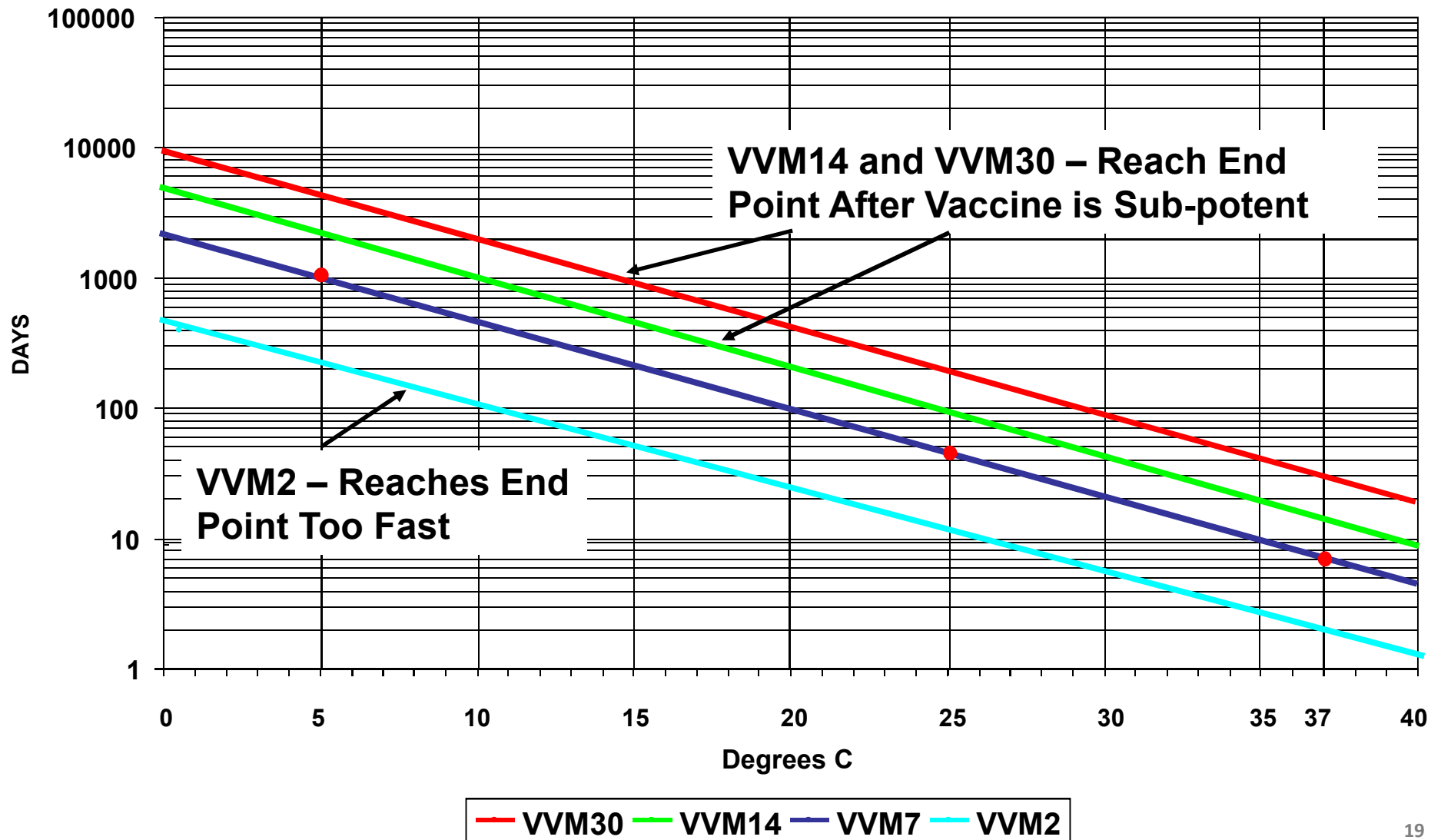
Product A Stability Data and VVM Categories

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

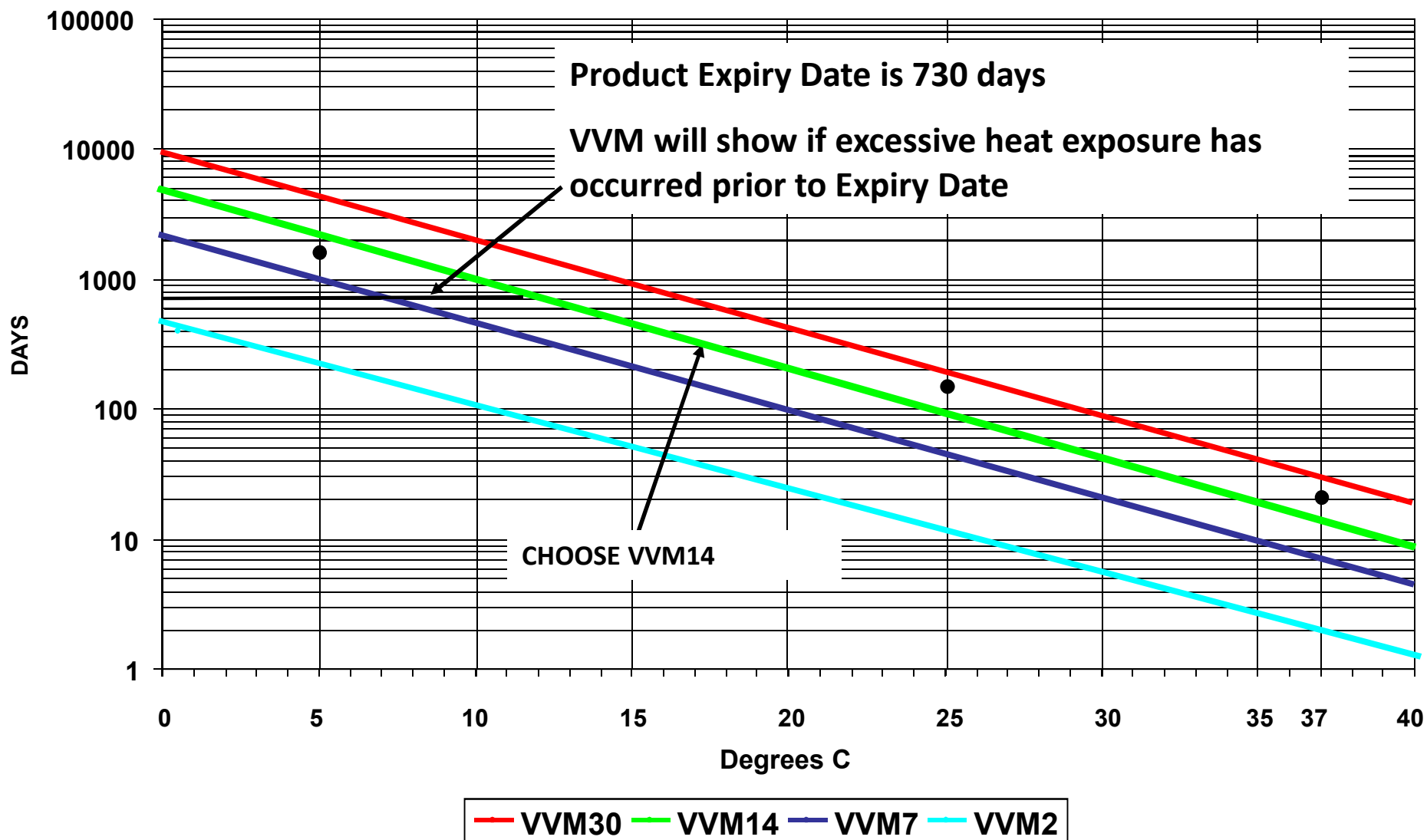
Step 1: Summarize stability data

- 2 to 8°C¹: 1600 days
- 25°C: 150 days
- 37°C: 21 years
- Expiry Date: 2 years

¹2 to 8°C is treated as 5°C

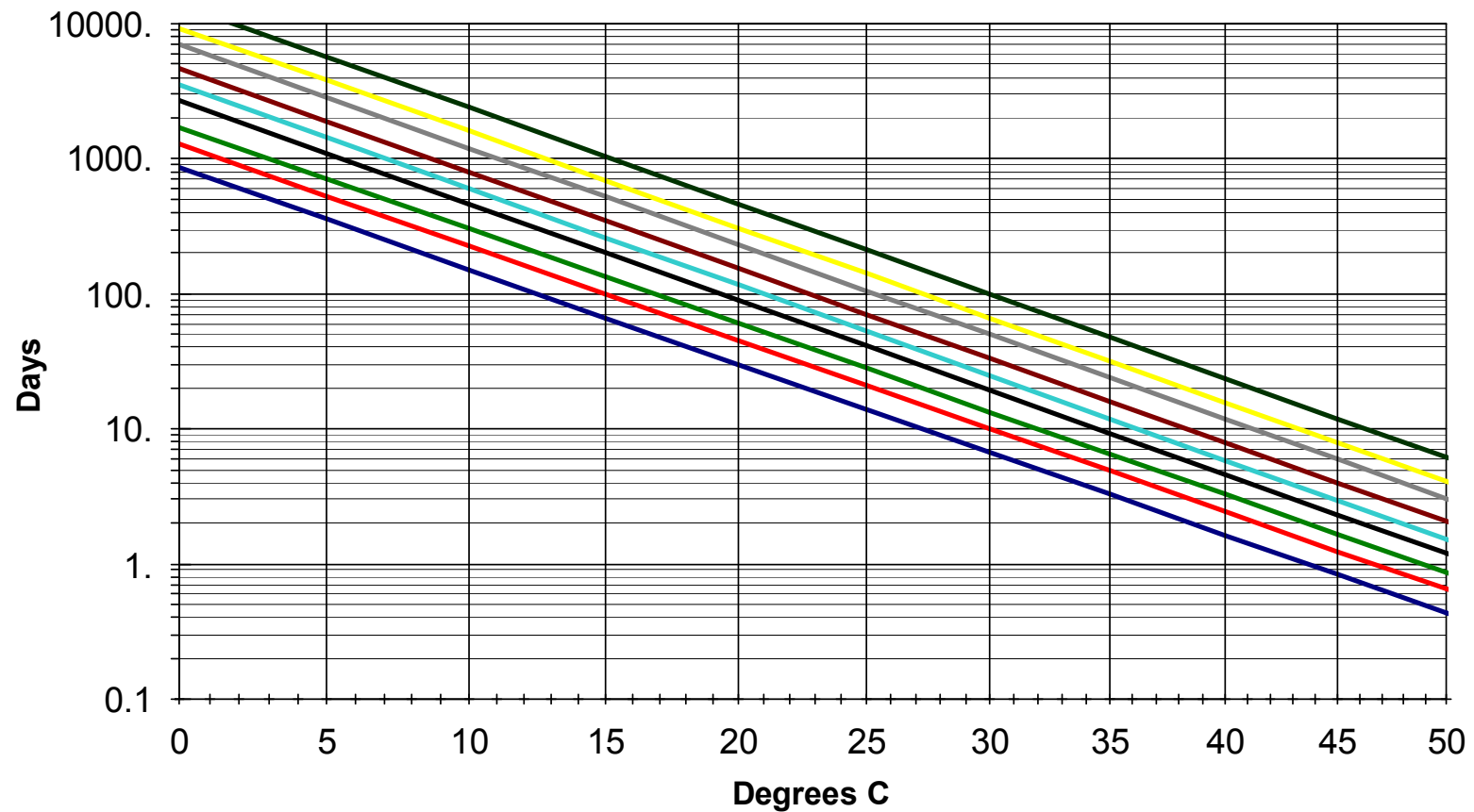
Product B Stability Data and VVM Categories

Step 2: Compare stability data with VVM categories



Other HEATmarker TTI Categories

HEATmarkers with UV Protection



Thank you!!!