Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs

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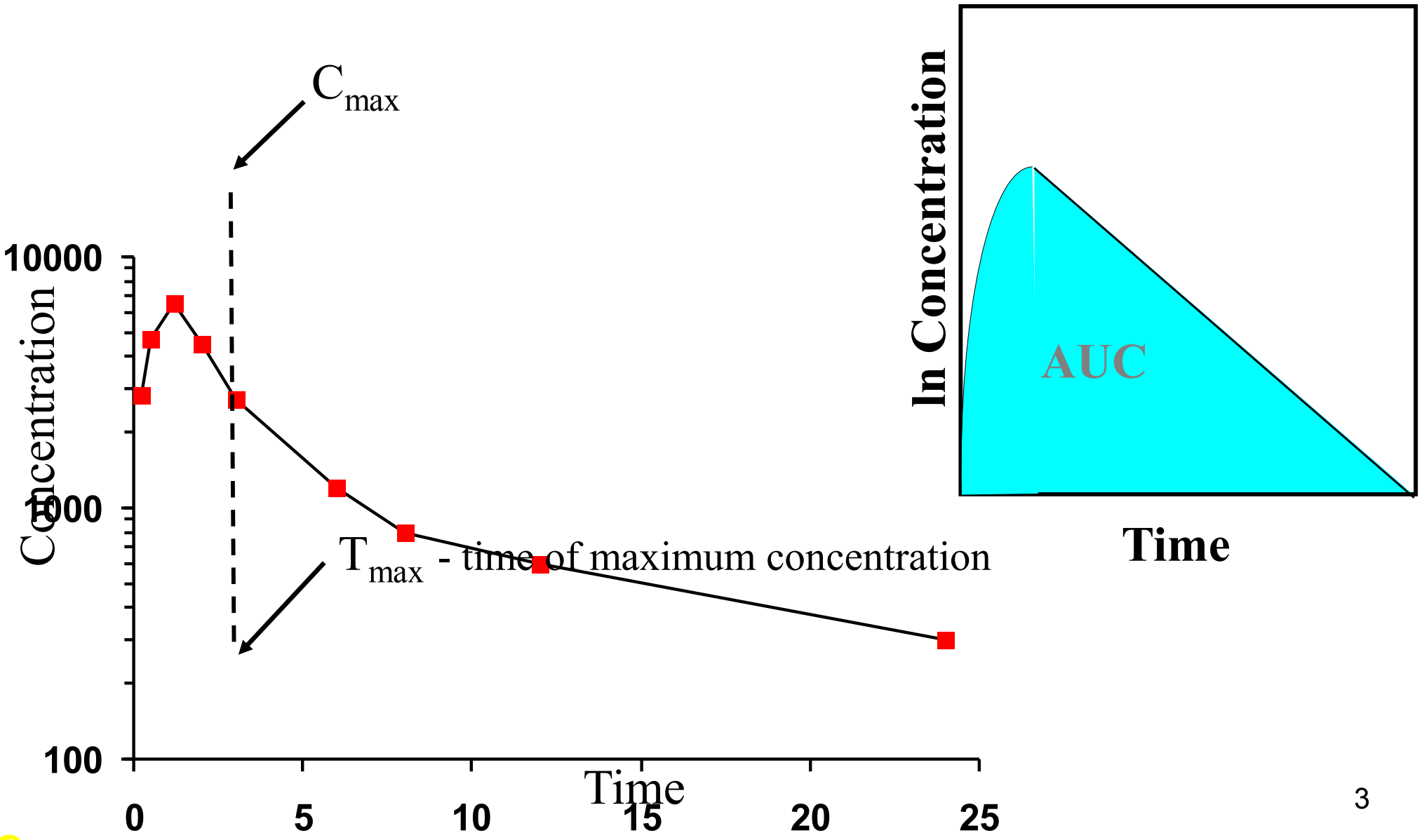
GPhA 2011 Fall Technical Workshop

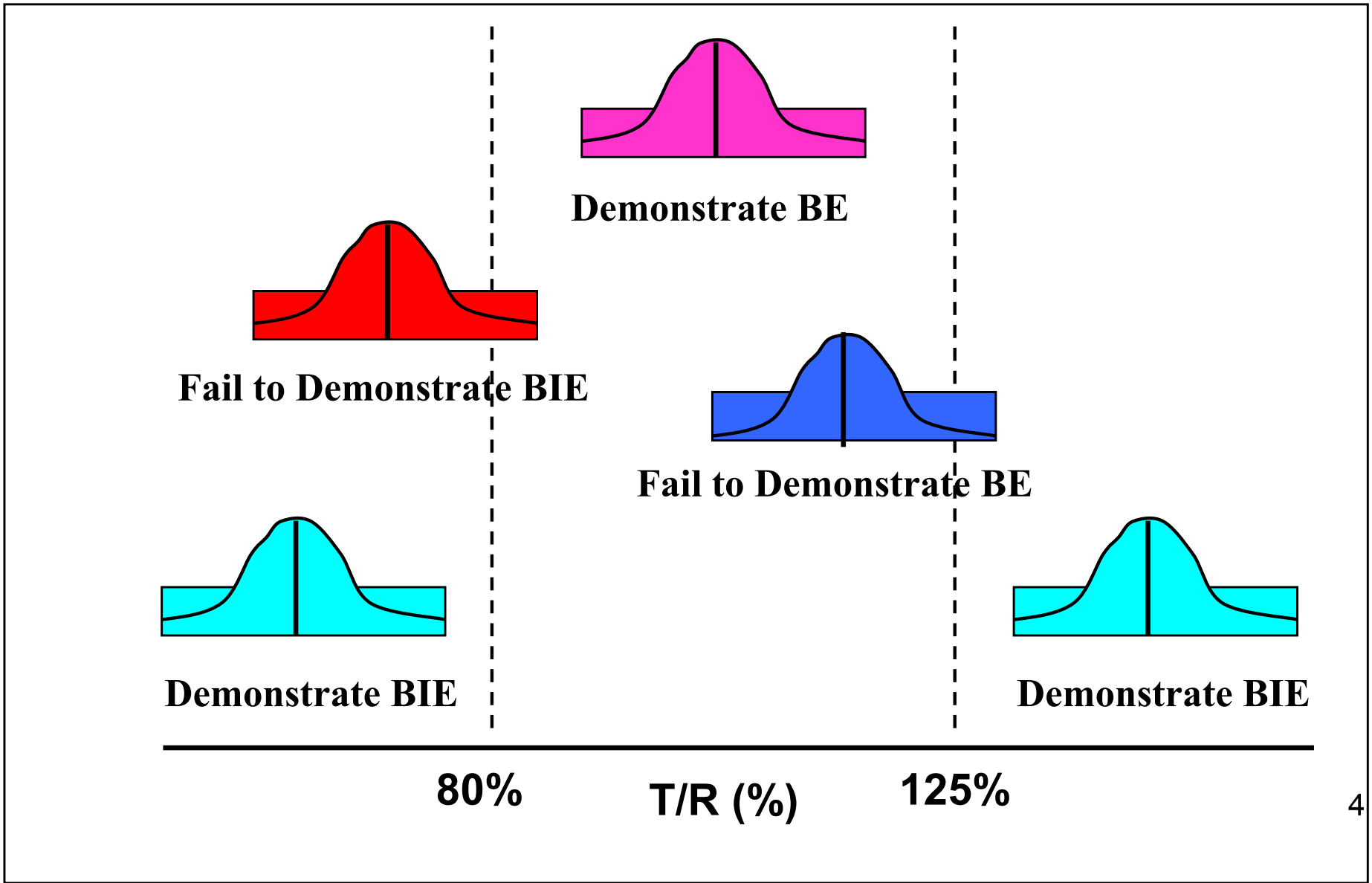
Bioequivalence

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study…" (21 CFR §320.1)

Plasma Concentration Profile



Possible Outcome of BE Studies



Bioequivalence

Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration

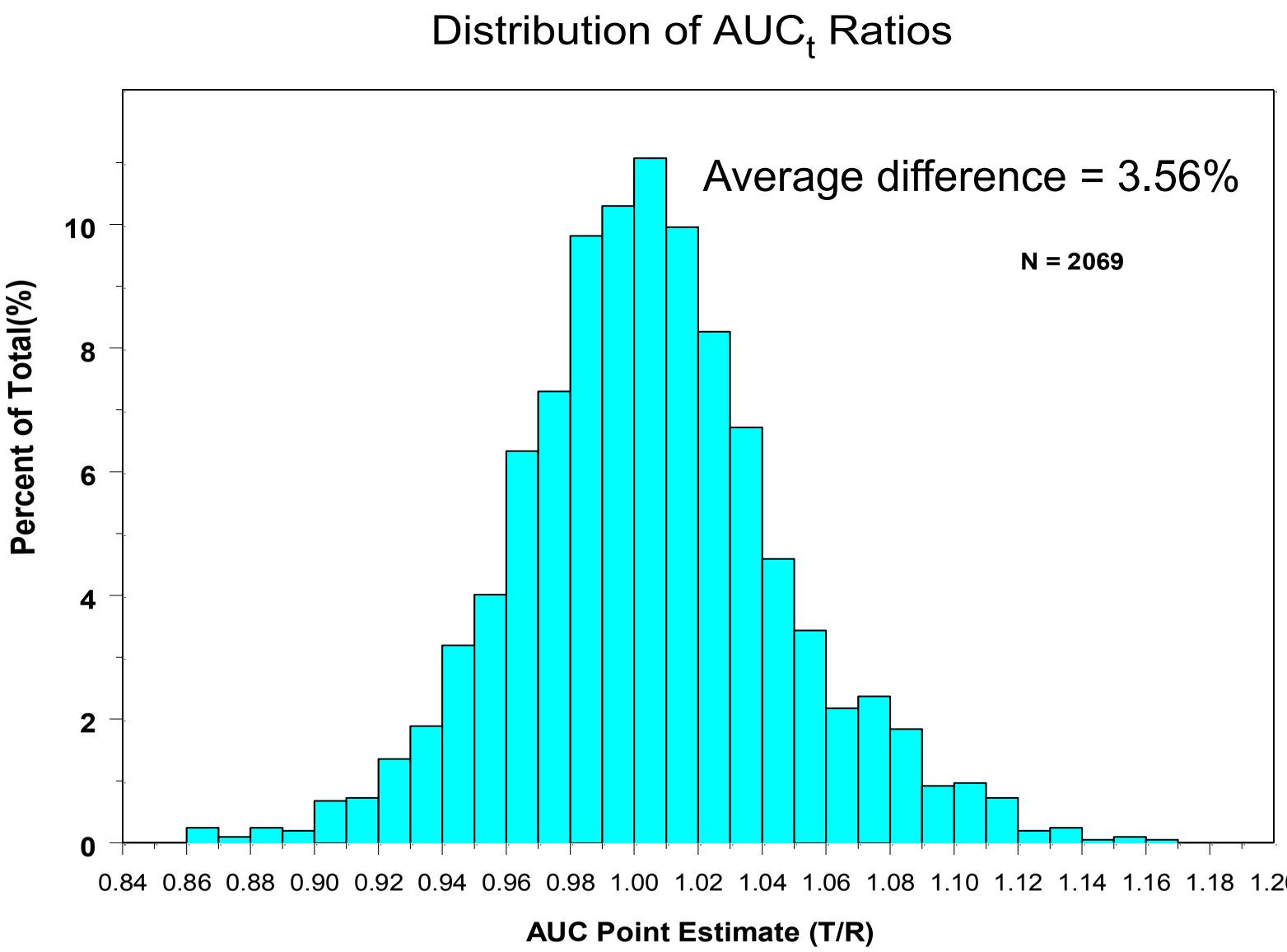
Barbara M Davit, Patrick E Nwakama, Gary J Buehler, Dale P Conner, Sam H Haidar, Devvrat T Patel, Yongsheng Yang, Lawrence X Yu, and Janet Woodcock

BACKGROUND: In the US, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the generic formulation provides the same rate and extent of absorption as (ie, is bioequivalent to) the innovator drug product. Thus, most orally administered generic drug products in the US are approved based on results of one or more clinical bioequivalence studies.

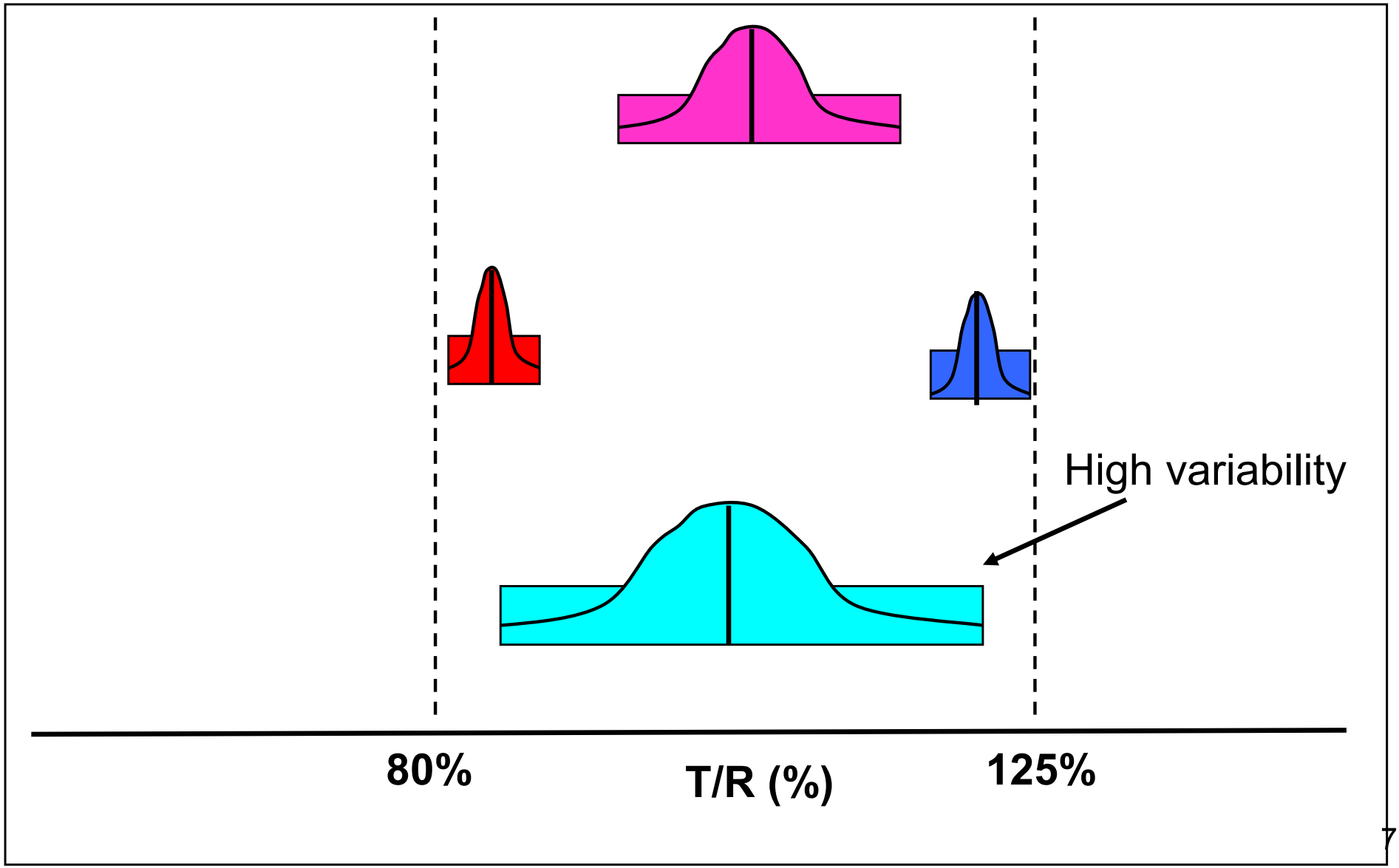
OBJECTIVE: To evaluate how well the bioequivalence measures of generic drugs approved in the US over a 12-year period compare with those of their corresponding innovator counterparts.

Generic pharmaceutical products play a vital role in US healthcare. Since the passage of the Drug Price Competition and Patent Term Restoration Act in 1984 (Hatch-Waxman Amendments),[1] which set the rules under which generic drugs could compete with innovator products, the Food and Drug Administra-

FDA 12 Year BE Data



Effect of Variability on BE Studies



Development of BE Standard for Highly Variable Drugs

4/2004	First presentation to the FDA Advisory Committee
10/2006	Second presentation to the FDA Advisory Committee
3/2007	Received the first ANDA which used the new FDA BE approach
5/2007	Critical Path Opportunities for Generic Drugs BE of HVD
1/2008	FDA OGD's first publication on BE of HVD (Pharm. Res.)
3/2008	FDA OGD's second publication on BE of HVD (AAPS J)
9/2008	FDA OGD's third publication on BE of HVD (AAPS J.)
1/2009	FDA OGD's fourth publication on BE of HVD (Generic Book)
5/2009	Third (final) presentation to the FDA Advisory Committee
4/2010	FDA OGD published guidance on BE of HVD drug
Present	Over 20 presentations at national and international meetings Numerous ANDAs have been approved

Pharmaceutical Research, Vol. 25, No. 1, January 2008 (© 2007)
DOI: 10.1007/s11095-007-9434-x

Commentary

Bioequivalence Approaches for Highly Variable Drugs and Drug Products

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Received June 9, 2007; accepted August 8, 2007; published online September 22, 2007

Abstract. Over the past decade, concerns have been expressed increasingly regarding the difficulty for highly variable drugs and drug products (%CV greater than 30) to meet the standard bioequivalence (BE) criteria using a reasonable number of study subjects. The topic has been discussed on numerous occasions at national and international meetings. Despite the lack of a universally accepted solution for the issue, regulatory agencies generally agree that an adjustment of the traditional BE limits for these drugs or products may be warranted to alleviate the resource burden of studying relatively large numbers of subjects in bioequivalence trials. This report summarizes a careful examination of all the statistical methods available and extensive simulations for BE assessment of highly variable drugs/products. Herein, the authors present an approach of scaling an average BE criterion to the within-subject variability of the reference product in a crossover BE study, together with a point-estimate constraint imposed on the geometric mean ratio between the test and reference products. The use of a reference-scaling approach involves the determination of variability of the reference product, which requires replication of the reference treatment in each individual. A partial replicated-treatment design with this new data analysis methodology will thus provide a more efficient design for BE studies with highly variable drugs and drug products.

KEY WORDS: bioequivalence; highly variable drugs; highly variable drug products; scaled average bioequivalence; statistical approach; study design.

The AAPS Journal (© 2008)
DOI: 10.1208/s12248-008-9053-4

Research Article

Themed Issue: Bioequivalence, Biopharmaceutics Classification System, and Beyond
Guest Editors: James E. Polli, Bertil S. Abrahamsson, and Lawrence X. Yu

Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs

Sam H. Haidar,[1,4] Fairouz Makhlouf,[2] Donald J. Schuirmann,[3] Terry Hyslop,[1] Barbara Davit,[1] Dale Conner,[1] and Lawrence X. Yu[1]

Received 22 March 2008; accepted 11 July 2008

Abstract. Various approaches for evaluating the bioequivalence (BE) of highly variable drugs (CV≥ 30%) have been debated for many years. More recently, the FDA conducted research to evaluate one such approach: scaled average BE. A main objective of this study was to determine the impact of scaled average BE on study power, and compare it to the method commonly applied currently (average BE). Three-sequence, three period, two treatment partially replicated cross-over BE studies were simulated in S-Plus. Average BE criteria, using 80–125% limits on the 90% confidence intervals for C_{max} and AUC geometric mean ratios, as well as scaled average BE were applied to the results. The percent of studies passing BE was determined under different conditions. Variables tested included within subject variability, point estimate constraint, and different values for σ_{w0}, which is a constant set by the regulatory agency. The simulation results demonstrated higher study power with scaled average BE, compared to average BE, as within subject variability increased. At 60% CV, study power was more than 90% for scaled average BE, compared with about 22% for average BE. A σ_{w0} value of 0.25 appears to work best. The results of this research project suggest that scaled average BE, using a partial replicate design, is a good approach for the evaluation of BE of highly variable drugs.

KEY WORDS: bioequivalence; highly variable drugs; scaled bioequivalence; simulations.

The AAPS Journal, Vol. 10, No. 1, March 2008 (© 2008)
DOI: 10.1208/s12248-008-9015-x

Research Article

Themed Issue: Bioequivalence, Biopharmaceutics Classification System, and Beyond
Guest Editors: James E. Polli, Bertil S. Abrahamsson, and Lawrence X. Yu

Highly Variable Drugs: Observations from Bioequivalence Data Submitted to the FDA for New Generic Drug Applications

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Received 18 September, 2007; accepted 28 January, 2008; published online 5 March 2008

Introduction. It is widely believed that acceptable bioequivalence studies of drugs with high within-subject pharmacokinetic variability must enroll higher numbers of subjects than studies of drugs with lower variability. We studied the scope of this issue within US generic drug regulatory submissions.

Materials and Methods. We collected data from all *in vivo* bioequivalence studies reviewed at FDA's Office of Generic Drugs (OGD) from 2003–2005. We used the ANOVA root mean square error (RMSE) from bioequivalence statistical analyses to estimate within-subject variability. A drug was considered highly variable if its RMSE for C_{max} and/or AUC was ≥0.3. To identify factors contributing to high variability, we evaluated drug substance pharmacokinetic characteristics and drug product dissolution performance.

Results and Discussion. In 2003–2005, the OGD reviewed 1,010 acceptable bioequivalence studies of 180 different drugs, of which 31% (57/180) were highly variable. Of these highly variable drugs, 51%, 10%, and 39% were either consistently, borderline, or inconsistently highly variable, respectively. We observed that most of the consistent and borderline highly variable drugs underwent extensive first pass metabolism. Drug product dissolution variability was high for about half of the inconsistently highly variable drugs. We could not identify factors causing variability for the other half. Studies of highly variable drugs generally used more subjects than studies of lower variability drugs.

Conclusion. About 60% of the highly variable drugs we surveyed were highly variable due to drug substance pharmacokinetic characteristics. For about 20% of the highly variable drugs, it appeared that formulation performance contributed to the high variability.

KEY WORDS: bioequivalence; generic drugs; highly variable drugs; presystemic drug metabolism;

FDA OGD Scaled Average BE Approach for Highly Variable Drugs

- Three-period BE study
  - Provide reference product (R) twice and test product (T) once
  - Sequences = TRR, RRT, RTR
- When the variability from the study $CV_{WR} \geq 30\%$,
  - BE criteria scaled to reference variability
  - BE Limits (upper, lower) = EXP ($\pm 0.223\ \sigma_{WR}/\ \sigma_{WO}$),, $\sigma_{WO} = 0.25$
  - [80%, 125%] as a point estimate constraint
- When the variability from the study $CV_{WR} < 30\%$,
  - use unscaled average bioequivalence
- Both AUC and C_{max} should meet BE acceptance criteria
- The minimum number of subjects is 24

Contains Nonbinding Recommendations

Draft Guidance on Progesterone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Progesterone

Form/Route: Capsule/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Partial or fully replicated crossover design *in-vivo*
   Strength: 200 mg
   Subjects: Healthy males and postmenopausal females, general population. As many postmenopausal women as possible should be included in the study.
   Additional Comments: Please measure baseline progesterone levels at -1.0, -0.5, and 0 hours before dosing. The mean of the pre-dose progesterone levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. Please analyze the data using both uncorrected and corrected data. Applicants may consider using a reference-scaled average bioequivalence approach for progesterone. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or C_{max} (i.e., within-subject variability $\geq$ 30%). For detailed information on this approach, please refer to the published book chapter, *Davit B, Conner D.* Reference-scaled average bioequivalence approach. In: Kanfer I, Shargel L, eds. Generic Drug Product Development – International Regulatory Requirements for Bioequivalence. New York, NY: Informa Healthcare, 2010: 271-272.

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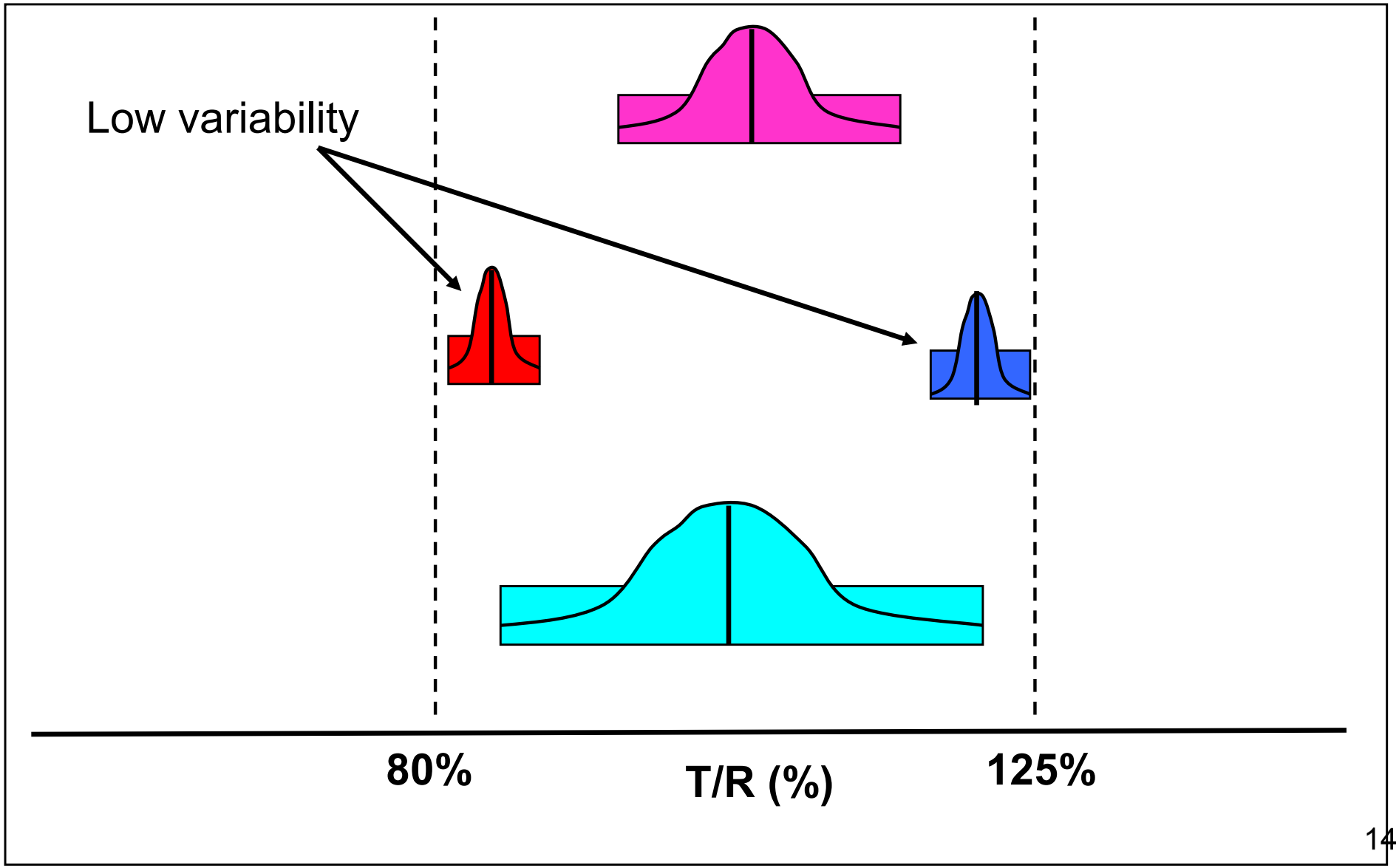
2. Type of study: Fed
   Design: Partial or fully replicated crossover design *in-vivo*
   Strength: 200 mg
   Subjects: Healthy males and postmenopausal females, general population.
   Additional Comments: Please see additional comment above.

Analytes to measure (in appropriate biological fluid): Progesterone in plasma

Bioequivalence based on (90% CI): Progesterone

Effect of Variability on BE Studies

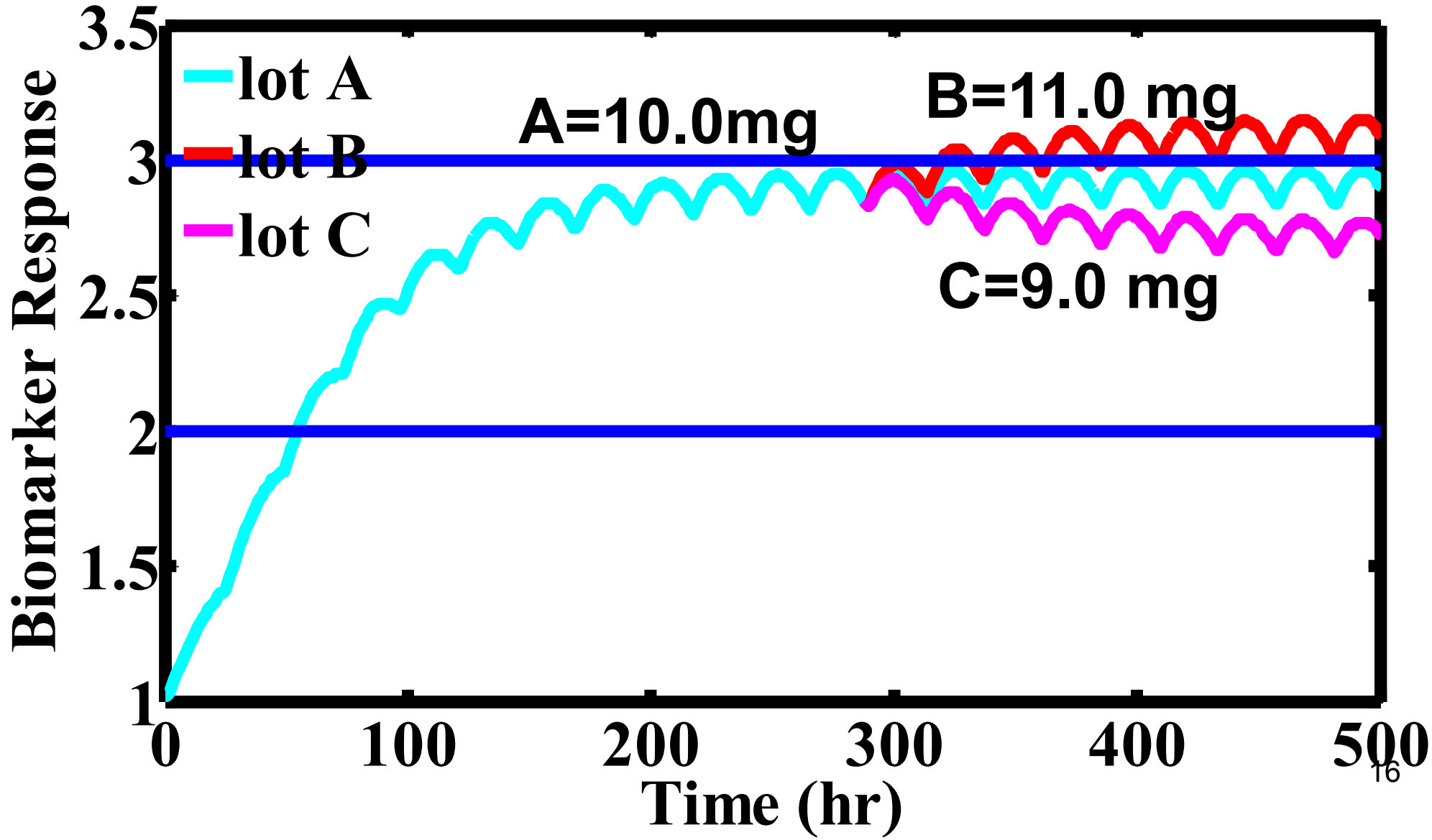


Narrow Therapeutic Index Drugs Have Low Within-Subject Variability

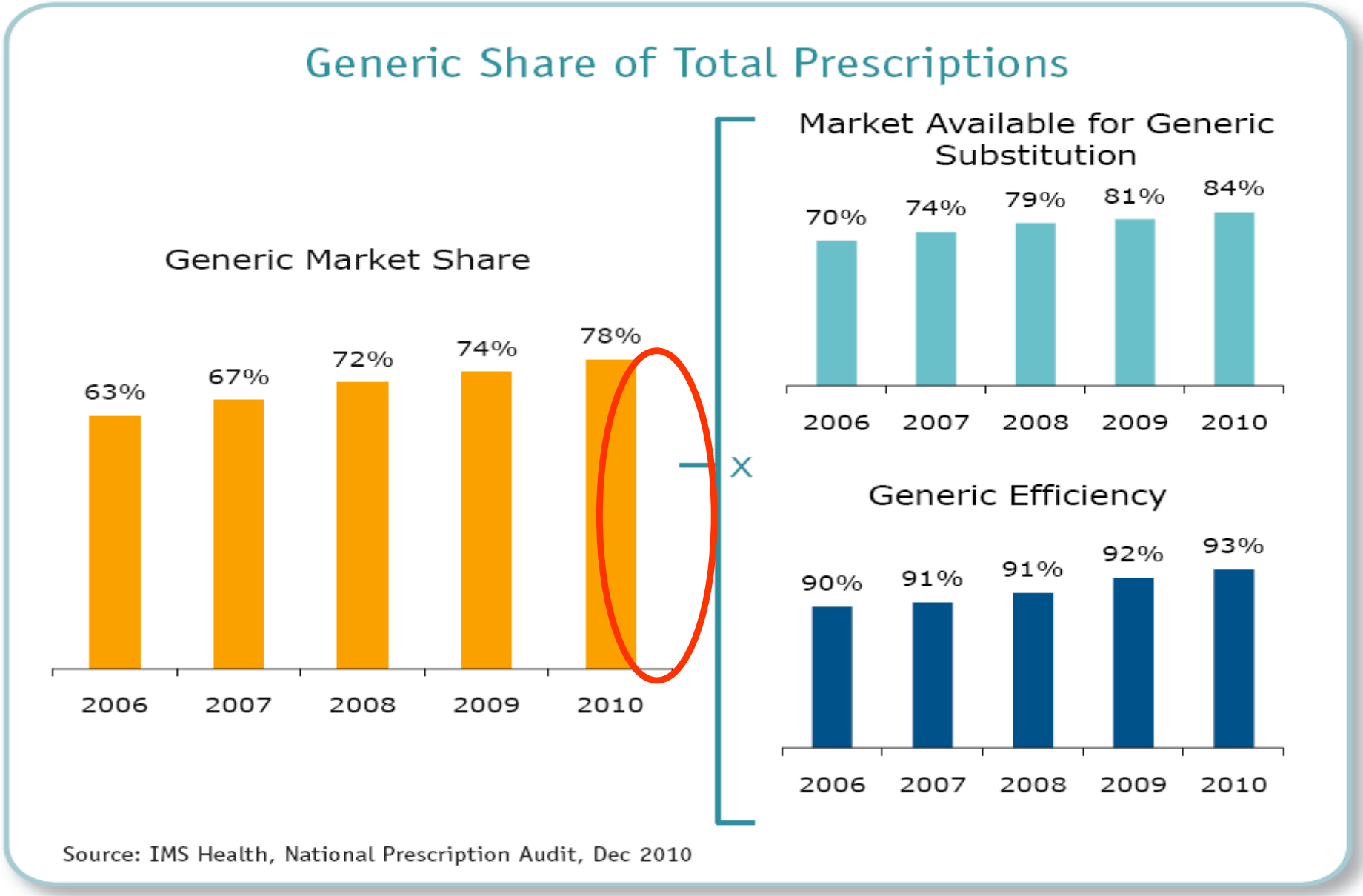
Summary of Residual Variability (% CV) from ANDAs reviewed between 1996-2008

	AUC_{0-t}		C_{max}	
Drugs	**Mean**	**Range**	**Mean**	**Range**
Warfarin (n=29)	5.7	3.3, 11.0	12.7	7.7, 20.1
Levothyroxine (n=9)	9.3	3.8, 15.5	9.6	5.2, 18.6
Carbmazepine (n=15)	8.0	4.4, 19.4	8.7	5.2, 17.6
Lithium Carbonate (n=16)	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin (n=5)	21.7	13.1, 32.2	21.0	14.3, 26.1
Phenytoin (n=12)	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline (n=3)	17.9	12.8, 24.2	18.2	11.8, 25.8

PK-PD Modeling: 90.0-110.0% Assay Limits Insufficient to Ensure Target Response



Total Prescription Drugs Dispensed in the United States



DHHS Assistant Secretary for Planning and Evaluation Issued Generic Use Brief December 1, 2010

- Barriers to Greater Savings from Generic Drug Use
  - …limit generic substitution by the pharmacist for drugs with a Narrow Therapeutic Index (NTI)…NTI drugs include some anti-epileptic drugs, warfarin, and digoxin…some states require that generic versions can not be substituted for NTI drugs without the prescriber's consent.

Patient, Pharmacist, and Physician Perception

- Overall, patient, pharmacist, and physician have a great of concerns on the use of generic NTIs
  - Physicians caring for epileptic patients
    - 606 physicians responded to survey
    - 88% concerned about breakthrough seizures with formulation switch (65% had seen this occur)
    - 55% prescribed AED “brand only”

Canada – Health Canada

- Usual BE Acceptance Criteria
  - AUC – 90% Confidence Interval (CI) of T/R ratio should fall within 80.0 – 125.0%
  - Cmax – T/R point estimate should fall within 80 – 125%
- Recommended BE Acceptance Criteria for Generic CD Drugs
  - Both AUC and Cmax – 90% CI of T/R ratios should meet acceptance criteria
  - AUC – 90.0 – 112.0%
  - Cmax – 80.0 – 125.0%
- Drugs considered NTI

Cyclosporine	Digoxin	Flecainide	Lithium
Phenytoin	Sirolimus	Theophylline	Warfarin

European Union – EMEA

- Usual BE Acceptance Criteria

  Both AUC and Cmax – 90% CI of T/R ratios should fall within 80 – 125%

- Recommended BE Acceptance Criteria for Generic NTI Drugs

  AUC: 90.00-111.11%

  Cmax: 90.00-111.11% should also be applied for Cmax where Cmax is of particular importance for safety, efficacy or drug level monitoring

- Has No Listing of NTI Drugs

Japan – NIHS

- Usual BE Acceptance Criteria

  Both AUC and Cmax – 90% CI of T/R ratios should fall within 80 – 125%

- Recommended BE Acceptance Criteria for Generic NTI Drugs

  No change in acceptance criteria for AUC and Cmax;

  however, if dissolution profiles of lower strengths of modified-release NTI drugs are not “equivalent” (f2 analysis) to corresponding reference product profiles, then in vivo studies must be done (no biowaivers)

- List of 26 NTI Drugs – includes Digoxin, Lithium, Phenytoin, Tacrolimus, Theophylline, Warfarin; adds others such as Carbamazepine, Ethinyl Estradiol, Quinidine

FDA's Effort

2010 FDA Advisory Committee for Pharm. Sci. Meeting

- At the conclusion of the April 2010 ACPS meeting on NTI drugs, the Committee recommended, 13-0, that the FDA develop a list of NTI drugs with clear, specialized criteria for including drugs on the list. In addition, the committee voted 11-2 that the current bioequivalence standards are not sufficient for critical dose or NTI drugs and it was suggested that the standards need to be stricter

2010 FDA Advisory Committee for Pharm. Sci. Meeting (continued)

- The Committee commented:
  - Replicate studies are important
  - The Agency should look at manufacturing data on excipients from existing formularies
  - The requirements for confidence intervals should perhaps be narrower (90-111%) and should include 100% (or 1.0)
- The ACPS Committee recommended future research, including pharmacodynamic (PD) modeling and therapeutic failure causes

Proposed NTI Drug Definition

- Narrow therapeutic index (NTI) drugs are defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening, possibly resulting in hospitalization, disability, or even death. Example NTI drugs include warfarin, levothyroxine, carbamazepine, digoxin, lithium carbonate, phenytoin, and theophylline.

- NTI drugs generally have the following characteristics:
  - Steep drug dose-response relationship within the usual dose range or narrow span between effective drug concentrations and concentrations associated with serious toxicity
  - Subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures to ensure safe and effective use of the drug, and
  - Small within subject variability.

Simulation Studies

- BE study design
  - Two, three, and four way crossover study designs
- BE limit
  - 80-125% and 90-111%
- Bioequivalence approach
  - Reference scaled average bioequivalence
  - σ_{WO} = 0.10 or 0.25
- Variability comparison

Recommended BE Study Design for NTI Drugs

- Four-way crossover, fully replicated design
- Test product given twice
- Reference product given twice
- This design will provide the ability to
  - Scale a criterion to the within-subject variability of the reference product; and
  - Compare test and reference within-subject variances to confirm that they do not differ significantly.

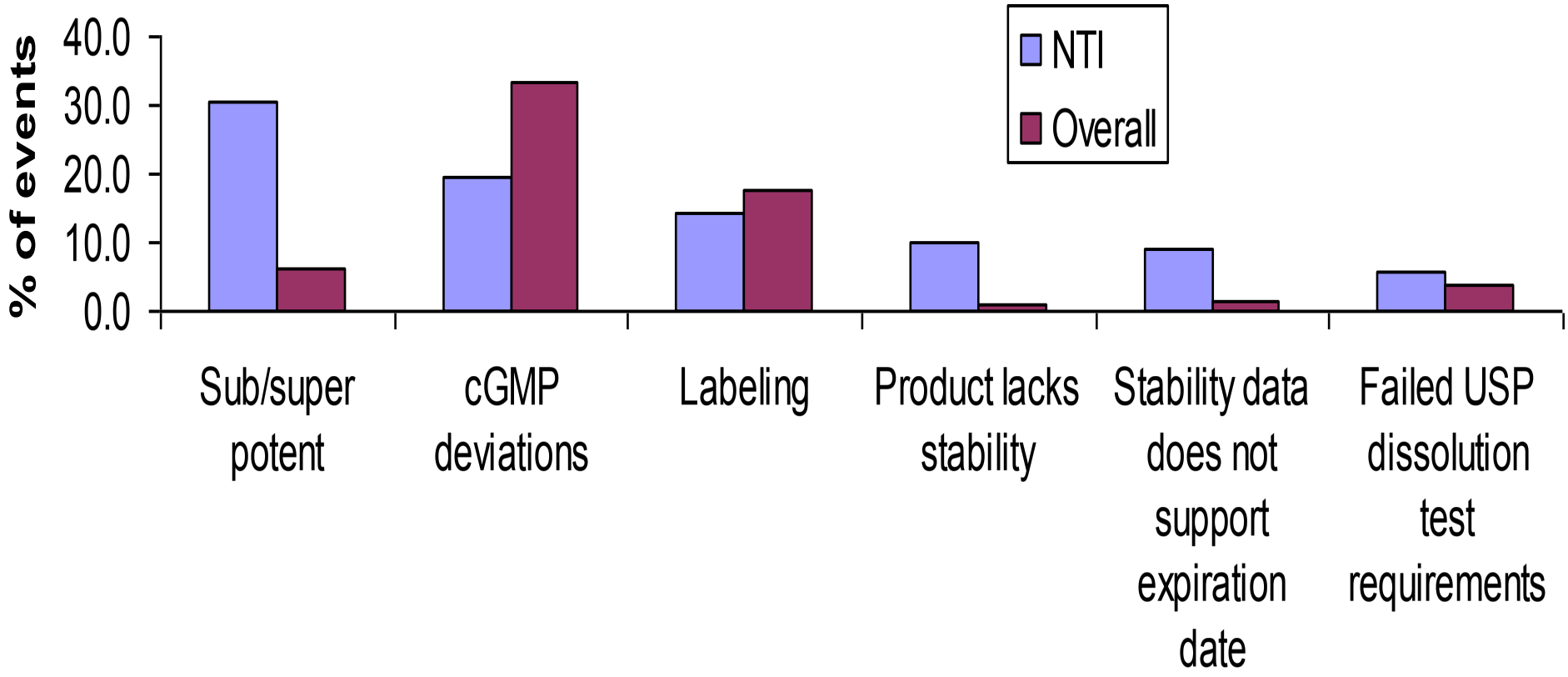
Recommended BE limits for Generic NTI Drugs

- BE limits will change as a function of the within-subject variability of the reference product (reference-scaled average bioequivalence ("reference-scaled ABE"))
- If reference variability is ≤10%, then BE limits are reference-scaled and are narrower than 90-111.11%
- If reference variability is > 10%, then BE limits are reference-scaled and wider than 90-111.11%, but are capped at 80-125% limits
- This proposal encourages development of low-variability formulations

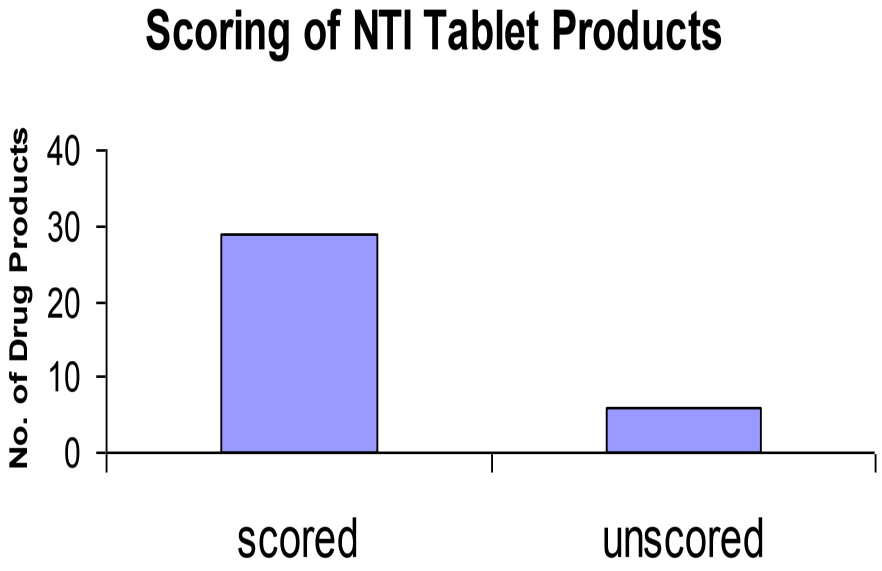
FDA's Survey on Quality and Standard

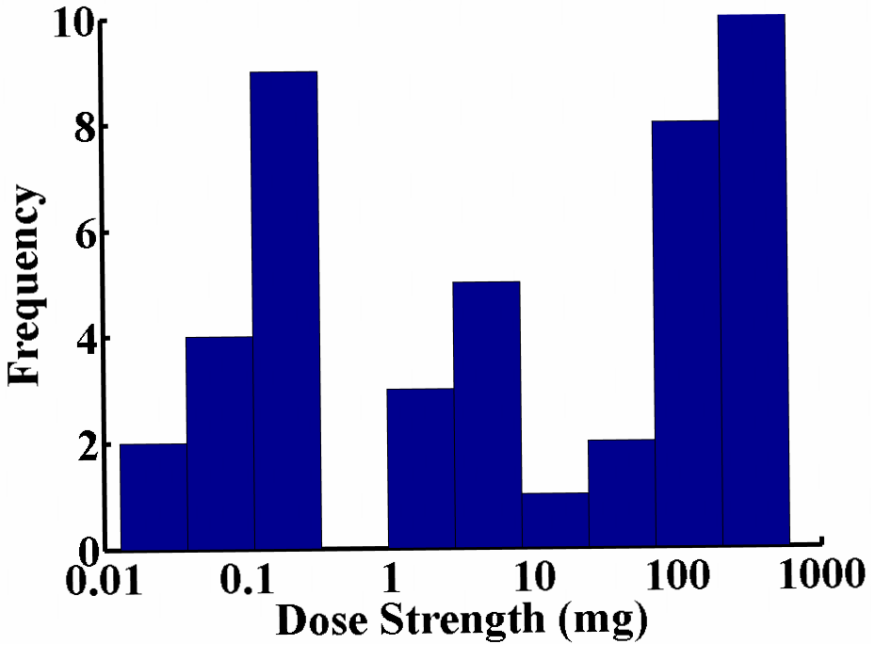
- Product design and manufacturing
- Drug assay
- Content Uniformity
- Dissolution
- Stability
- Recall
- Field Alert, MedWatch, Adverse Event Reporting System (AERS), and Drug Quality Reporting System (DQRS)

Major Recall Rates of Surveyed NTI Compared with Overall Drugs



Content Uniformity with NTI drugs





- Many surveyed NTI drugs are scored and have low dose strength

- NDA/ANDA applicants often use the USP content uniformity standards as the specification limits for drug product batch release and did not provide CU and dissolution data of split tablets.

- NDA/ANDA applicants rarely report detailed content uniformity data in their annual reports

Proposed potency specifications for NTI products

- Generic versions of NTI drug products will be expected to meet assayed potency specifications of 95.0% to 105.0%
- This will assure that switching between brand-to-generic or generic-to-generic will provide comparable doses
- This will also help ensure consistency of the dose delivered throughout shelf life

2011 FDA Advisory Committee for Pharm. Sci. Meeting

- The FDA Advisory Committee for Pharm. Sci. supports
  - the FDA's draft definition of NTI drugs (YES: 11 NO: 0 ABSTAIN: 2)
  - the two-treatment, four-period, fully replicated crossover design (YES: 12 NO: 1 ABSTAIN: 0)
  - the reference-scaled average bioequivalence approach (YES: 12 NO: 0 ABSTAIN: 1)
  - tighten the assayed potency standard for NTI drugs to 95.0 – 105.0% (YES: 13 NO: 0 ABSTAIN: 0)

Future Development

- Conduct variability simulation studies and develop an approach for variability comparison
- Propose an approach for content uniformity
- Publish the draft FDA's approach for NTI drugs (warfarin etc) at the FDA individual product bioequivalence guidance

Conclusion

- The FDA's new quality and bioequivalence standards for NTI drugs will bring the US into harmony with other regulatory agencies and improve public confidence in quality and switchability of generic drugs

Acknowledgements

- Dale Conner
- Barbara davit
- Stella Grosser
- Wenlei Jiang
- Robert Lionberger
- Rachelle Lubin
- Fairouz Makhlouf
- Laurie Muldowney
- Devvrat Patel
- Don Schuirmann
- Sriram Subramaniam
- Xinyuan Zhang