Going hither and yon: ICH Q1E Stability modeling in practice

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Outline

- The "Hither" part
  - Overview of statistical modeling of stability studies
    - Some history
    - Regulatory Guidances, emphasis on Q1E
    - Stability Study – Objective, Shelf life, Design
      - Kinetic Models
    - Statistical Models
      - Fixed
        - Pooling according to ICH Q1E
- The "Yon" Part
  - Mixed model
    - Bayesian Modeling
  - Managing risk - Release limits
- The more Yon part - Accelerated Studies and modeling
- ***Summary***

Carstensen, 1976 JPS Journal

Terminology Regarding Labeled and Contained Amounts in Dosage Forms

Keyphrases □ Dosage forms—terminology regarding labeled and contained amounts, definitions suggested for the terms shelflife, outdate, expiration date, label date □ Terminology—regarding labeled and contained amounts in dosage forms, definitions suggested for the terms shelflife, outdate, expiration date, label date

To the Editor:

Dating of pharmaceutical preparations has become standard practice in this country. To this end, an acceptable nomenclature for various phases of the decay cycle of a product is of essence; we should like to suggest definitions for the terms "shelflife," "outdate," "expiration date," and "label date."

As pointed out by Crout (1), concise definitions of terms are necessary for the sake of rational debate. The difficulties encountered without such definitions are, for instance, evident in Canadian Regulations C.01.004[7]. Here, such statements are used as:

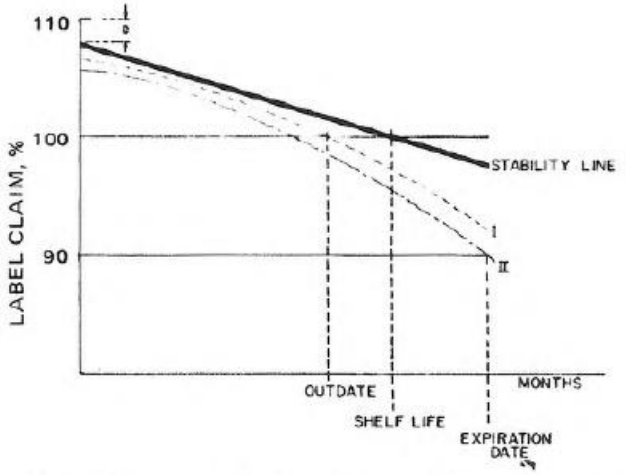
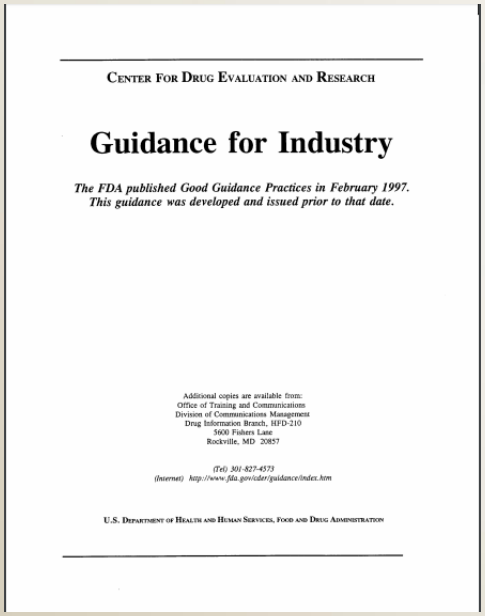


Figure 1—*Plot of stability of product, starting at (110 − e)% label claim.*

the example in Fig. 1, the excess is $(10 - e)\%$; *i.e.*, the initial content is $(100 - e)\%$ label claim[2]. The point where the stability line reaches 100% is denoted shelflife in our definition. In reality, the stability line

Three Stability Guidances


CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

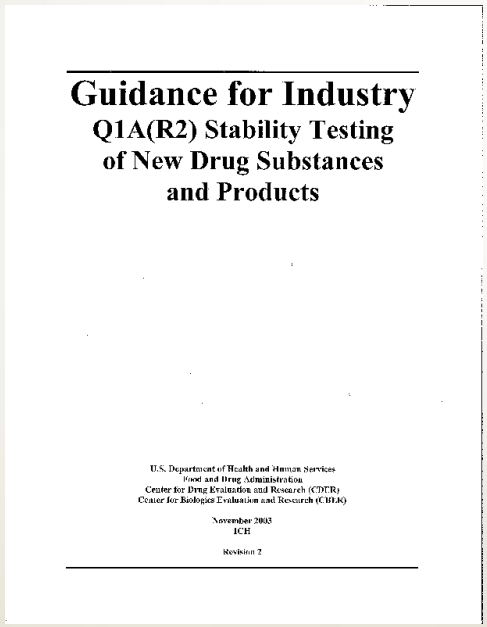
The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

1987


Guidance for Industry

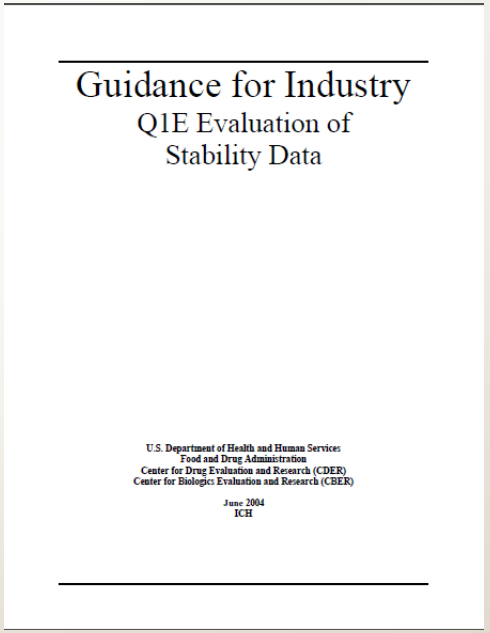
Q1A(R2) Stability Testing of New Drug Substances and Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2003
ICH

Revision 2

(R2)2003;
(R1)2000;
1993


Guidance for Industry

Q1E Evaluation of Stability Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2004
ICH

2004

Relevant Regulatory Guidances (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 and Matrixing Designs for Stability Testing of New Drug Substances and Products *(2003)*
- **Q1E – Evaluation for Stability Data** *(2004)*

  Recommendations how to establish shelf life or retest period based on stability studies performed.

- **Q5C** – Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products *(Step 5 version;1996)*

Stability Study

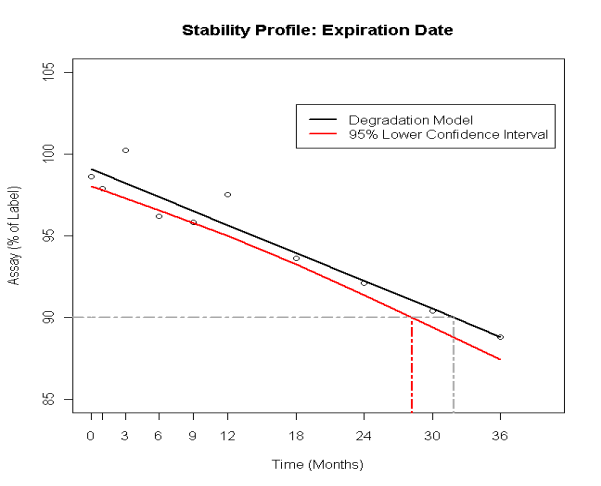
Objective

- To provide 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, light, container)
- *Establish a shelf life for the drug substance or the drug product (or DS re-test period for small molecules)*

Shelf life Q1A(R2) definition

'The time period during which a drug product is expected to remain within the approved specifications, provided that it is stored under conditions defined on the container label.'

- Recommend storage conditions



$$LSL = A + b_i \times T_{ED} - t_{(\alpha,df)} \sqrt{Var(A + b_i \times T_{ED})}$$

Stability Studies - Basic Design

- Randomly select dosage units/vials/syringes at time of manufacture, minimum of 3 batches, stored at specified conditions related to zones I,II,III,IV requirements
- At specified times 0,1,3,6,9,12,18,24,36,48,60 months, randomly select dosage units and perform analytical testing
- Basic Factors : Batch, Strength, Storage Condition, Time, Position, Container/closure and/or Fill
- Reduced study designs
  - Matrixing and bracketing

Kinetic Models (API) (Underlying Mechanism)

- Orders 0,1,2

$$C^{(0)}(t) = C_0 - k_0 \cdot t$$

$$C^{(1)}(t) = C_0 \cdot e^{-k_1 \cdot t}$$

$$C^{(2)}(t) = \left\{ \left(\frac{1}{C_0} \right) + k_2 \cdot t \right\}^{-1}$$

where C_0 is the assay value at time 0 and k_i = Degradation Rate for i^{th} order

- When k_1 and k_2 are small,

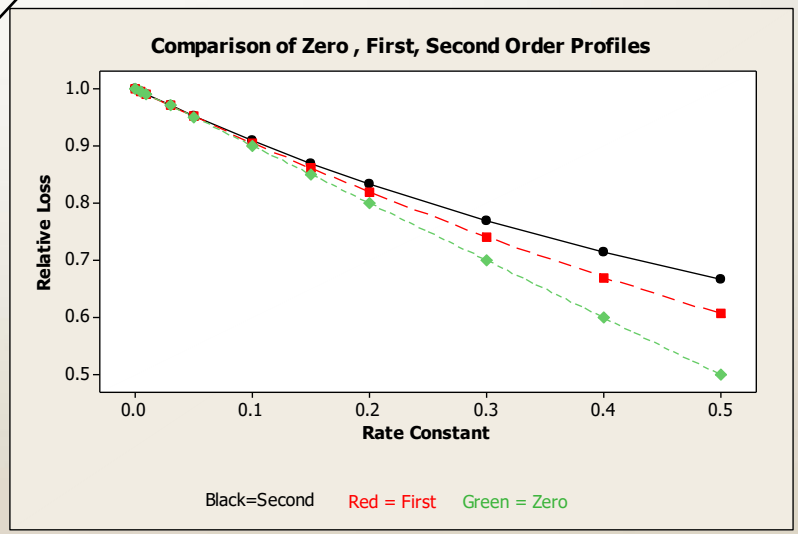
$$C^{(1)}(t) \approx C_0 - C_0 \cdot k_1 \cdot t \quad and \quad C^{(2)}(t) \approx C_0 - C_0^2 \cdot k_2 \cdot t$$

Kinetic Models

Comparison of Relative Degradation vs Kinetic Order

k	Concentration Second	Concentration First	Concentration Zero	Zero Order Difference (%) First	Zero Order Difference (%) Second
0	1	1	1	0	0
0.005	0.995	0.995	0.995	0	0
.01	0.990	0.990	0.99	-0.01	-0.01
.03	0.971	0.970	0.97	-0.1	-0.1
.05	0.952	0.951	0.95	-0.1	-0.3
.10	0.909	0.905	0.90	-0.5	-1
.15	0.870	0.861	0.85	-1	-2
.20	0.833	0.819	0.80	-2	-4
.30	0.769	0.741	0.70	-6	-9
.40	0.714	0.670	0.60	-10	-16
.50	0.667	0.607	0.50	-18	-25

Range of Small Difference



Statistical Models (n_b Batches, n_c Conditions)

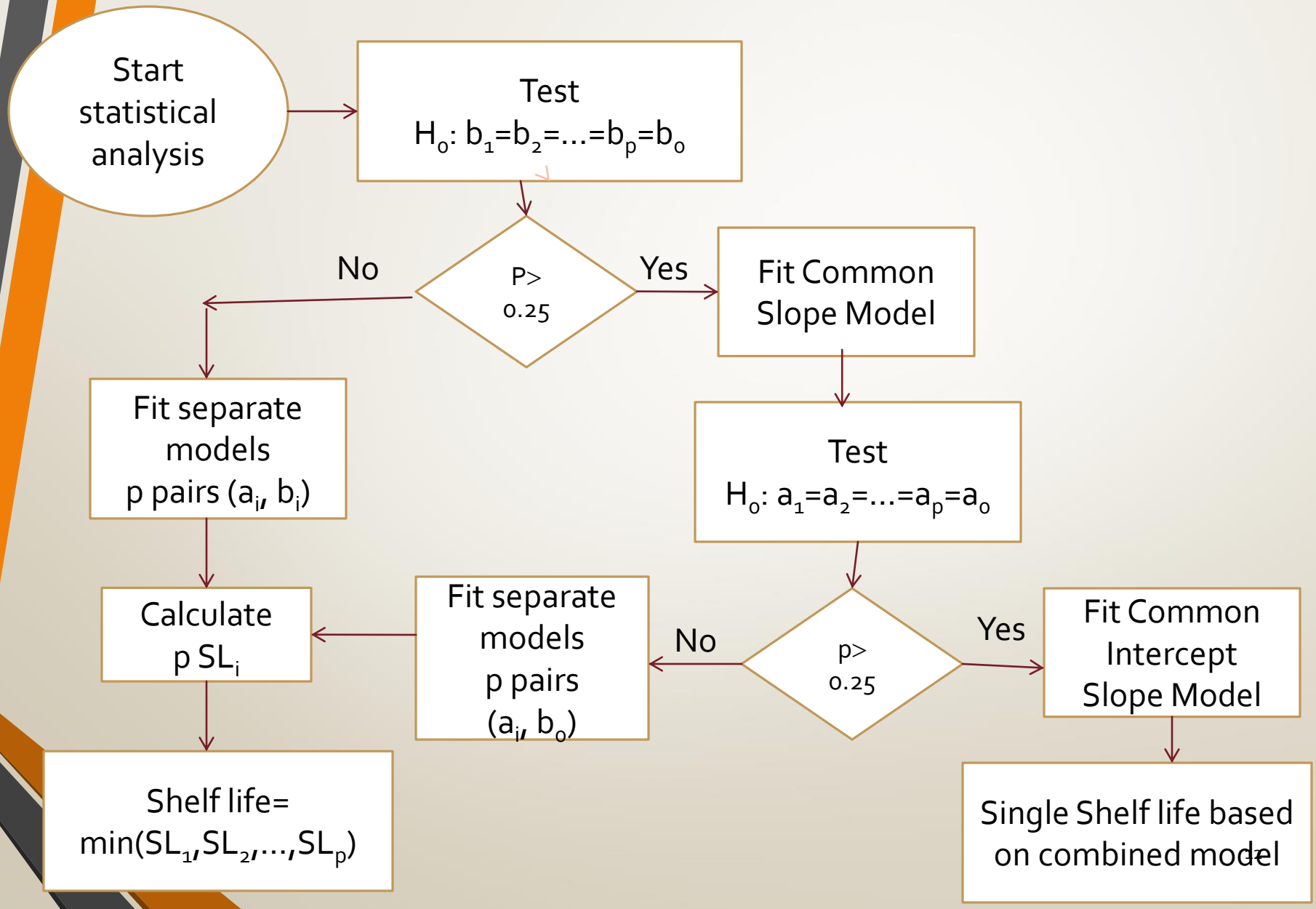
Model Specification				
Type	Number	Form	Number Fixed Parameters	Number Variance Parameters
Fixed	1	$y_{ijk} = A_{ij} + B_{ij} \times T_{ijk} + \varepsilon_{ijk}$	$2*n_b*n_c$	n_b*n_c
	2	$y_{ijk} = A_{i} + B_{ij} \times T_{ijk} + \varepsilon_{ijk}$	$n_b*n_c+n_b$	n_b
	3a	$y_{ijk} = A_{i} + B_{ij} \times T_{ijk} + \varepsilon_{ijk}$	$n_b*n_c+n_b$	1
	3b	$y_{ijk} = A_{i} + B_{j} \times T_{ijk} + \varepsilon_{ijk}$	n_c+n_b	1
Mixed	4	$y_{ijk} = (\mathrm{A}_0 + \alpha_i) + B_j \times T_{ijk} + \varepsilon_{ijk}$	n_c+1	2
	5	$y_{ijk} = (\mathrm{A}_0 + \alpha_i) + \left(B_j + \beta_i\right) \times T_{ijk} + \varepsilon_{ijk}$	n_c+1	3

Index Definitions: i=Batch, j=Condition, k=Time

Statistical Models (n_b Batches, n_c Conditions)

- Models 1,2,3 (Fixed Terms only)
  - 1. Fit individually by Batch and Condition (n_b * n_c models)
  - 2. Fit by Batch, include all Conditions (fit n_b constrained intercept models)
  - 3. Fit all Batches and Conditions (fit 1 model, constrained batch intercepts, with/without constrained slopes)
- Models 4, 5 (Mixed Models, with 1 or 2 Random Terms)
  - 4. Random Term in the Intercept
  - 5. Random Terms in Intercept and Slopes

Flowchart of pooling rules Q1E



Pooling across batches (API)

- Pooling from Model $1 - 3b$
  - Two Steps
    - Pool across Intercepts, then slopes
    - Pool across Slopes, then Intercepts ($Q1E$)
  - Pool in a single step
  - No best way, multiple error terms, multiple steps applying the same criterion, what is being controlled?
  - Rewards imprecise assays, penalizes precise assays
    - Same set of observed batch slopes could fail poolability for a small molecule but pass for a biologic
- Other problems
  - Using the residual error term for pooling across Intercepts – Why is this the right criterion?
  - $P=0.25$ ignores levels of process and analytical variability
  - Cannot power a stability study design – emphasis is on limited resources/feasibility
- Equivalence approach not a way out
- These issues set the stage for the mixed model approach (either Bayesian or Frequentist)

Example of NDA Stability Protocol

Introduction

The purpose of this protocol is to describe the analytical requirements and conduct of the NDA stability studies for DRUGX, Prolonged Release (PR) Tablets 50 mg, 100 mg, 150 mg, 200 mg and 250mg made by the direct compression (DC) process and packaged in HDPE Bottles and Aclar blister packaging.

Drug Product Manufacture Information

DP Batch No.	DP Mfg Site	Final Blend Batch Size	DS Batch No.	DS Mfg Site	DS Batch Size
PD1	S PA	100 Kg	DSA	HA	85 Kg
PD2	S PA	100 Kg	DSB	HA	92 Kg
PD3	S PA	100 Kg	DSC	HA	85 Kg
PD4	S PA	100 Kg	DSA	HA	85 Kg
PD5	S PA	100 Kg	DSB	HA	92 Kg
PD6	S PA	100 Kg	DSC	HA	85 Kg
PD7	S PA	100 Kg	DSA	HA	85 Kg
PD8	S PA	100 Kg	DSB	HA	92 Kg
PD9	S PA	100 Kg	DSC	HA	85 Kg

Batches and Containers

Study No.	DP Batch No.	Strength	DP Formula No.	Container Closure (Package)	Status
A1-B1	PD1	50 mg	019	C1, C2, C3, C4, C5	A,P
A2-B2	PD2	50 mg	019	C1, C2, C3, C4, C5	A,P
A3-B3	PD3	50 mg	019	C1, C2, C3, C4, C5	A,P
A4-B4	PD4	100 mg	020	C1, C2, C3, C4, C5	A,P
A5-B5	PD5	150 mg	021	C1, C2, C3, C4, C5	A,P
A6-B6	PD6	200 mg	022	C1, C2, C3, C4, C5	A,P
A7-B7	PD7	250 mg	023	C1, C2, C3, C4, C5	A,P
A8-B8	PD8	250 mg	023	C1, C2, C3, C4, C5	A,P
A9-B9	PD9	250 mg	023	C1, C2, C3, C4, C5	A,P

Time/Storage Condition Scheme and Schedule

	Storage Condition				Accelerated/Stress Condition		
Months	5 °C	25 °C/ 60% RH	30°C/ 75% RH	30 °C/ 65% RH	50 °C	40 °C/ 75% RH	Light
0	NA	ABC	NA	NA	NA	NA	NA
8 hr	NA	NA	NA	NA	NA	NA	AB
3	AB	AB	AB	AB	AB	AB	NA
6	AB	AB	AB	AB	NA	AB	NA
9	AB	AB	AB	AB	NA	NA	NA
12	ABC	ABC	ABC	ABC	NA	NA	NA
18	AB	AB	AB	AB	NA	NA	NA
24	ABC	ABC	ABC	ABC	NA	NA	NA
36	ABC	ABC	ABC	ABC	NA	NA	NA

A = Assay Active, Degradants, Dissolution P=Passive
B = Moisture C = Microbiology

Example NDA Stability Protocol

- Covariance Structure
  - 3 drug substance lots used to manufacture 9 drug product lots at 5 strengths in an incomplete block pattern

DS Lot	Strength				
	50	100	150	200	250
DS2	X	X			X
DS3	X		X		X
DS4	X			X	X

  - Each drug product lot is studied in 5 different packages at 7 different Storage Conditions, ICH fixed model $\Rightarrow$ 7(Conds)x5(Packs)x9(Batch) + 9 = 324 terms
  - Ultimately, something approaching independence is traced back to only 3 DS lots

Empirical support for foregoing pooling tests on slope (small molecules API assay)

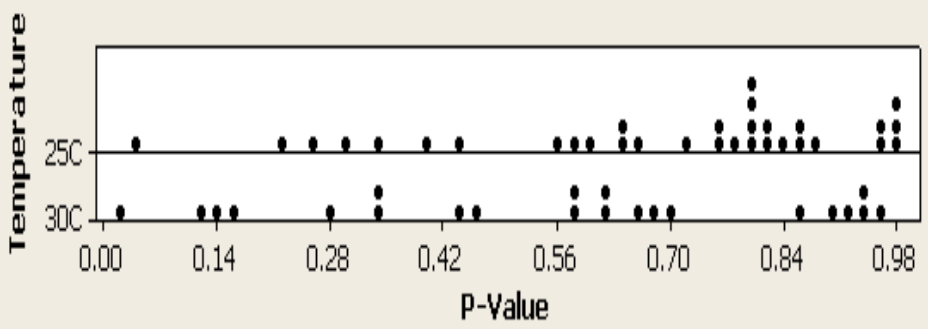
Statistical Review of 33 recent stability studies representing both development and marketed compounds in various dosage forms

- Apply ICH model and test for poolability
  - Median p-value for test of poolability = 0.670
  - 13% of p-values <0.25

    5% of p-values <0.10

    70% of p-values >0.50
- The low occurrence of p<0.25 tends to support assumption of a common fixed slope for assay.

Dot Plot of p-values



Proportion of p-values <0.25 by Time of Statistical Analysis

Real Time Data (mo.)	25C		30c	
	Observed	Expected*	Observed	Expected*
12	2/33	8/33	4/22	5/22
18	4/28	7/28	3/16	4/16
24	3/21	5/21	4/12	3/12
36	0/11	3/11	0/3	1/3

*Under the assumption of parallelism

Pooling across batches (API)

- Does it serve a useful purpose?
  - When chemistry is independent of batch a single fixed rate constant is applicable
- Are the regulatory guidelines reflective of current technology and statistical practice?
- QbD says exploit the science – is this the right time to question the pooling paradigm?

Bayesian Mixed Model – the "Yon" part

- Random Intercept Model

$$Y_{ijk} = \mu + \alpha_i + \beta_j X_{ijk} + \varepsilon_{ijk}$$

$$Y_{ijk} \sim N(\mu + \alpha_i + \beta_j X_{ijk}, \sigma_\varepsilon{}^2)$$

$$\alpha_i \sim N(0, \sigma_\alpha{}^2)$$

- **Add (prior) distribution on the unknown parameters, μ, β_j, σ_ε^2, σ_α^2** *(Controversial)*

Prior Distributions

Expert opinion (small molecule example)

- Overall mean is between 99% and 101%
- A 99% confidence interval of lot to lot variability is between 0.1 and 0.5
- The yearly degradation rate at 25C/60RH is 1.2% (0.1 monthly)
- The yearly degradation rate at 30C/65RH is 2.4% (0.2 monthly)
- Degradation rate variability is assumed to have a coefficient of variation of 20%
- A 99% confidence interval of analytical variability is between 0.1 to 1.0

Prior Distributions

- Provides a flexible framework for incorporating scientific and expert judgment, exploiting past experience with similar products and processes

$$\mu \sim N(100, 0.1)$$

$$\sigma_\alpha^{\,2} \sim \Gamma^{-1}(10, 2)$$

$$\beta_{25C} \sim N(-0.1, \sigma_\beta^2), \;\; \beta_{30C} \sim N(-0.2, \sigma_\beta^2)$$

$$\sigma_\beta^{\,2} \sim \Gamma^{-1}(60, \;\; 0.008)$$

$$\sigma_\varepsilon^{\,2} \sim \Gamma^{-1}(6, 2)$$

Managing risk with Internal Release Limits - Consumer and Producer risk

- Internally derived and are the responsibility of the manufacturer, lot acceptance limits
- Apply only at time of lot release
- Account for changes over time and uncertainties due to process variability
- Intended to provide a high level of assurance that a lot falling within release limits will conform to quality requirements over the shelf life of the product
- Important to the customer

➢ ***Given Release Limits and Specifications how can we assess manufacturing risk?***

Manufacturing Risk Estimation

- Given Release Limits and Specifications, manufacturing risk can be described through a 2x2 table given below:

	End of Shelf Life		
Release	Pass (%)	Fail (%)	Total (%)
Pass (%)	C_{11}	C_{12}	R_1
Fail (%)	C_{21}	C_{22}	R_2
Total (%)	C_1	C_2	100

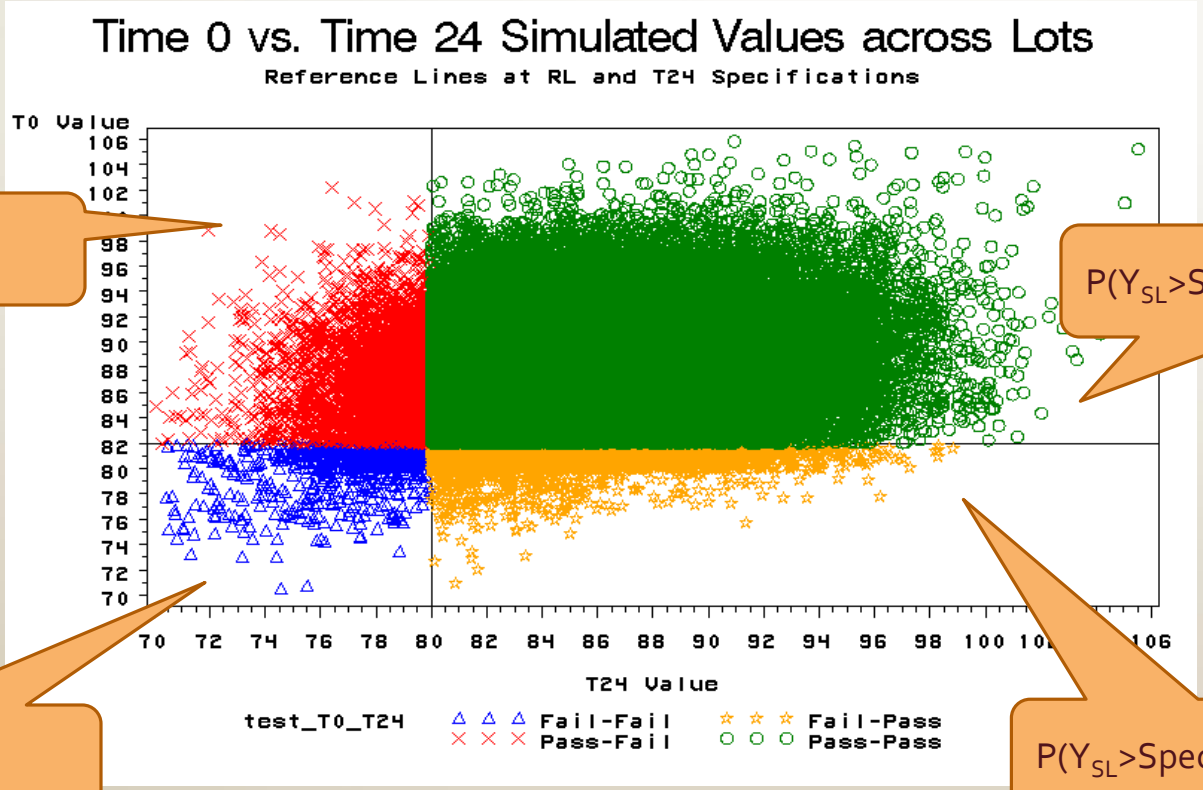
$C_{12}/R_1 = P(Y_{SL} < Spec_{SL} | Y_0 \geq RL)$
cost to the consumer

cost to the company

- Probabilities associated with the above 2x2 table can be estimated through a Bayesian posterior predictive distribution approach

Manufacturing Risk Estimation

Using simulated lot data at T_0 and T_{SL}, calculate the probabilities of future lots falling into each of the 4 possible outcomes in relation to pass and fail at Release and end of Shelf Life .



$P(Y_{SL}<Spec_{SL}|Y_0 \geq RL)$

$P(Y_{SL}>Spec_{SL}|Y_0 \geq RL)$

$P(Y_{SL}<Spec_{SL}|Y_0<RL)$

$P(Y_{SL}>Spec_{SL}|Y_0<RL)$

Y_j = Lot mean at *j-th* time point, SL=shelf life

Accelerated Stability Testing – Going even more yonder

Product is subjected to stress conditions.

- Temperature and humidity are the most common stress factors.
- Purpose is to predict long term stability and shelf life but is only supportive in establishing a shelf life claim.
  - The shelf-life is obtained by extrapolation from the high temperature/humidity conditions to the recommended storage condition.
  - Imperative to understand the underlying statistical models and science of the experimental protocols/models applied to get the shelf-life.
- Arrhenius equation captures the kinetic relationship between rates and temperature (KKF or Garrett 2-stage models).
  - The usual fixed and mixed models ignore any relationship between rate and temperature.

Arrhenius Equation

Named for Svante Arrhenius (1903 Nobel Laureate in Chemistry) who established a relationship between temperature and the rates of chemical reaction

$$k_T = k(T) = Ae^{-\frac{E_a}{R \cdot T}}$$

where k_T = Degradation Rate

A = Non-thermal Constant

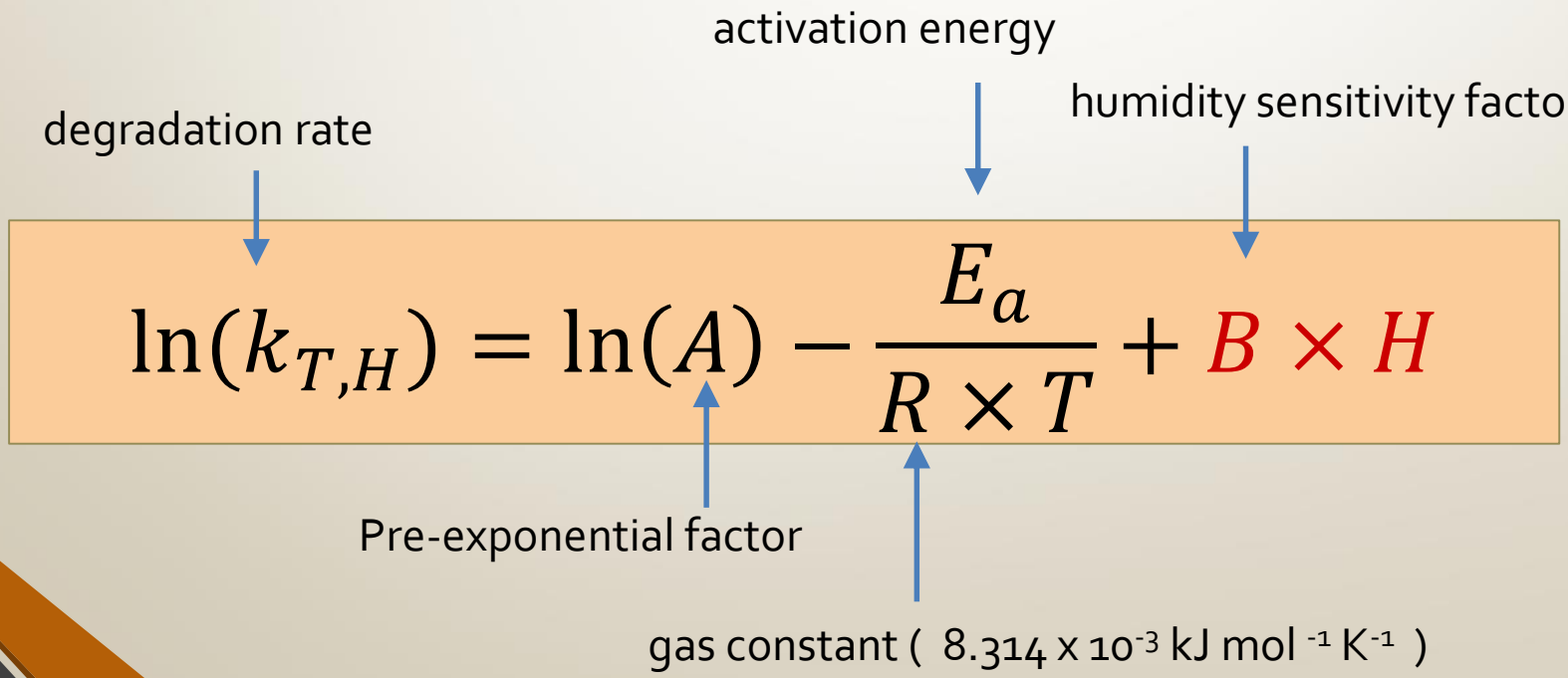
E_a = Activation Energy

R = Universal Gas Constant (8.314×10^{-3} kJ mol^{-1} K^{-1})

T = Absolute Temperature

Arrhenius Equation with Humidity Term

A humidity term with coefficient B is introduced to account for the effect of relative humidity on rate parameter.



King-Kung-Fung Model* (1984)

- Kinetic rate-based reparameterization of the Arrhenius model
- Accommodates zero and first order kinetic models
- Nonlinear regression analysis employed to provide parameter estimates of shelf-life, E_a and C_0.
  - Allows direct statistical prediction of shelf-life using observed values of drug content, **time** and **temperature**
  - Statistical non-linear numerical modeling leads to appropriate estimates of uncertainty in estimate of shelf life. Lower 95% confidence bound on shelf life parameter chosen for shelf life, consistent with ICHQ1E definition.

*Shang-Ying P. King, Min-Shya Kung and Ho-Leung Fung, *Statistical Prediction of Drug Stability Based on Nonlinear Parameter Estimation*, *Journal of Pharmaceutical Sciences*, Vol. 73, No. 5, p.657–662, May 1984

Nonlinear Parameterization (King-Kung-Fung Model)

$$k_T = Ae^{-\frac{E_a}{R \cdot T}}$$

Let $T = 298^oK$ (25^oC)

$$A = k_{298}e^{\frac{E_a}{298 \cdot R}}$$

$$k_T = k_{298}e^{\frac{E_a}{R}\left(\frac{1}{298}-\frac{1}{T}\right)}$$

$\{C(t) = C_0 - k \cdot t\}$

$$C_T(t) = C_0 - \underbrace{k_{298}e^{\frac{E_a}{R}\left(\frac{1}{298}-\frac{1}{T}\right)}}_{k_T} \cdot t$$

Extended King-Kung-Fung Model

The King-Kung-Fung (KKF) model modified to express the formation of degradant:

Assuming zero order kinetics, total degradation is:

$$D_t = D_0 + k_{T,H} \times t$$

$$k_{T,H} = Ae^{-\frac{E_a}{R \times T} + B \times H}$$

Let $T = 298^oK\ (25^oC)$, $H = 60$

$$A = k_{298,60} e^{\frac{E_a}{298 \times R} - B \times 60}$$

$$k_{T,H} = k_{298,60} e^{\frac{E_a}{R}\left(\frac{1}{298} - \frac{1}{T}\right) + B(H-60)}$$

$$k_{298,60} = \frac{Q - D_0}{t_{SL}}$$

$$D_t = D_0 + \frac{Q - D_0}{t_{SL}} \times t \times e^{\frac{E_a}{R} \times \left(\frac{1}{298} - \frac{1}{T}\right) + B \times (H-60)} + \varepsilon$$

- Estimate Shelf Life at 25C/60%RH and its uncertainty w.r.t spec = Q
- Parameter estimates are calculated based on the Arrhenius relationship conditional on an assumed zero order kinetic

Linearized Arrhenius Model

- Two-stage approach (Garrett, 1955)
  - Assume a zero order kinetic model
  - Stage 1 : fit a pseudo zero order kinetic model to the concentration measurements;

$$D_T(t) = D_0 + k_T \cdot t$$

  - Stage 2 : Model the rate estimates according to Arrhenius relationship Generalized Least Squares approach

$$\log k_T = \underbrace{\log A}_{\beta_0} + \underbrace{\frac{E_a}{R}}_{\beta_1} \cdot \frac{1}{T} + B \cdot H$$

  - Expressed as linear regression problem

$$\log k_T = \beta_0 + \beta_1 \cdot \frac{1}{T} + \beta_2 \cdot H + \zeta$$

Accelerated Stability Testing in practice

Small Molecules

- Temperatures range typically from 50°C to 80°C
- Humidity range as low as 10% to as high as 75% .
- The exposure time can range from less than 7 days to 3 months; however, most protocols last 14 to 21 days.
- A 6-month study at 40°C is equivalent to a 2-year long term study at 25°C
- Requires extended Arrhenius model
- KKF and Garrett 2-stage models work well in practice

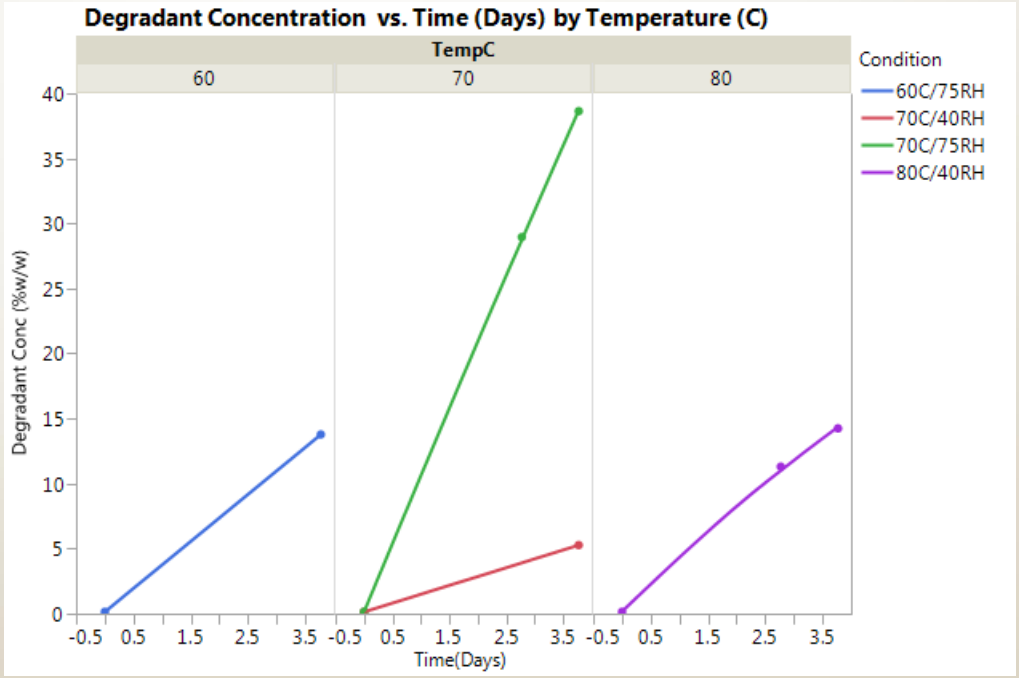
Large Molecules

- Typically 5°C, 25°C , 40°C, limited by unfolding temperature – studied through thermal calorimetry
- Humidity generally not a factor (containers protecting them against humidity)
- A 1-month study at 25°C is equivalent to a 1-year long term study at 5°C
- Complex degradation mechanisms involving deamidation or desialylation, and physical changes in 3-dimensional structure and aggregation may interfere with simple zero order kinetic assumptions
  - Arrhenius plots for biologics could have two different linear regions with a much steeper slope at higher temperatures – need to stay below unfolding temperature

Case Study (tablet formulation) of Degradant under Accelerated Conditions

Data Table

day	Temp	RH	Deg
0	**60**	**75**	0.1471
3.771	60	75	13.79
3.771	70	40	5.279
2.771	70	75	28.957
3.771	70	75	38.64
2.771	80	40	11.315
3.771	80	40	14.254



Accelerated Degradant Study Results

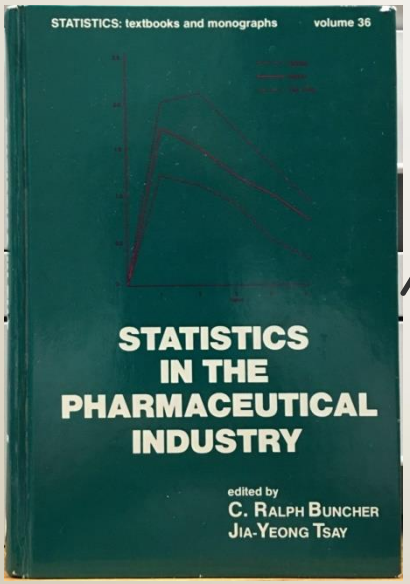
Parameter	King,Kung, Fung	Garrett Two-Stage	Bayesian Posterior Estimates		
			Mean	Median	5%
$C_{initial}$	0.27 (se=0.40)	0.36 (se=0.50)	0.33	0.31	0.05
E_a (kJ Mol^{-1})	100.5 (se=3.9)	100.4 (se=4.4)	100.8	100.8	97.58
B (RH)	0.06 (se=0.002)	0.06 (se=0.002)	0.06	0.06	0.056
$t_{SL,\ 25C/60\%RH}$ (in days)	127 (SL^1: 72)	122 (SL: 56)	127	126	(SL: 107)
$t_{SL,\ 30C/75\%RH}$ (in days)	28 (SL^1: 17)	26 (SL: 14)	27	27	(SL: 23)
MSE	0.21	0.27	0.14	0.12	0.07

SL=Shelf Life

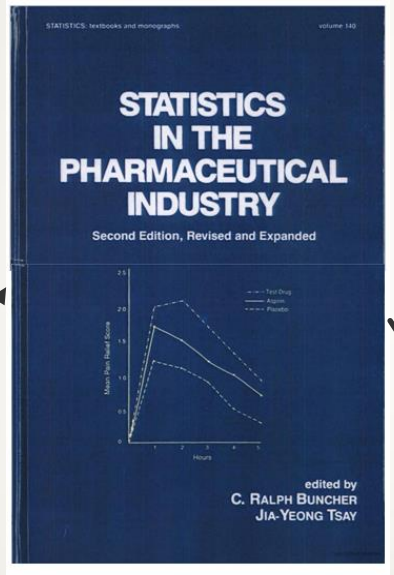
[1] Lower 95% Confidence bound

Statistics In the Pharmaceutical Industry

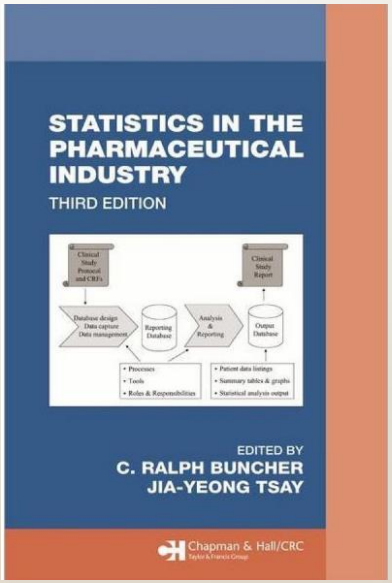
Charles Ralph Buncher, Jia-Yeong Tsay



First Edition 1981
Accelerated Studies



Second Edition 1991
RT and Accelerated



Third Edition 2006
RT Studies

Summary

- Stability evaluation of pharmaceutical products is both a regulatory and commercial requirement in assuring product quality
- Current regulatory guidances do not reflect current statistical approaches to RT or accelerated stability modeling
  - Q1E fixed model pooling rules are being challenged
  - Mixed modelling with a Bayesian perspective is a natural representation of the sources of inherent variability in the manufacturing process
    - Sets the stage for a coherent risk control and assessment strategy acknowledging consumer and producer risk in relation to release limits
- Accelerated stability studies hold the potential to provide a rapid assessment of stability properties and recently emerging statistical tools for their modeling and analysis can be used along with science understanding

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3. Guideline on declaration of storage conditions: a) in the product information of medicinal products b) for active substances (CPMP/QWP/609/96 rev 2)
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