HOW DO YOU MAKE BETTER DEVELOPMENT DECISIONS FASTER?

ICH STABILITY REQUIREMENTS
Overcoming the Challenges

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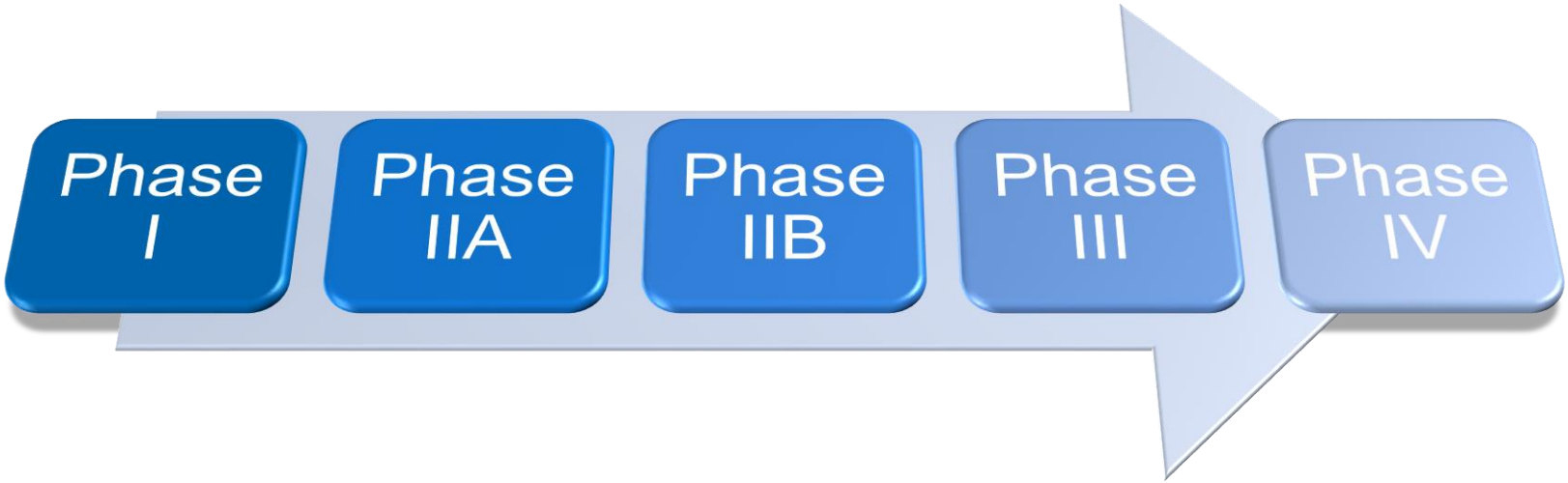
Stability Is Defined By…

- “resistance or the degree of resistance to chemical change or disintegration” – dictionary.com
- “the capacity of a drug product to remain within specifications established to ensure its identity, strength, quality and purity” – FDA, 1987, 1998
- “evidence on how the **quality** of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as **temperature, humidity, and light**, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.” – ICH Q1A

Factors That Influence Stability

- DP/DS Characteristics
  - Particle Size
  - Surface Area
  - Formulation
    - Excipients
    - pH
    - Preservatives
    - Solvents
  - Polymorphs
  - Crystalline Structure
- Environmental
  - Light
  - Heat
  - Oxygen
  - Humidity
- Container/Closure System
- Packaging

Stability Evolution



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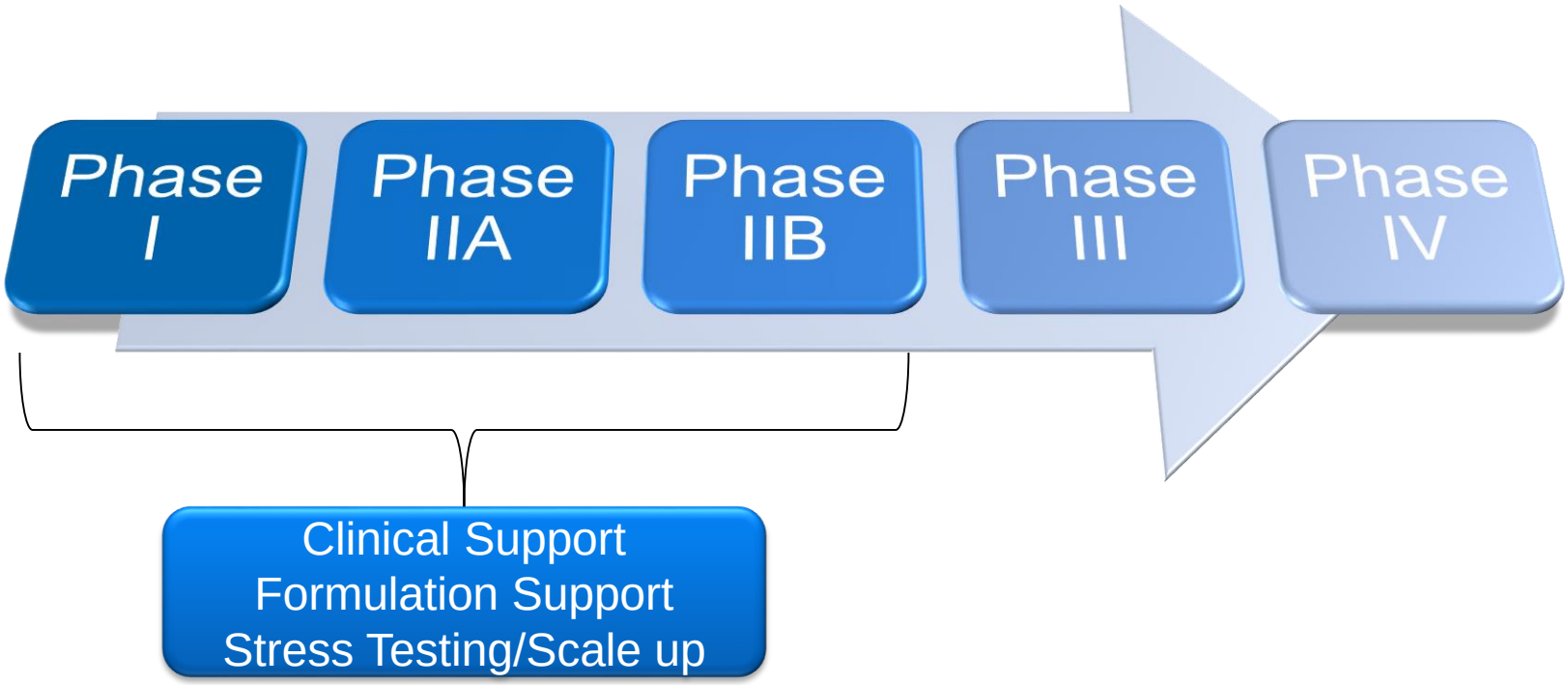

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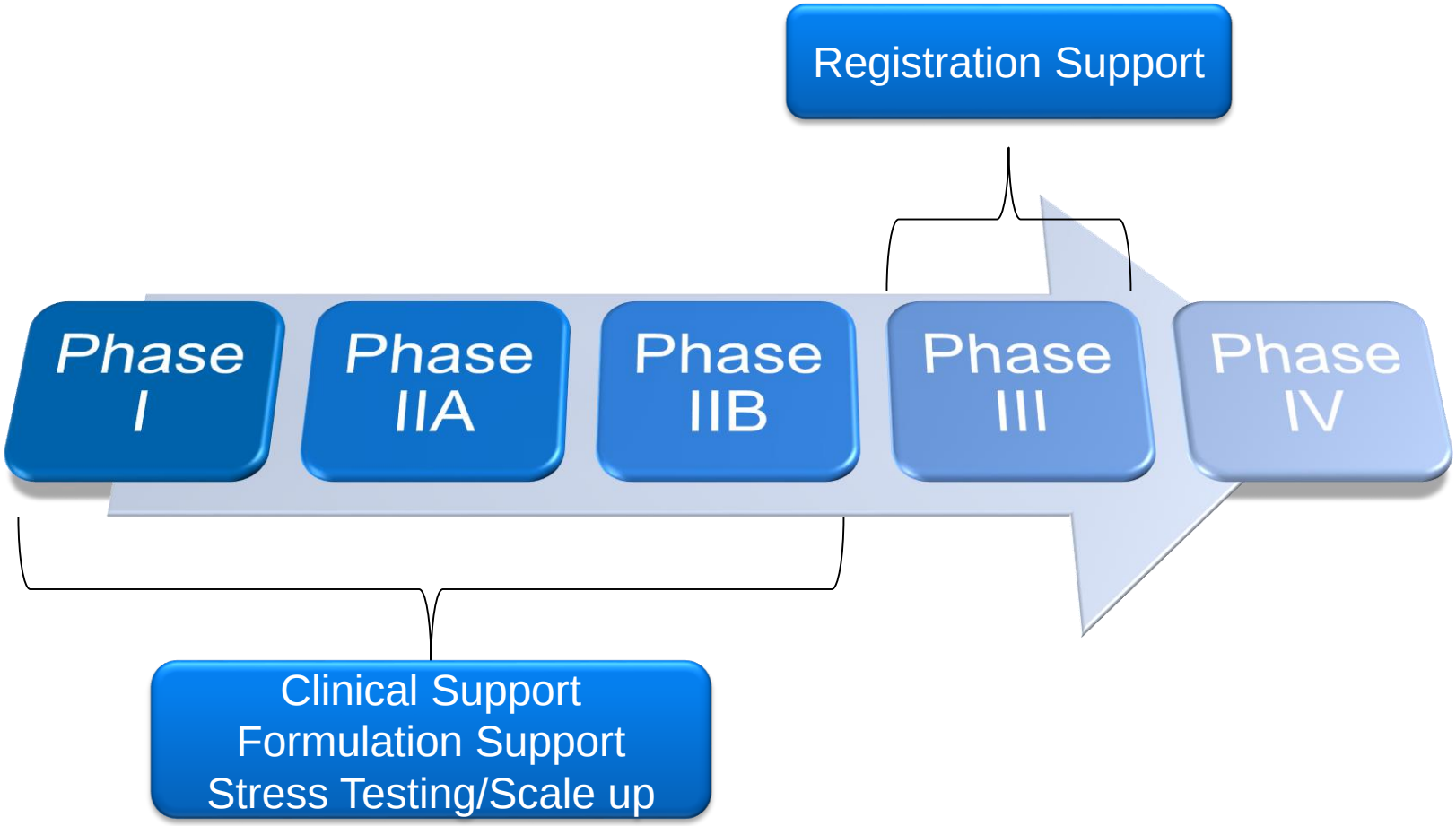

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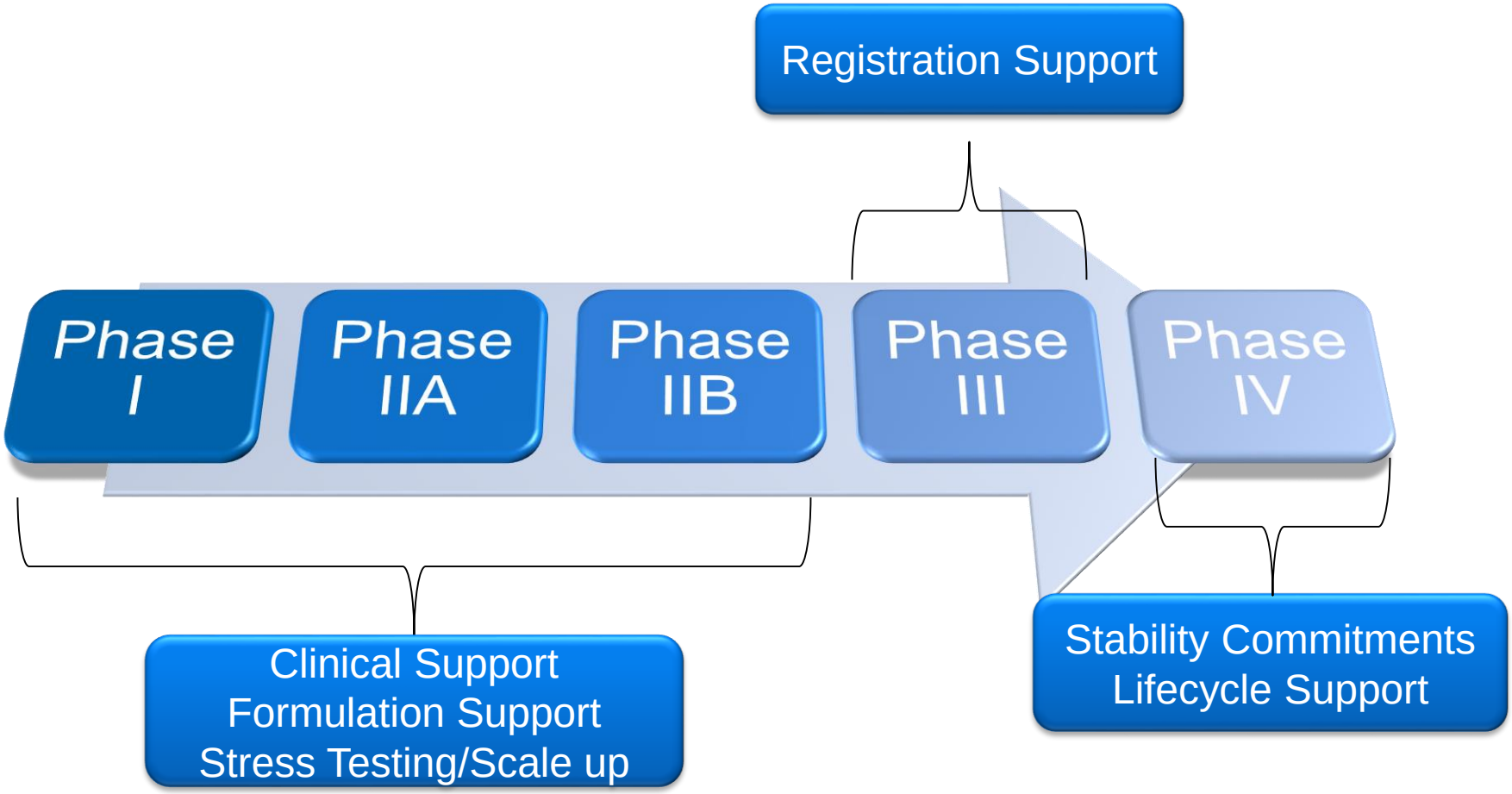


Who Is the ICH?

International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- **Japan:** Ministry of Health, Labour and Welfare, and Japan Pharmaceutical Manufacturers Association
- **Europe:** European Union and European Federation of Pharmaceutical Industries and Associations
- **USA:** Food and Drug Administration and Pharmaceutical Research and Manufacturers of America
- **Observers:** World Health Organization, European Free Trade Association, and Health Canada

What Is the Goal of ICH?

To increase international harmonization of technical requirements

- Reduce unnecessary duplication
- Reduce animal testing
- Reduce development costs

ICH issues *Guidance—NOT* REGULATIONS

ICH Guidelines

- **Q1A (R2)** – Stability testing of New Drug Substances and Products
- **Q1B** – Stability Testing: Photostability Testing of New Drug Substances and Products
- **Q1C** – Stability Testing for New Dosage Forms
- **Q1D** – Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- **Q1E** – Evaluation of Stability Data
- **Q1F** – Stability Data package for Registration Applications in Climatic Zones III and IV - Withdrawn
- **Q5C** – Stability Testing of Biotechnological/Biological Products

Goals Of the Guidelines

- Provide evidence on how quality varies with
  - Time
  - Heat
  - Light
  - Humidity
- Establish re-test period for DS
- Establish Shelf Life

Climactic Zone

	Zone 1	Zone II	Zone III	Zone IV
Description:	Moderate	Mediterranean	Hot/Dry	Very Hot/Moist
Average Temp:	21 °C	25 °C	30 °C	30 °C
Average %RH:	45% RH	60% RH	35% RH	70% RH

ICH Q1A (R2)

- Guideline applies to zones I and II
  - EU, Japan and US
    - ✓ Data generated in any region is applicable to other two regions
  - Does not apply to ROW
    - ✓ WHO guidelines
- Defines recommended stability data for registration

Stability Study Types

- Long term
  - “normal” target storage conditions
- Intermediate
  - Stability condition which is designed to moderately increase the rate of degradation
- Accelerated
  - Stability condition which can be used as a potential worst case predictive condition for the long term conditions
- Stress testing
  - Intentional degradation by various chemical and non-physical stressing conditions
- Photostability
  - Determination of impact of light on the stability of the product

Stability Conditions

	Long Term	Intermediate	Accelerated
General Storage	25 °C/60% RH (12 months)	30 °C/65% RH (6 months)	40 °C/75% RH (6 months)
Refrigerated Storage	5 °C (12 months)	NA	25 °C/60% RH (6 months)
Frozen Storage	- 20 °C	NA	NA
Below -20 °C	Case-by-case		
Semi-Permeable	25 °C/40% RH Or 30 °C/35% RH (12 months)	30 °C/65% RH (6 months)	40 °C/ NMT 25% RH (6 months)

Drug Substance Requirements

- 3 Primary Batches
  - Same process and synthetic route as final procedure
  - Quality should be same as production scale
  - container/closure should be the same or representative of proposed storage

Drug Product

- 3 primary batches
  - On each DP configuration
    - Unless bracketing/matrixing
  - Batches made by same process as filed
  - Each batch recommended to be made with different DS batches
  - Container/Closure should be same as proposed marketing packaging
    - Include secondary if needed

Testing Frequency

- Long Term
  - 1st year: every 3 months
  - 2nd year: every 6 months
  - Yearly after
- Accelerated
  - Three time points
  - 0, 3, and 6 months
- Intermediate
  - Every three months for 1 year
  - If needed as a result of Significant Change

Significant Change

- Drug Substance
  - Failure of specification
- Drug Product
  - 5% change in assay from initial value
  - Degradation specification failure
  - Failure for appearance, functional or physical attributes

What To Test?

- Attributes which are susceptible and may “influence quality, safety, and/or efficacy”
- Critical Quality Attributes
- Physical, Microbial, Chemical

Typical Quality Attributes

- Chemical
  - Loss of Efficacy
    - Assay/Potency
  - Increase in toxicity
    - Impurities
- Microbial impact
  - Sterility
- Change in Elegance
  - Taste
  - Smell
  - Color

- Physical
  - Dissolution
  - Hardness
  - Precipitation
  - Reconstitution
- Packaging Failures
- Loss of functionality
- Semi-Permeable
  - Water Loss

Stress Testing

- Degradation Pathway determination
  - Acid, Base, Oxidation, Heat, Humidity, Light Stress
  - Determination of potential impurities
  - Determination of potential susceptibilities
- Analytical Methods
  - Help to direct method development/validation
    - Mass Balance
    - Stability Indicating Determination

Analytical Methods

- Perform GAP analysis on early phase methods
  - Ensure proper development for phase III expectations
- Employ stability indicating method(s)
- Methods should be validated
  - ICH Q2
  - FDA guidance (Feb 2014): Analytical Procedures and Methods Validation for Drugs and Biologics

ICH Q1B - Photostability

- 1.2 million lux overall exposure
- Integrated UV of NLT 200 watt hours/m^2

Option I

- "Sun" lamp: D65 (ISO 10977)
- Temperature exposure a concern

Option II

- Cool white fluorescent and near UV fluorescent lamps
- Longer stressing times

Photostability - DS

- Forced Degradation
  - Determination of photodegradation pathways
  - Analytical method support
- Confirmatory
  - Handling, packaging and labeling
- Presentation
  - Minimize physical changes
    - ✓ Evaporation, sublimation, etc.
  - Transparent container, i.e. Quartz
  - Solid, NMT 3mm thick

Photostability - DP

- Stepwise Procedure
  - Direct Exposure
    - ✓ If applicable
    - ✓ If acceptable change may stop
  - Immediate Pack
    - ✓ Primary container/closure
    - ✓ Orient to get uniform exposure
    - ✓ If acceptable change may stop
  - Marketing Pack
    - ✓ Secondary packaging/marketing packaging
    - ✓ If unacceptable change, reformulation/repackage

ICH Q1C – New Dosage Form

- Same API as existing product but in a different form
  - Different route of administration
    - ✓ Oral to parenteral
  - New Functionality
    - ✓ Immediate release to Sustained release
  - Different dosage form
    - ✓ Tablets to capsules
- Follow ICH Q1A and Q1B
  - Reduced testing may be justified

ICH Q1D – Reduced Testing

- Bracketing
  - Only extremes of ranges are tested
    - ✓ 1, 3, 5, 7 mg tablets
    - ✓ Only test 1 and 7 mg tested at all time points
    - ✓ Intermediate levels represented by extremes
- Matrixing
  - Subsets of samples are tested at time points
    - ✓ Assumes each subset is representative of all subsets

ICH Q1E - Evaluation

- Main Topics
  - How to analyze the data generated by ICH Q1A
  - When to use extrapolation
  - How to set retest/shelf life

Case 1 – No Change

- Accelerated Condition: No significant change
- Long Term Condition: No significant change
- Room Temperature
  - Statistical Evaluation may not be needed
  - Extrapolation of shelf life can be double but no more than 12 months beyond long term data
- Refrigerated
  - Extrapolation of shelf life can be 1.5 times but no more than 6 months beyond long term data

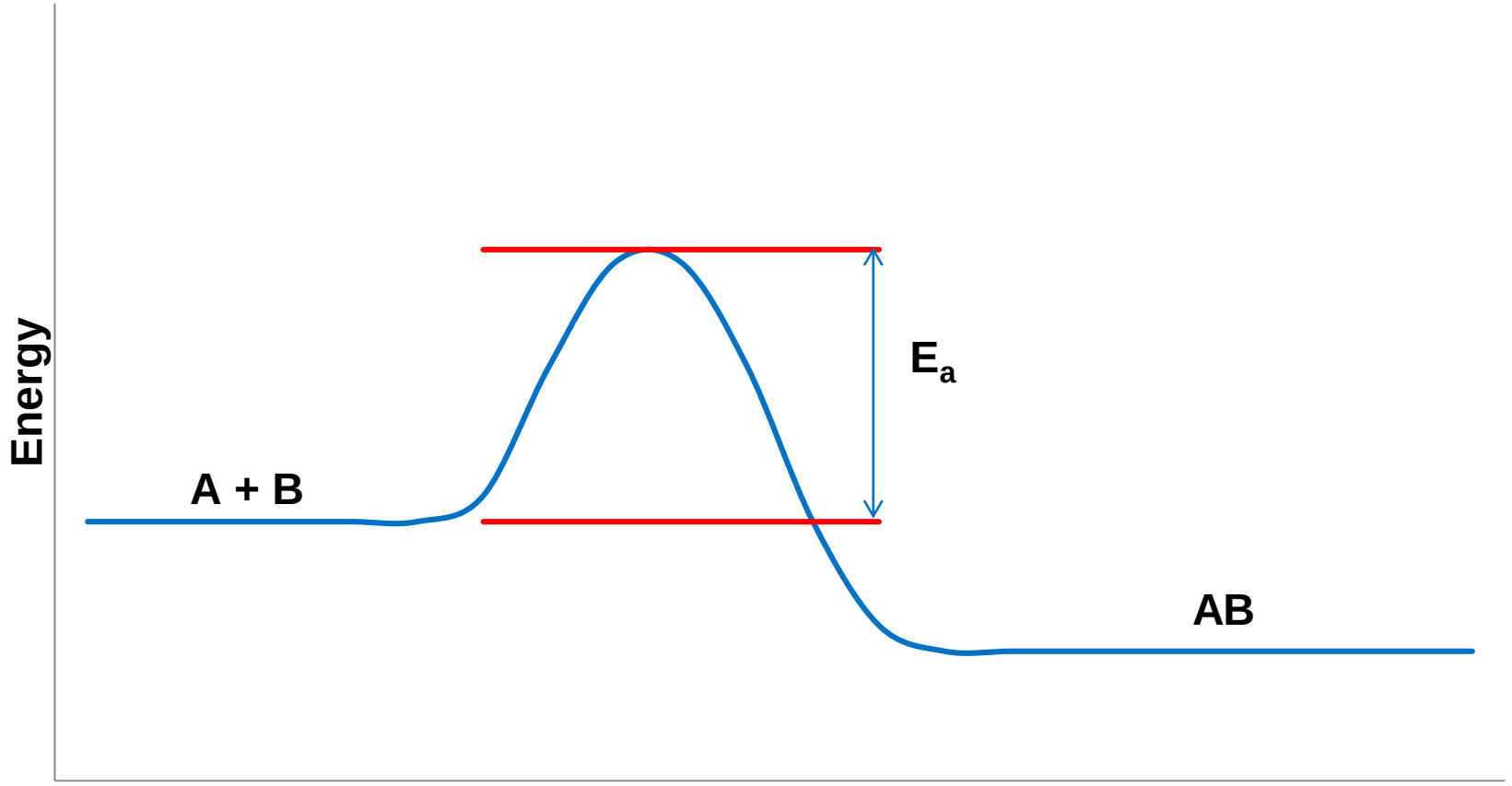
Case 2 – Some Change/Variability

- Accelerated Condition and/or Long Term Condition show change/variability
  - Data not amendable to interpretation
    - ✓ Supporting data may be used
    - ✓ Developmental batches
    - ✓ Extrapolation of shelf life can be 1.5 times but no more than 6 months beyond long term data
    - ✓ Refrigerated: shelf life can no more than 3 months beyond long term data
  - Data amenable to interpretation
    - ✓ Extrapolation of shelf life can be double but no more than 12 months beyond long term data
    - ✓ Refrigerated: shelf life can be 1.5 times but no more than 6 months beyond long term data

Case 3 – Significant Change

- Accelerated Condition: Significant change
- Intermediate Condition: No significant change
- Room Temperature
  - Long term data not amenable
    - ✓ Extrapolation of shelf life no more than 3 months beyond long term data
    - ✓ If backed up by supporting data
  - Long term data amenable
    - ✓ Extrapolation of shelf life can be 1.5 times but no more than 6 months beyond long term data
- Refrigerated
  - Extrapolation is not appropriate
  - Retest/Shelf life based on long term data

Why Accelerated Not Always Predictive



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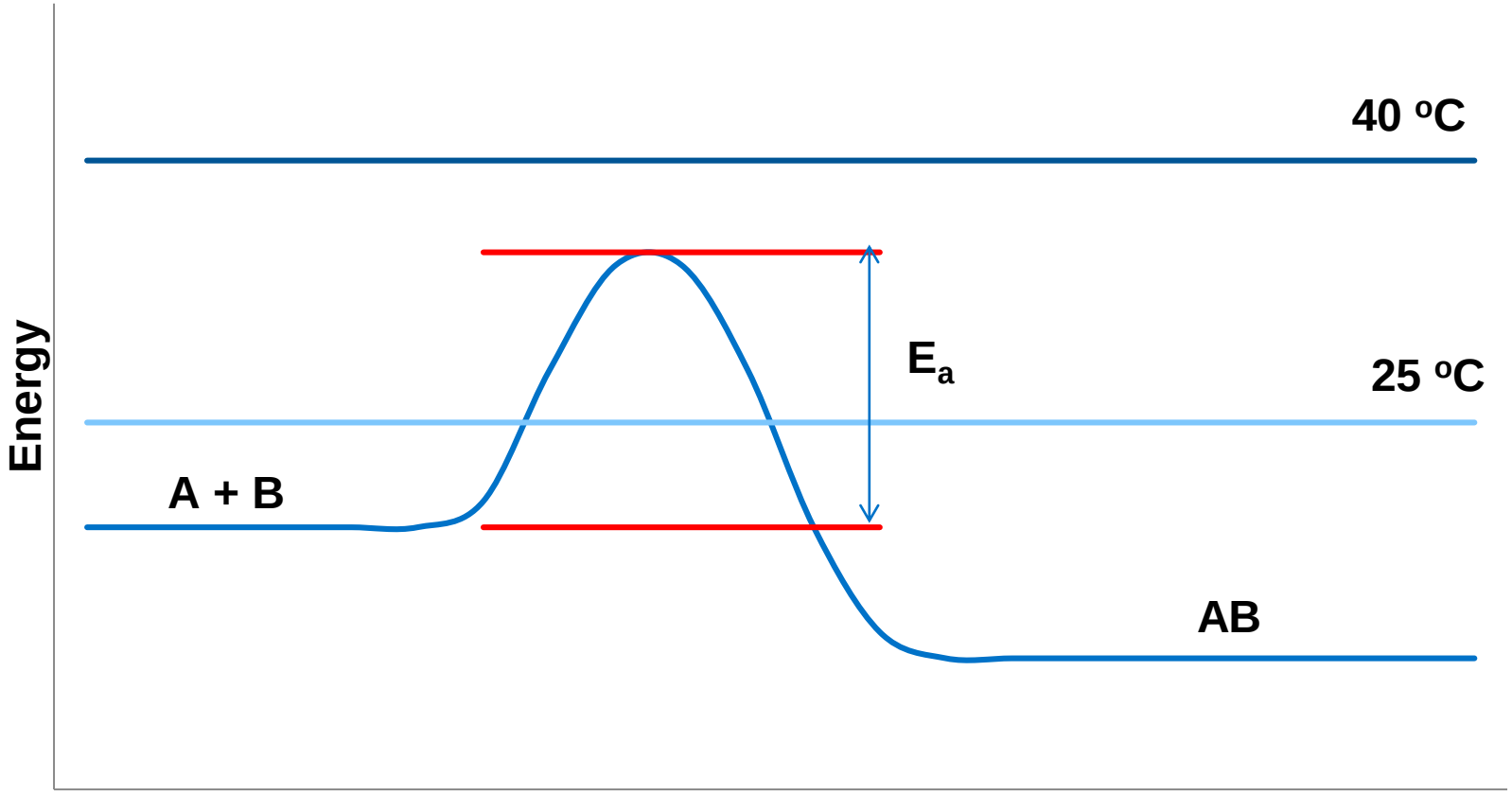


Case 4 – Significant Change

- Accelerated Condition: Significant change
- Intermediate Condition: Significant change
- Evaluation
  - Retest/Shelf life cannot exceed long term data

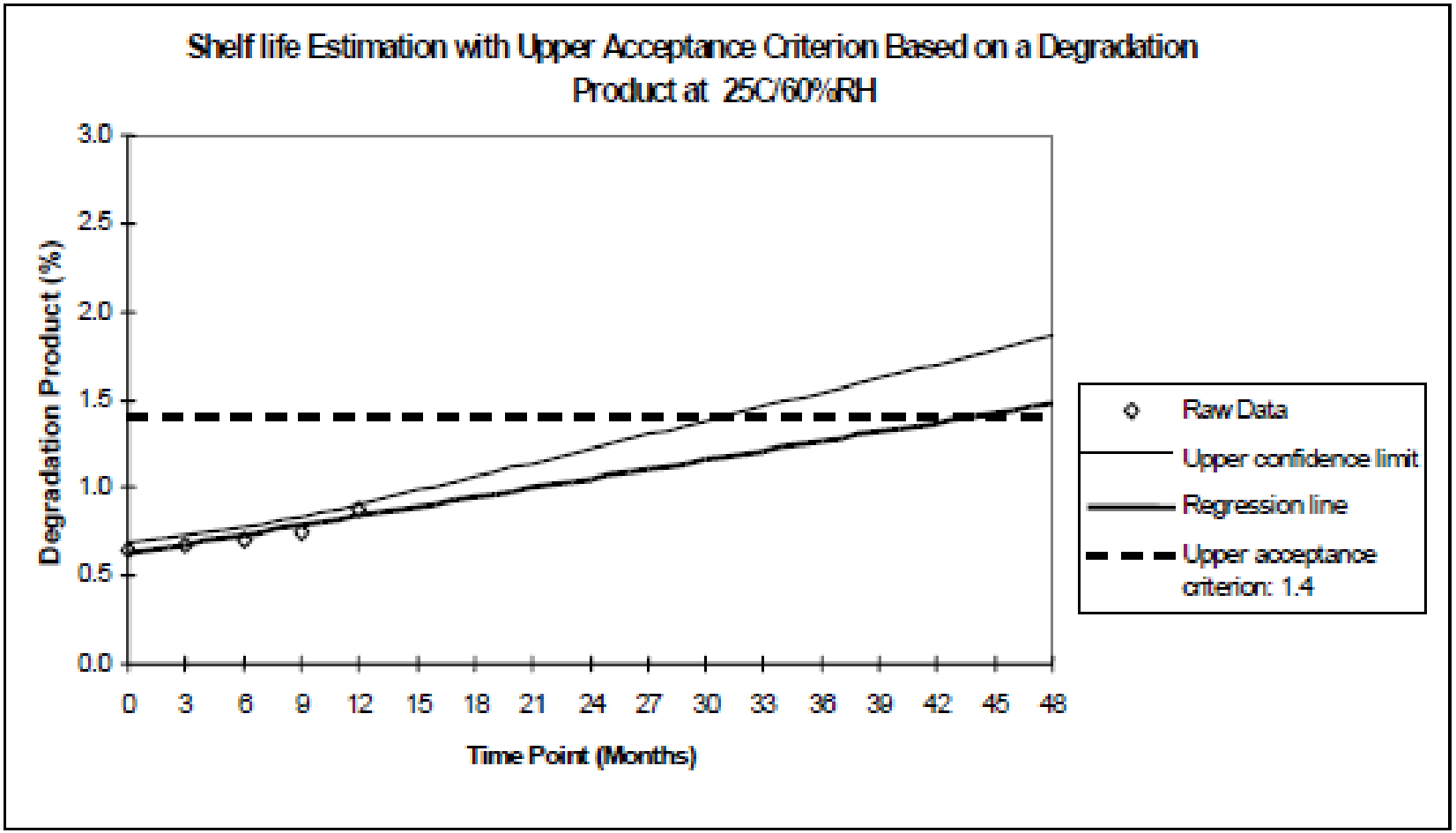
Frozen Storage

- Retest/Shelf life based on long term data
- Testing on single batch at 5 ^{o}C or 25 ^{o}C recommended for excursions
- For storage below -20 ^{o}C
  - Addressed on case-by-case basis
  - Retest/Shelf-life based on long term data

Statistical Approaches

- Regression Analysis
  - May be linear or non-linear
  - Plot intersection of 95% confidence interval with proposed specification
    - ✓ One-sided or two-sided confidence intervals
  - SAS, Slimstat, JMP, etc
  - Analysis should take into account study design to ensure statistical significance

Example Plot



ICH Q5c

- In general ICH Q1A can be applied
  - Special Considerations should be made
    - ✓ Complexity of stability indicating methods
    - ✓ Availability of lots
    - ✓ Retest/Expiry based on long-term, real-time data

Case Study 1

- Accelerated/Long Term stability both demonstrated a loss of mass balance (HPLC method)
  - Scenario 1: Impurities with different spectral properties
  - Scenario 2: Inappropriate methods
- Both Scenario 1 and 2
  - Stress studies inadequate
  - Degradation Pathway not understood
  - Method development didn't use appropriately stressed samples
  - New methods developed using alternate detection techniques

Case Study 2

- Impurity peak grew over 6 months then decreased
  - Trending at 6 months would have had expiry at 12 months
  - Impurity decreased at 9 and 12 month time points
- Isolation and ID performed
  - Impurity was an intermediate
    - ✓ $A + B \rightarrow C$
    - ✓ $C \rightarrow D$
  - Reaction product (D) found in the solvent front
    - ✓ New method developed

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