Bayesian approach to risk assessment for dissolution testing of a marketed drug product

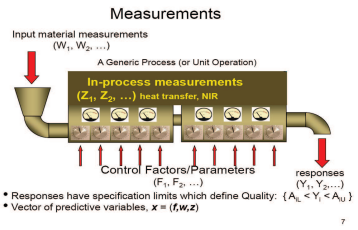
Nonclinical Statistics & Computing

Biostatistics and Programming

Coppenolle Hans, Altan Stan, Chen Juan, Manola Areti, Shen Yan, Shoung Jyh-Ming

Pharmaceutical quality

- A **Critical Quality Attribute (CQA)** is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (product purity, strength, drug release and stability)
  - CQA's of drug substance, excipients, intermediates, drug product
  - Link to clinical safety, efficacy, ...



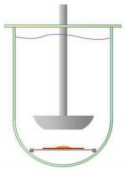
Outline

- Introduction
  - Pharmaceutical quality
  - Dissolution testing
  - Stability study
- Marketed product case study
  - Data description
  - Stability modeling
  - Risk assessment at time of manufacture and end of shelf life
- Analytical design strategy for dissolution testing
- Quality by Design

Drug release

- **Clinical quality**: release of active ingredient from drug product and dissolution of the drug under physiological conditions
  - Rate and extend of drug release depends mainly on
    - Manufacturing process parameters
    - Material attributes
- **In vitro test method** is used to determine drug release over dissolution time
  - Rate of release is believed to be linked to in vivo performance
  - Useful for assessing manufacturing quality

Dissolution testing

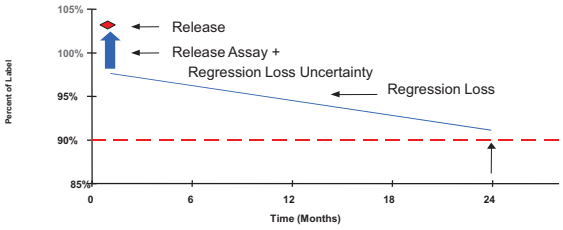


- Dissolution testing procedure
  - Dissolution after time x is of interest
  - 6 vessels per dissolution bath
  - 1 analytical run = 6 vessels
- Analytical testing reference (**U**nited **S**tates **P**harmacopeia)
  - Apparatus, procedure and interpretation

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

Stability study

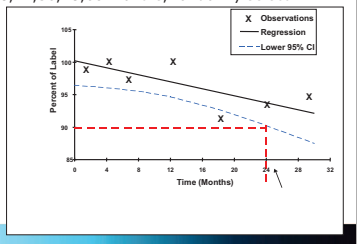
- **Release limits**
  - The bounds of intervals on the true lot mean formed on the basis of given specifications and real time stability data so that a future lot whose measured value at time of manufacture falls within these limits has a high level of assurance that its mean will remain within specifications throughout shelf life



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

Stability study

- **Stability** is defined as the capacity of a drug substance or a drug product to remain within **specifications** established to ensure its identity, strength, quality, and purity throughout the **retest period** or **expiration dating period**
- Design of stability studies
  - Typical variables are lot, strength, condition, time, package, position, supplier, manufacturing site, …
  - Randomly select containers/dosage units at time of manufacture (minimum of 3 batches) and store at specified conditions related to zones I,II,III,IV requirements
  - At specified stability times 0,1,3,6,9,12,18,24,36,48,60 months, randomly select dosage units and perform assay testing
- Dissolution testing procedure
  - Stage testing
  - 6 vessels per dissolution bath
  - 1 analytical run = 6 vessels



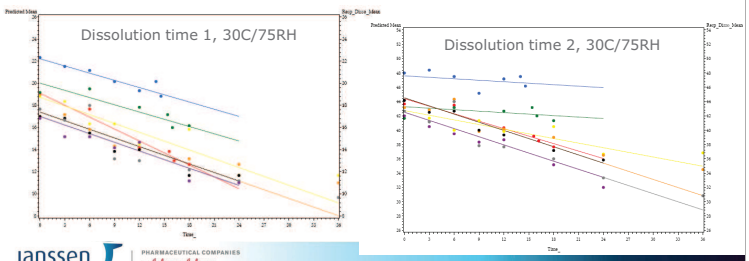
Marketed product case study

- Construction & review of the dataset
  - Different dissolution time points
  - 24 months real time stability data (25C, 30C, 40C) of dissolution for 3 study lots
  - 18 months stability data (25C, 30C, 40C) of dissolution for 3 commercial lots
  - Data at time of manufacture of dissolution for 47 commercial batches
  - An analytical run was defined as a set of 6 vessels jointly assessed in a single dissolution bath

		25C/60RH	30C/75RH	40C/75RH
Lot Type	Lot	Time (Months)		
Study	A	0,3,6,9,12,18,24,36	3,6,9,12,18,24,36	1,3,6
	B	0,3,6,9,12,18,24,36	3,6,9,12,18,24,36	1,3,6
		0,3,6,9,12,18,24	3,6,9,12,18,24	1,3,6
	C	0,3,6,9,12,18,24,36	3,6,9,12,18,24,36	1,3,6
		0,3,6,9,12,18,24	3,6,9,12,18,24	1,3,6
Commercial	D	0,6,12,16.2,18	6,12,15.6,16.2,18	6
	E	0,6,12,16.0,18	6,12,15.4,16.0,18	6
	F	0,3,6,9,12,14.6	3,6,9,12,14,14.6	1,3,6

Marketed product case study

- Lot-specific study of stability data
- Observed differences in the stability profiles raised the statistical concern of poolability
  - Question of whether changes in process parameters, changes in material attributes or analytical run variation was contributing to the diffuse picture seen in the stability profiles
  - Process engineers are possibly aware of issues and are tweaking the process to address observed stability changes



Marketed product case study

$$y_{v(tijkl)} = \mu_t + \alpha_{i(t)} + S_{jk} \times T_{ijkl(t)} + \gamma_{ijkl(t)} + \varepsilon_{v(tijkl)}$$

- Release limit calculation (ADG method)

(Allen, Dukes, & Gerger, 1991. Determination of Release Limits: A General Methodology.)

$$RL_{jk} = LSL - S_{jk} \times T_{shelf} + t_{1-\alpha,df} \times \sqrt{Var(S_{jk} \times T_{shelf}) + \sigma_\gamma^2 + \frac{\sigma_\varepsilon^2}{6}}$$

- The popular ADG method does not address risk in a statistically derived probability sense
  - Applies to individual lots as manufactured
  - More decision rule rather than risk control strategy
- Current technology allows the application of a Bayesian approach in a fairly direct and uncomplicated way

Marketed product case study

- The manufacturing process was analyzed based on stability data of the study lots and data of the commercial lots at time of manufacture by dissolution time

$$y_{v(tijkl)} = \mu_t + \alpha_{i(t)} + S_{jk} \times T_{ijkl(t)} + \gamma_{ijkl(t)} + \varepsilon_{v(tijkl)}$$

  - $Y_{v(tijkl)}$: dissolution of v^{th} vessel for i^{th} lot within t^{th} type at j^{th} group, k^{th} condition, l^{th} stability time point
  - μ_t: process mean for t^{th} type at time of manufacture (study and commercial lots)
  - $\alpha_{i(t)}$: random effect of i^{th} lot within t^{th} type : ~ $N(0,\sigma_\alpha^2)$
  - S_{jk}:rate of change at j^{th} group, k^{th} condition
  - $T_{ijkl(t)}$: l^{th} stability time of v^{th} vessel for i^{th} lot within t^{th} type at j^{th} group, k^{th} condition
  - $\gamma_{ijkl(t)}$: run-to-run and unknown source of variability ~ $N(0,\sigma_\gamma^2)$
  - $\varepsilon_{v(tijkl)}$: vessel-to-vessel variability : ~ $N(0,\sigma_\varepsilon^2)$

Marketed product case study

- Generate **a posterior sample** representing a set of process parameters from the posterior distribution of the parameters from the mixed model. This represents a random commercial process, indexed by *s* , with parameters: μ_{ts}, S_{jks}, $\sigma_{\alpha s}^2$, $\sigma_{\gamma s}^2$, $\sigma_{\varepsilon s}^2$
  1. 100 random **batches at time of manufacture** representing the commercial process were generated
     - 12 error terms representing **vessel-to-vessel variability** were added to the batch means such that for each batch 6 stage 1 vessels and 6 stage 2 vessels at time of manufacture were obtained ⇒ vessels were sampled with replacement from the complete set of residuals of the fitted linear mixed model.
     - A random run effect sampled based on the posterior sample of the model parameter representing **run-to-run variability** was added to the 2 constructed sets of 6 vessels for each batch
  2. Data for the 100 generated **batches at 24 months** were constructed by also adding the total change in dissolution after 24 months shelf life based on the posterior sample of the rate of change parameter for the considered condition

  These steps were repeated for each of the 2000 posterior samples

Note: Independence Chain Metropolis-Hastings algorithm used in SAS Proc Mixed procedure

Bayesian simulation approach

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
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- USP rules at stage 1 and 2 were applied to
  - The simulated batches at time of manufacture and information on pass/fail at each stage was retained
  - The simulated batches at 24 months and information on pass/fail at each stage was retained

Based on above algorithm, the percentage of the total of 200,000 batches allocated to factor levels pass and fail after stage 2 dissolution testing of the cross-classifying factors time of manufacture and 24 months shelf life was calculated by dissolution time and storage condition

Bayesian simulation approach

- Failure rate calculations
  - P(FR)=P(FR1)×P(FR2|FR1)
  - P(FS|PR)=P(FS1|PR)×P(FS2|PR,FS1)
  - P(F)=P(FR)+((1-P(FR))xP(FS|PR))
- A cross-tabulation of the percentage of commercial batches that pass/fail stage 2 testing at time of manufacture and 24 months shelf life at given dissolution time and condition

%		24 Months Shelf Life	
		PASS	FAIL
Release	PASS	74.47	24.81
	FAIL	0.69	0.03

Risk of Product Recall

Risk of Loss to Company

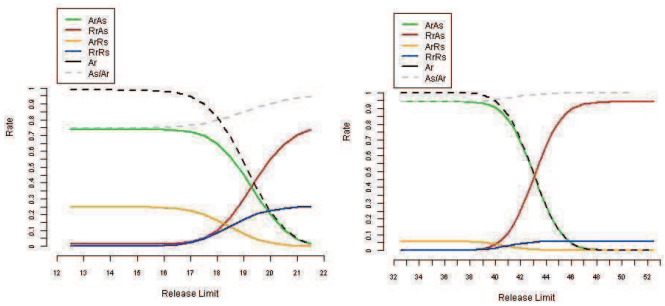
Bayesian simulation approach to risk assessment

- The probability of pass/fail stage testing at time of lot manufacture and end of shelf life after stage 2 dissolution testing was also calculated based on
  - USP rules at stage 1 and 2 (time of manufacture, shelf life)
  - A release limit applied at time of manufacture based on the mean of 6 vessels

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

Tables constructed for series of possible release limits applied at time of manufacture based on the mean of 6 vessels

Bayesian simulation approach to risk assessment



Bayesian simulation approach to risk assessment

- **Bayesian posterior predictive approach** addresses manufacturing risk by allocating measured outcomes into categories of acceptable and unacceptable lots at both time of manufacture and end of shelf life given specifications and release limits
  - Predictive posterior distribution of future lots can be easily generated ⇒ a natural interpretation of manufacturing risk as a probability
  - The risks associated with the manufacturing process are expressed via 2x2 tables displaying joint time of manufacture and end of shelf life outcomes as probabilities
  - Release limits as a control strategy can be assessed by calculating the OC curve corresponding to the 2x2 table outcomes generated across a range of release point values or intervals
  - Natural calculation of both consumer and producer risk
  - Costs to the company associated with the risks can be calculated
  - Provides elements of a comprehensive risk control strategy missing in the ADG method
- Expert opinions, historical data from diverse sources and prior knowledge may be integrated into a prior distribution

Analytical design strategy

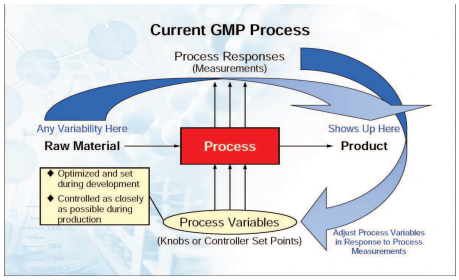
- Alternative analytical design at each stability time is proposed to mitigate the possible effects of local biases due to analytical run interfering with the characterization of the stability profile
- Example Latin square design with vessel number and analytical run as blocking factors (3 lots, 2 conditions)
  - A combination of lot and condition is allocated to each vessel and to each analytical run exactly once

		Analytical run					
		1	2	3	4	5	6
Vessel	1	B / 30C	A / 25C	C / 25C	A / 30C	B / 25C	C / 30C
	2	A / 25C	B / 30C	A / 30C	C / 25C	C / 30C	B / 25C
	3	A / 30C	C / 25C	B / 25C	C / 30C	A / 25C	B / 30C
	4	C / 25C	A / 30C	C / 30C	B / 25C	B / 30C	A / 25C
	5	B / 25C	C / 30C	B / 30C	A / 25C	A / 30C	C / 25C
	6	C / 30C	B / 25C	A / 25C	B / 30C	C / 25C	A / 30C

  - The lot mean estimates at a given condition will benefit from having local biases averaged across 6 analytical runs

Process state

- End-product quality is not the issue
  - Quality tested into products



- This process map is not in line with cGMPs for 21st Century
  - Product and process understanding discouraged, compliance not science
  - Manufacturing processes often "frozen" following regulatory approval, any change is bad ↔ risk based approach
  - Product failures with possibly clinical impact → rework and regulatory action
  - Opportunities for improvement offered by new technologies are often missed
  - Internatinal collaboration is not promoted

Quality by Design

- Change in culture away from a 'compliance' driven paradigm to a science based paradigm (documented quality)
- FDA's Vision and the ICH desired state (ICH Q8/Q9/Q10)

Comparison of Conventional Pharmaceutical Development with QbD		
	Conventional	QbD
Approach	Mainly empirical, focus on process reproducibility	Systematic, focus on process robustness, understanding and controlling variability
Quality Assurance	End product Testing, IPC	Product/Process understanding, upstream controls through PAT
Process	Fixed, changes discouraged	Flexible within Design Space, continuous improvement

Thank you!

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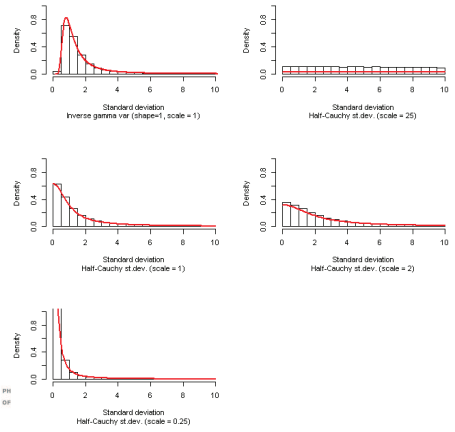
Bayesian simulation approach to risk assessment

- Some knowledge about variability can be obtained from scientists who formulate the drug



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