

Mechanism for an integrated approach to Formulation Research, Knowledge Management, & Knowledge sharing with FDA & Industry

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The Complexity of Formulation Science

- Performance
 - Scientific Reliability
 - Formulation Stability & State of Control
 - Bioavailability/Bioequivalence
 - Safety, Efficacy & Therapeutic Equivalence
- Processes
 - Design/Design Control
 - Characterization & Assessment
 - Utility of prior knowledge
 - Approval and compliance decisions

Issues

- Fundamental understanding and knowledge of formulations
- Development report describes operationally what happens but may not provide adequate understanding
 - Structure
 - Solid state chemistry/Solution chemistry
 - Reactions & interaction of components in the composition
 - Design and mechanism of operation/structure/performance/behavior/function of formulation
 - Examples
 - Acid-base reactions/salt switches
 - Nanoparticles – Abraxane, coated nanoparticles
 - Emulsion formulations
 - Controlled release

Issues

- Specific populations; e.g., Pediatric formulations
- Nuances and critical aspects of manufacturing and how processes influence formulations
- Stability and potential stability issues
- Failure modes often not fully explored
- Frame the right questions in QbR

Example Complex/Problem Formulations

- Controlled/Sustained Release
 - Bupropion/Wellbutrin
 - Methylphenidate/ADHD drugs
- Emulsion- Based
 - Neoral
- Nanoparticles/Abraxane
- BCS Class 2
 - Ritonavir
 - Efavirenz
- Failure Mode Analysis
 - Acid-base reactions in formulations
 - Abuse deterrent formulations

Understanding these formulations requires fundamental scientific understanding

Neoral – microemulsion formulations

Mixtures of Neoral and SangCya with Diluent



- Neoral – a microemulsion formulation
- SangCya – a non-microemulsion formulation
- QbR – Importance of QTPP and structure differences of two formulations

Bupropion/Wellbutrin 300 mg Product

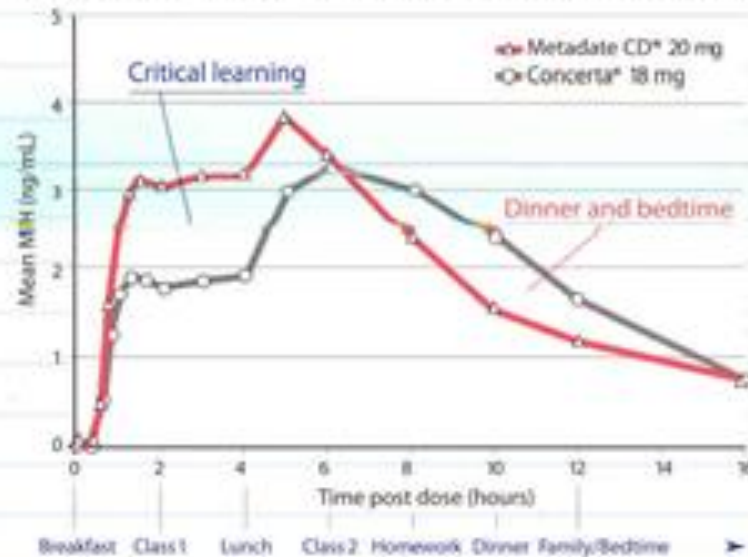
Bupropion XL 300 mg and Wellbutrin XL 300 mg

- Between January 1 and June 30, 2007, FDA received 85 post-marketing reports in which patients who switched from Wellbutrin XL 300 mg to Teva's bupropion formulation (Budeprion XL 300 mg) experienced an undesirable effect.
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm153270.htm>
- Withdrawal of Generic Budeprion for Non-bioequivalence.
<http://www.nejm.org/doi/full/10.1056/NEJMp1212969>
- A Drug Recall That Should Frighten Us All About The FDA.
<http://www.forbes.com/sites/davidmaris/2012/10/10/fda-recall-points-to-serious-problems-at-the-fda/#27da54cf357d>

- Bupropion XL300 – matrix release product prone to dose dumping
- Wellbutrin XL300 – membrane technology releasing bupropion over 5 hours. Not prone to dose dumping.
- QbR – Importance of BE study for highest dose

Metadate CD® delivers peak exposure during critical learning hours

Rapid 30-minute measurable plasma levels with continuous delivery*†



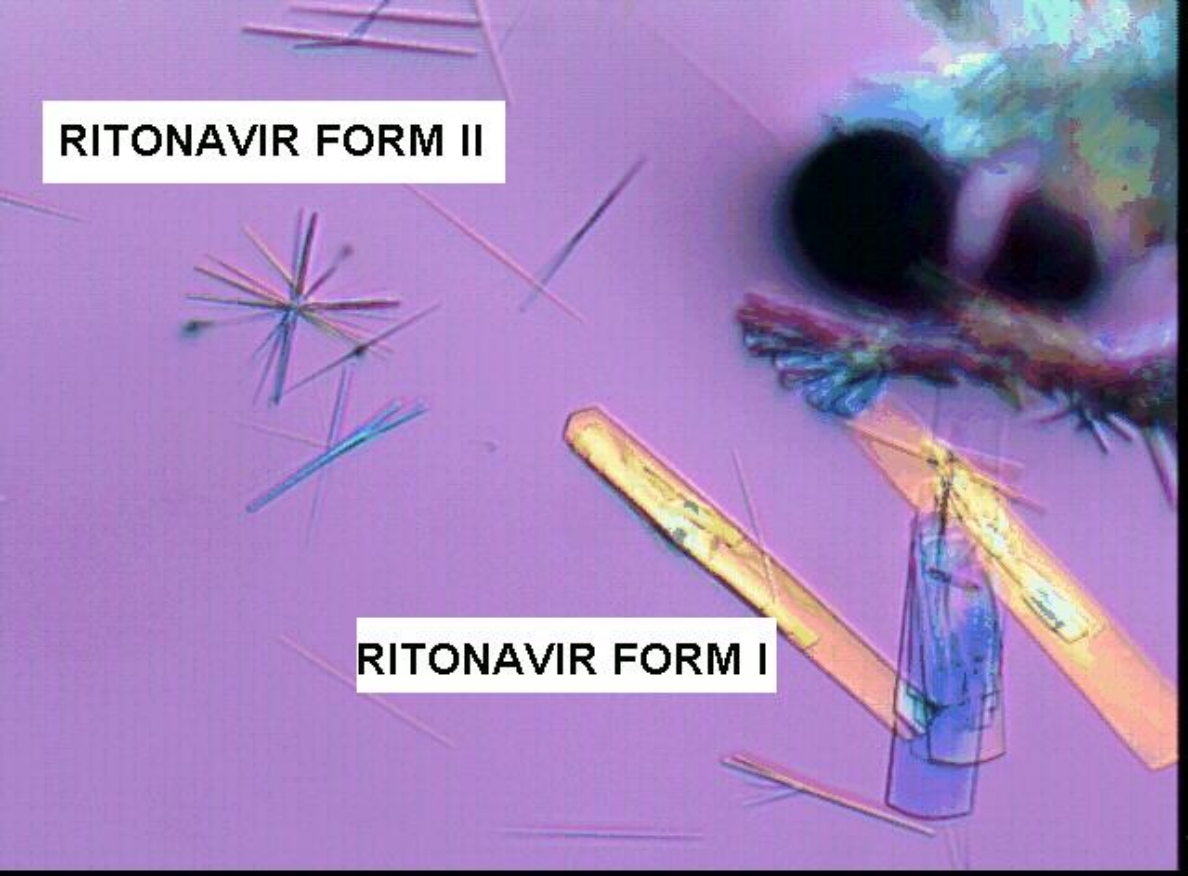
Mean MPH plasma concentration in fasting adult volunteers (N=36) following administration of one dose. The PK profiles of MPH in adults and children are qualitatively similar.²

- In pediatric studies, Metadate CD® achieved peak plasma levels at approximately 1.5 and 4.5 hours post dose
 - Peak exposure during critical academic learning hours

***Study Design:** A single-dose, randomized, 2-way, crossover study designed to compare the rate and extent of absorption of methylphenidate from 2 extended-release products—a 20-mg Metadate CD® capsule and an 18-mg Concerta® tablet—in 36 healthy adult male and female subjects under fasted conditions. Blood samples were collected over 24 hours, and methylphenidate plasma concentrations were used to calculate pharmacokinetic parameters for each treatment.²

†Metadate CD® should be administered once daily in the morning before breakfast. Consumption of a high-fat breakfast may affect the absorption rate of Metadate CD®.

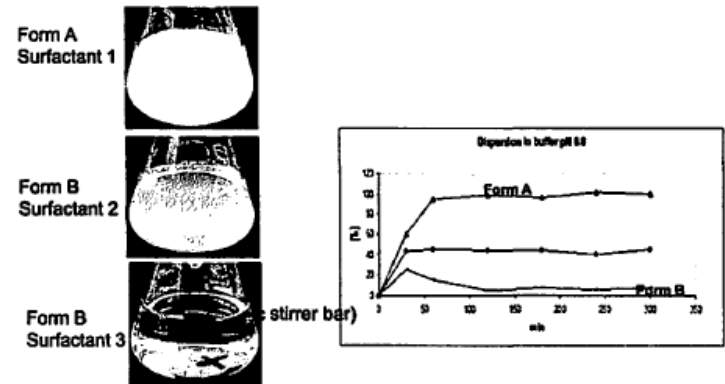




Ritonavir

- Soft Gel – Form 2 precipitated
- Reformulated SEC
- Reformulated as melt extruded tablet with special surfactant – sorbitan monolaureate
- QbR – importance of structure and manufacturing method (CQA)
- Importance of CQA - excipient

Formulation screening (e.g., choice of surfactant):



54th Annual International Pharmaceutical Research and Development Conference
11-15th of June 2012

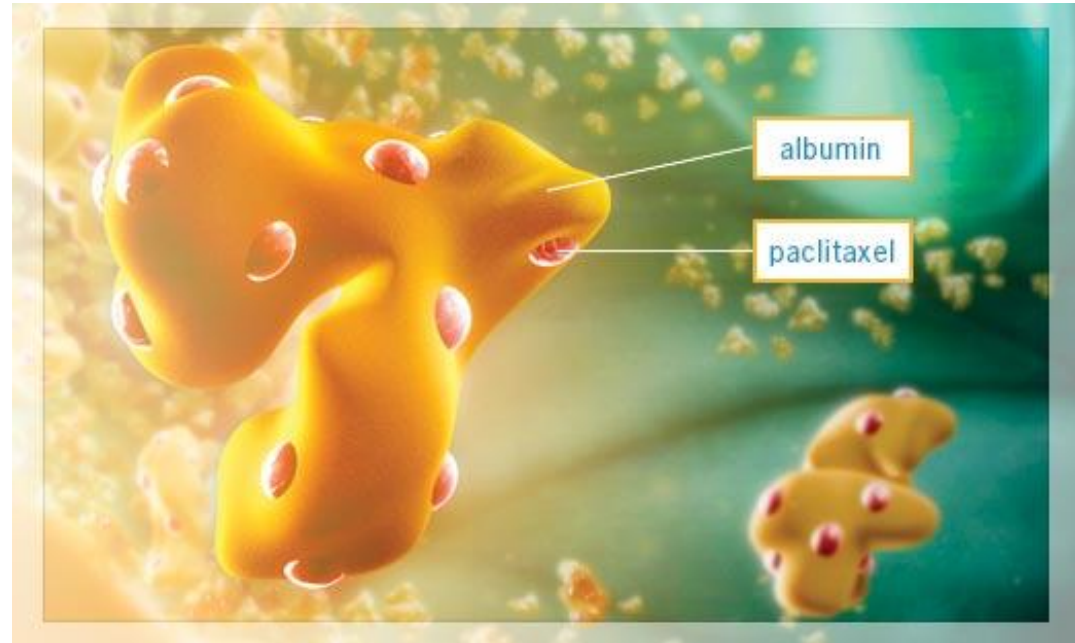
Dr. Gerd Woschke
Global Pharmaceutical Sciences
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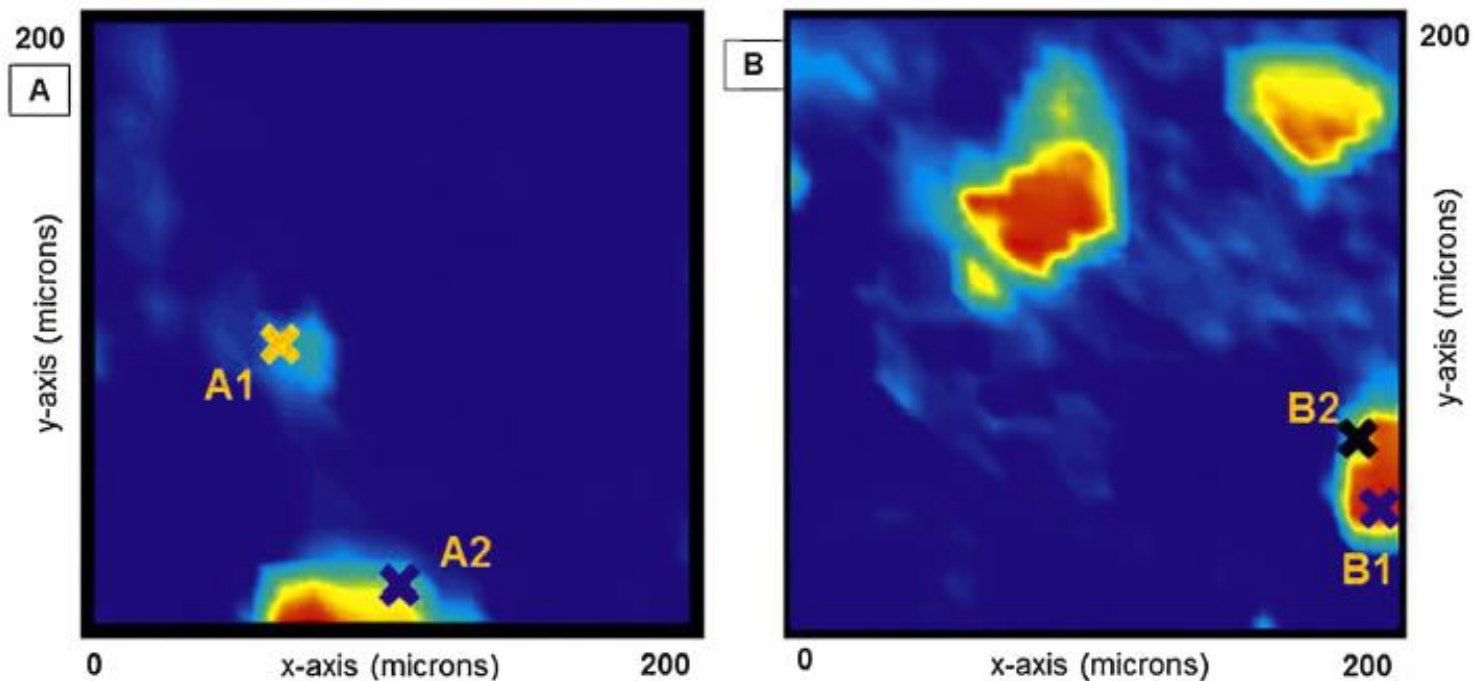
Abbott

Abraxane

- Structure
- Manufacturing method
- QbR - CQAs



Salt Disproportionation in Pioglitazone HCl Tablets



Steps to outlining a mechanism

- Case studies
 - Analysis: What didn't occur as it should have (e.g., identification of failure modes)
 - What if/should: Experimental research (e.g., evaluating options for optimal integration of product/process design with analytics)
- Transdisciplinary synthesis
 - What: Right questions @ right time
 - How: Right questions @ right time
 - Classification systems (e.g., NTI Quality) and decision trees, orthogonal methods (e.g., Utility of R&D Analytics, QC Tests and Effective Investigations)
- Process & system for knowledge acquisition & curation
 - Identify knowledge and/or resource gaps and process to fill these
 - Building the knowledge base
- Deliverables (Examples)
 - Targeted white papers & scientific publication
 - What if/should research to evaluate option for optimal integration
 - System for transdisciplinary elaboration to inform Question Based Review and recommendations on product specific recommendations for regulatory guidance
 - Training programs
 - Curated knowledge base

Summary

NIPTE Point of View:

Confidence in Generics: Need for an Integrated approach to Formulation Research and Knowledge Management (Ajaz Hussain)

Integrated approach for evolving standard for analytical characterization - case example excipient variability (Eric Munson)

Integrated approach for evolving standards for formulation design - case example NTI's (Ken Morris)

Mechanism for an integrated approach to Formulation Research, Knowledge Management, & Knowledge sharing with FDA & Industry (Steve Byrn)

- In their allocation of FY 2017 funding for regulatory science research, the FDA is urged to consider prioritizing efforts towards development of knowledge bases and standards to guide optimal integration of multifaceted scientific evidence of Therapeutic Equivalence.
- Mechanism for such an integrated approach can/should include: Analysis (Looking back), Synthesis (Looking forward) and building of knowledge bases
- Deliverables, for example, may include:
 - Targeted white papers & scientific publication
 - What if/should research to evaluate option for optimal integration
 - System for transdisciplinary elaboration to inform Question Based Review and recommendations on product specific recommendations for regulatory guidance
 - Training programs, and
 - Curated knowledge base