QBR as an Organizing Principle for the Pre-approval Development of Generic Drugs

FY 2016 Regulatory Science Initiatives Part 15 Public Meeting

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Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA)
Testimony of Janet Woodcock, M.D.
Before the Committee on Oversight and Government Reform
United States House of Representatives, February 4, 2016

Ongoing Challenges

…"Second, there is a need for more research in the generics space. Some drugs lack generic competition because there is no convincing bioequivalence test method available. … *Similarly, methods for showing chemical sameness for certain complex drugs are not available*…"

What does QBR as an Organizing Principle Mean?

QbR and QbD are complimentary not independent

QbD is the framework/control strategy and QbR is the logistics/execution

- A Development History captured in the Report is the key to both guiding development and being ready for QbR.
- Essential aspects of the *DH* include:
  - The rationale for all phases of development
    - Fundamental principles, prior knowledge, heuristics
    - Q8 and Q6 principles are implicit in *DH*
  - The knowledge base created
    - Makes the *DH* an electronic living document with all changes captured
    - Usage of new and prior knowledge to make decisions
    - Capturing of failure modes and sharing of knowledge between *FDA* review and inspection

"Historical" Example:

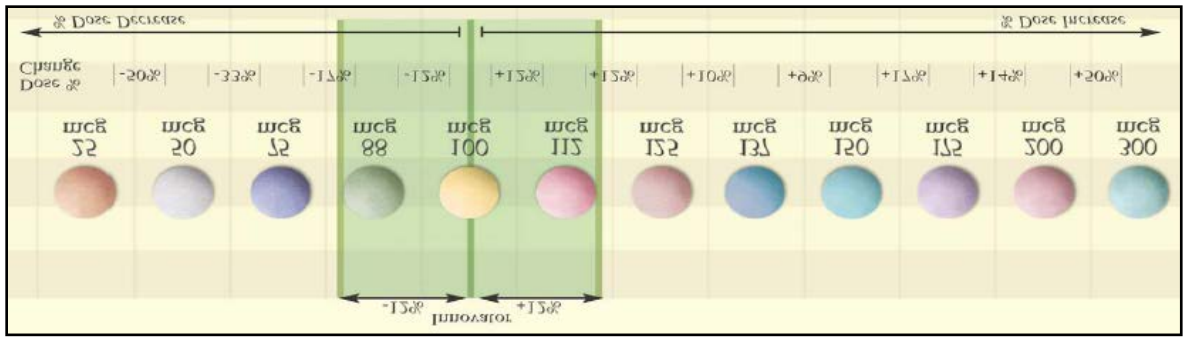
FDA Advisory Committee for Pharmaceutical Science—March 13, 2003

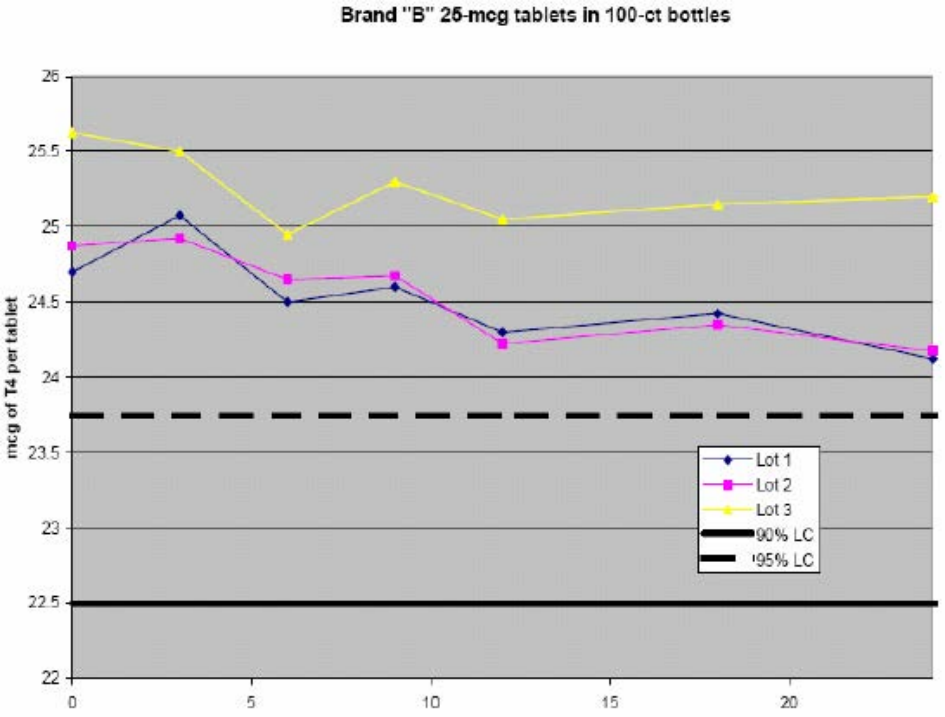
Carlos R. Hamilton, Jr. MD, FACE

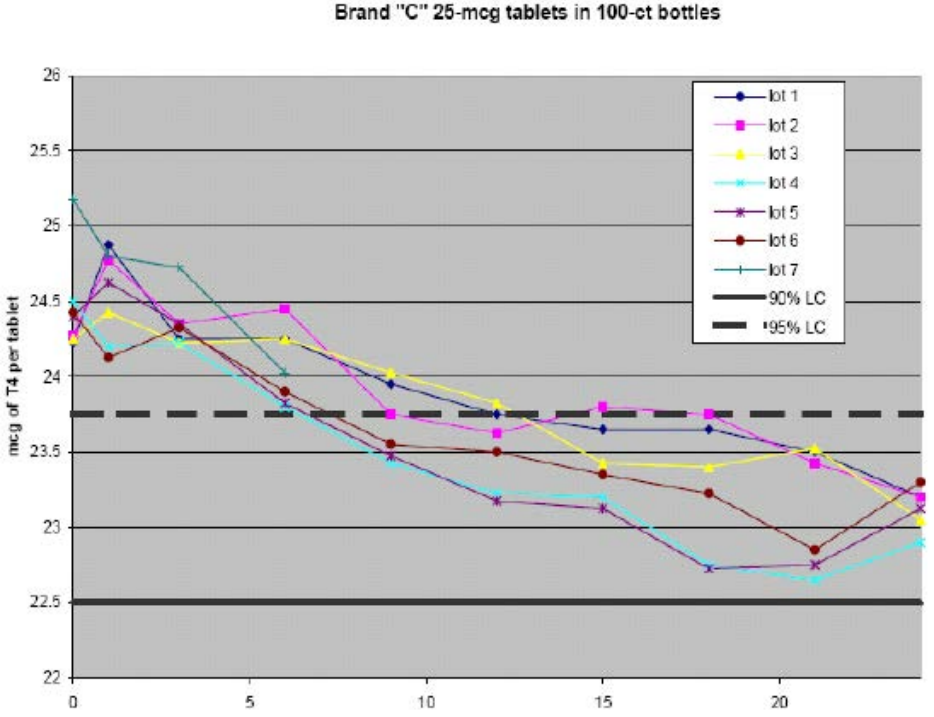
American Association of Clinical Endocrinologists—VP

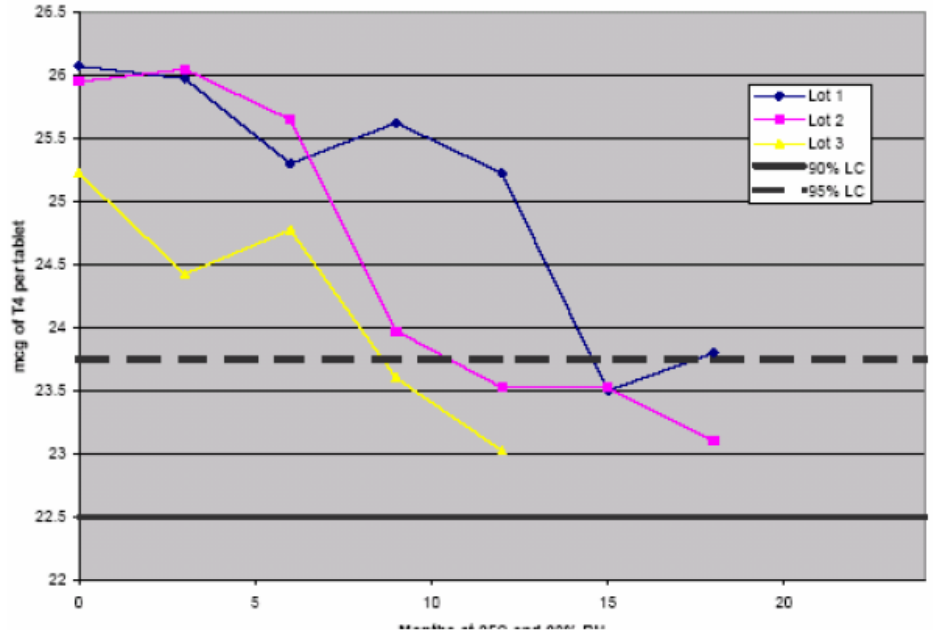
UT Houston, Executive Vice-President for Clinical Affairs

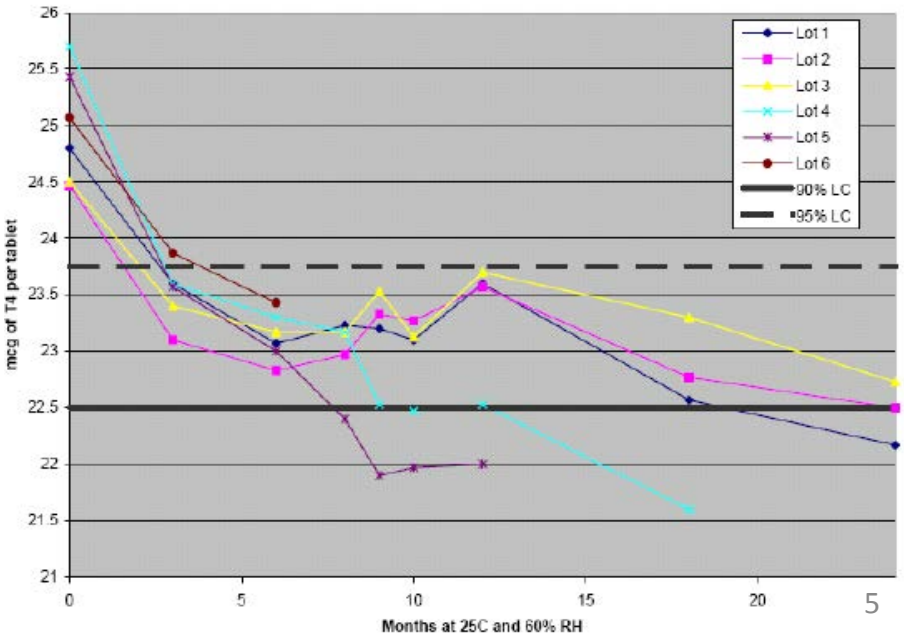
Dosage Changes of as Little as 12.5 to 25 Micrograms of Oral L-Thyroxine Daily Have Significant Effects on Serum TSH











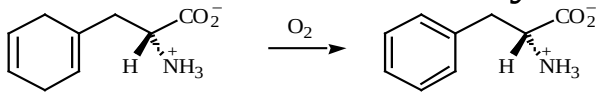
Eric Duffy – CDER-FDA

Impact of the Solid State on Chemical Stability: Dehydration (*Solid State Chemistry of Drugs*, Byrn 1999)

16.11 Oxidation Reactions Preceded by Loss of Solvent

Although not extensively studied, there are several solid-state oxidation reactions that are preceded by and may indeed require prior loss of solvent of crystallization.

A. Dihydrophenylalanine

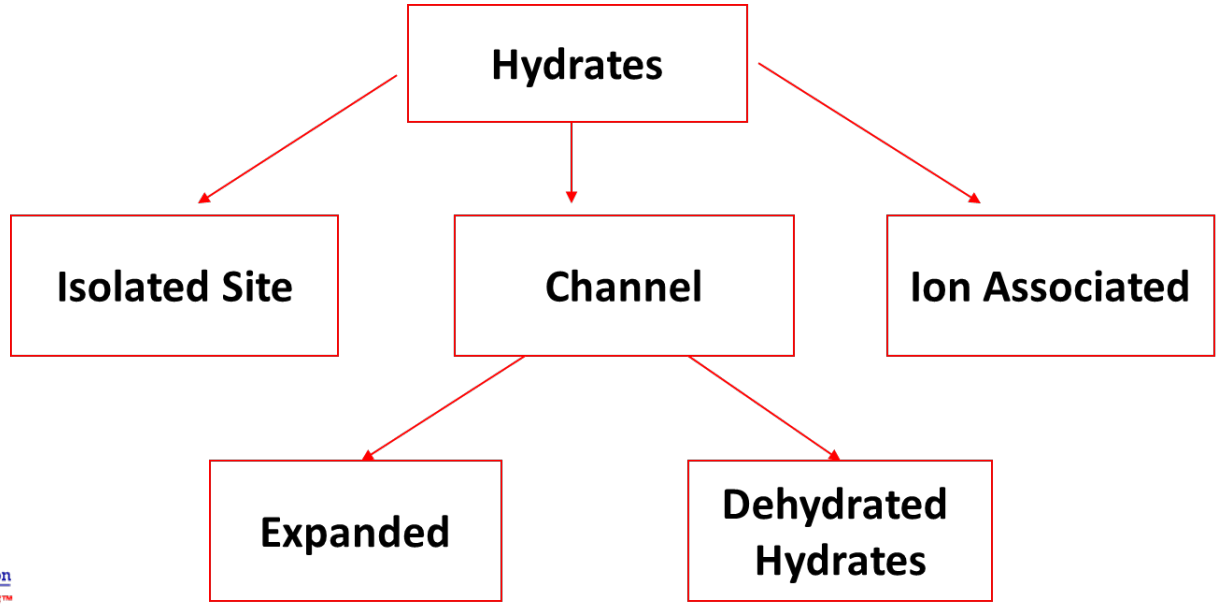


dihydrophenylalanine phenylalanine

Impact of the Solid State: Crystalline Hydrate Classification System

(Morris and Rodriguez 1993, Morris and Brittain1998)

Dehydration can lead to amorphous material, new crystal structures, dehydrated hydrates which maintain the packing motif of the original structure, or mixed structures



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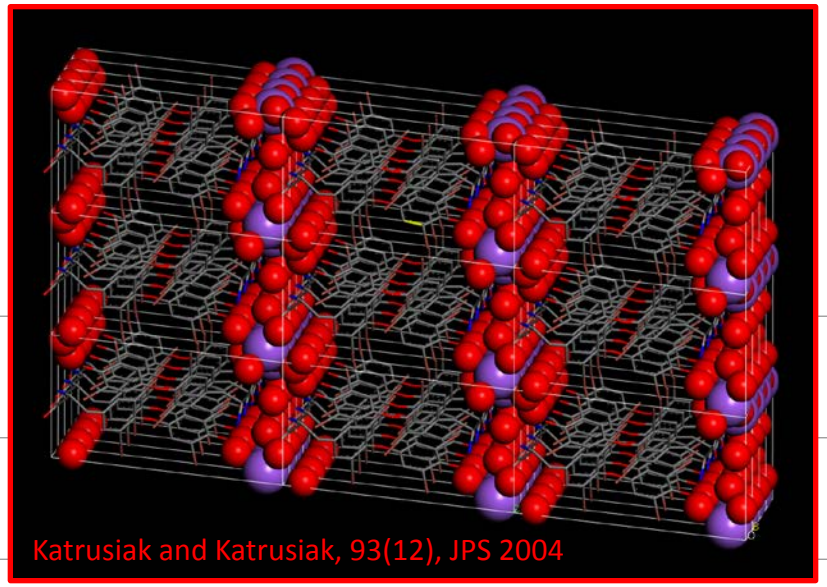
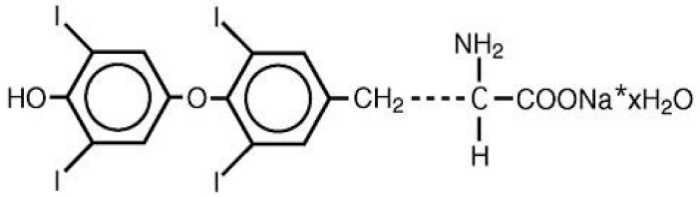
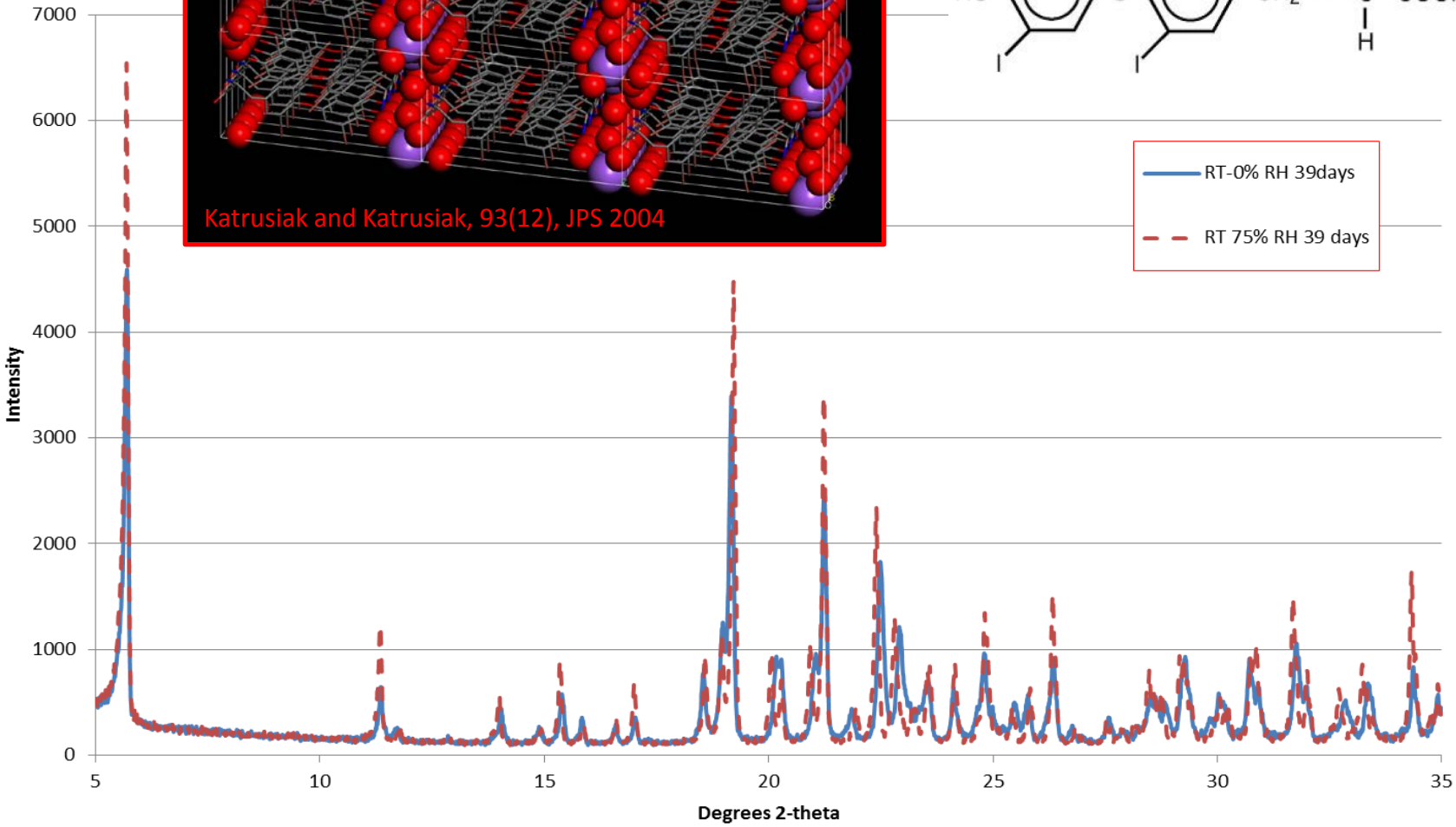
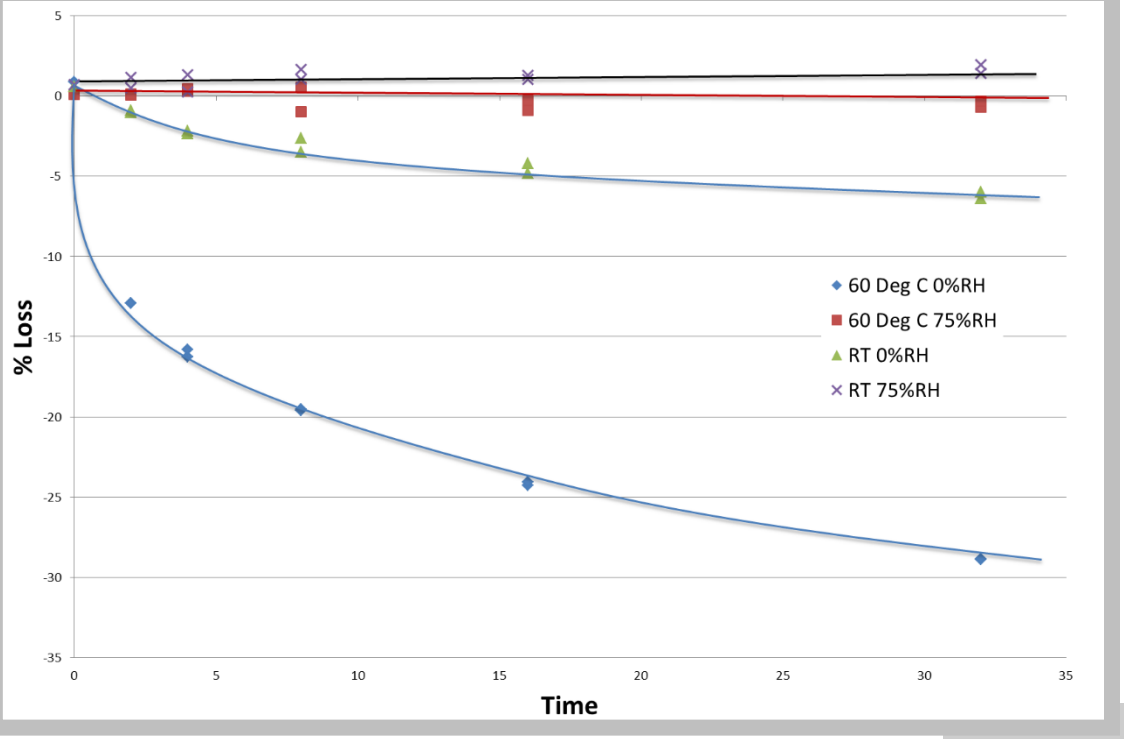
Dehydration of LTH can produce a dehydrated hydrate which maintain the packing motif of the original structure as shown





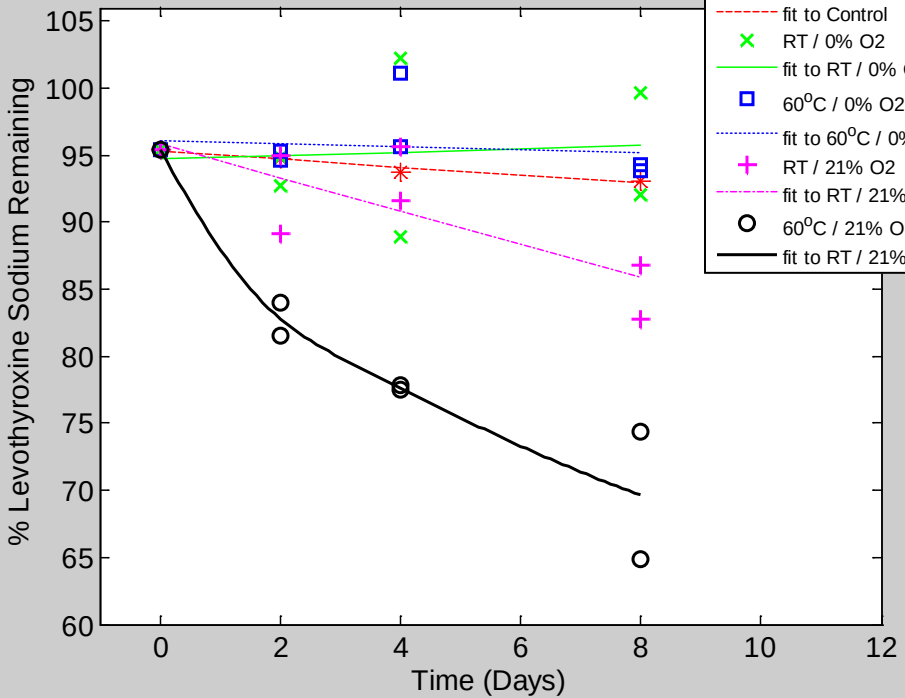




Does Dehydration Precede Degradation?

Does O_2 Cause Degradation?

Pharm Dev and Tech Vol. 20(3), pgs.314-319 May 2015



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So a lot was known or discoverable about levo's properties and issues

- NTI (narrow therapeutic index drug)
- Very low dose, 25-300ug
- Chemically labile: formulation failure modes
  - Stable if hydrated but oxidized if dehydrated/disordered
  - Processing effected stability (ala structure) – Patel Cincinati thesis
  - Excipient interaction (often via pH), Mansoor's papers
- Long *PK* $t_{1/2}$ of approximately 7 days

Yet many products were developed and approved <u>apparently</u> oblivious of the prior knowledge and/or logical concerns

Note - this pre-dates most of the "Q's" QbD, QbR, Q8 etc…so no Dev. Report in US

What does the example teach?

- The dosage form quality specs need to be developed at the **preclinical or pre-bio-study stage** (QTPP – Q8 -ala Q6A) to know what variability is due to the patient variability or PD
  - *An opportunity to leverage **pre-ANDA** meetings*
  - *Specs established as a basis for product design not decided after the fact*
- The development process has to be ***INTEGRATED*** to understand how fundamental property changes propagate variability downstream
  - *Orthogonal analytics and BE must be "connected" to formulation design*
  - *Scaling-up amplifies but seldom solves problems (paraphrased from Steve Byrn)*
- Designing a process/product and creating a sound Development History is its own reward in product quality and for efficient review

An Integrated NTI *Quality* Classification

- The problems facing NTI development and use are based on the **general hypothesis** that the lack of IVIVC (and the phenomenon of a NTI itself) is a broad category,
  - i.e., the lack of IVIVC is a symptom with many different possible root causes.
  - It is proposed that these root causes fall into a finite number of predictable categories with variable but assignable contributions to the observed effect.
- Data mining and creation of an NTI quality-clinical response, adverse event, metabolism, and drug physico-chemical properties knowledge base **will be a major element of classification**. The data will be compiled into a fully relational knowledge base (FDA as a partner). This will not only serve to inform (right question at the right time) but to direct experimentation and modification strategies

NTI quality classification: *knowledge base* development

Drug	Oral Dose (mg)	Stability	Cp $t_{1/2}$ (hr)	Solubility (mg/mL)	Product Recall Basis (2012 - 2016)	Mol. Wt (g/mol)
Prazosin	1	Light Sensitive	2.5	0.5 (HCl salt)	-	383.4
Warfarin	1	Temperature sensitive	40	0.017	Super potetnt, CU, Stability	308.33
Clonidine	0.1	+	14	50	-	230.09
Valproic Acid	125	Light and Temperature Sensitive	12.5	50	Failed Dissolution	144.21
Digoxin	0.05	Light Sensitive	42	0.0648	-	580.94
Levothyroxine	0.025	Light Sensitive, Oxidation	168	0.000105 0.15 (salt)	Subpotent, stability, (45)	776.87
Phenytoin	30	Temperature sensitive	17	0.032	Failed dissolution	252.27
Isoetharine Mesylate	0.35	Temperature sensitive		3.18	-	335.42
Disopyramide	100	+	6.7	0.0449	Failed dissolution	339.47

Many more descriptors are relatively straight forward to obtain or generate with concerted effort of teams of graduate students!

Summary: Opportunities for FDA Support

- Research on ***integrated*** product development ***by category***, across disciplines/investigators, for pharmaceutical and therapeutic equivalence and *guidance contribution*
  - NTI quality matrix example
  - Complex Dosage Forms
  - Combination products
  - Complex APIs …
- Support for ***Knowledge Base*** *R&D* for formulation design
  - Elucidate fundamental phenomena associated with Dosage Form categories
  - Facilitate modeling, e.g. *ontologies*; FDA-NIPTE excipient database
  - Prepare the ground for *pre-ANDA* meetings
- Development of ***programs for training and expert support*** for Generic Companies and Reviewers
  - Identify knowledge and/or resource gaps
  - Development report rationale and design