Bioequivalence – Still a Quality Achilles' Heel?

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INSIGHT, ADVICE & SOLUTIONS LLC

Achilles' Heel = A vulnerable point.

TYPE I ERROR = INCORRECTLY CONCLUDE EQUIVALENCE

TYPE II ERROR = INCORRECTLY CONCLUDE NON-EQUIVALENCE

Pharmaceutical Equivalence is the Achilles' Heel

LESSONS I HAVE LEARNED

Lessons I have learned

Opening the Door To Follow-on Proteins?

When the FDA approved the follow-on protein Omnitrope in May, it gave generic drug makers the wedge they were hoping for. With pressure building in Washington, did Omnitrope push the door open – or was it just an anomaly? **BY STEPHEN BARLAS**

When the U.S. Food and Drug Administration last May approved Sandoz's Omnitrope — a follow-on protein to Pfizer's Genotropin, the leading biotech human growth hormone — hope sprung in the generic drug community that perhaps the agency had finally seen it their way, setting a precedent that would allow for the production and sale of follow-on proteins in the United States.

Omnitrope (somatropin) is the first follow-on protein from a generic pharmaceuticals company that the FDA has ever approved.

Equally significant — and troubling to the biotechnology industry — is the FDA's near-withering 52-page reply to two biotech manufacturers and the Biotechnology Industry Organization, whose citizen petitions had marshaled a phalanx of legal and regulatory arguments intended to persuade the agency not to approve Omnitrope. Essentially, the three petitions said the FDA could not approve Omni-

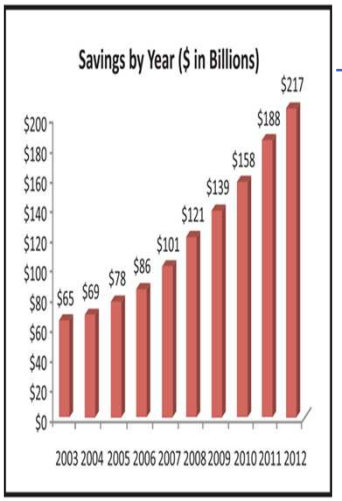
PHOTOGRAPH BY ROB CRANDALL

"You won't see 80–90 percent discounts on biogenerics because of the complexity of the product, the extensive development efforts to show it is identical to the innovator drug, and the manufacturing costs," says Ajaz Hussain, vice president and global head for biopharmaceutical development at Sandoz.

OCTOBER 2006 · BIOTECHNOLOGY HEALTHCARE 47

- Complex generic & biosimilar development share common challenges
- Pharmaceutical Equivalence is the Achilles' Heel
- Quality by Design requires an early investment in analytics
- QTPP should be based on RLD's CQA's and variability
- RLD TPP needs to be considered

Generic Drugs Savings [USA]



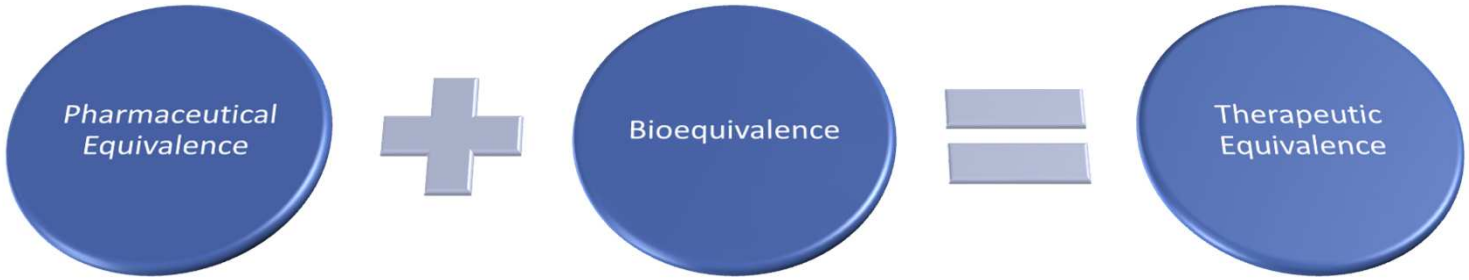
Over the 10-year period 2003 through 2012, generic drug use has generated more than $1.2 trillion in savings to the health care system

- In 2012, generics saved the U.S. health system $217 billion, up from $188 billion in 2011
- Nervous system and cardiovascular treatments account for 60 percent of cost savings.

http://www.gphaonline.org/media/cms/2013_Savings_Study_12.19.2013_FINAL.pdf

Therapeutic Equivalents

Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.



Also, they are adequately labeled; and are manufactured in compliance with CGMP

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf

Pharmaceutical Equivalents

Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules).

Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Bioequivalent Drug Products

This term describes pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(7)(B) of the Act describes one set of conditions under which a test and reference listed drug shall be considered bioequivalent:

- The rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses;
- Or, the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.
- Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate.
- Bioequivalence may sometimes be demonstrated using an in vitro bioequivalence standard, especially when such an in vitro test has been correlated with human in vivo bioavailability data.
- In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

Peroral Systemic Delivery: FDA Guidance Documents

1986
- FDA BE task force; report (1989): +/- 20%

1992
- 80-125 CI on log - trasformed metrics

2000
- FDA BA/BE general guidance; BCS biowaiver guidance

2001
- Statistical approaches to establishing BE

2002
- Food effect BA/BE guidance

2003
- Revision 1 of BA/BE general guidance

2009
- Partial AUC requirement

2010
- Guidance for HVDP (progesterone product guidance): RSABE

2012
- Guidance for NTI drugs (warfarin product guidance)

2013
- Separate BE guidance for PK endpoint studies for ANDAs

2014
- Separate BA/BE guidance for INDs, NDAs

Complex Generics

LMWH, peptides, complex mixtures, natural source products	Generic Enoxaparin (2011)
Liposomes, iron colloids	Generic Sodium Ferric Gluconate (2011) & Doxorubicin HCl liposome injection (2013)
Locally acting drugs	Generic Acyclovir topical ointment (2013)
DPI, MDI, nasal spray, transdermal system	Generic Advair®?

Confidence in Generic Drug Substitution [FDA]

Patients should have confidence that the generic drugs they are prescribed in the United States can be effectively substituted for the brand product or another generic product.

Through new bioequivalence study designs for narrow therapeutic index (NTI) drugs and postapproval studies of generic substitution, the US Food and Drug Administration's (FDA's) ongoing generic drug regulatory science activities are designed to ensure successful generic substitution for all drug products.

Clinical Pharmacology & Therapeutics **94**, 438-440 (October 2013)

Affordability & Availability

In the United States (U.S.), drug products are considered therapeutically equivalent if they meet regulatory criteria of pharmaceutical equivalence and bioequivalence.

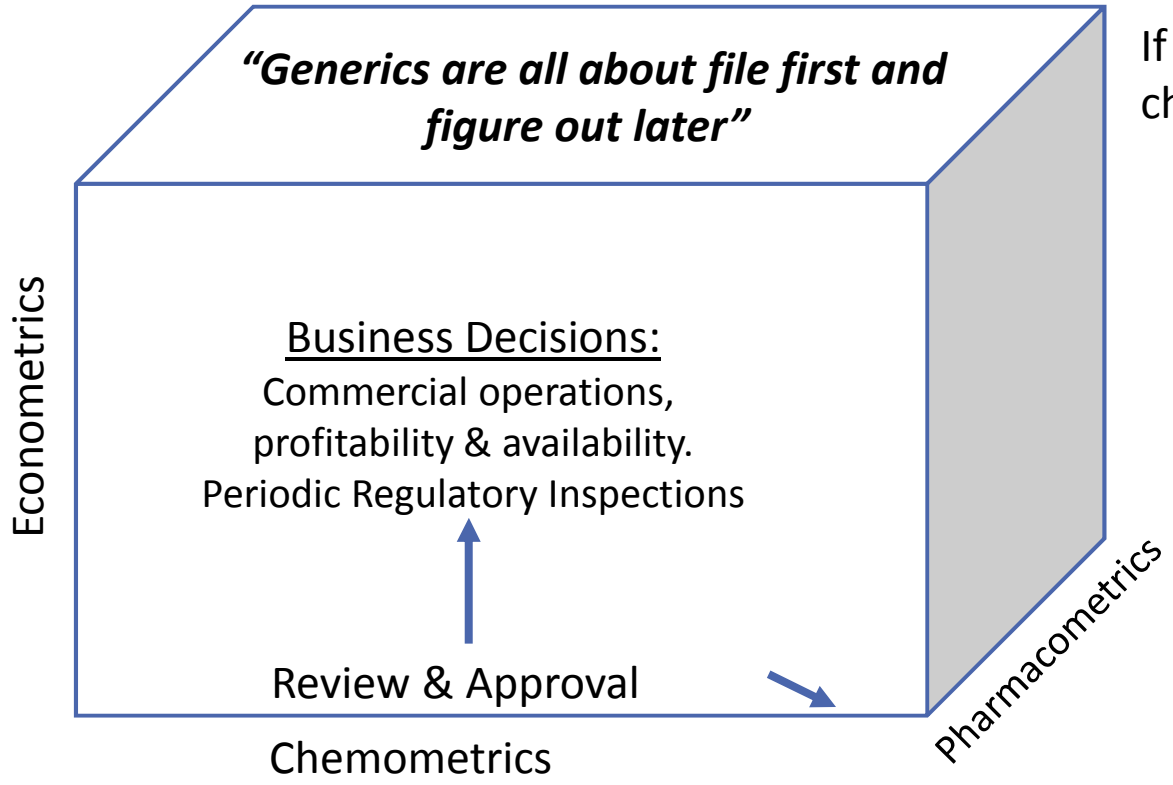
These requirements can be traced back to 1977 when the U.S. Food and Drug Administration (FDA) published the regulations on bioavailability and bioequivalence.

Over the years, to keep up with the advancement in science and technology, the FDA has been constantly updating the regulatory approaches to assessing and ensuring equivalence.

A systems approach – not just a one-time bioequivalence test – is critical for maintaining confidence in the overall system.

A vulnerable point

Ted Fuhr, McKinsey & Company. 17 July 2011: FDA Advisory Committee Presentation.



If so, this must change!

Effective Regulatory System: Importance of Process Understanding and Quality by Design

Ajaz S. Hussain, Ph.D.
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Pharmaceutical Quality Forum: 3rd Symposium
November 2004, Tokyo, Japan

San Francisco Chronicle

Prescription for trouble
How flaw in FDA safety net may pose risk to public with generic drugs
Sunday, December 22, 2002
Tom Abate, Todd Wallack, Chronicle Staff Writers

FDA castigated over generic drug loophole
Tuesday, December 24, 2002

LETTERS TO THE EDITOR
Wednesday, December 25, 2002
IN THE DARK AT FDA
JOHN BUFFUM
Pharmacy Planning Services, Inc.
Assoc. clinical professor of pharmacy
UCSF San Francisco

http://www.nihs.go.jp/drug/PhForum/documents041122/Hussain041122.pdf

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Question-Based Review for Pharmaceutical Quality Assessment

Lawrence X. Yu, Ph.D.
Deputy Director (acting)
Office of Pharmaceutical Science
Food and Drug Administration

Excipient Fest Americas
April 30 – May 1, 2013

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U.S. Food and Drug Administration
Protecting and Promot
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http://ipecamericas.org/system/files/KeyNoteEF13May11LawrenceYu(FDA).pdf

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Mixtures of Neoral and SangCya with Diluent

Are we asking the right questions & insisting on the right answer?

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Current (2005) CMC Review: Issues

- Quality by end product testing
  - Little or no scrutiny on
    - Product design
    - Process design and scale-up
  - In process testing
- Product specifications by test data from one/three batches
  - Little or no mechanistic understanding
  - "Overly conservative specifications"

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http://ipecamericas.org/system/files/KeyNoteEF13May11LawrenceYu(FDA).pdf

Biopharmaceutics and Drug Product Quality: Performance Tests for Drug Products, A Look Into the Future

Ajaz S. Hussain, Ph.D.
Deputy Director, Office of Pharmaceutical Science, CDER, FDA

USP Annual Scientific Meeting
"The Science of Quality"
September 26–30, 2004
Sheraton at Woodbridge Place, Iselin, NJ

A Look Into the Future: The future is upon us!

- Increased importance of physical performance characteristics of drug delivery systems
  - Complex drug delivery systems
  - Combination systems (e.g., drug-device)
  - Nanotechnology
- The Science of Quality – a critical dimension is the ability to understand, control, and manage variability

Performance Tests?

- Physical performance
  - Delivery to a site of action (e.g., target organs, tissues and cells)
    - Size, shape, density, (aero or hydro) dynamics, surface chemistry (e.g., charge),…
  - Residence time at the site of action or administration and biological interactions
  - Drug release mechanisms (e.g., passive or triggered)
  - Others

OOS or Exceptions Further Increase Cycle Times (Source: G. K. Raju, M.I.T. FDA Science Board Meeting, November 16, 2001)

Pharmaceutical Manufacturing: Impact of Exceptions

(Detailed Analysis of 2 Products)

PERFORMANCE MEASURE	VALUE
• **Average Cycle time**	**95 days**
• **Std dev**(Cycle time)	**> 100 days**
• **Exceptions** increase cycle time by	**> 50 %**
• **Exceptions** increase variability by	**> 100%**
• **Capacity Utilization** of "System"	**LOW**

Dissolution

NEED FOR FUNDAMENTAL TECHNOLOGY

MIT PHARMACEUTICAL MANUFACTURING INITIATIVE (PHARMI)

Dissolution Experience at the FDA Division of Pharmaceutical Analysis

- Dissolution testing with USP Apparatus 1 and 2 requires diligent attention to details: mechanical and chemical
- Dosage forms can respond differently to small variations in apparatus set up or degassing
- Large differences in dissolution results are possible unless all parameters are carefully controlled
- Differences in reproducibility can often be traced to improper mechanical calibration and/or degassing

Cindy Buhse
Director, Division of Pharmaceutical Analysis
FDA/CDER/OPS/OTR

Process Capability and Measurement Capability: Dissolution Test

- When we evaluate process capability by measuring variability in the product produced
- Total variability σ^2_{Total}
  - Assuming independent variable (if not independent for example interaction between measurement and product a covariance term needs to be included)
  - $\sigma^2_{Total} = \sigma^2_{Product} + \sigma^2_{Measurement}$
  - $\sigma^2_{Measurement} = \sigma^2_{Repeatability} + \sigma^2_{Reprodicibility}$

In an OOS Situation – the question is what went wrong?

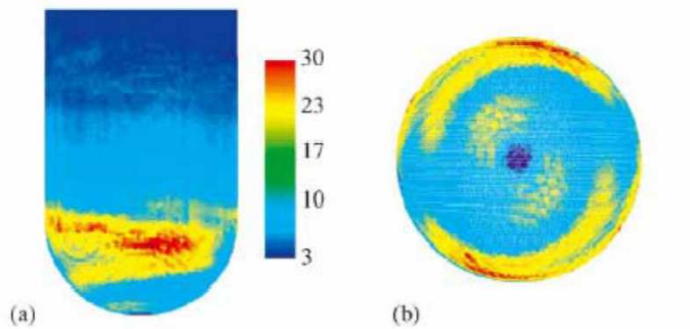
- Repeatability – inherent precision of the test procedure (did this change?)
- Reproducibility – different operator, different time period, different environment,… (is this a problem?)
- Destructive sample – what should we use to evaluate repeatability and reproducibility?
  - A USP Dissolution Calibrator Tablet?
  - Tablets from clinical batch?
    - Statistical approaches are available for ensuring appropriate sample of reference
  - Difficult questions; a need exists for further discussion on this topic

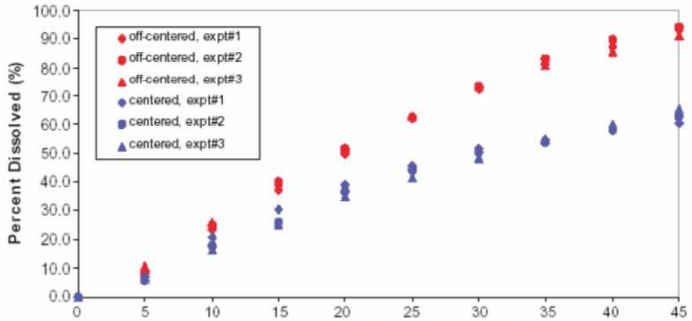
Difficult questions faced by Manufacturing Groups and Regulators…

- If we chose to use a calibrator tablet for a Gauge R&R study….
- $\sigma^2_{(\text{Total for Calib.})}$
  - $= \sigma^2_{(\text{Calib.})} + \sigma^2_{\text{C*Measurement}}$
  - What is the measurement for the Calibrator and what is its variability? $\sigma^2_{(\text{C*Measurement})}$
  - Since $\sigma^2_{(\text{Calib.})}$ is not known; we have to use $\sigma^2_{(\text{Total for Calib.})}$
- $\sigma^2_{\text{Total for Product}} = \sigma^2_{\text{Product}} + \sigma^2_{\text{Total for Calib.}}$

Difficult questions faced by Manufacturing Groups and Regulators…

- Assumption of independent variable?
- Another aspect – is the measurement capability for a Calibrator tablet representative of the drug product? What if there are differences such as disintegration mechanism and buoyancy between the Calibrator and the drug product?





J. Kukura, J.L. Baxter, F.J. Muzzio* International Journal of Pharmaceutics 279 (2004) 9–17

Mechanical Calibration

Pharmaceutical Science Advisory Committee Meeting, October 25-26, 2005, transcript available at http://www.fda.gov/ohrms/dockets/ac/cder05.html#PharmScience

ASTM E 2503-07, Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus.

FDA Guidance. The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP). 2010.

CNN.com

More U.S. Marines contract Malaria

Wednesday, September 10, 2003 Posted: 9:25 AM EDT (1325 GMT)

WASHINGTON (CNN) -- Ten more U.S. military personnel serving as part of the peacekeeping mission in Liberia are showing signs of having contracted malaria.

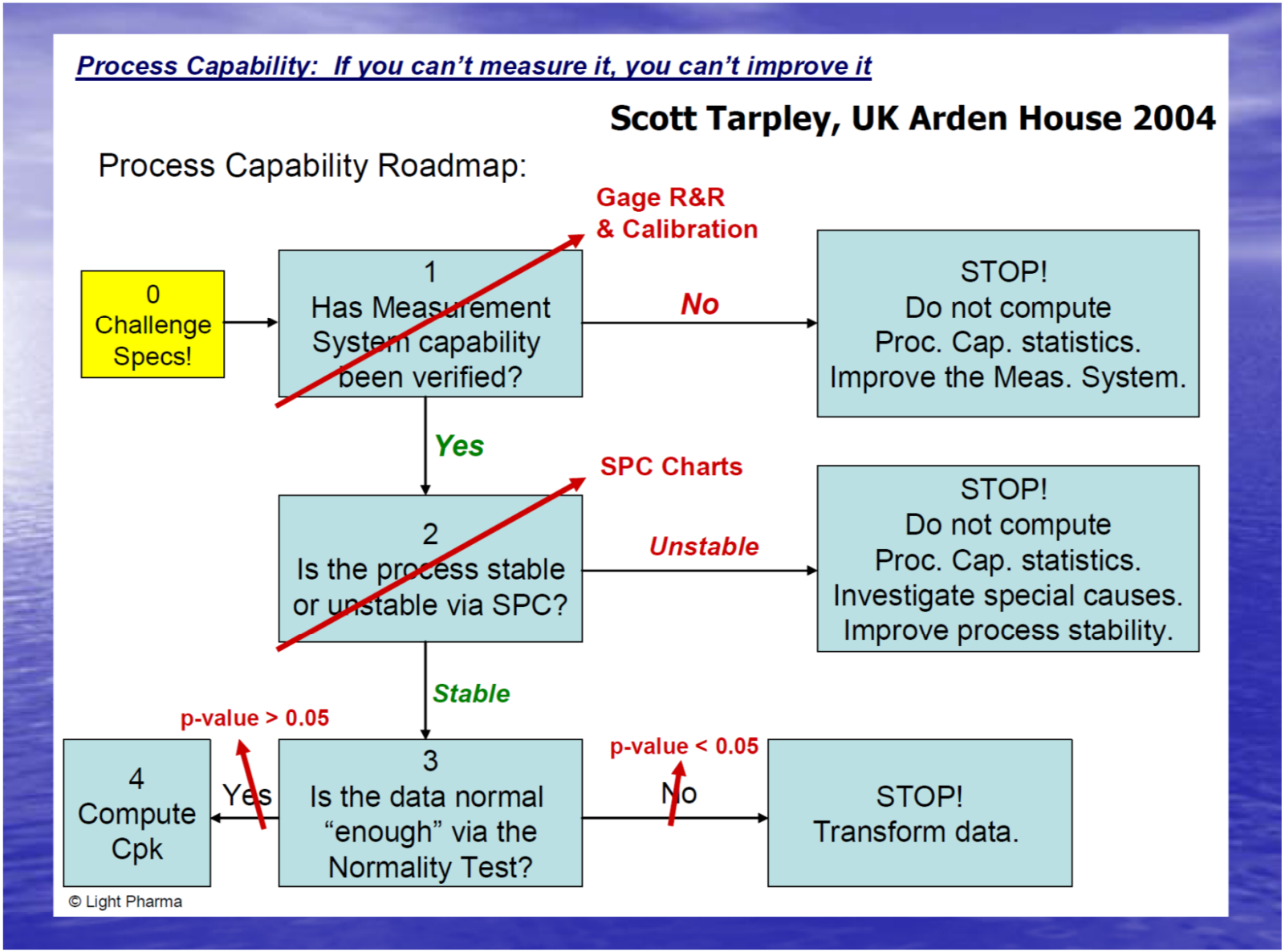
Prophylaxis compliance and not pharmaceutical quality was the reason

We faced significant challenges in our analysis: Unexpected inter-laboratory differences that highlighted limitation of the current calibration procedure

"We are at a loss to explain the difference between DPA's and PHI-DO's initial results. …….

We further contend that the Helium sparging does not remove dissolved air as well as the vacuum procedures and therefore could account for the additional 5 or 6% increase in the dissolution results. And finally, for this formulation basket wobble can significantly increase the dissolution values."

DPA/CDER/FDA Memo B. J. Westenberger, 17 October 2003


Process Capability: If you can't measure it, you can't improve it
Scott Tarpley, UK Arden House 2004
Process Capability Roadmap:
Gage R&R & Calibration
0 Challenge Specs!
1 Has Measurement System capability been verified?
No
STOP! Do not compute Proc. Cap. statistics. Improve the Meas. System.
Yes
SPC Charts
2 Is the process stable or unstable via SPC?
Unstable
STOP! Do not compute Proc. Cap. statistics. Investigate special causes. Improve process stability.
Stable
p-value > 0.05
p-value < 0.05
4 Compute Cpk
Yes
3 Is the data normal "enough" via the Normality Test?
No
STOP! Transform data.
© Light Pharma

A Warning Letter

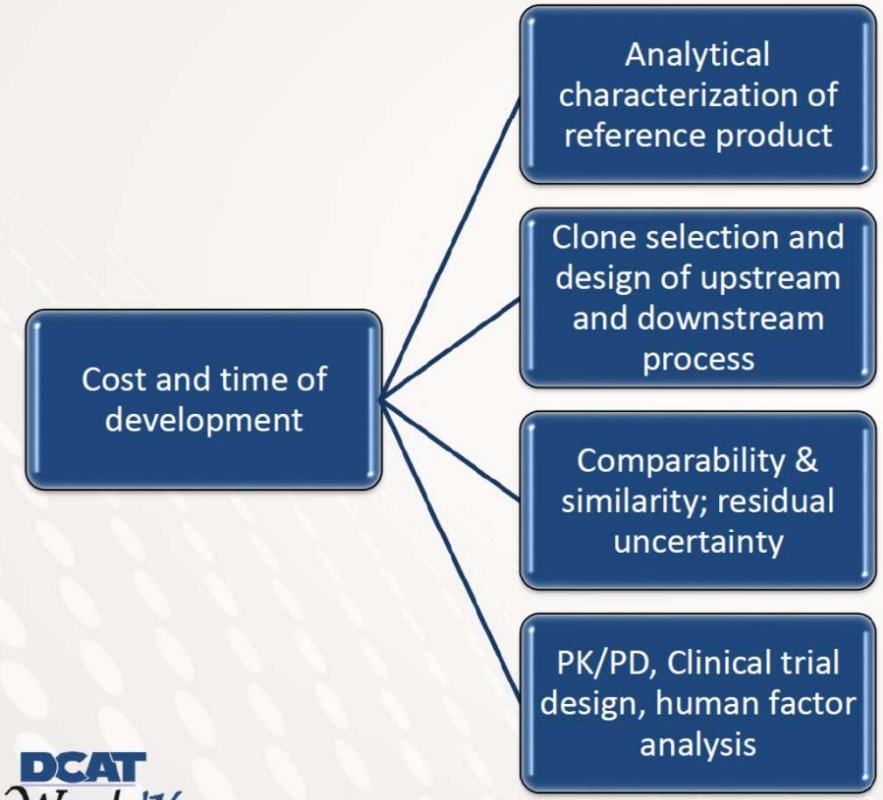
There is no assurance that the written production and process control procedures established for coating the are sufficient to produce a product that has the quality it is purported or represented to possess. The duration of each coating cycle is determined by the pan operators and is based on a visual determination that the coating solutions are evenly distributed before proceeding to the next step. It was noted that of [redacted] batches made in , and of [redacted] batches made in were rejected due to in-process dissolution failures.

The partial release of various products even though there was no data to invalidate out-of-specification (OOS) results. Some examples include:

a) lot #' was only partially rejected due to a failing in-process dissolution rate of from at the dissolution timepoint. Some partial releases were noted for this product for the period .

This can be catastrophic for the business and availability of Important drugs

Determinants of success



- Indications & evidence
- Clinical data vs. extrapolation across indications
- Interchangeability (USA)

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TPP & QTPP

What is the specific purpose of TPP & QTPP in biosimilar development?

- Why add TPP?

How to leverage lot to lot variability in the reference medicinal product?

- How many lots; when to characterize?

Which differences are acceptable while ensuring ability to demonstrate similarity?

- Understanding clinical relevance

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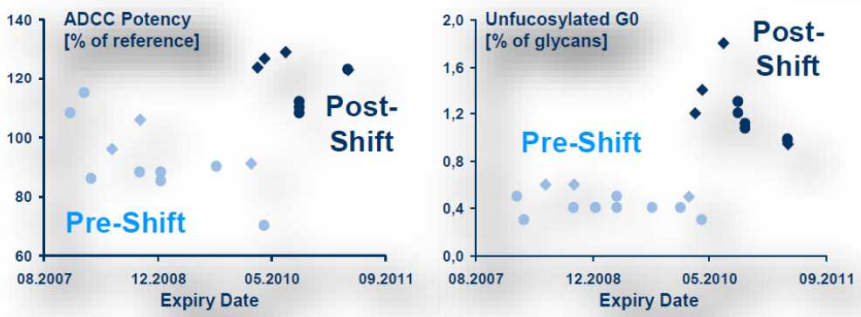
QTTP

- Define the targets for biosimilar development
  - Prior-knowledge (structure function, clinical,..) & RLD
- Define 'similar' - acceptance criteria
  - Clinical endpoints & variability in reference product
- QTPP should identify attributes most relevant
  - Facilitates development of meaningful target & acceptance criteria

"This [enoxaparin] approval represents a major development in US regulatory science and policy that will likely affect several other complex drug products...the extensive analytical characterization, as carried out for enoxaparin, will be important in the evaluation of protein products and may help to reduce the scope and extent of animal and clinical studies for biosimilars."
Sau Lee, et. al., Scientific Considerations in the Review and Approval of Generic Enoxaparin in the United States. Nature Biotechnology. Volume 3, 220-226 (2013)



Schiestl, M., *et al.*: Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals. *Nature Biotechnology*, 29: 310-312, 2011

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Key areas for consideration

Multiple disciplines & stakeholders

Overcoming the 'blind spots'

- Sampling and statistical criteria (starting with RLD samples)

Analysis of knowledge

- Pertaining to analytical characterization and comparability acceptance criteria

Evidence logic & communication

- Argumentation is a central means by which the community assesses the promise of conjectures and the validity of claims

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Blind spots take you on a 'roller costar' ride – not good for the patients and the business

Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS)

Certain methylphenidate hydrochloride extended-release tablets (generic products for the trade name Concerta)	Lack of therapeutic effect, possibly related to product quality issues	FDA is continuing to evaluate this issue to determine the need for any regulatory action.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm391572.htm

Need to avoid "roller coaster" rides

"We Did It! Concerta Generics on FDA Watch List"

To all ADHD Roller Coaster blog readers who took the time to complete the FDA's complaint form after experiencing adverse effects from the new Concerta generics: ***Good job! You have helped to place these generics on the FDA's Watch List, as of April 21, 2014.*** *But this is an incremental victory, so we should stay vigilant and continue to advocate on this issue.*

http://adhdrollercoaster.org/the-basics/we-did-it-concertas-generics-on-fda-watch-list/#.VD89kvmSwXg

Leverage the right analytical tool at the right time

PHARMACEUTICAL TECHNOLOGY

Delayed Release Tablet Dissolution Related to Coating Thickness by Terahertz Pulsed Image Mapping

JOHN A. SPENCER,[1] ZONGMING GAO,[1] TERRY MOORE,[1] LUCINDA F. BUHSE,[1] PHILIP F. TADAY,[2] DAVID A. NEWNHAM,[2] YAOCHUN SHEN,[2] ALESSIA PORTIERI,[2] AJAZ HUSAIN[3]

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[2]TeraView Ltd., Cambridge, CB4 0WS, UK

[3]Sandoz, Princeton, New Jersey

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RLD Variability

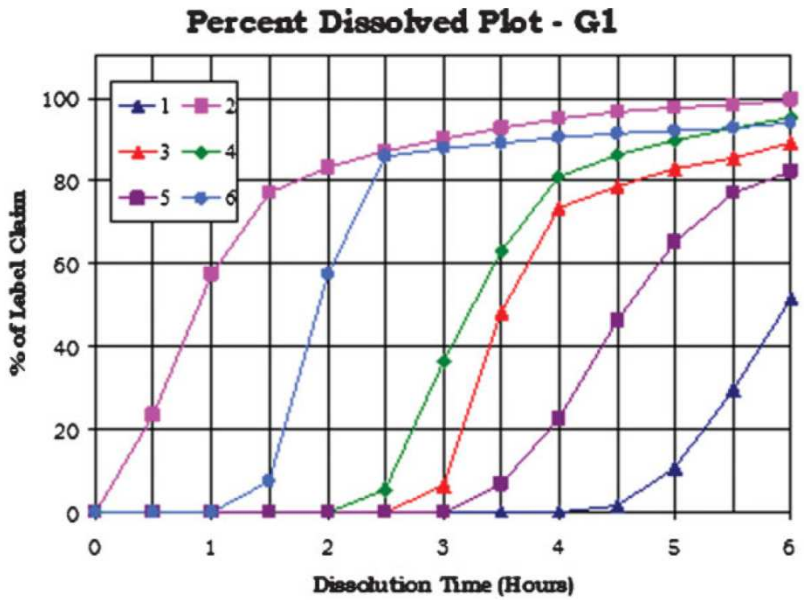

Figure 5. Typical dissolution curves - Run G1 observed fully scanned tablets for 6 h.

Knowing variability in the RLD provides a sound scientific rationale for designing a therapeutic equivalent generic product

Comprehensive development plan and effective regulatory communication strategy is critical

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 97, NO. 4, APRIL 2008

Pharmaceutical Equivalence can be the Achilles' Heel

LESSONS I HAVE LEARNED – QBD IS IN THE BEST INTEREST OF THE PATIENT & THE BUSINESS.

ASK THE RIGHT QUESTION WITH THE TIGHT ANALYTIC TOOL AT THE RIGHT TIME.