Forced Degradation Conditions and ‘Endpoints’: Review, Industry Benchmarking, and Recommendations

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September 20, 2022

Philadelphia, PA USA

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STABILITY - PURITY - QUALITY

IFDC
International Forced Degradation Community

Evaluating Stress Testing Endpoints

ANVISA Workshop, 16 May 2022

Presented by: International Forced Degradation Community (IFDC)

Outline

1. Scope
2. Introduction to forced degradation
3. Problem Statement and Study Objectives
4. Forced degradation endpoints – current landscape
   - Scientific literature
   - Regulatory guidance including ANVISA
   - Consortia internal best practices
5. IFDC stress testing endpoint recommendations

Scope

- In Scope: Today's endpoints discussion is derived from drug substance and solid drug product stress testing data

- Out of Scope: Endpoint considerations for non-solid dosage forms
  - Drug substance: stress testing study design independent of dosage form type
  - Drug product: forced degradation conditions and experimental details can vary based on drug product type (e.g. parenteral formulations), however, the same endpoint principles apply

What is Forced Degradation?

- Also referred to as “stress testing”
- ICH Q1A(R2) is the gold standard for defining stress testing
- Exposing drug substances and products to severe conditions designed to induce “potential” degradation pathways
- Conditions include pH extremes, oxidative stress, photolytic stress, thermal stress, exposure to high humidity, etc.
- Conditions tend to be more severe than accelerated stability, and is not necessarily a GMP activity

Reasons to Conduct a Forced Degradation Study

- Help understand the intrinsic stability of the drug substance
- Underpin method development and validation of stability indicating methods
- Provide information to guide the development of stable formulations
- Aid in determining pharmaceutically relevant degradation pathways which provide insight into potential control strategies
- Assist with structure elucidation of both potential (those formed in stress testing) and actual (those formed in ICH registration stability studies) degradation products
- Regulatory requirement

All forced degradation has a similar overarching purpose (*and challenge*)

- Objective: induce, within a short period of time, pharmaceutically relevant degradation pathways that have the potential to occur during manufacture, long-term storage, distribution and use
- Challenge: design a comprehensive forced degradation study plan that is sufficiently severe/rigorous to identify all pharmaceutically relevant degradation pathways
  - **Too severe** or conditions that are not scientifically justified risks generating non-pharmaceutically relevant degradation products and over engineering purity methods*
  - **Too mild** of conditions and actual degradation products formed in accelerated and real time stability samples of the final packaged products may be missed

*R. Singh, Z. Rehman. Current trends in forced degradation study for pharmaceutical product development. J Pharm Educ Res 2012; 3: 54-63

Problem Statement and Study Objectives

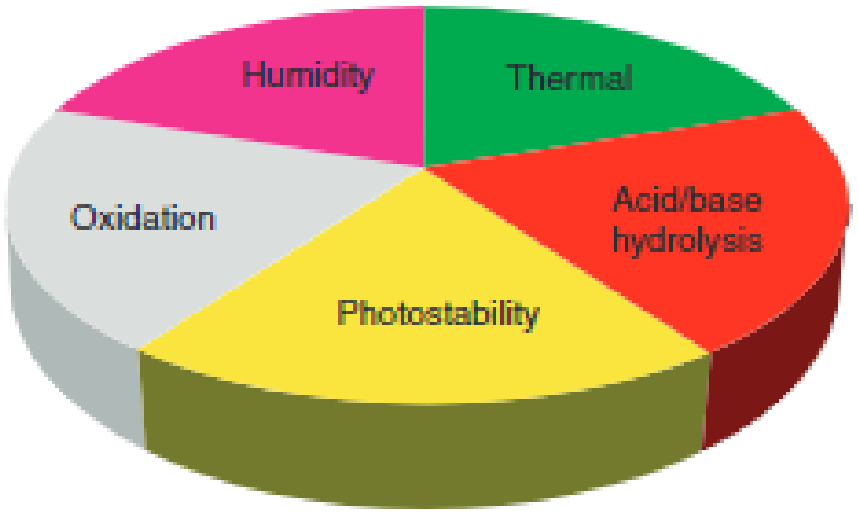
Problem statement

- When performing stress testing studies there is a lack of clarity and agreement in the scientific literature and regulatory guidance as to what constitutes an appropriate endpoint
- It is unclear what represents a suitable justification for declaring a drug substance (DS) or drug product (DP) **stable** to a specific stress testing condition or degradation pathway

Study Objectives

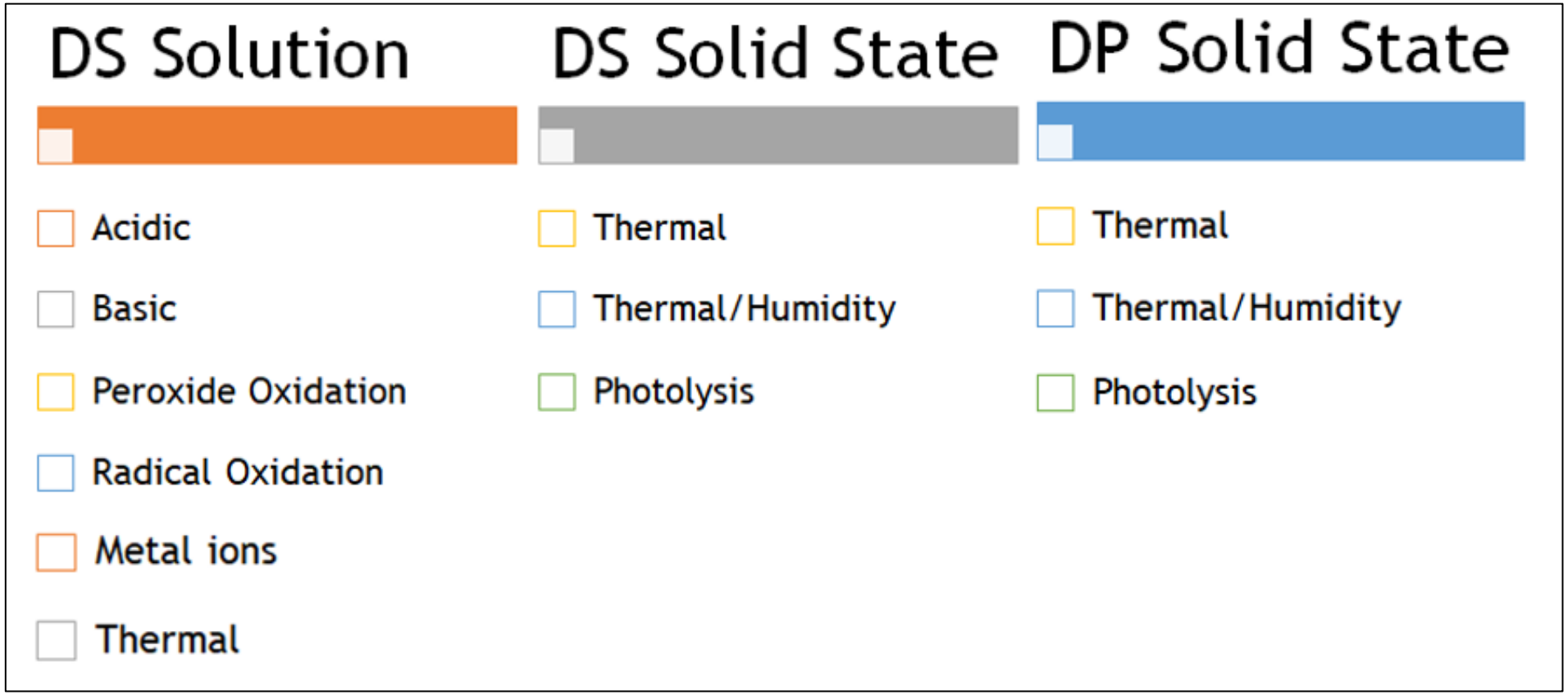
- Provide technical recommendations for forced degradation endpoints for specific conditions
  - For a ***reactive*** drug substance and drug product
  - For a ***stable*** drug substance and drug product: the maximum amount of pharmaceutically relevant stress required to prove a drug substance or drug product is stable to a specific stress condition

Pharmaceutically Relevant Degradation Pathways



- There are five main pharmaceutically-relevant stress conditions
- A well-designed stress testing study will evaluate the potential for these conditions to induce degradation in the DS and DP
- Not all the conditions will necessarily lead to degradation during stress testing studies
- DS and DP can be classified as stable or reactive for particular conditions when appropriate forced degradation endpoints are applied

Stress Testing Study Design in Line with Industry Best Practices for Solid Drug Products



- Solution phase stress testing of solid drug products not recommended
- IFDC. J Pharm. Sci. 2022 https://doi.org/10.1016/j.xphs.2021.06.012

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Literature Assessment of Endpoints

- The literature contains a large variety of publications citing a diversity of forced degradation conditions and endpoints*
- Extreme conditions have been employed that go beyond the recommendations in this presentation and that exceed pharmaceutically relevant handling, storage and distribution of materials
- There is little guidance on the recommended endpoints

*The diversity of conditions and endpoints historically used are best described in these two publications:

(1) Chapter 1, Baertschi SW, Reynolds DW, in Pharmaceutical Stress Testing: Predicting Drug Degradation, 2nd edition Baertschi SW, Alsante KM, Reed RA, Eds, Informa Healthcare, London (2011).

(2) Singh S, Bakshi M, Guidance on conduct of stress tests to determine inherent stability of drugs, Pharm. Technol. On-Line, p. 1-14, April (2000)

A Brief Overview of Regulatory Requirements

Relevant Regulatory Guidance

ICH:

Q1A(R2) - STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS - **2003**

Q1B - PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS - **1996**

Q1C - STABILITY TESTING FOR NEW DOSAGE FORMS - **1996**

Q1D - BRACKETING & MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSANCE AND PRODUCTS - **2002**

Q1E - EVALUATION OF STABILITY DATA - **2003**

Q1F - STABILITY DATA PACKAGE FOR REGISTRATION APPLICATION IN CLIMATE Zones III and IV - **Withdrawn**

Q2(R1) - VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY - **2005, in review**

Q3A(R2) - IMPURITIES IN NEW DRUG SUBSTANCES - **2006**

Q3B (R2) - IMPURITIES IN NEW DRUG PRODUCTS - **2006**

Q6A - SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES - **1999**

Q7 - GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS - **2000**

M7 R1) - ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK - **2017**

- https://www.ich.org/page/quality-guidelines;
- https://www.who.int/medicines/areas/quality_safety/quality_assurance/stblty-testing-APIsandFPPS-QAS17-694_12012017.pdf
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents

WHO:

TRS 1010, Annex 10 - Stability testing of active pharmaceutical ingredients and finished pharmaceutical products - **2018**

FDA:

FDA-1999-D-0030 - INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls. Guidance for Industry - **2003**

FDA-2015-N-0007 - Analytical Procedures and Methods Validation for Drugs and Biologics: Guidance for Industry - **2015**

Analysts on Inspection. In: ORA Laboratory Manual. Volume III, Section 5, **2019**

EMA:

CPMP/QWP/122/02, rev 1 corr. - Committee for Proprietary Medicinal Products (CPMP). Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products - **2003**

CHMP/QWP/185401/2004 final - Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials - **2006**

ANVISA:

RDC 53 - degradation products in drug products with synthetic and semi-synthetic active substances, classified as new, generic and similar – **2015**
Guideline 04 – Supports RDC 53 – **2015**
Q&As RDC 53 – **2016, 2017, 2018, 2019**
RDC 318 – Stability Studies – **2019**
RDC 166 – Analytical Method Validation - **2017**

Overview of Regulatory Guidance: ICH and WHO

- **ICH Guidance (Q1A(R2), Q3A(R2), Q3B(R2))**
  - No specific targets for endpoints (% degradation or time / temperature, reagent conc.)
  - Q1B Photostability guideline implies photostress > confirmatory exposures

- **WHO Guidance**
  - 10-30% total degradation
  - Absence of deg products after 10 days, the API is considered stable under the particular stress condition.

Singh S et al., Trends in Analytical Chemistry, 49, 71-88 (2013)

Table 1
WHO suggested pre-formulation stress testing protocol for the development of FDC-FPP [12]

Stress factor	Conditions	Concentration of APIs[a]	Time
Heat	60°C	1:1 with diluent[b]	1–10 days
Humidity	75% RH or greater	Solid state	1–10 days
Acid	0.1 N HCl	2:1 in 0.1 N HCl	1–10 days
Base	0.1 N NaOH	2:1 in 0.1 N NaOH	1–10 days
Oxidation	3% H_2O_2	1:1 in 3% H_2O_2	1–3 hours
Photolysis	Metal halide, mercury, xenon or ultraviolet-B fluorescent lamp	1:1 with diluents[b]	1–10 days
Metal ions (optional)	0.05 M Fe^{2+} or Cu^{2+}	1:1 with solution of metal ions	1–10 days

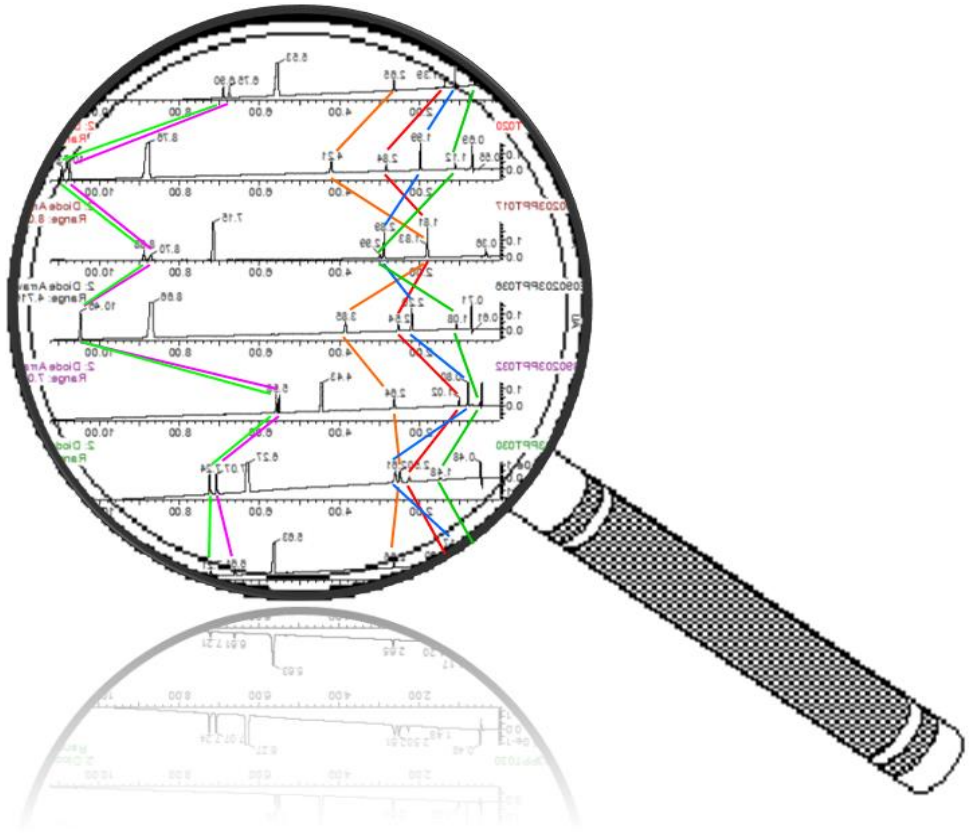
[a] When testing degradability of APIs in combination, the APIs should be in the same ratio as in the FDC-FPP.
[b] In each case, the diluent is either an excipient or all excipients in the formulation in the same ratios as in the formulation. Other ratios of diluent may also be appropriate, for example, the approximate ratio in which the drug and excipients will be used in a formulation.

Requirements of RDC 53/2015 and Guide No. 4/2015

- **RDC 53/2015**
  - Art.6 ° forced degradation studies should promote degradation to the extent sufficient to allow evaluation of formation of degradation products.
    - § 1: The tests should promote degradation greater than 10% (ten percent) and less than that which would lead to complete degradation of the sample.
    - § 2: In tests where degradation is less than 10% (ten percent), the company must provide technical justification.

- **Guide No. 4/2015**
  - Section 8. EXPERIMENTAL PART OF THE DEGRADATION PROFILE
    - The conditions should be varied so that a decrease in the main peak area of at least 10% is reached, optimally without occurring generation of secondary degradation products.
    - As justification for not reaching the minimum of 10% degradation under a certain condition, the company may demonstrate that the condition used is compatible with the maximum recommended in scientific literature.
    - The study parameters should be varied so that the acceptable degradation is reached in every condition or until the maximum recommended in scientific literature is reached.

IFDC - Forced Degradation Endpoint Best Practices



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Definition of Terms

- Endpoint
  - Solution phase stress: In drug substance and drug product stress testing studies an appropriate endpoint is either a % total degradation target outcome (**reactive**) OR a maximum amount of pharmaceutically relevant stress imparted to the drug substance or drug product (**stable**)
  - Solid phase stress endpoints are determined by
    - Thermal: Greater than or equal Kinetic Equivalence to 6M at accelerated conditions
    - Photo: In EXCESS of confirmatory light exposure (ICHQ1B)

- Verified endpoint range
  - The 2021 benchmarking forced degradation study design, including endpoints, gave coverage for accelerated and real time stability degradation products for 62 drug products

IFDC. Assessing the Relevance of Solution Phase Stress Testing of Solid Dosage Form Drug Products: A Cross-Industry Benchmarking Study. J Pharm. Sci. 2022 https://doi.org/10.1016/j.xphs.2021.06.012

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Building the Endpoint Data Set

Knowledge Landscape:

- Scientific literature
- Regulatory guidance (including ANVISA)
- IFDC company best practices

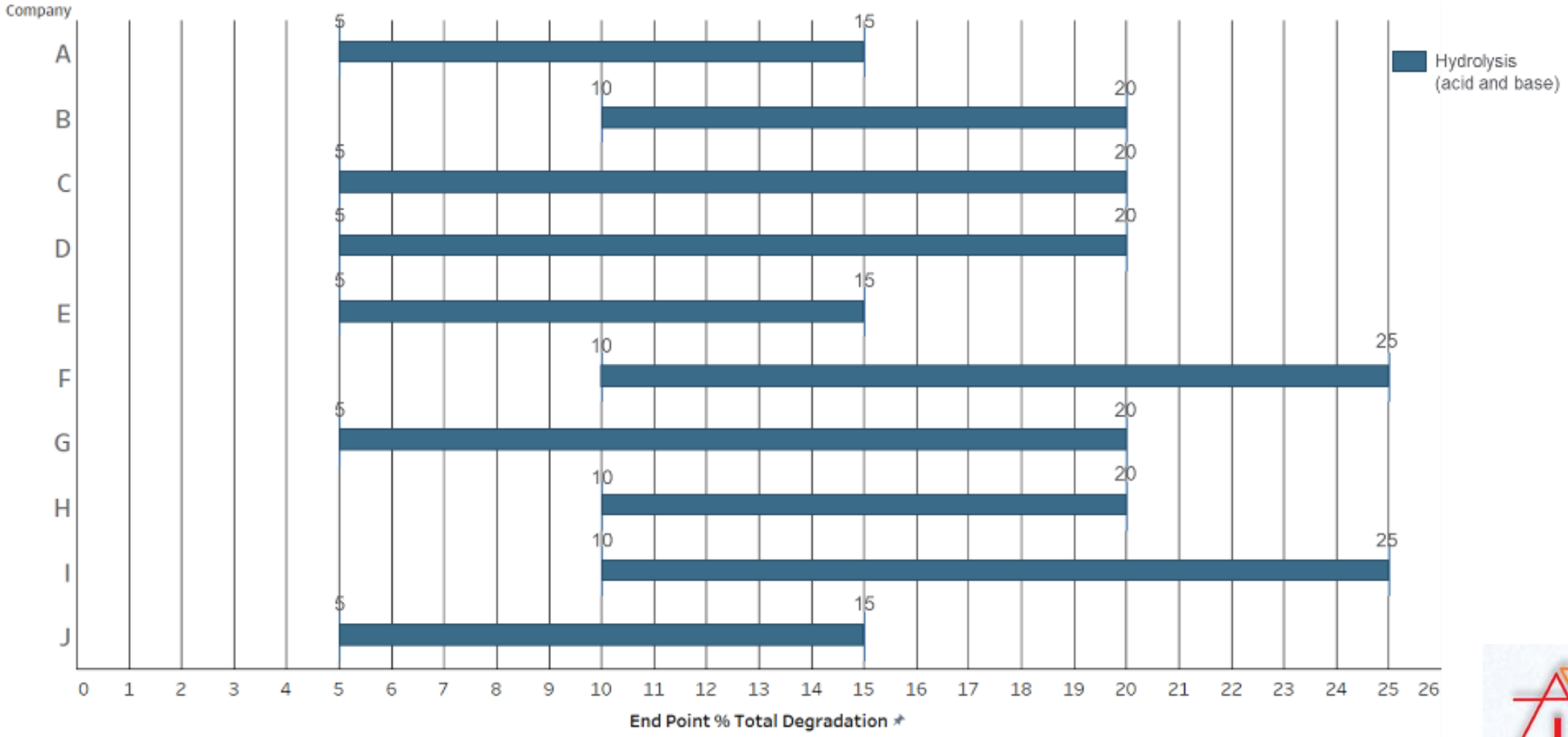
Focused on high quality, anonymized data from reputable organizations:

- Internal forced degradation and endpoint best practices from ten large pharmaceutical companies
- Focus on comprehensive stress testing study design and endpoints, with comparisons to real time stability results

Path to IFDC recommendations:

- Data visualization of data from IFDC companies
- **Reactive** vs. **stable** drug substance/drug product

Solution Phase Forced Degradation Study Endpoint for a **reactive** drug substance



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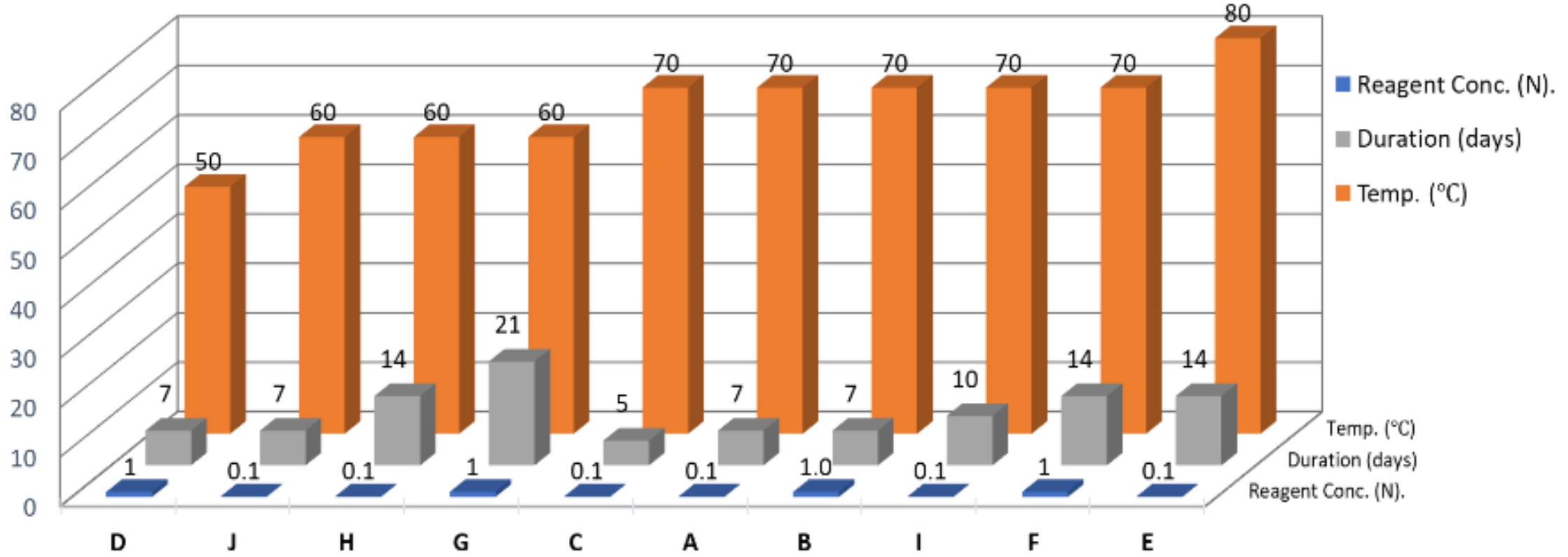
Hydrolysis Stress Testing Endpoints for a **Stable** Drug Substance [same Endpoints for both Acid (HCl) and Base (NaOH)]



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Drug Substance Hydrolysis Stress Testing Endpoints Summary

Key points and interpretation

- The range of endpoints have been verified to be 5-25% total degradation for a **reactive** drug substance
- To prove a drug substance is **stable** the maximum amount of pharmaceutically relevant stress is applied
- HCl and NaOH are most widely used
- The worst-case combination of 1N, 80°C and 21 days is not a recommended endpoint

Verified Endpoint Ranges

Endpoint target - **reactive** drug substance	Total deg	5-25%
Endpoint target - **stable** drug substance	Acid reagent	0.1-1 N (pH 1 to 0)
	Base reagent	0.1-1 N (pH 13 to 14)
	Temperature	50-80°C
	Duration	7-21 days
	Total deg	report

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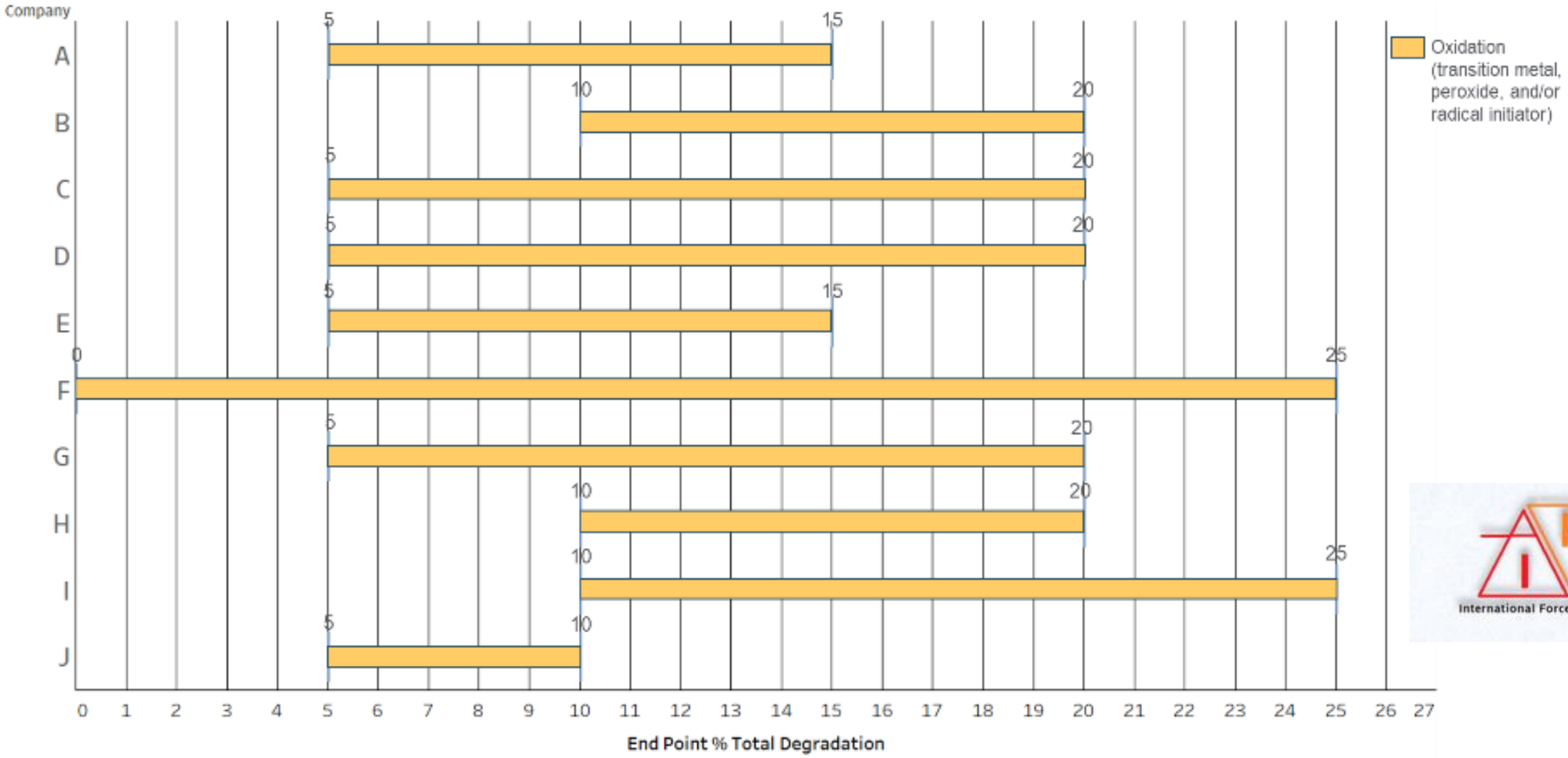
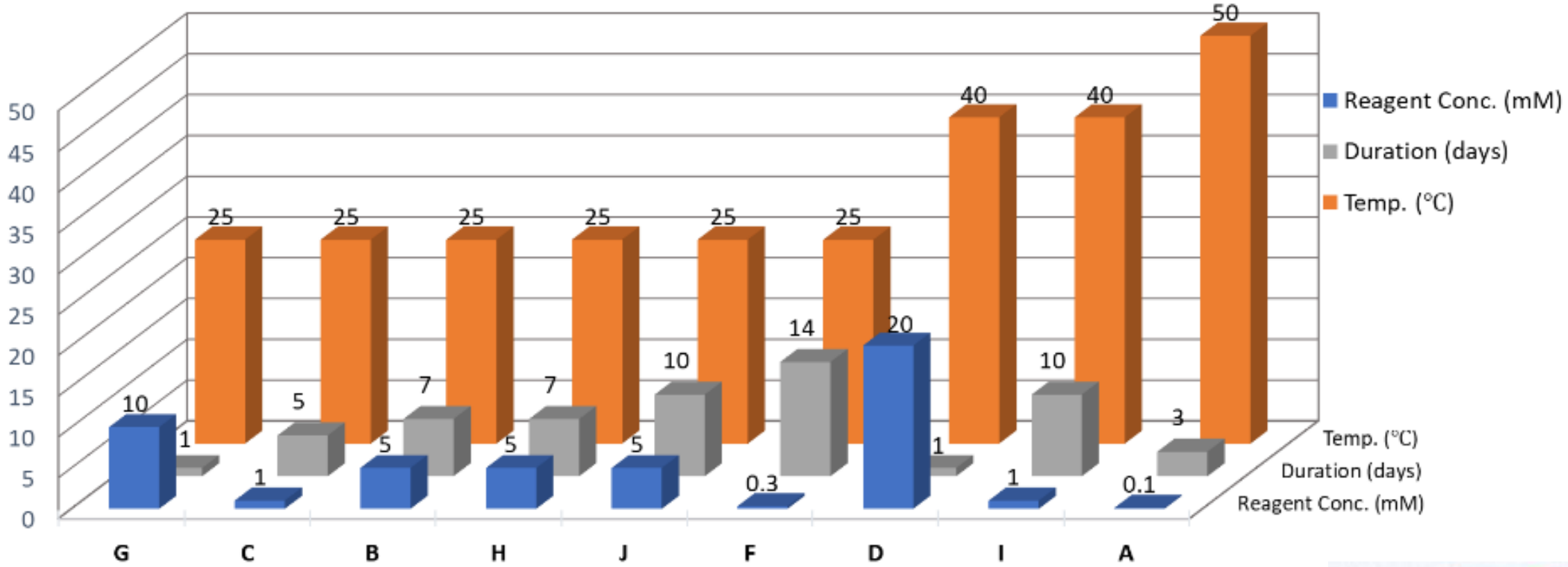
Solution Phase Forced Degradation Study Endpoint for a **reactive** drug substance



Transition Metal Oxidative Stress Testing Endpoints for a **Stable** Drug Substance



Same endpoints for both Fe(III) and Cu(II)

*Note: No solution state oxidation transition metal from company E

Drug Substance Transition Metal Oxidative Stress Testing Endpoints Summary

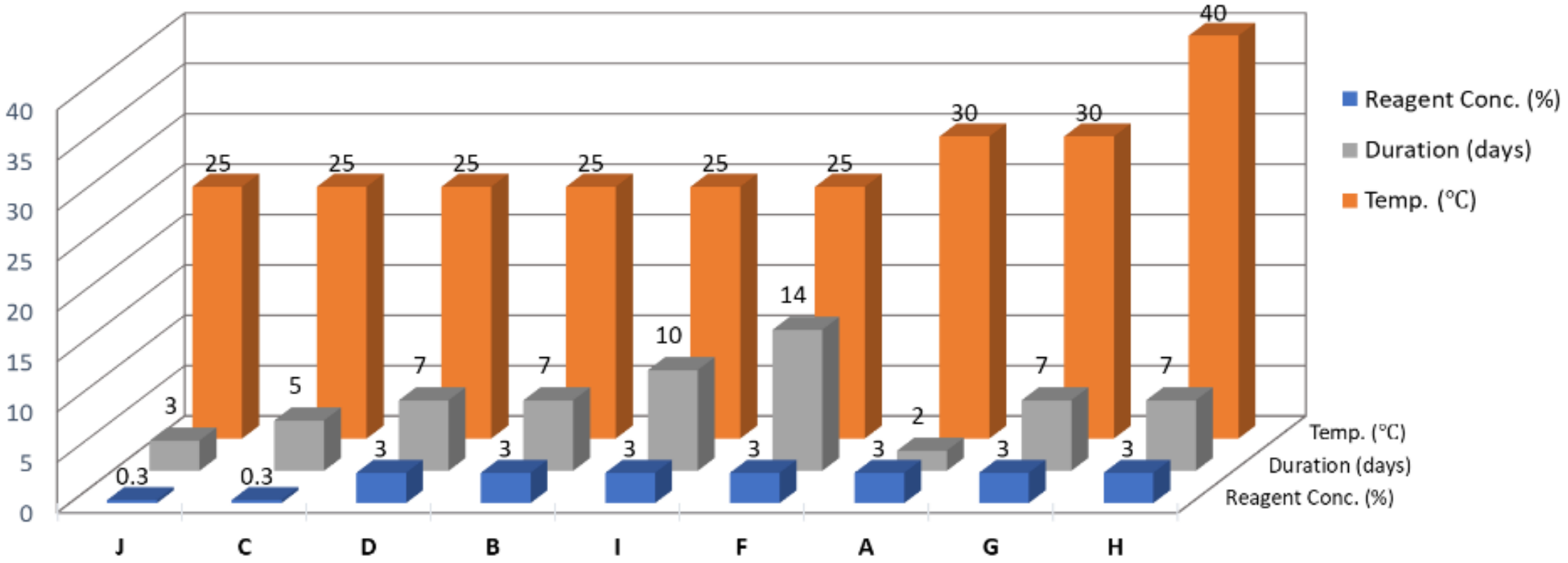
Key points and interpretation

- The range of endpoints have been verified to be 5-25% total degradation for a **reactive** drug substance
- To prove a drug substance is **stable** the maximum amount of pharmaceutically relevant stress is applied
- Fe (III) and Cu (II) are most widely used
- Recommended temperature range is 25-40°C
- The worst-case combination of 20mM, 50°C and 14 days is not a recommended endpoint

Verified Endpoint Ranges

Endpoint target - **reactive** drug substance	Total deg	5-25%
Endpoint target - **stable** drug substance	Reagent conc.	0.1-20 mM
	Temperature (verified)	25-50°C
	Temperature (recommended)	25-40°C
	Duration	1-14 days
	Total deg	report

Peroxide Oxidative Stress Testing Endpoints for a **Stable** Drug Substance



Note: Data from company E is not presented. Company E utilizes alternative reagents/conditions to probe peroxide-mediated oxidative degradation pathways

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Drug Substance Peroxide Oxidative Stress Testing Endpoints Summary

Key points and interpretation

- The range of endpoints have been verified to be 5-25% total degradation for a **reactive** drug substance
- To prove a drug substance is **stable** the maximum amount of pharmaceutically relevant stress is applied
- The most common reagent is hydrogen peroxide
- Recommended temperature 25°C
- A condition of 3%, 40°C and 14 days is not a verified endpoint

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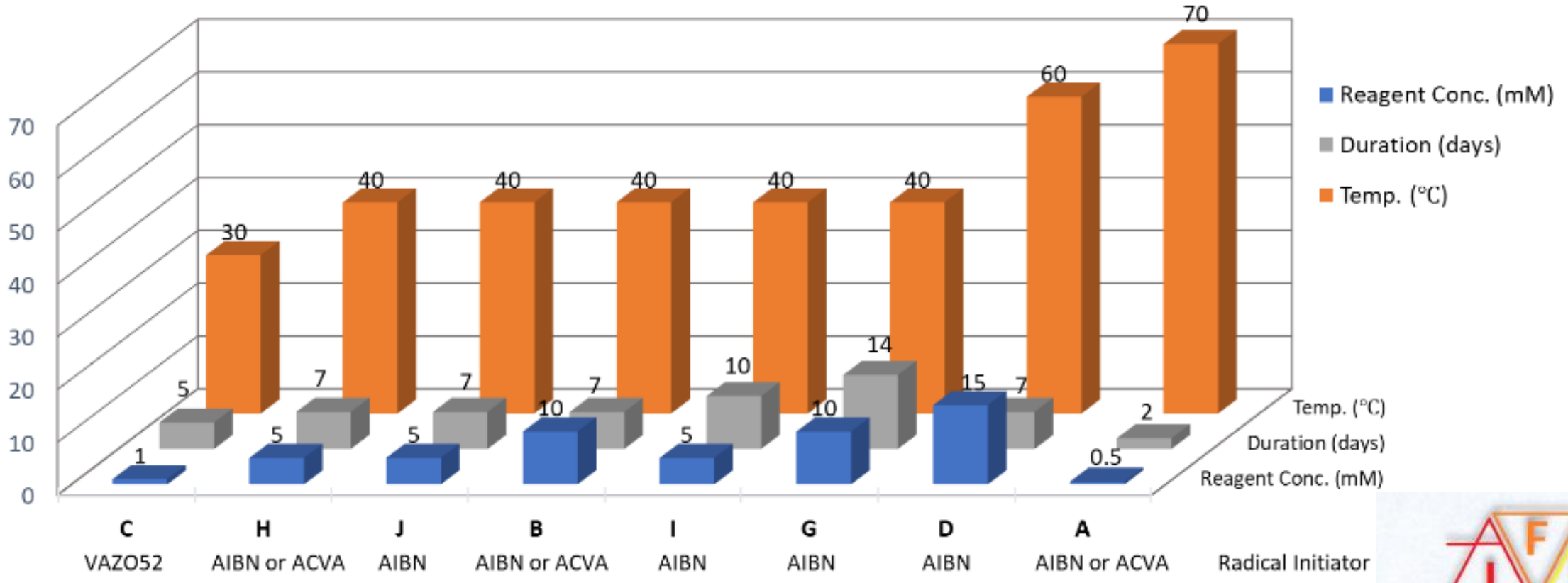
Verified Endpoint Ranges

Endpoint target - **reactive** drug substance	Total deg	5-25%
Endpoint target - **stable** drug substance	Reagent concentration (H_2O_2)	0.3-3%
	Temperature (verified)	25-40°C
	Temperature (recommended)	25°C
	Duration	2-14 days
	Total deg	report

Radical Initiator Oxidative Stress Testing Endpoints for a **Stable** Drug Substance



Note: Data from company E is not presented. Company E utilizes alternative reagents/conditions to probe radical-mediated oxidative degradation pathways

Drug Substance Radical Initiator Oxidative Stress Testing Endpoints Summary

Key points and interpretation

- The range of endpoints have been verified to be 5-25% total degradation for a **reactive** drug substance
- To prove a drug substance is **stable** the maximum amount of pharmaceutically relevant stress is applied
- The most common reagent is AIBN or ACVA
  - NMP used by one company as an alternative oxidant
- Recommended temperature 40°C for AIBN
- The worst-case combination of 15mM, 70°C and 14 days is not a recommended endpoint

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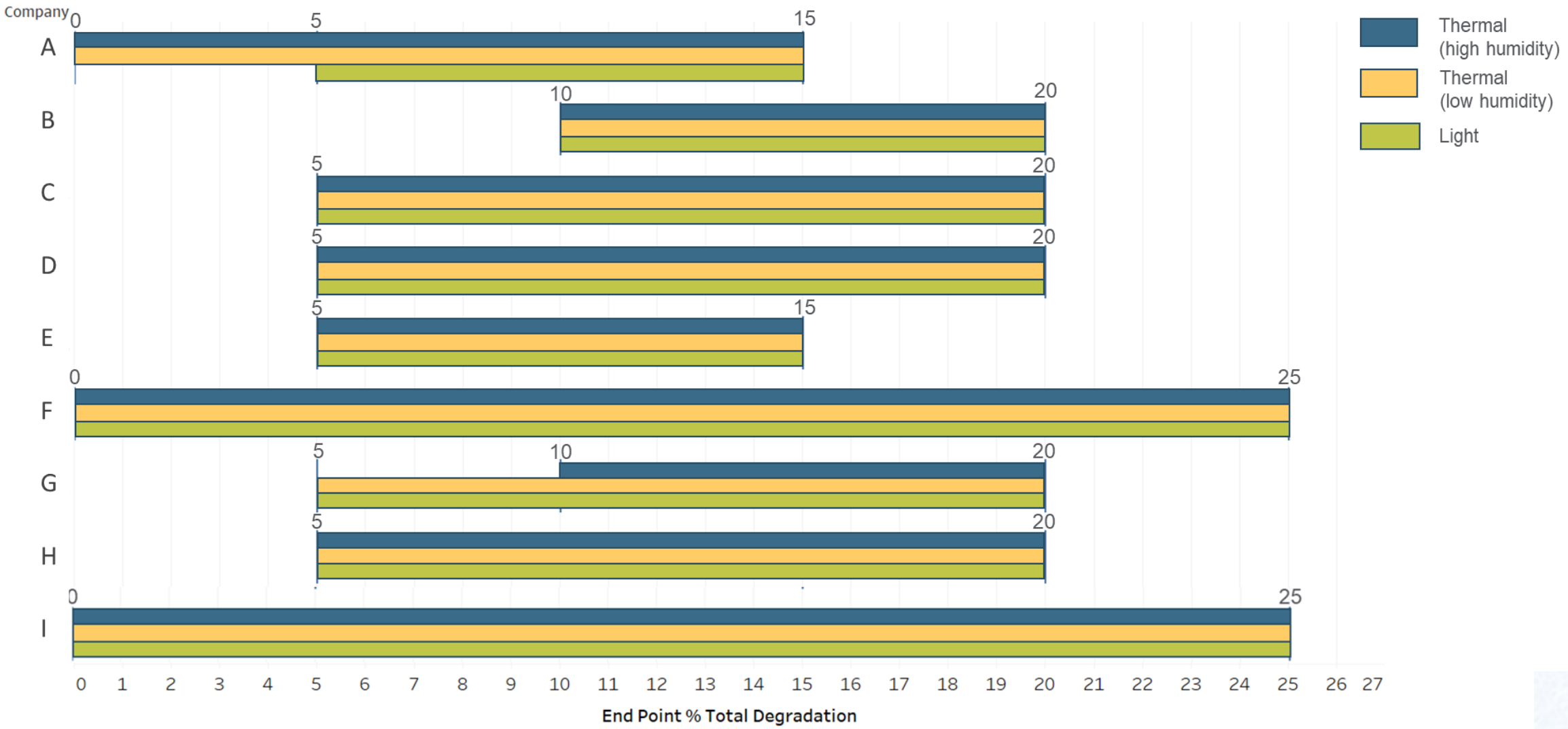
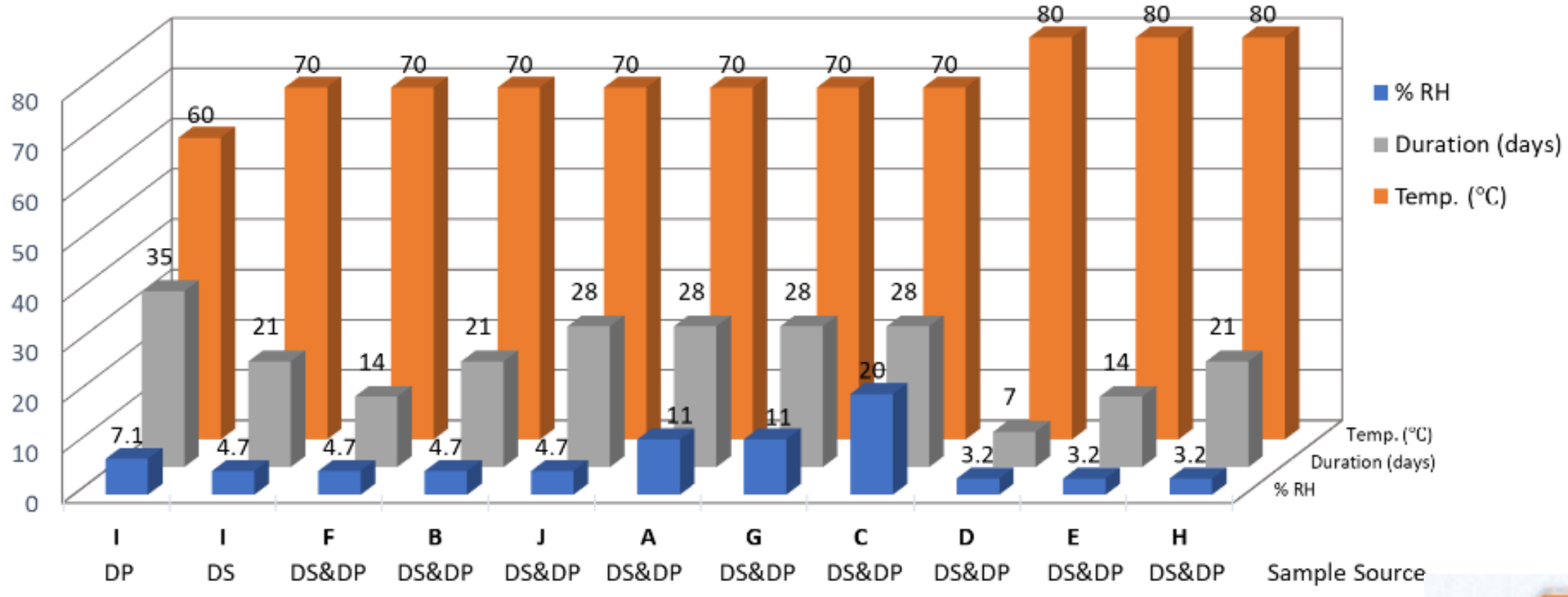
Verified Endpoint Ranges

Endpoint target - **reactive** drug substance	Total deg	5-25%
Endpoint target - **stable** drug substance	Reagent concentration (azonitrile)	0.5-15 mM
	Temperature (verified)	30-70°C
	Temperature (recommended for AIBN)	40°C
	Duration	5-14 days
	Total deg	report

Drug Substance and Drug Product Dosage Form: “**Reactive**” Solid Phase Stress % Total degradation Endpoint comparison



Solid Phase Thermal Stress (**Low Humidity**) Endpoints: Drug Substance and Solid Drug Product



Drug Substance and Solid Drug Product Dosage Form: Solid Phase Thermal Stress (**Low Humidity**) Endpoints Summary

Key points and interpretation

- The range of endpoints have been verified to be 0-25% total degradation for a **reactive** drug substance
  - <5% degradation typically observed
- To prove a drug substance is **stable** the maximum amount of pharmaceutically relevant stress is applied
- The maximum stress temperature and duration should provide a minimum kinetic equivalence equal to accelerated stability: e.g., 40°C/6 mo
- The worst-case combination of 80°C and 35 days is not a recommended endpoint

Verified Endpoint Ranges

Endpoint target - **reactive** drug substance/API	Total degradation	5-25%
Endpoint target - drug **stable** substance/API	Temperature (verified)	60-80°C
	Humidity	3.2-30%
	Duration	7-35 days
	Total degradation	report

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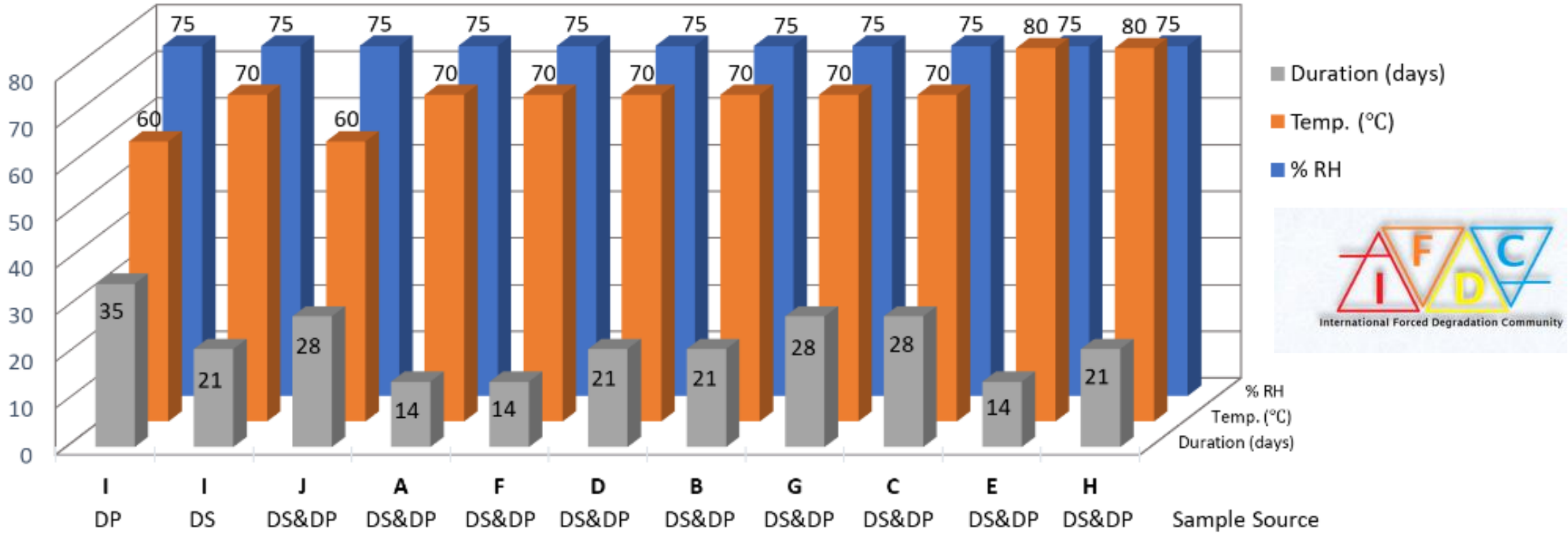
Solid Phase Thermal Stress (**High Humidity**) Endpoints: Drug Substance and Solid Drug Product



Drug Substance and Solid Drug Product Dosage Form: Solid Phase Thermal Stress (**High Humidity**) Endpoints Summary

Key points and interpretation

- The range of endpoints have been verified to be 0-25% total degradation for a **reactive** drug substance
  - <5% degradation typically observed
- To prove a drug substance is **stable,** the maximum amount of pharmaceutically relevant stress is applied
- The maximum stress temperature and duration should provide a minimum kinetic equivalence equal to accelerated stability: 40°C/75%RH/6 mo
- The worst-case combination of 80°C, 75%RH and 35 days is not a recommended endpoint

Verified Endpoint Ranges

Endpoint target - **reactive** drug substance/API	Total deg	5-25%
Endpoint target - **stable** drug substance/API	Temperature (verified)	60-80°C
	Humidity	75%
	Duration	14-35 days
	Total deg	report

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Solid Phase Light Stress Endpoints: Drug Substance and Solid Drug Product

Light-Drug Substance and Drug Product Solid

Exposure Amount (xICH)	Light Source	
	Option 1	Option 2
1	■●	
2	■●■●■●	■●
3	■●■●	■●
4	■●	■●
6	●	
8	■	

Sample Source
- ■ Drug Product - Solid Dosage Form
- ● Drug Substance

Company
- A
- B
- C
- D
- E
- F
- G
- H
- I
- J

Note: with xenon or metal halide Option 1 sources, 1x ICH will approximately have a UV exposure 2-3X the minimum confirmatory recommendations

Drug Substance and Solid Drug Product Dosage Form: Solid Phase Light Stress Endpoints Summary

Key points and interpretation

- The range of endpoints have been verified to be 0-25% total degradation for a **reactive** drug substance
  - <5% degradation typically observed
- To prove a drug substance is **stable** the maximum amount of pharmaceutically relevant stress is applied
- The most common condition is option 1 or 2 with 2X ICH exposure

Verified Endpoint Ranges

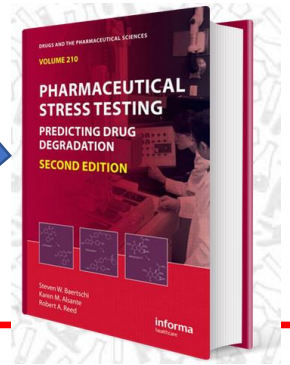
Endpoint target - **reactive** drug substance/API	Total deg	5-25%
Endpoint target - **stable** drug substance/API	Light Source	Option 1 or 2
	Light exposure	1-8X ICH Confirmatory (Confirmatory = 1.2M lux-hr visible and 200 W-h/m^2 UVA)

Summary

- Successful implementation of stress testing Endpoints are dependent on a well-designed, comprehensive and a sufficiently rigorous stress testing study design that includes both the drug substance and drug product
- The scope of today's endpoints discussion: drug substance and solid DP
- Problem Statement in relation to scientific literature and regulatory guidance
  - Maximum stress recommended in scientific literature show examples of extreme endpoints
- Two endpoint categories were discussed
  - **"Reactive"** vs. "**Stable"** drug substance and drug products
- Verified endpoint ranges from nine IFDC companies were presented
  1) **Reactive** drug substance and drug product endpoint: % total degradation target
  2) **Stable** drug substance and drug product endpoint: maximum amount of pharmaceutically relevant stress required to prove a drug substance or drug product is stable. Various ranges were verified to be acceptable for each stress condition.

Recommendations (made to ANVISA)

- Align with ICH Q1A(R2) definition of stress along with ICH Q1B
- Avoid mandating specific, definitive requirements; instead, make recommendations or guidelines
- Adopt the concept of different endpoints for **stable** and **reactive** drug substances and products as outlined in the presentation
  - For **stable** drugs: Verified range of maximum stress conditions and timepoints.
  - For **reactive** drugs: Verified range of degradation (5-25%). Requiring a minimum of 10% is not needed to ensure comprehensive coverage
- Extreme stress testing and endpoint recommendations in *some* scientific literature references should be avoided
  - **The Gold Standard:**



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Backup slides

Diversity in Literature References

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