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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

Proceeding	91202898
Party	Defendant Mikhail Levitin T/A Mikhail Levitin Institute
Correspondence Address	MIKHAIL LEVITIN PO BOX 102 REEDERS, PA 18352-0102 UNITED STATES vitality@ptd.net, mslevitin@verizon.net
Submission	Defendant's Notice of Reliance
Filer's Name	Mikhail Levitin
Filer's e-mail	vitality@ptd.net
Signature	/Mikhail Levitin/
Date	07/10/2013
Attachments	IN THE UNITED STATES PATENT AND TRADEMARK OFFICE070913.pdf(57288 bytes ) ExhibitA FDA accuses LOreal from Business by Luxury.pdf(178732 bytes ) ExhibitB Inspections FDA vs L'Oreal.pdf(281276 bytes ) ExhibitC FDA Issues Warning Letter to L.pdf(161283 bytes ) ExhibitD FDA Issues Warning Letter to L.pdf(125269 bytes ) ExhibitE FDA Issues Warning Letter to L.pdf(114137 bytes ) ExhibitF L'Oreal's false Ads, Suit Claims.pdf(132026 bytes ) ExhibitG FDA Issues Warning Letter to L.pdf(168106 bytes ) ExhibitH FDA Issues Warning Letter by MedicalXpress.com.pdf(78108 bytes ) ExhibitI FDA Issues Warning Letter to L.pdf(71904 bytes ) ExhibitJ FDA Issues Warning Letter by Knopfler Lab.pdf(170322 bytes ) ExhibitK US Law Firm Investigates Cosmetic Brands LOreal for Using False.pdf(110913 bytes ) ExhibitL US Food and Drug Administration claims LOreal by The China Post.pdf(103193 bytes ) ExhibitM US Food and Drug Administration claims LOreal by The Australian.pdf(63658 bytes ) ExhibitO FDA UCM266777 pp10-11.pdf(5129597 bytes )

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

**L'Oréal S.A. and L'Oréal USA, INC.,**  
Opposer,  
vs.

In the Matter of Application  
Serial No: 85/270,272  
Re: Mark: FOREAL FOR'EAL  
BY MIKHAIL

**MIKHAIL LEVITIN T/A**  
**MIKHAIL LEVITIN INSTITUTE,**  
Applicant

APPLICANT'S NOTICE OF RELIANCE

Pursuant to Trademark Trial and Appeal Board Manual of Procedure  
("TBMP") #704.02 and 37 CFR ## 2.120 and 2.122 Applicant hereby  
offers into evidence and intends to rely on the following:

1. Exhibit A / FDA accuses L'Oreal and Lancôme of misleading claims in advertising anti-aging products Sep 13, 2012;
2. Exhibit B / FDA- Inspections, Compliance, Enforcement, and Criminal Investigations;
3. Exhibit C / FDA Issues Warning Letter to L'Oreal about Drug-like Claims for Anti-aging Creams from SpecialChem;
4. Exhibit D / **L'Oreal Accused of Misleading Anti-Aging Ads**  
by US Agency / DRISHYA NAIR;
5. Exhibit E / Lancôme Anti-Aging Cream Marketing Claims Draw

FDA Warning, Published by Russell Maas;

6. Exhibit F / L'Oreal Anti-Aging Creams Rely On False Ads, Suit Claims, TwitterFacebookLinkedIn by Juan Carlos Rodriguez;

7. Exhibit G / L'Oreal faces Lancôme anti-ageing dispute in the US, from: *AFP*, September 12, 2012 10:10AM

8. Exhibit H / US agency accuses L'Oreal of misleading marketing, *MedicalXpress.com*, September 12, 2012;

9. Exhibit I / US authorities warn L'Oreal over 'misleading' anti-aging cream marketing, Big News Network (ANI) Wednesday 12th September, 2012;

10. Exhibit J / L'Oreal's Lancôme gets hammered by FDA for stem cell cosmetics offered at Nordstrom: good, but why kid gloves for transplant clinics? Posted on September 11, 2012 by admin;

11. Exhibit K / US Law Firm Investigates Cosmetic Brands for Using False & Misleading Anti-aging Claims, *SpecialChem* - Feb 18, 2013;

12. Exhibit L / US Food and Drug Administration claims L'Oreal misled its customers, *AFP* September 13, 2012, 12:08 am TWN

13. Exhibit M / US agency accuses L'Oreal of misleading, from: *AAP* September 12, 2012 4:02PM;

14. Exhibit O / FDA, *Advisory Committee for Pharmaceutical Science*, July 26, 2011.

While major arguments in the case are subjective, Opposer made an attempt at a quantitative factor in the arguments but failed in simple arithmetic, stated that it is only one character different among six (mistake again) in **L'Oréal** compared with Foreal.

In fact, in the alleged key word Foreal, Applicant has five similar characters from seven in Opposer's brand mark.

The identity factor in this case would be 71.4%.

The precedence for the case has been brought by FDA when considered relevance between a brand and generic drug with minimum 90% (see Exhibit O, page 10 – 11).

It means that not less than 90% from brand formulation is allowed in the generic form to consider the relevance.

FDA, with this tool and regulations, is controlling the industry where Opposer is conducting his business. It is obvious that 71.4 less than 90, so the relevance according FDA is not established.

English grammar existed before **L'Oréal** came on the market and it is still the same.

Blaming a similarity between two marks **L'Oréal** (Opposer) and FOREAL FOR'EAL BY MIKHAIL (Applicant) from English grammar's point of view does not stand a chance.

That fact has been proofed in the Applicant's answer on  
September 3, 2012, ##21, 22.

In conclusion, according to Opposer's statement, an impressive  
amount of money was spent for advertising its products.

Ironically, the significant amount of these funds was spent to  
mislead and confuse the public and definitely "diminished and  
diluted Opposer's good will" and attempted to blame this on  
Applicant.

Applicant voluntarily withdraws from discussions offered by his  
representative, Larry Stempel, CPA, in 1970 applicants idea and  
product samples, on an anti aging product line.

Applicant withdraws it due to an uncomfortable discovery about  
Opposer:

**Liliane Bettencourt**, 88, the France's richest woman  
who inherited the L'Oreal cosmetics fortune, was told that she  
had dementia and Alzheimer's and is no longer mentally fit to run  
her business affairs.

(Re: <http://www.bellenews.com/2011/10/17/world/europe-news/liliane-bettencourt-loreal-heiress-is-mentally-unfit-a-judge-rules/#ixzz2CS0Q7U2o>).

Dated: July 10, 2013

Respectfully submitted,

By: /Mikhail Levitin/  
Mikhail Levitin  
P.O. Box 102  
Reeders, PA 18352  
(570) 872-7962

CERTIFICATE OF SERVICE

I hereby certify that the foregoing copy of APPLICANT'S  
NOTICE OF RELIANCE has been served this day of July 10, 2013 by

U.S. mail upon Plaintiff's Attorney on record:

Robert L. Sherman  
Paul Hastings, LLP  
75 East 35<sup>th</sup> Street  
New York, NY 10022,

**Natalie Furman, Associate, Litigation Department** at [nataliefurman@paulhastings.com](mailto:nataliefurman@paulhastings.com).

**Edith R. Lopez | Paralegal**

Paul Hastings LLP | 75 East 55th Street, New York, NY 10022 | Direct: +1.212.318.6779 |  
Main: +1.212.318.6000 | Fax: +1.212.230.5133 |  
[edithlopez@paulhastings.com](mailto:edithlopez@paulhastings.com); [www.paulhastings.com](http://www.paulhastings.com)

The company and address designated for such service.

Mikhail Levitin

Date

\_\_\_\_\_07/10/2013\_\_\_\_\_

# FDA accuses L’Oreal and Lancome of misleading claims in advertising anti-aging products

Sep 13, 2012

The U.S. Food and Drug Administration (FDA) has sent a letter to French cosmetics giant [L’Oreal](#) in regard to the advertisement being used its [Lancome](#) products. The US regulators have alleged the company for using misleading claims in regard to Lancome products, which consists of anti-aging products.

The FDA condemns Lancome’s advertising for its cosmetic anti-aging products which it claims are able to modify the functions or structure of the human body in a similar way that a medical drug could do (according to U.S. legislation). The Lancome product, which claims of doing so, is the *Genifique Youth Activating Concentrate*. FDA cites among others a sentence stating that the product “stimulates the activity of genes and production of youth proteins.”. Another Lancome product, which is cited is the *Genifique Repair Youth Activating Night Cream*. Lancome claims that the cream can increase the production of genes.



Lancome Genifique Youth Activating Concentrate

The FDA has not taken any formal action against L'Oreal, the owner of the Lancome brand and has given the company 15 days to correct the misleading claims. Failure to make the requested corrections, would result, the FDA says in its letter, in legal action against the manufacturers and distributors as well as the withdrawal from the U.S. market of the illegal products.

# Inspections, Compliance, Enforcement, and Criminal Investigations



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## Lancome 9/7/12



Department of Health and Human Services

Public Health Service  
Food and Drug Administration

College Park, MD 20740

**WARNING LETTER**

SEP 7 2012

VIA CERTIFIED MAIL

Mr. Serge Jureidini

President

Lancôme USA

575 Fifth Avenue

New York, NY 10017

Re: 273596

Dear Mr. Jureidini:

This is to advise you that the Food and Drug Administration (FDA) reviewed your website at the Internet address <http://www.lancome-usa.com> in August 2012. Based on this review, your products Génifique Youth Activating Concentrate, Genefique Eye Youth Activating Eye Concentrate, Genefique Cream Serum Youth Activating Cream Serum, Génifique Repair Youth Activating Night Cream, Absolue Precious Cells Advanced Regenerating and Reconstructing Cream SPF 15 Sunscreen, Absolue Eye Precious Cells Advanced Regenerating and Reconstructing Eye Cream, Absolue Night Precious Cells Advanced Regenerating and Reconstructing Night Cream, and Rénergie Microlift Eye R.A.R.E.™ Intense Repositioning Eye Lifter appear to be promoted for uses that cause these products to be drugs under section 201(g)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(C)]. The claims on your web site indicate that these products are intended to affect the structure or any function of the human body, rendering them drugs under the Act. The marketing of these products with these claims evidencing these intended uses violates the Act.

Examples of some of the claims observed on your web site include:

Génifique Youth Activating Concentrate, Génifique Eye Youth Activating Eye Concentrate, and Génifique Cream Serum Youth Activating Cream Serum

- “[B]oosts the activity of genes and stimulates the production of youth proteins.”

Génifique Repair Youth Activating Night Cream

- “[B]oosts the activity of genes.”

Absolue Precious Cells Advanced Regenerating and Reconstructing Cream SPF 15 Sunscreen

- “A powerful combination of unique ingredients – Reconstruction Complex and Pro-Xylane™, a patented scientific innovation-- has been shown to improve the condition around the stem cells and stimulate cell regeneration to reconstruct skin to a denser quality.”
- “See significant deep wrinkle reduction in UV damaged skin, clinically proven.”

Absolue Eye Precious Cells Advanced Regenerating and Reconstructing Eye Cream and Absolue Night Precious Cells Advanced Regenerating and Reconstructing Night Cream

- “A powerful combination of unique ingredients – Reconstruction Complex and Pro-Xylane™, a patented scientific innovation-- has been shown to improve the condition around the stem cells and stimulate cell regeneration to reconstruct skin to a denser quality.”

Rénergie Microlift Eye R.A.R.E.™ Intense Repositioning Eye Lifter

- “Immediate lifting, lasting repositioning. Inspired by eye-lifting surgical techniques . . . helps recreate a younger, lifted look in the delicate eye area.”
- “[U]nique R.A.R.E. oligopeptide helps to re-bundle collagen.”

Your products are not generally recognized among qualified experts as safe and effective for the above referenced uses and, therefore, the products are new drugs as defined in section 201(p) of the Act [21 U.S.C. § 321(p)]. Under section 505(a) of the Act (21 U.S.C. § 355(a)) a new drug may not be legally marketed in the U.S. without prior approval from FDA in the form of an approved New Drug Application (NDA). A description of the new drug approval process can be found on FDA's internet website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDeveloped><sup>1</sup>

[andApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDeveloped/Approved/ApprovalApplications/NewDrugApplicationNDA/default.htm)<sup>2</sup>. Any questions you may have regarding this process should be directed to the Food and Drug Administration, Division of Drug

Information, Center for Drug Evaluation and Research, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

This letter is not an all-inclusive statement of violations associated with your products or their labeling, and we have not attempted to list here all of the products that are promoted on your website for intended uses that cause them to be drugs. It is your responsibility to ensure that all products marketed by your firm comply with the Act and its implementing regulations. We advise you to review your website, product labels, and other labeling for your products to ensure that the claims you make for your products do not reflect intended uses that cause the distribution of the products to violate the Act.

We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter. Failure to do so may result in enforcement action without further notice. The Act authorizes injunctions against manufacturers and distributors of illegal products and seizure of such products.

Please notify this office in writing within fifteen (15) working days of the receipt of this letter as to the specific steps you have taken to correct the stated violations, including an explanation of each step being taken to identify violations and make corrections to ensure that similar violations will not recur. If you do not believe that your products are in violation of the Act, include your reasoning and any supporting information for our consideration. If the corrective action cannot be completed within fifteen working days, state the reason for the delay and the time frame within which the corrections will be implemented.

Please direct your written reply to Rob Genzel, Jr., Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Compliance, Division of Enforcement(HFS-608), 5100 Paint Branch Parkway, College Park, Maryland 20740-3835.

Sincerely,

/S/

Michael W. Roosevelt

Acting Director

Office of Compliance

Center for Food Safety and Applied Nutrition

# FDA Issues Warning Letter to L'Oreal about Drug-like Claims for Anti-aging Creams

SpecialChem - Sep 13, 2012

Food and Drug Administration (FDA) issued a warning letter to cosmetic giant L'Oreal for its Lancome unit after reviewing its website for Genefique skin care product range. Based on this review, FDA found that these products appear to be drugs under section 201(g)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(C)].

According to a warning letter posted on the website, the claims indicate that these products are intended to affect the structure or any function of the human body, rendering them drugs under the Act. The marketing of these products with these claims evidencing these intended uses violates the Act. The products include Génifique Youth Activating Concentrate, Genefique Eye Youth Activating Eye Concentrate, Genefique [Cream](#) Serum Youth Activating [Cream](#) Serum, Génifique Repair Youth Activating Night Cream, Absolue Precious Cells Advanced Regenerating and Reconstructing Cream [SPF 15 Sunscreen](#), Absolue Eye Precious Cells Advanced Regenerating and Reconstructing Eye Cream, Absolue Night Precious Cells Advanced Regenerating and Reconstructing Night Cream, and Rénergie Microlift Eye R.A.R.E.™ Intense Repositioning Eye Lifter.

Lancome claims that Genefique products "boost the activity of genes and stimulates the production of youth proteins" and "boosts the activity of genes". Also products contain a powerful combination of unique ingredients to improve the condition around the stem cells and stimulate cell regeneration to reconstruct skin to a denser quality.

The agency said that these products are not generally recognized among qualified experts as safe and effective, therefore, the products are new drugs as defined in section 201(p) of the Act [21 U.S.C. § 321(p)]. Under section 505(a) of the Act (21 U.S.C. § 355(a)) a new drug may not be legally marketed in the U.S. without prior approval from FDA in the form of an approved New Drug Application (NDA).

## About Lancôme

Lancôme Paris is a French luxury cosmetics house. Owned by L'Oréal since 1964, Lancôme is part of the Luxury Products division, which offers skin care, fragrances, and makeup at higher-end prices.

## **About L'Oréal Group**

L'Oréal, the world's leading beauty company, has catered to all forms of beauty in the world for over 100 years and has built an unrivalled portfolio of 27 international, diverse and complementary brands. With sales amounting to 20.3 billion euros in 2011, L'Oréal employs 68,900 people worldwide. Regarding sustainable development, Corporate Knights, a Global Responsible Investment Network, has selected L'Oréal for its 2012 ranking of the Global 100 Most Sustainable Corporations in the World. L'Oréal has received this distinction for the 5th consecutive year.

## **About Food and Drug Administration**

The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), and veterinary products. The FDA also enforces other laws, notably Section 361 of the Public Health Service Act and associated regulations, many of which are not directly related to food or drugs. These include sanitation requirements on interstate travel and control of disease on products ranging from certain household pets to sperm donation for assisted reproduction.

*Written by : SpecialChem Editorial Team  
Based on Information Displayed on [www.fda.gov](http://www.fda.gov)*

# L'Oreal Accused of Misleading Anti-Aging Ads by US Agency

[DRISHYA NAIR](#)

Update Date: Sep 12, 2012 07:20 AM EDT



L'Oreal (Photo : Flickr)

L'Oreal, the French cosmetic giant and the world's largest cosmetics manufacturer, has been accused by US regulators of misleading claims in marketing its Lancome line of anti-aging products, according to a letter released Tuesday.

Addressed to the president of L'Oreal-owned Lancome USA, the letter by the Food and Drug Administration says that under US law, some Lancome products advertised online "are intended to affect the structure or any function of the human body, rendering them drugs."

The products under the scanner is the Genifique Youth Activating Concentrate which claims to boost "the activity of genes and stimulate the production of youth proteins," according to the letter, reported AFP.

Another product is the Genifique Repair Youth Activating Night Cream, which claims to boost "the activity of genes."

Lancome has to respond to the FDA warning within 15 days with specific steps it would taken to correct the violations, according to the letter dated Friday.

"We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter," wrote the FDA's Michael W. Roosevelt of the Center for Food Safety and Applied Nutrition.

"Failure to do so may result in enforcement action without further notice."

# Lancome Anti-Aging Cream Marketing Claims Draw FDA Warning



By: Russell Maas | Published: September 12th, 2012

Marketing claims made in connection with various of Lancome anti-aging cream products have resulted in a warning letter from the U.S. Food and Drug Administration (FDA), which has indicated that the advertising violates federal law by promoting medical benefits that have not been established or approved by the drug regulatory agency.

In an FDA warning letter sent to Lancome USA on September 7, the agency told the subsidiary of L’Oreal to stop marketing the skincare products with language that makes them sound like drugs, by suggesting that the products affect the structure or any function of the human body.

The FDA pointed to marketing materials published by the company that indicate their skincare products can “reconstruct skin to denser quality” or “stimulate cell generation” to create a younger look around the eyes.

Because the products are not generally recognized among qualified experts as safe and effective for the claimed uses, the FDA has indicated that the marketing claims make the anti-aging creams a new drug under federal law, requiring the manufacturer to submit a New Drug Application (NDA) to the FDA before they may legally market them in the United States.

Some of the products identified in the warning letter include **Genifique Youth Activating Concentrate, Genifique Eye Youth Activating Eye Concentrate and Night Cream, Absolue Precious Cells Advanced Regenerating Cream SPF 15 Sunscreen, Renergie Microlift Eye R.A.R.E. Intense Repositing Eye Lifter and Absolue Eye Precious Cells Advanced Regenerating and Reconstructing Eye Cream and Absolue Night Precious Cells Advanced Regenerating and Reconstructing Night Cream.**

Other claims advertised for the Genifique Youth Activating Concentrate suggest that the product “boosts the activity of genes” and “stimulates production of youth proteins”.

The FDA has requested that Lancome take immediate action to correct the violations associated with the advertising of the products, and notify the agency within 15 working days of the steps that have been taken.

Although no reported injuries have been reported in connection with the product, the FDA has warned L’Oreal’s Lancome unit that failure to fix the advertising claims may lead to further enforcement actions such as seizures of the products and injunctions against the manufacturers and distributors.

- See more at: <http://www.aboutlawsuits.com/lancome-anti-aging-cream-fda-warning-33229/#sthash.Nh1SOkzZ.dpuf>

# L'Oreal Anti-Aging Creams Rely On False Ads, Suit Claims

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Share us on: [Twitter](#)[Facebook](#)[LinkedIn](#) By **Juan Carlos Rodriguez**

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Law360, New York (September 24, 2012, 3:22 PM ET) -- L'Oreal USA Inc. on Friday was hit with a proposed class action in Florida federal court that alleges there is no scientific evidence to back up the advertised claims of its Lancome brand anti-aging creams and serums.

Plaintiff Constanza Nino says L'Oreal and Lancome have profited by misleading the public with claims that the products “boost the activity of genes and stimulate the production of youth proteins,” and promising “visibly younger skin in seven days.” The lawsuit follows a recent U.S. [Food and Drug Administration](#) warning to the company that its Internet advertisements for many of its skin care products give the impression they are drugs, even though they have no such approval.

“Defendants prey upon consumers who fear the effects of aging and believe there are products that can make their skin and features youthful again, and halt or turn back the inevitable march of time,” Nino said in the complaint.

The products included in the lawsuit are Genifique, Renergie, Absolue, Visionnaire and High Resolution.

Nino said L'Oreal's claims of superiority over lesser-priced wrinkle creams are based on breakthroughs in science and purported breakthrough scientific discoveries of unique formulas that penetrate deeply into skin and boost the activity of the consumer's genes.

“Defendants claim that they have proven this with such things as ‘in-vitro tests on genes’ and extensive clinical studies and research,” the complaint said. “Defendants knew or should have known that their representations about a skin cream or serum being able to alter gene activity, as one example, were false, and defendants purposely misrepresented and failed to disclose such falsities to consumers.”

The lawsuit also says the defendants have taken no meaningful steps to clear up consumer misconceptions about its products.

In a Sept. 11 warning letter to L'Oreal, the FDA claims made on Lancome's website indicate

the products are intended to affect the structure or function of the human body, rendering them drugs under the Federal Food, Drug and Cosmetic Act, the agency says.

“The marketing of these products with these claims evidencing these intended uses violates the act,” the FDA said.

The agency said that because the products are not generally recognized among qualified experts as safe and effective for the advertised uses, they are new drugs as defined in the Food, Drug and Cosmetic Act. It warned Lancome to make sure the claims and intended uses reflected on its labels and website don't break the act, or else it could face enforcement action.

Nino said the allegedly false claims have caused consumers to pay a premium price for Lancome's products when there are other moisturizers and creams at lower prices, because they believe Lancome's products are unique and better.

“But actually, upon information and belief, defendants' products contain fundamentally the same ingredients and provide no superior results or benefits when compared to the lower priced creams and serums,” Nino said. “Thus, defendants have engorged themselves with profits based upon their false and deceptive practices to the detriment of consumers.”

Nino is represented by Matthew T. Moore and Jeremy W. Alters of Alters Law Firm PA and Benedict P. Morelli and David S. Ratner of [Morelli Ratner PC](#).

Counsel information for L'Oreal was not immediately available.

The case is Constanza Nino v. L'Oreal USA Inc., case number [1:12-cv-23462](#), in the U.S. District Court for the Southern District of Florida.

--Editing by Lindsay Naylor.

# L'Oreal faces Lancome anti-ageing dispute in the US

- From: *AFP*
- September 12, 2012 10:10AM



Customer at the Lancome cosmetics counter at a department store in Sydney. Picture: Jane Dempster *Source: The Daily Telegraph*

**REGULATORS have accused French cosmetics giant L'Oreal of misleading claims in marketing its Lancome line of anti-ageing products.**

In a letter released on Tuesday, addressed to the president of L'Oreal-owned Lancome USA, the Food and Drug Administration said some Lancome products advertised online carry claims that "are intended to affect the structure or any function of the human body, rendering them drugs" under US law.

In February British regulators [banned a magazine advert for an anti-ageing moisturiser](#) by L'Oreal after upholding a complaint that the image of the model, actress Rachel Weisz, was misleading.

The products under scrutiny this time include the Genifique Youth Activating Concentrate, which claims to boost "the activity of genes and stimulates the production of youth proteins",

according to the letter.

Another singled out is the Genifique Repair Youth Activating Night Cream, which claims to boost "the activity of genes".

Lancome has 15 days to respond to the FDA warning with specific steps it has taken to correct the violations, according to the letter dated on Friday.

"We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter," wrote the FDA's Michael W Roosevelt of the Centre for Food Safety and Applied Nutrition.

"Failure to do so may result in enforcement action without further notice."

L'Oreal is the world's largest cosmetics maker.

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## US agency accuses L'Oreal of misleading marketing

US regulators accused French cosmetics giant L'Oreal of misleading claims in marketing its Lancome line of anti-aging products, according to a letter released Tuesday.

In the letter, addressed to the president of L'Oreal-owned Lancome USA, the [Food and Drug Administration](#) said some Lancome products advertised online carry claims that "are intended to affect the structure or any function of the [human body](#), rendering them drugs" under US law.

The products under scrutiny include the Genifique Youth Activating Concentrate, which claims to boost "the activity of genes and stimulates the production of youth proteins," according to the letter.

Another singled out is the Genifique Repair Youth Activating Night Cream, which claims to boost "the activity of [genes](#)."

Lancome has 15 days to respond to the FDA warning with specific steps it has taken to correct the violations, according to the letter dated Friday.

"We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter," wrote the FDA's Michael W. Roosevelt of the Center for [Food Safety](#) and Applied Nutrition. "Failure to do so may result in enforcement action without further notice."

L'Oreal is the world's largest cosmetics maker.



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## US authorities warn L'Oreal over 'misleading' anti-aging cream marketing

Big News Network (ANI) Wednesday 12th September, 2012

French cosmetics giant L'Oreal has been accused of misleading claims in marketing its Lancome line of anti-aging products.

The US' Food and Drug Administration said in a letter to the president of L'Oreal-owned Lancome USA, that its products advertised online carry claims that 'are intended to affect the structure or any function of the human body, rendering them drugs' under U.S. laws.

According to the letter, the products that under scrutiny include the Genifique Youth Activating Concentrate, which claims to boost "the activity of genes and stimulates the production of youth proteins".

Another ad singled out is the Genifique Repair Youth Activating Night Cream, which claims to boost "the activity of genes".

According to News.com.au, Lancome has 15 days to respond to the FDA warning.

"We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter," the FDA's Michael W Roosevelt of the Centre for Food Safety and Applied Nutrition wrote.

"Failure to do so may result in enforcement action without further notice," Roosevelt added. (ANI)

# L'Oreal's Lancome gets hammered by FDA for stem cell cosmetics offered at Nordstrom: good, but why kid gloves for transplant clinics?

Posted on [September 11, 2012](#) by [admin](#)

**Stem cell cosmetics is an exploding area** ranging from facial creams to face lifts to boob jobs to baldness treatments (see two key posts [here](#) and [here](#) for background and great stories).



The stem cell cosmetics field has not been held back by issues such as the fact that there is no science behind their expensive creams and treatments or that they do not have FDA approval.

Today the FDA gave the stem cell cosmetics field a wake up call in a big way.

The FDA issued warning letters (a very serious action by the FDA—see other examples here) to [Lancôme](#) and [Greek Island Labs](#).

Lancome, [owned by L'Oreal](#), was smacked down for a number of problems by the FDA related to several products claiming anti-aging efficacy. Just one example of a product mentioned by the FDA as problematic is shown in the image above.

Both companies received nearly identical verbiage in their letter indicating they had new drugs on their hands that they were pitching without FDA approval:

***Your products are not generally recognized among qualified experts as safe and effective for the above referenced uses and, therefore, the products are new drugs as defined in section 201(p) of the Act [21 U.S.C. § 321(p)]. Under section 505(a) of the***

***Act (21 U.S.C. § 355(a)) a new drug may not be legally marketed in the U.S. without prior approval from FDA in the form of an approved New Drug Application (NDA).***

The stem cell cosmetics companies should not by any means believe they can bluff their way out of this. The FDA means business as indicated by the cautionary passage in the warning letter (emphasis mine):

***We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter. Failure to do so may result in enforcement action without further notice. The Act authorizes injunctions against manufacturers and distributors of illegal products and seizure of such products.***

# US Law Firm Investigates Cosmetic Brands for Using False & Misleading Anti-aging Claims

SpecialChem - Feb 18, 2013

LOS ANGELES -- The national plaintiffs' law firm of Baron and Budd is investigating potential class action lawsuits against various luxury retail cosmetic brands for using false and misleading statements in connection with the advertising of their [anti-aging](#) products. After recently filing similar lawsuits against AVON regarding the company's Anew line of [anti-aging](#) products and L'Oreal regarding the company's Lancome Genifique, Absolue, and Renergie lines, the firm is now looking into the advertising claims made by Estée Lauder, Clinique, La Prairie, Dr. Perricone, ReVive, Naturabisse, Lancome, Clarins, Shiseido and Dr. Gross brands.

Baron and Budd attorneys Roland Tellis and Mark Pifko believe that these issues may be industry-wide, and that many other cosmetics brands are making claims similar to those discussed in the AVON and L'Oreal lawsuits. Other major anti-aging lines include the popular Estée Lauder "Repairwear," Clinique "Youth Surge," La Prairie "Cellular" and ReVive "Intensite" collections. The AVON and L'Oreal lawsuits allege that these companies purposely misled consumers about their products and profited handsomely as a result of the false claims.

"Our lawsuits assert that the advertisements for skincare brands prey on consumers' desire to find a safer and more cost-effective alternative to surgery to combat the effects of aging," said attorney Mark Pifko of Baron and Budd's California office. "But, companies go too far when their marketing materials use scientific-sounding claims about pharmaceutical technologies that purportedly operate on a molecular level to convince consumers to believe that their anti-aging products actually work. The truth is that these products are cosmetics, not drugs."

Tellis and Pifko are co-lead counsel in the lawsuit against AVON regarding deceptive labeling of the company's Anew anti-aging products. Last year, the FDA issued a warning claiming that the cosmetics company was making claims about some of their products that would classify the products as drugs under FDA regulations. The lawsuit alleges that AVON used predatory marketing techniques intended to mislead consumers into believing that the company's anti-aging products were capable of turning back time and offering at-home results to consumer that would usually require a dermatologist.

## About Baron & Budd

The law firm of Baron & Budd, with offices in Dallas, Baton Rouge, Austin and Los Angeles, is a nationally recognized law firm with over 35 years of "Protecting What's Right" for people,

communities and businesses harmed by negligence. Baron & Budd's size and resources enable the firm to take on large and complex cases. The firm represents individuals, governmental and business entities in areas as diverse as [water](#) contamination, Gulf oil spill, Qui Tam, California Proposition 65 violations, unsafe drugs and medical devices, Chinese drywall, deceptive advertising, consumer financial fraud, securities fraud and asbestos cancers such as mesothelioma.

*Source: Baron & Budd*

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# US Food and Drug Administration claims L'Oreal misled its customers

AFP

September 13, 2012, 12:08 am TWN



WASHINGTON -- U.S. regulators accused French cosmetics giant L'Oreal of misleading claims in marketing its Lancome line of anti-aging products, according to a letter released Tuesday.

In the letter, addressed to the president of L'Oreal-owned Lancome USA, the Food and Drug Administration said some Lancome products advertised online carry claims that “are intended to affect the structure or any function of the human body, rendering them drugs” under US law.

The products under scrutiny include the Genifique Youth Activating Concentrate, which claims to boost “the activity of genes and stimulates the production of youth proteins,” according to the letter.

Another singled out is the Genifique Repair Youth Activating Night Cream, which claims to boost “the activity of genes.”

Lancome has 15 days to respond to the FDA warning with specific steps it has taken to correct the violations, according to the letter dated Friday.

# US agency accuses L'Oreal of misleading

- From: *AAP*
- September 12, 2012 4:02PM

## **US regulators have accused French cosmetics giant L'Oreal of misleading claims in marketing its Lancome line of anti-aging products.**

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"We request that you take prompt action to correct all violations associated with your products, including the violations identified in this letter," wrote the FDA's Michael W Roosevelt of the Centre for Food Safety and Applied Nutrition. "Failure to do so may result in enforcement action without further notice."

L'Oreal is the world's largest cosmetics maker.



# Approaches to Demonstrate Bioequivalence of Narrow Therapeutic Index Drugs

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology  
July 26, 2011*

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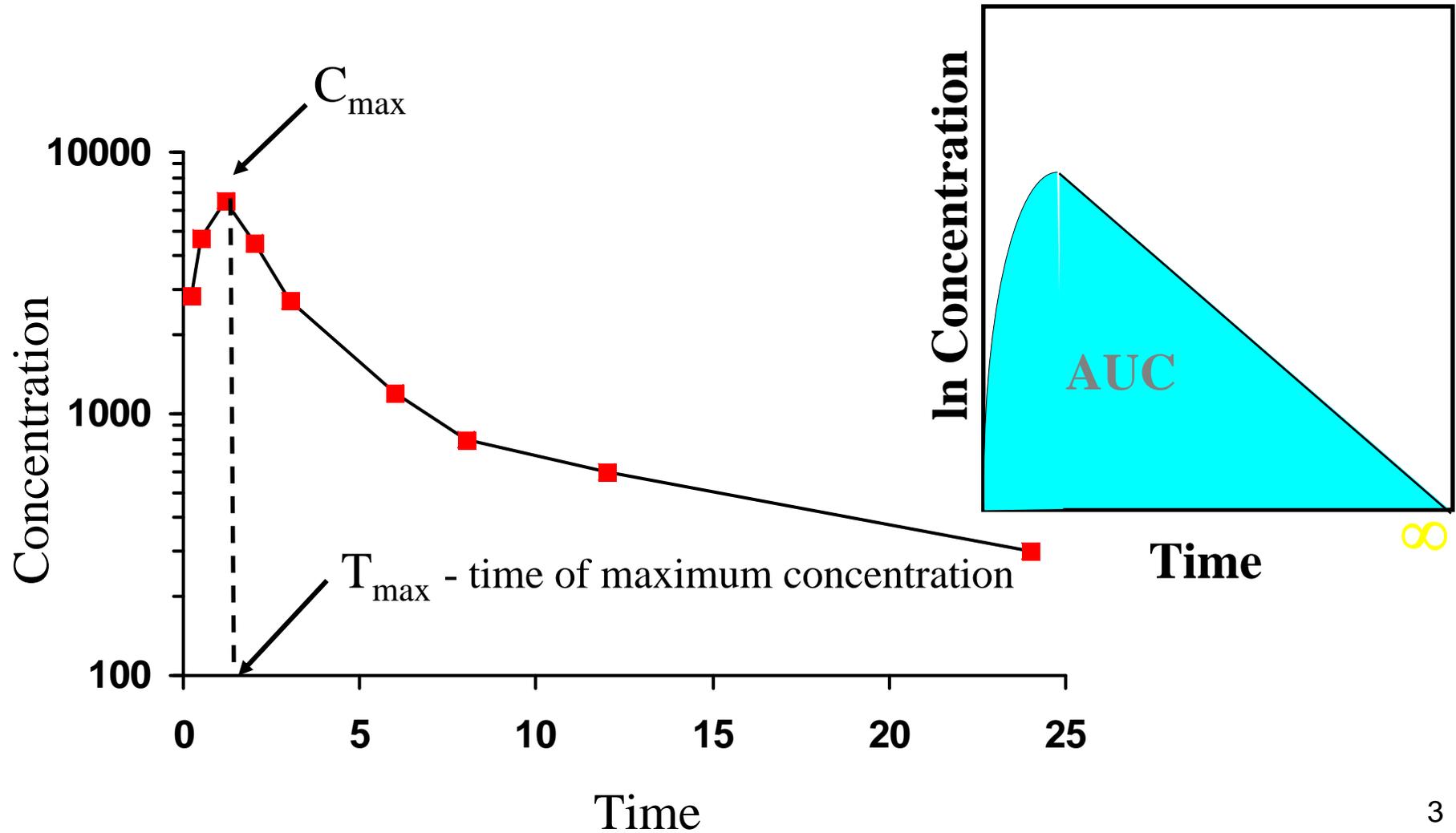
**Lawrence X. Yu, PhD.**  
**Deputy Director for Science and Chemistry**  
**Office of Generic Drugs**



# Bioequivalence

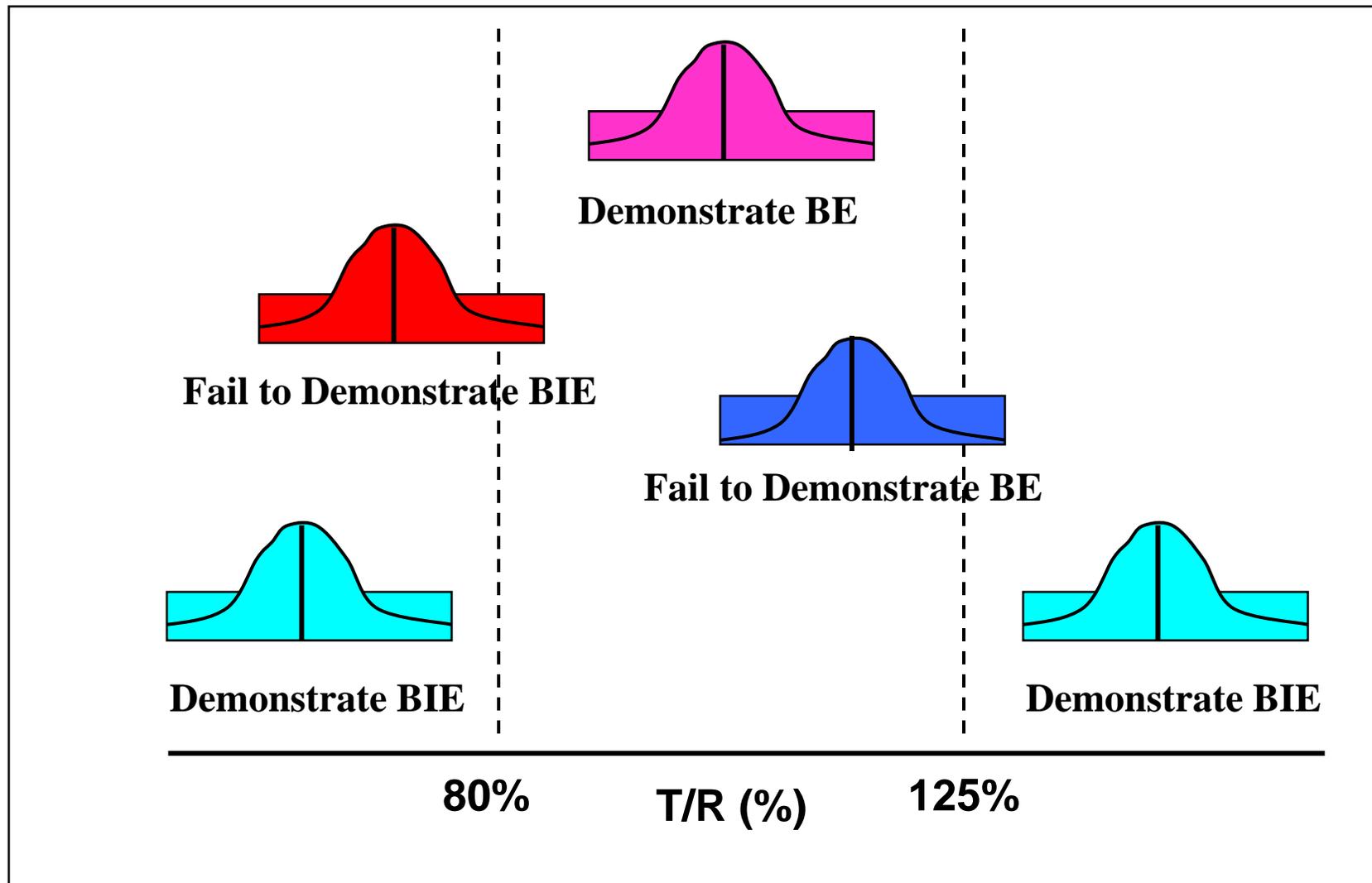
- The absence of **a significant difference** in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately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

# Plasma Concentration Profile





# Possible Outcome of BE Studies



### Bioequivalence

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# 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

**G**eneric 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),<sup>1</sup> which set the rules under which generic drugs could compete with innovator products, the Food and Drug Administra-

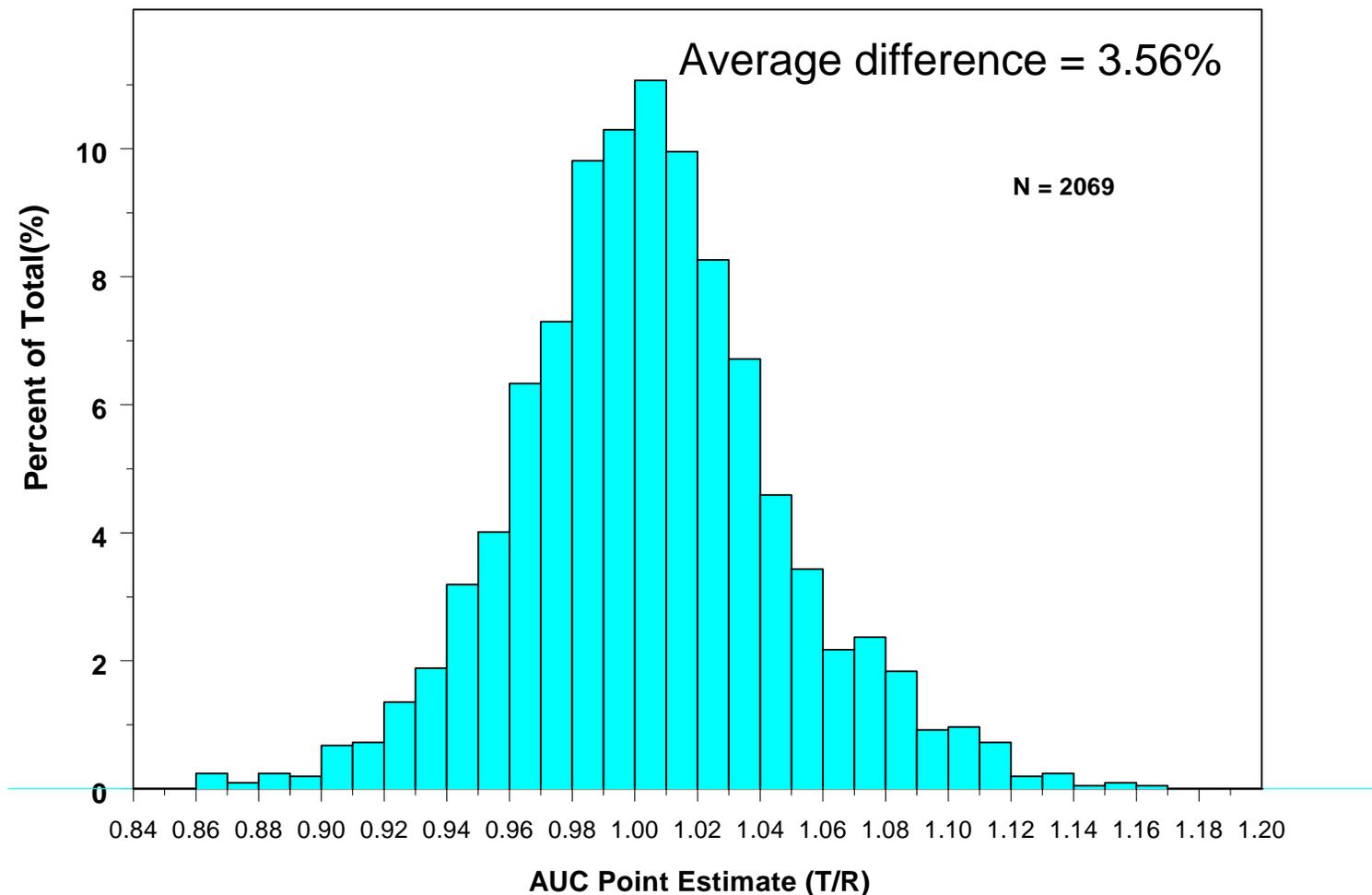
**BACKGROUND:** In the US, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the generic formulation provides the same rate and extent of absorption as (ie, is bioequivalent to) the innovator drug product. Thus, most orally administered generic drug products 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.

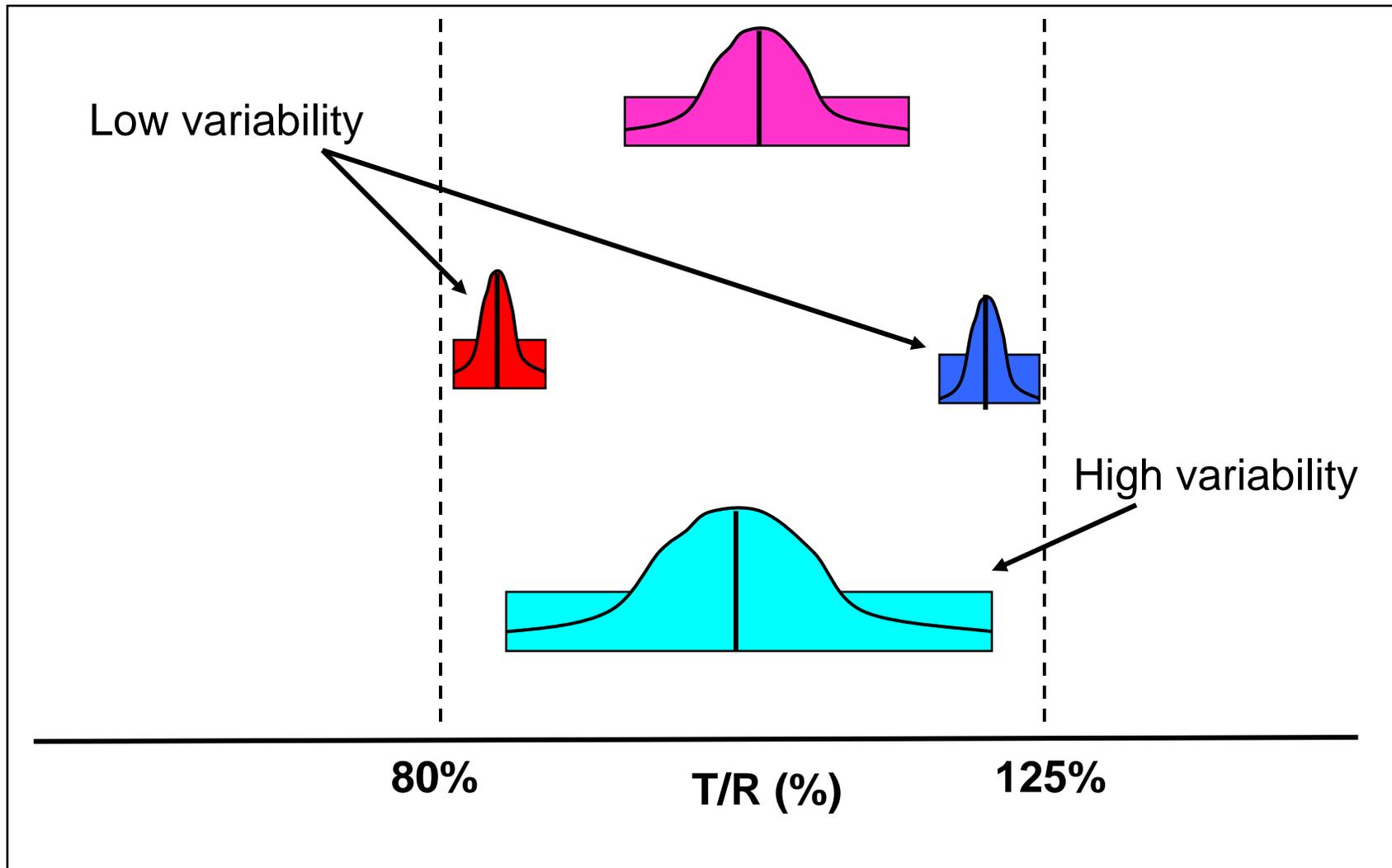


# FDA 12 Year BE Data

Distribution of  $AUC_t$  Ratios



# Effect of Variability on BE Studies





# Coefficient of Variation (CV) for NTI Drugs

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

Drugs	AUC <sub>0-t</sub>		C <sub>max</sub>	
	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
Carbamazepine (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

Not a comprehensive list of NTI drugs



## 2010 ACPS 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 ACPS 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



# FDA's Simulation Studies

- BE study design
  - Two, three, and four way crossover study designs
- BE limit
  - 80-125% and 90-111.11%
- Bioequivalence approach
  - Reference scaled average bioequivalence
  - $\sigma_{WO} = 0.10$  or  $0.25$
- Other constraints
  - Point estimate limit 5% or 10%
  - The 90% confidence interval includes 100%



# 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)



# FDA's Proposal

- Study design
- Reference-scaled average bioequivalence to compare mean
- BE limits
- Point estimate limit



# Proposed NTI Drug Definition

- Those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening. NTI drugs generally have the following characteristics:
  - Steep dose-response curves for both safety and efficacy in the usual dosing interval or close effective concentrations and concentrations associated with serious toxicity,
  - Subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures, and
  - Generally small within subject variability.



# Today's Agenda on NTI Drugs

- Topic Introduction: BE for NTI Drug Product  
**Lawrence Yu**
- Narrow Therapeutic Index Drugs: An Approach to Bioequivalence and Interchangeability **Kamal K. Midha**
- Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs **Donald Schuirmann**
- Pharmaceutical Quality of NTI Drugs **Wenlei Jiang**
- FDA Proposals for NTI Drugs **Barbara M. Davit**
- Committee Discussion **Lawrence Yu**



## ACPS-CP Questions

July 26, 2011

### Bioequivalence (BE) and Quality Standards for Narrow Therapeutic Index (NTI) Drug Products

1. Is the draft definition for narrow therapeutic index (NTI) drugs, proposed by the FDA, reasonable and appropriate?
  - If not, please suggest revisions
2. Should the following be used for bioequivalence studies of NTI drugs:
  - The two-treatment, four-period, fully replicated crossover design
  - The reference-scaled average bioequivalence approach
3. Is it appropriate to tighten the assayed potency standard for NTI drugs to 95.0-105.0%?

# **Narrow Therapeutic Index Drugs: An Approach to Bioequivalence and Interchangeability**

Kamal K. Midha<sup>1</sup>, Gordon McKay<sup>1,2</sup>,  
Meir Bialer<sup>3</sup> and Maureen Rawson<sup>2</sup>

<sup>1</sup>University of Saskatchewan, College of  
Pharmacy and Nutrition, <sup>2</sup>Pharmalytics Ltd.

<sup>3</sup>The Hebrew University of Jerusalem,  
School of Pharmacy

# Outline

- Bioequivalence
  - Current practice is ABE based on 90%CI
  - Examples where current ABE approach requires change(s)
- Narrow Therapeutic Index (NTI) drugs as introduced by Dr. Lawrence Yu
- Antiepileptic drugs constitute a special class of drugs; a proposal to establish BE through scaled ABE will be presented based on Bialer and Midha, *Epilepsia*, 2010
- Simulations
- Discussion
- Conclusions

## Abbreviations

- BE = bioequivalence
- BEL = bioequivalence limits
- ABE = average bioequivalence
- NTIs = narrow therapeutic index drug products  
(also termed NTR or Critical Dose Drugs)
- HVD = highly variable drug (ANOVA-CV  $\geq$  30%)
- HVD/P = HVD or highly variable drug product
- WSV = within subject variability

# Bioequivalence and Therapeutic Equivalence

Pharmaceutical Equivalence



**Bioequivalence**



- Pharmacokinetic endpoint
- Pharmacodynamic endpoint
- Clinical endpoint
- In vitro endpoint

Therapeutic Equivalence/Interchangability

- **Bioequivalence is a surrogate for therapeutic equivalence**
- **Focus is on the documentation of bioequivalence by appropriate pharmacokinetic endpoints (in the majority of situations)**
- At present generic NTIs, once proven to be bioequivalent are regarded therapeutically interchangeable without loss of efficacy and safety.

## Conventional BE/ABE

- Typically test and reference products are administered to healthy volunteers in crossover studies and collected biological samples are assayed and subjected to PK analyses.

## Conventional BE/ABE

- Total exposure (AUC), peak exposure (C<sub>max</sub>) and time to C<sub>max</sub> (t<sub>max</sub>) are compared by analysis of variance (ANOVA) and the computed 90% confidence intervals (CI) of the geometric mean ratio (GMR) of each pharmacokinetic parameter are required to fall within 80-125% except t<sub>max</sub>.
- This approach has served us well in the majority of cases.
- However, its universal applicability has been questioned especially for HVD/P and now for NTIs and AEDs.

## Conventional ABE: 2-Treatment, 2-Period Design

- The residual mean square in ANOVA contains several variance components:
  - Within subject variability in absorption, distribution, metabolism and elimination (plus an element of analytical variability )
  - Within formulation variability
  - Subject by formulation interaction
  - Random unexplained variation

## Conventional ABE: 2-Treatment, 2-Period Design

- In a 2-treatment, 2-period design, the components of the residual mean square arising from ANOVA cannot be separated (therefore we will not know if the variance of test and reference products are similar or different).
- The residual mean square is used...
  - In the calculation of the ANOVA-CV (an estimate of within subject variability but confounded)
  - In the calculation of the 90%CI

## The 90% Confidence Interval

- In ABE based on 2-treatment, 2-period designs, the width of the 90% confidence interval depends on...
  - The magnitude of the ANOVA-CV
  - The number of subjects in each sequence

## Issues concerning interchangeability (switchability) for NTIs; How can we alleviate the issues?

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- For NTIs therapeutic issues can arise when a patient is maintained on brand itself (within brand or between two lots of a brand) or is switched from a brand to a generic as well as from one generic to another generic. This suggests that PK variability (within brand, within generic, between brand and generic and between generic1 and generic2) may be the root cause of therapeutic failure. We need to correct this situation as much as possible.

## Issues concerning interchangeability (switchability) for NTIs; How can we alleviate the issues?

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- Clearly PK variability (WSV) observed within the brand product and lots of the brand is at present operational and accepted. Therefore our efforts should be directed that PK variability within the generic product(s) ( $WSV_T$ ) and between generic and brand should be equal or no greater than what we observe for the brand to brand ( $WSV_R$ ).

## Number of Generics for two NTIs in the market

**Table 1** Number of generic manufacturers of carbamazepine and phenytoin

Brand name, dose	Generic name	Number of Generic Manufacturers
Dilantin, 100mg	phenytoin sodium	7
Tegretol, 200mg	carbamazepine	6

Adapted from Megan Barrett, J.Amer.Acad.Nurse Prac., 22, 300-304, 2010

# A Case Reports of Generic Substitution for two NTIs

## NTIs used by patients in Case Reports

AED before switch	N	AED at time of seizure	n
Dilantin	14	Phenytoin	15
Phenytek	1		
Tegretol	5	Carbamazepine	7
Carbetrol	1		
Tegretol XR	1		

- Therefore clinicians and patients are reluctant to switch to generics.

Adapted from: Berg et al, 2008, *Neurology* 71 525-530

# An ABE approach to reduce therapeutic risk due to PK variability

*Epilepsia*, 5 (6), 941-950, 2010

## CRITICAL REVIEW AND INVITED COMMENTARY

### Generic products of antiepileptic drugs: A perspective on bioequivalence and interchangeability

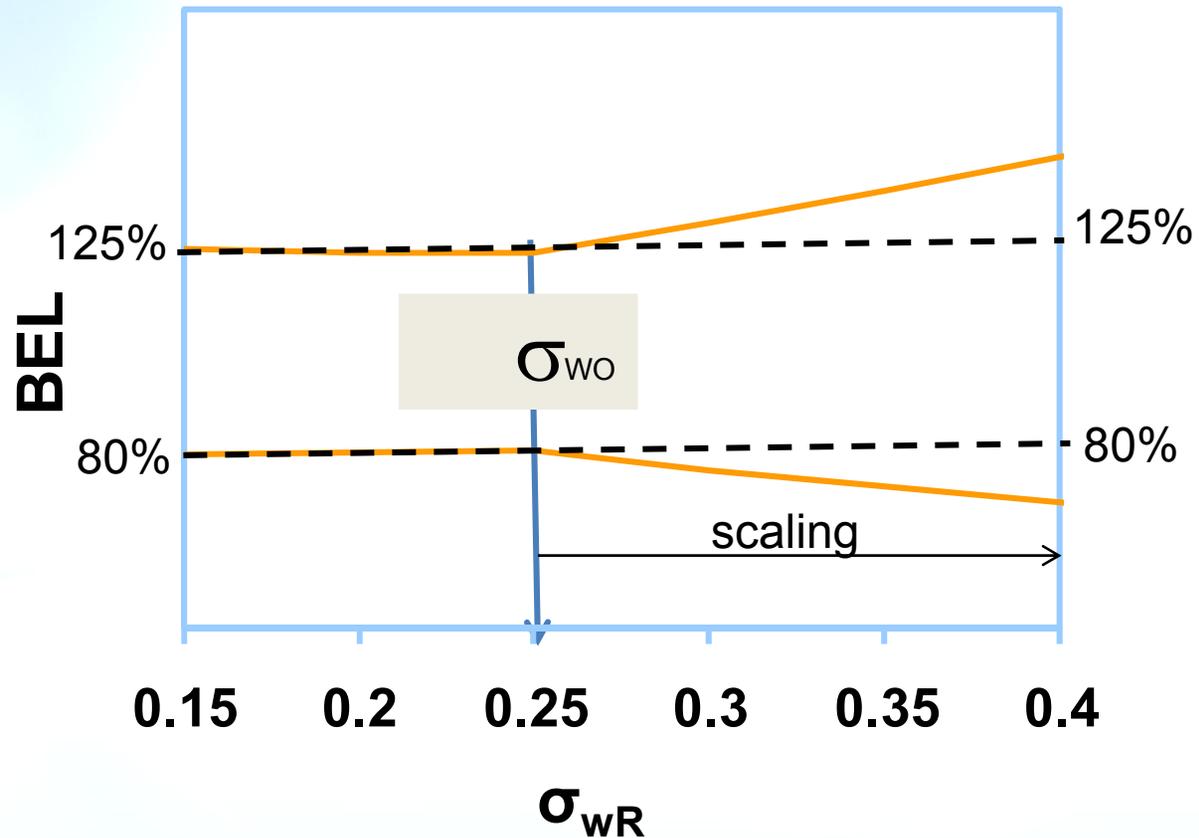
Meir Bialer and Kamal K. Midha

- We propose a scaled average bioequivalence approach that will ensure that fluctuations in plasma levels are no greater than those experienced within the brand reference product.

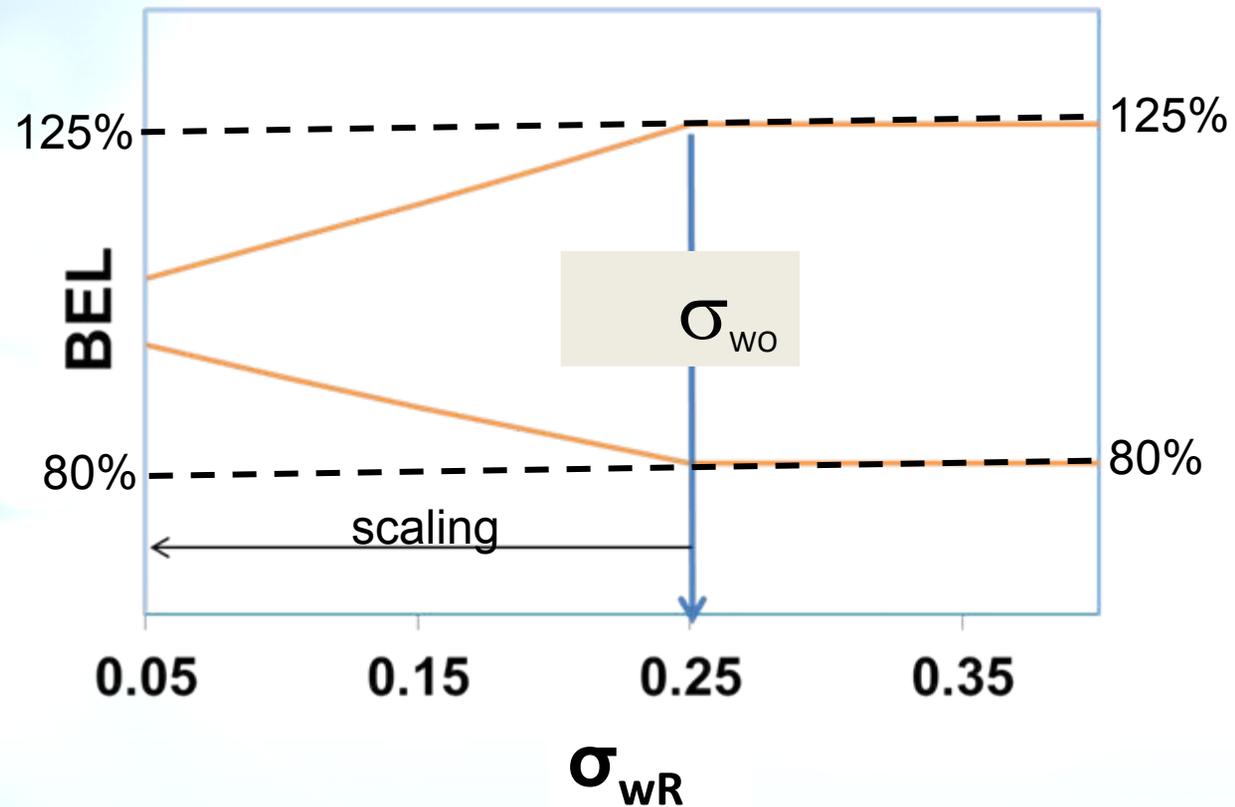
## What Is Scaled Average Bioequivalence (sABE)

- sABE is an approach in which ABE is scaled based on a variance component.
- The most recent and highly cited example is sABE for highly variable drugs.
- The BE Limits are scaled based on reference to reference variance from a replicate design study. Alternately the kinetic parameters obtained within a BE study may be scaled using the same variance just mentioned.

# A pictorial representation of scaling in BE for HVDs



# A pictorial representation of scaling in BE for NTIs

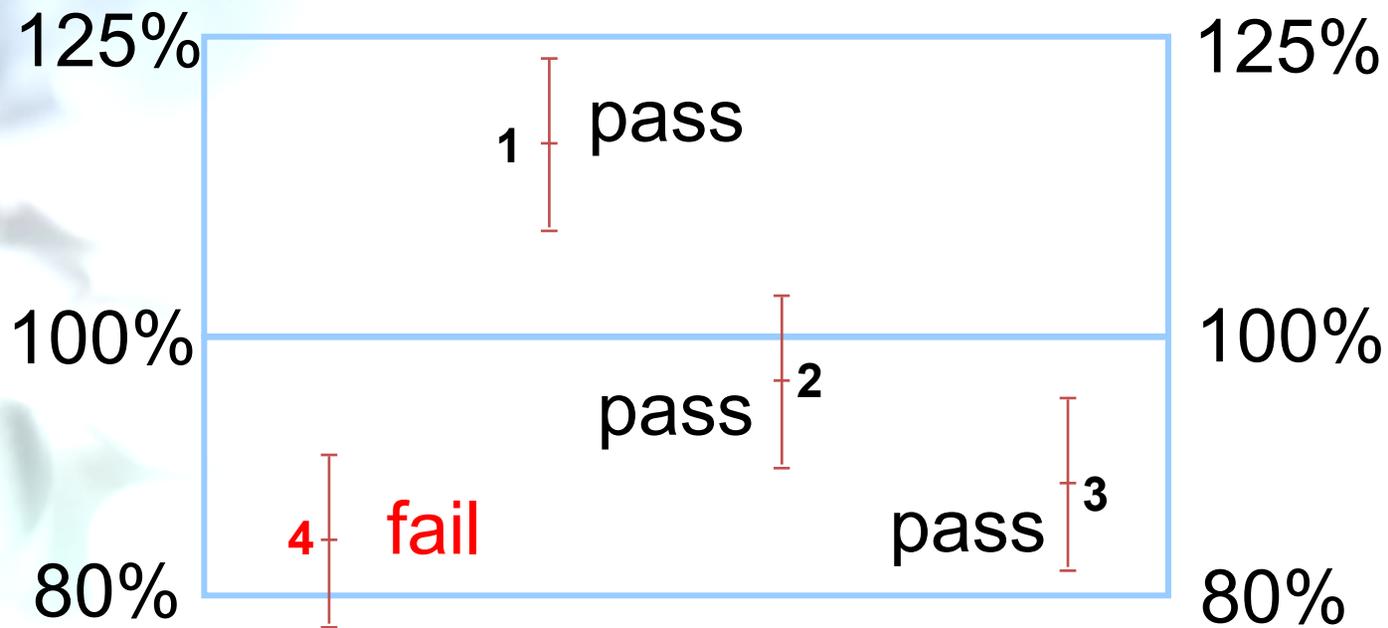


## **ANOVA-CV and its interplay with point estimates and the 90% CI**

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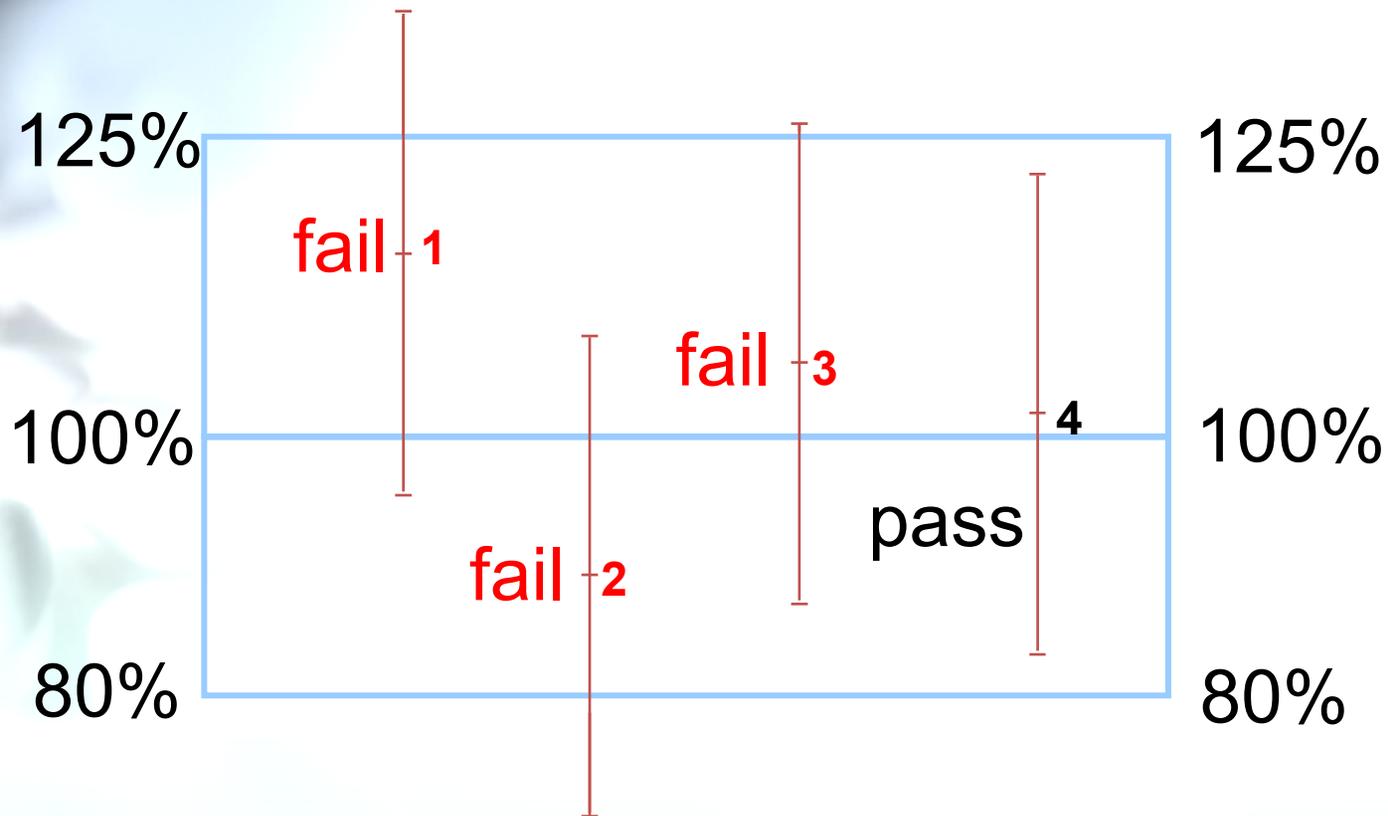
- The following 2 slides depict confidence intervals in 4 BE studies in which the width of the 90% CI is the same, but the GMR (point estimate) varies
- Traditional ABE: 2-treatment, 2-period design
- A low variability drug ANOVA-CV 14%
- A high variability drug ANOVA-CV 43%

## ANOVA-CV 14%, 24 subjects



GMR may deviate a long way from 100%

## ANOVA-CV 43%, 37 subjects



GMR must be close to 100% to fit in BE limits

## Replicate Designs

- Both 3 and 4 period replicate designs are possible. In the case of 3 period design (HVDs) only the reference is replicated.
- In 4 period replicate designs, the Test and Ref products are both replicated.

# Replicate Designs

- We propose doing a true replicate design employing:
  - 4-period, 2-sequence designs
    - e.g., TRTR and RTRT (where T & R represent the test and reference formulations)
    - Statisticians encourage the use of only two sequences to avoid compounding sequence effects

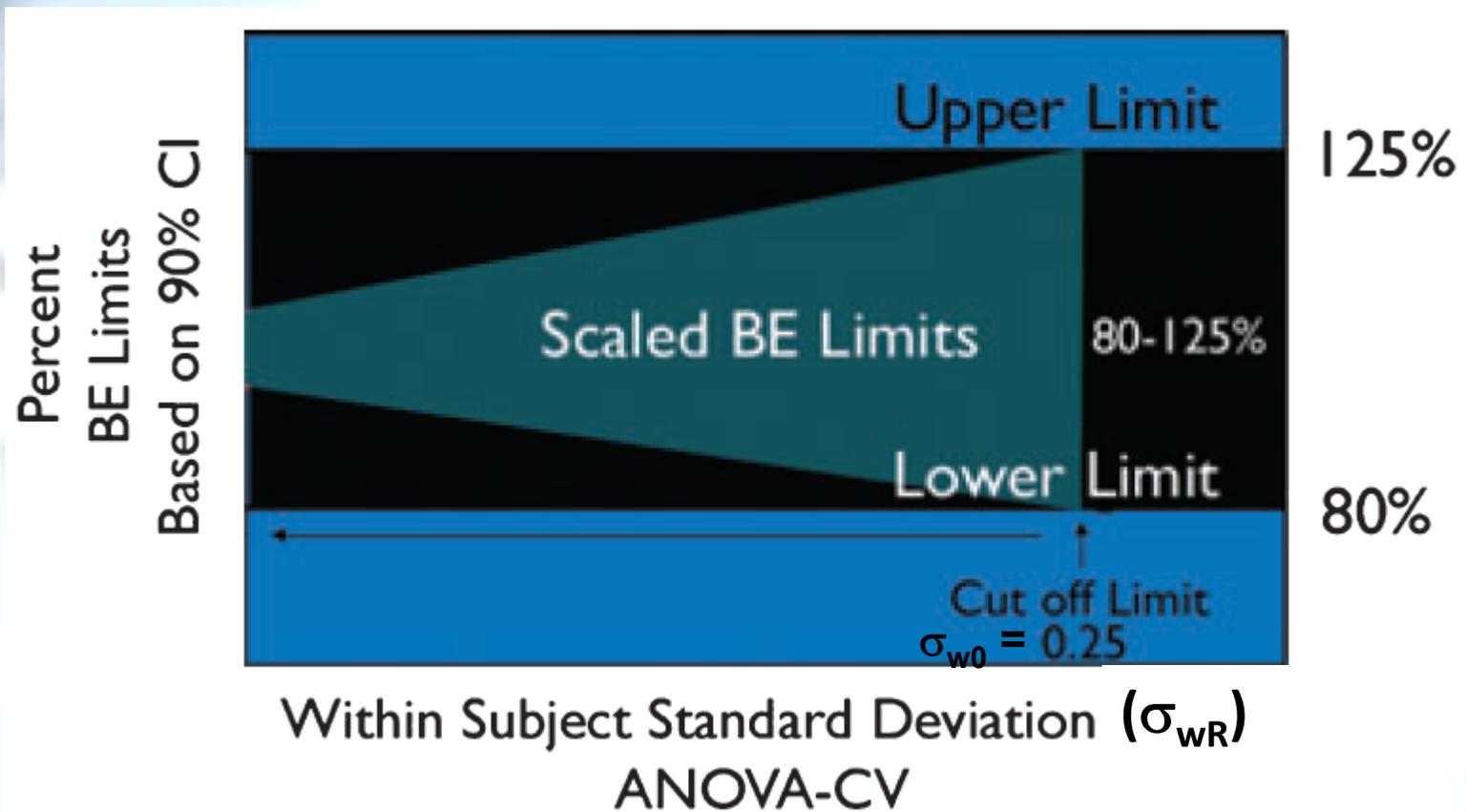
## Advantages of Replicate Designs

- Permits separate estimation of the variance associated with the test and ref formulations (Test vs Test and Ref vs Ref)
- This facilitates a better understanding of the pharmaceutical quality of the Test and Ref formulations which is based on the magnitude of the variance – larger the variance the poorer the pharmaceutical quality of the product.

## Advantages of Replicate Designs

- Ideally the test product should not be of poorer pharmaceutical quality than the reference product. It means that the magnitude of the Test to Test variance should not be greater than that of the Ref to Ref variance, if at all variance value should be less than the Ref to Ref variance.

# Reference sABE for AEDs/NTIs



## Ref scaled ABE by scaling the BEL

- The BE Limits based on the reference to reference WSV are scaled using the following formula:

$$\text{BEL} = \exp \left[ \frac{\pm (\ln 1.25) \sigma_{wR}}{\sigma_{w0}} \right]$$

# Simulations

- USFDA has suggested a reference scaled regulatory criteria for determination of reference scaled individual bioequivalence (1)
- Simulations were performed using previously published methodology which has been adapted for sABE four period two sequence designs (2).
- Simulations assumed a true within subject CV of the reference product,  $\sigma_{WR}$  at three levels, 6, 12 and 22%.

1. USFDA, Statistical approaches to establishing bioequivalence-guidance for industry, CDER, 2001
2. Tothfalusi et al, Pharm. Res., 18, 728-733, 2001

# Simulations

- The between subject variance and the variance for the test were set equal to that of the reference.
- Each study had 24 subjects, the true GMR (T/R%) was gradually increased from 100% until no further studies were acceptable.
- 500 simulations were performed under each selected condition detailed above.

## Simulations cont'd

- The number of studies which met acceptance criteria based on traditional unscaled ABE and sABE with  $\sigma_{w0}=0.2$  and  $0.25$  were examined.
- 90% CIs were calculated by an adaptation of Hyslop et al, 2000.
- For each simulation the true GMR was plotted against the % of studies that met the acceptance criteria.

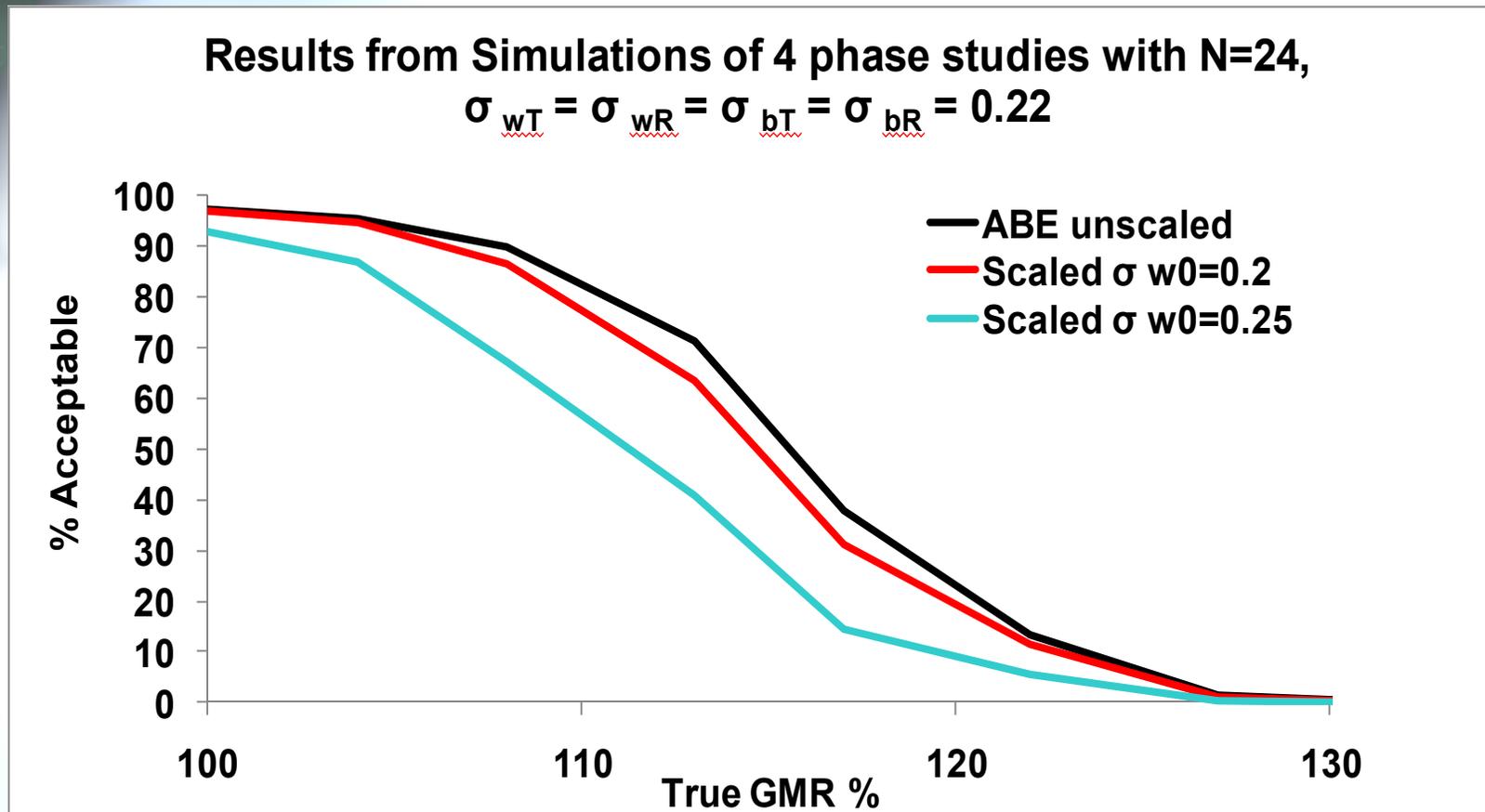
Hyslop et al, Stat. Med., 19, 2885-2897, 2000

## Referenced scaled ABE applied to the 90% confidence intervals

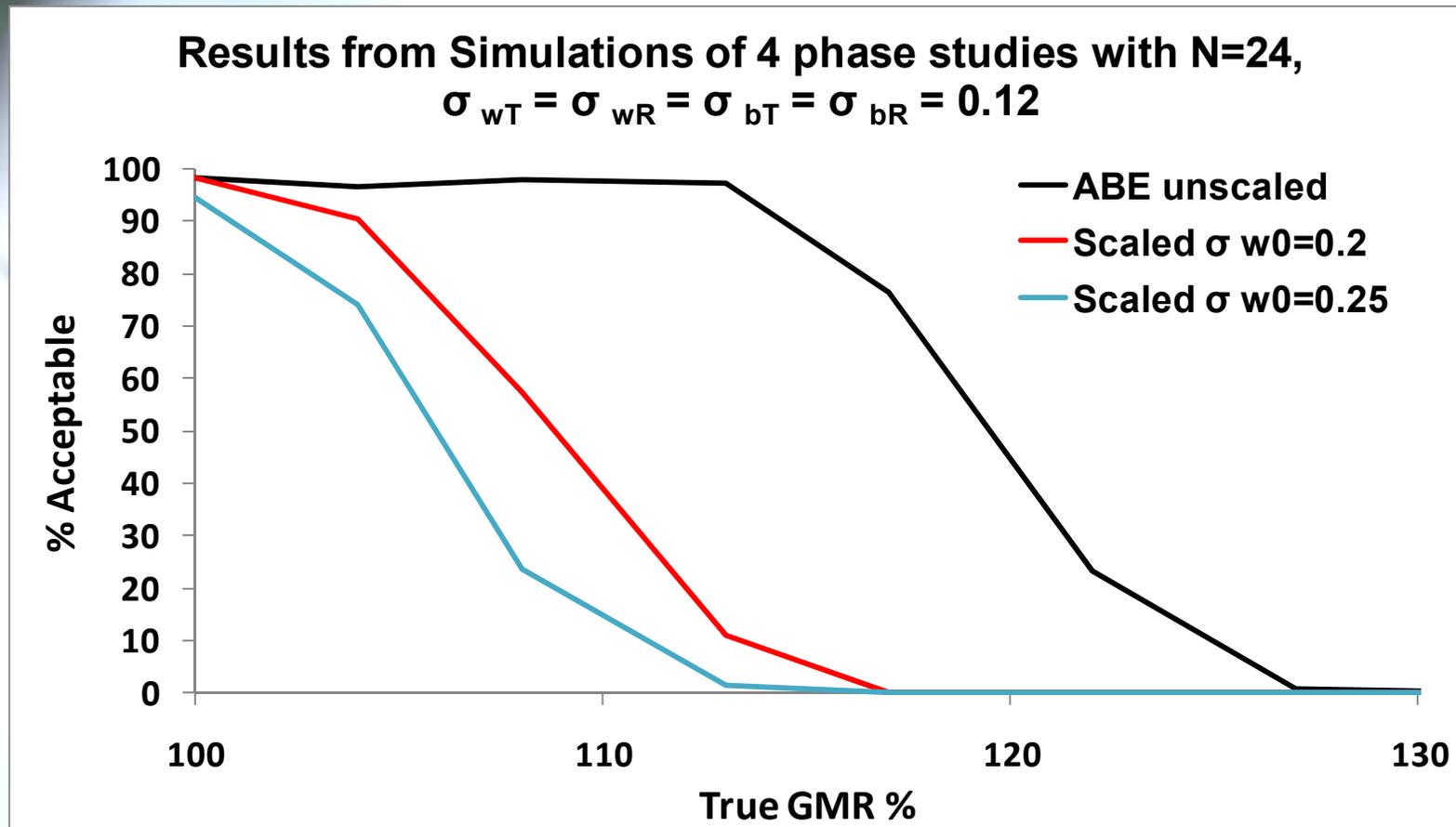
- 24 Subject, 4 period, 2 sequence studies were simulated
- Scaled ABE - 
$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \frac{(\ln(1.25))^2}{\sigma_{w0}^2}$$
- Rearranged as - 
$$(\mu_T - \mu_R)^2 - \sigma_{WR}^2 \left[ \frac{(\ln(1.25))^2}{\sigma_{w0}^2} \right] \leq 0$$
- An adaptation of Hyslop et al was used to calculate the upper CI, based on t-test as usual for the first term and  $\chi^2$  test for the variance term

Hyslop et al, Stat. Med., 19, 2885-2897, 2000

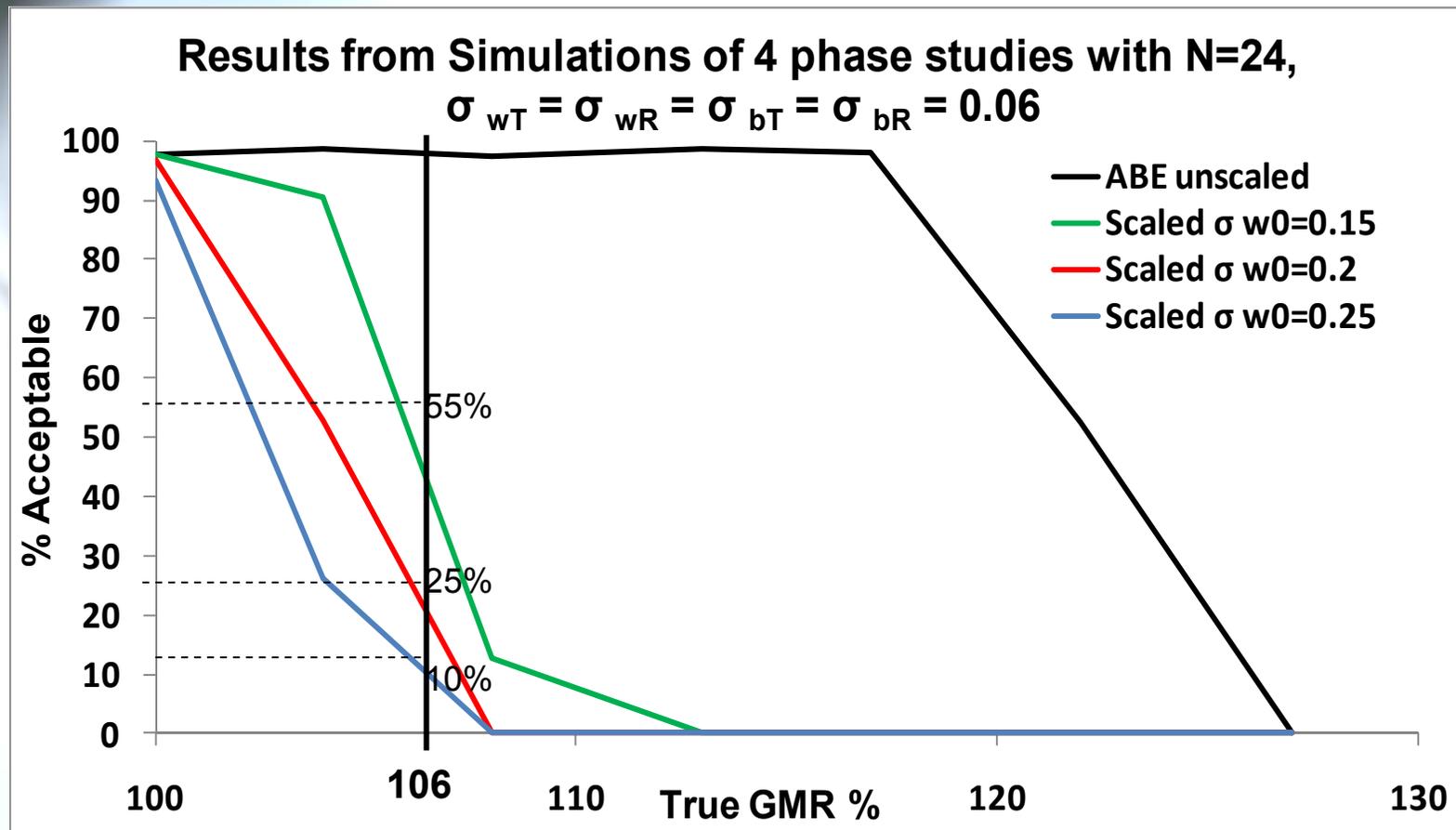
# Power Analysis $\sigma_{wR} = 0.22$



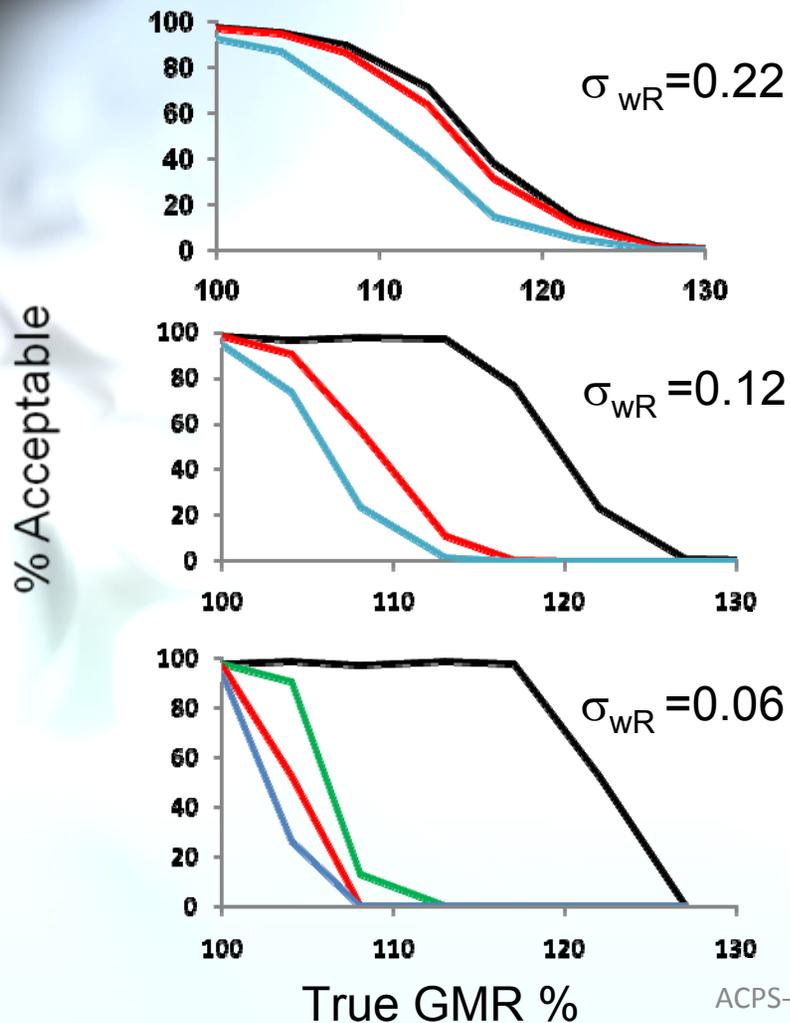
# Power Analysis $\sigma_{wR} = 0.12$



# Power Analysis $\sigma_{wR} = 0.06$

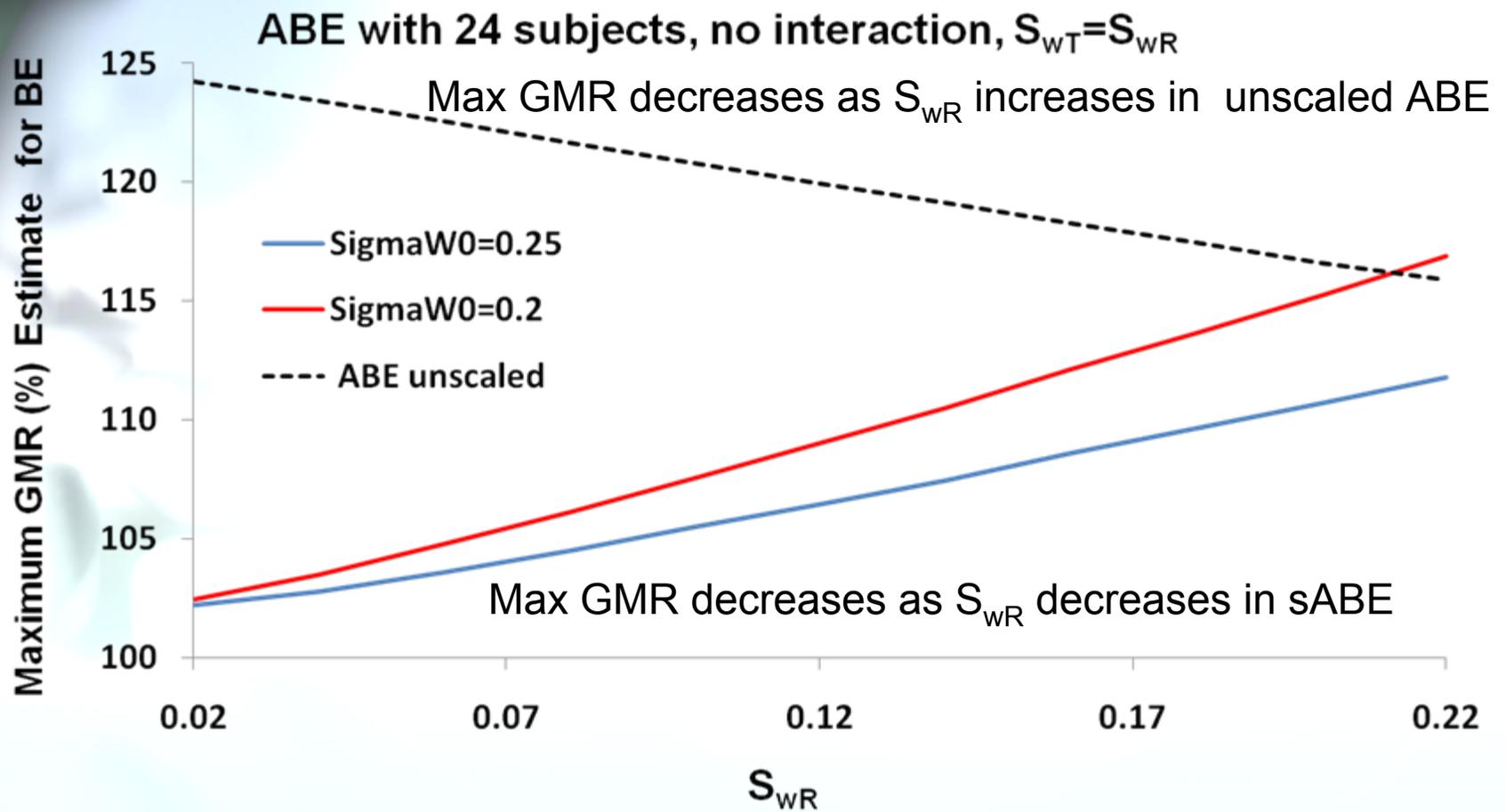


# The influence of $\sigma_{WR}$ on Scaling and its interplay with the maximum allowable GMR



- Scaling with ref to ref variability with a judiciously selected value for  $\sigma_{w0}$ , has a profound influence in controlling the BE outcome.
- It can restrain the 90% CI to give tighter BE Limits.
- In addition it can control the deviation of GMR from the ideal of 100%

# Maximum GMR allowable



## Conclusions

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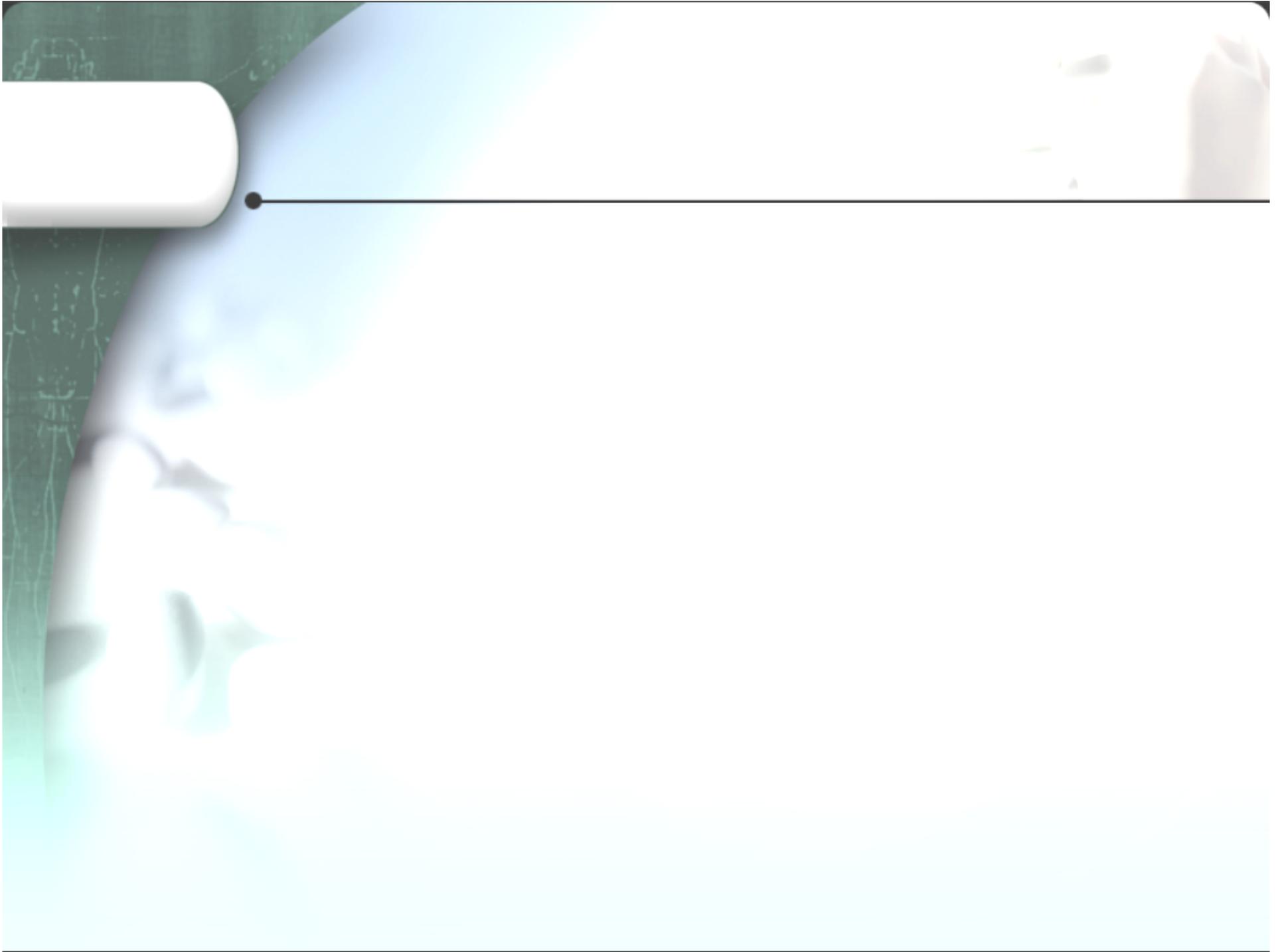
- We propose 4-Period two sequence designs in which both Test and Ref are replicated for NTIs and sABE using Ref to Ref variance.
- Replicate designs will provide separate estimates of Test vs Test and Ref vs Ref variances which will allow us to assess the pharmaceutical quality of each of the formulations.

## Conclusions

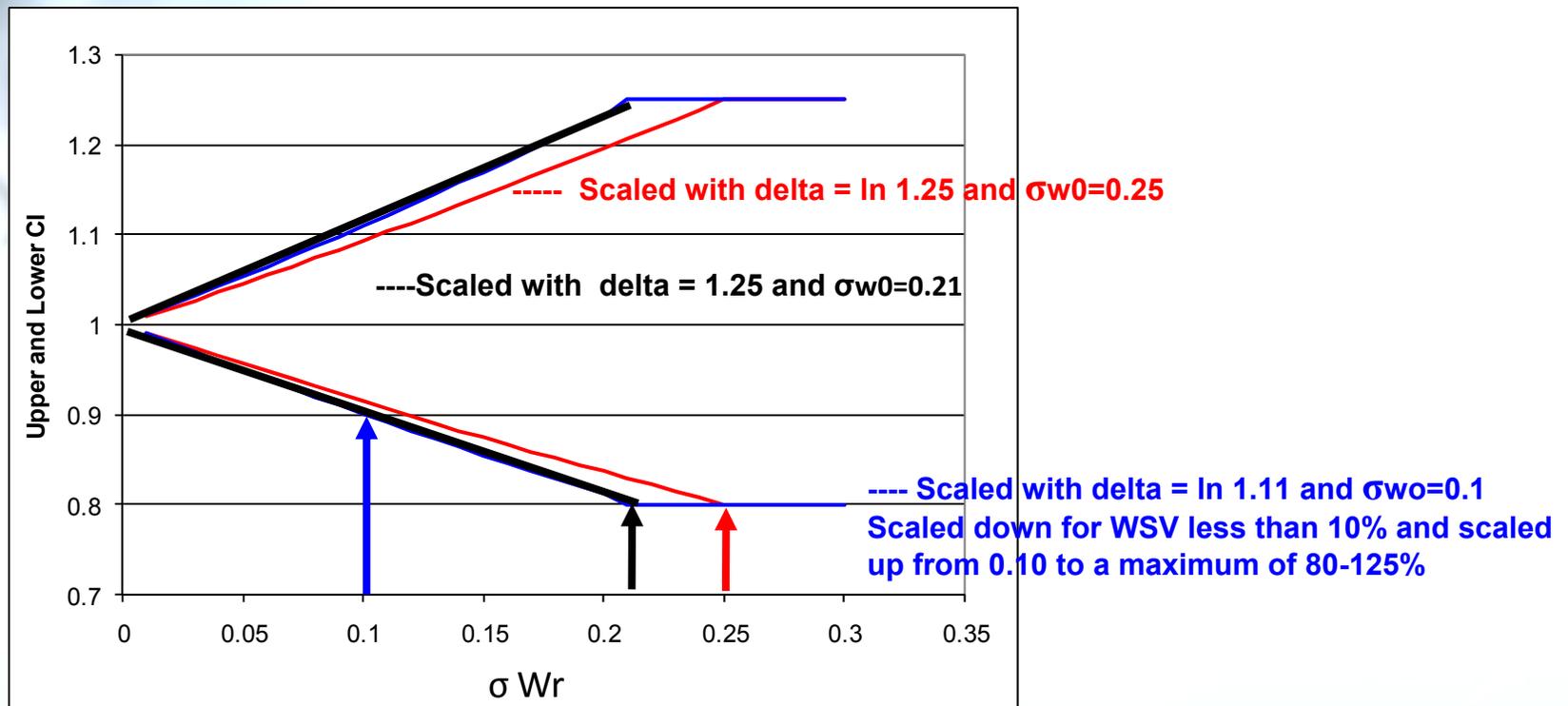
- We also propose that Test to Test variance should be less than or not significantly different than the Ref to Ref variability (F-test or equivalent)
- Ideally we propose that 2 lots of each the Test and Ref product be tested in the 4-period replicate study.

## Conclusions

- In our opinion there is no need to add additional constraints around the point estimate since the WSV will in itself limit the maximal allowable GMR in the final analysis.
- We believe the issues related to switchability between brand-bioequivalent generics (generic1 and generic2) can be minimized by constraining the 90%CI to include 100%.



## Conventional sABE versus BEL re-defined and scaling up and down from that limit based on WSV





# Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology  
July 26, 2011*

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**Donald J. Schuirmann**  
**Expert Mathematical Statistician**  
**Office of Biostatistics, OTS, CDER**



## Simulation Effort

The Office of Generic Drugs (OGD) Working Group, in collaboration with members of the Office of Biostatistics, carried out extensive simulations to investigate the properties of various approaches to bioequivalence (BE) assessment for Narrow Therapeutic Index (NTI) drug products.

## Simulation Effort (cont'd.)

- log-transformed PK endpoints (i.e.  $\ln(\text{AUC})$  and  $\ln(\text{Cmax})$ ) were assumed to be normally distributed
- $\mu_R$  and  $\mu_T$  are the population means for the Reference product (i.e. the RLD) and Test product (i.e. the proposed generic) log endpoints. The performance of the approaches considered depends on  $\mu_T - \mu_R$ , which is the log of the Geometric Mean Ratio (GMR.)

## Simulation Effort (cont'd.)

- Within-subject standard deviations for the log-transformed endpoints, for the Reference and Test products and denoted  $\sigma_{WR}$  and  $\sigma_{WT}$  respectively, may differ.
- The within-subject standard deviation ( $\sigma$ ) for the log-transformed endpoint is related to the within-subject coefficient of variation (CV) for the untransformed endpoint by the formulae

$$CV = \sqrt{e^{\sigma^2} - 1} \quad \text{or} \quad \sigma = \sqrt{\ln(1 + CV^2)}$$



## Simulation Effort (cont'd.)

- A more complete description of the assumed statistical model may be found in the January 2001 CDER guidance document *Guidance for Industry - Statistical Approaches to Establishing Bioequivalence*
- The parameter  $\sigma_D$  (described in the January 2001 Guidance) was assumed equal to zero in all simulations. However, the effect of having  $\sigma_D > 0$  is similar in many cases to having  $\sigma_{WT} > \sigma_{WR}$ , which we did consider



## Simulation Effort (cont'd.)

- Simulations were carried out in the *S-Plus*, *R*, or *APL* computer programming languages
- Each estimated probability based on one million (1,000,000) simulated studies



# Approaches Considered

- Scaled Average BE
- Regular Unscaled Average BE, but with tighter limits – 90-111.11% instead of 80-125%
- Point Estimate Constraints (PEC) in addition to the above
- Requiring the usual 90% confidence interval to contain 1.0



## NTI Drugs Show a Range of Variability

Residual Variability (% CV) from ANDAs reviewed between 1996-2008				
Drugs	AUC <sub>0-t</sub>		C <sub>max</sub>	
	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
Carbamazepine (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

Not a comprehensive list of NTI drugs

# Scaled Average BE

- scaled average BE criterion

$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

- $\theta$  defined as

$$\theta = \frac{[\ln(\Delta)]^2}{\sigma_{W0}^2}$$

$\sigma_{W0}$  is a regulatory constant.  $\Delta$  is the upper BE limit (e.g. 1.25) that applies when  $\sigma_{WR} = \sigma_{W0}$

## Scaled Average BE (cont'd.)

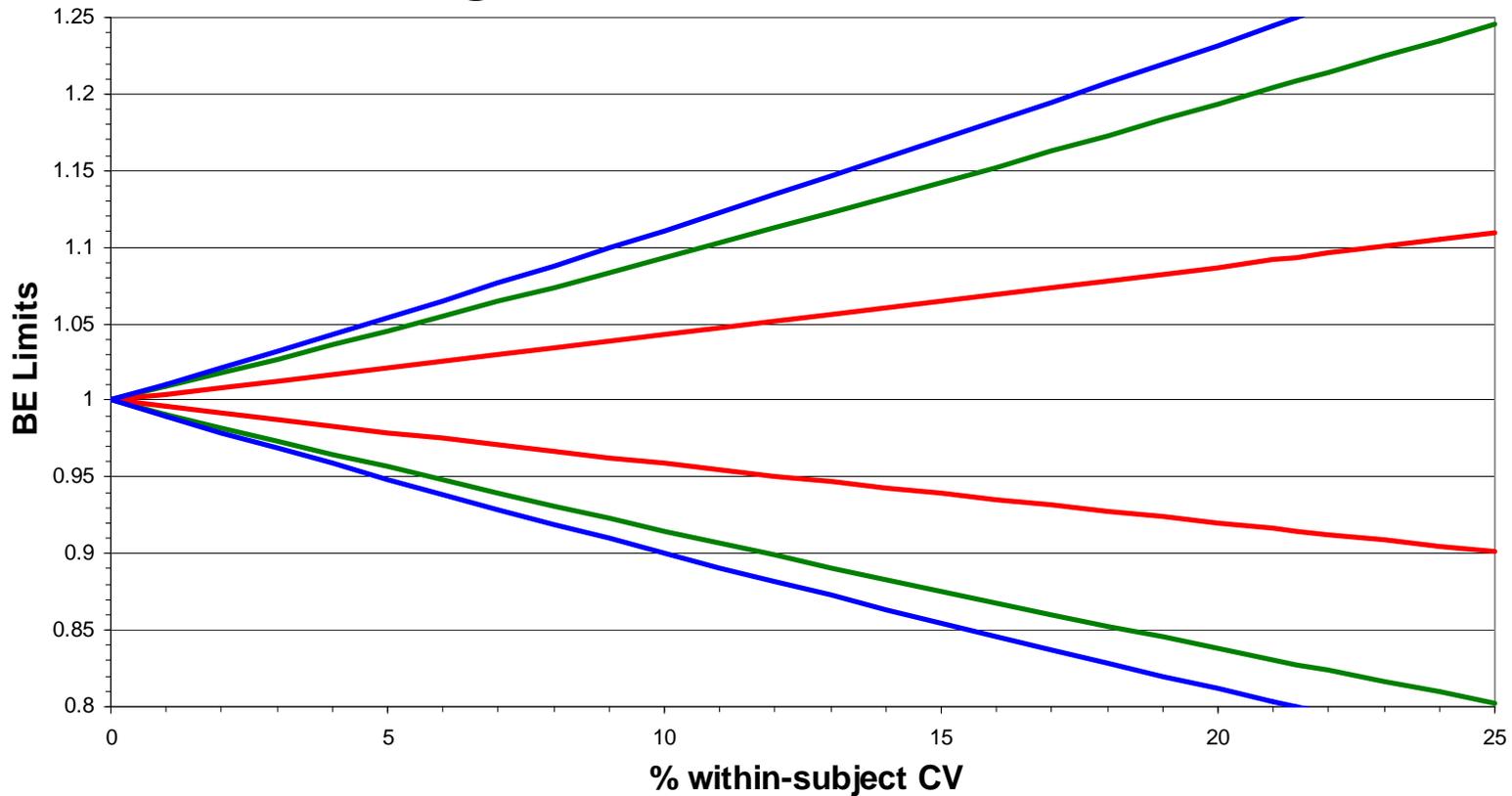
The OGD Working Group considered three cases

- Case 1:  $\Delta = 1.25$   $\sigma_{W0} = 0.25$   
(same as currently used for highly variable drugs)
- Case 2:  $\Delta = 1.11111$   $\sigma_{W0} = 0.25$   
(note  $1.11111 = 1/0.9$ )
- Case 3:  $\Delta = 1.11111$   $\sigma_{W0} = 0.10$



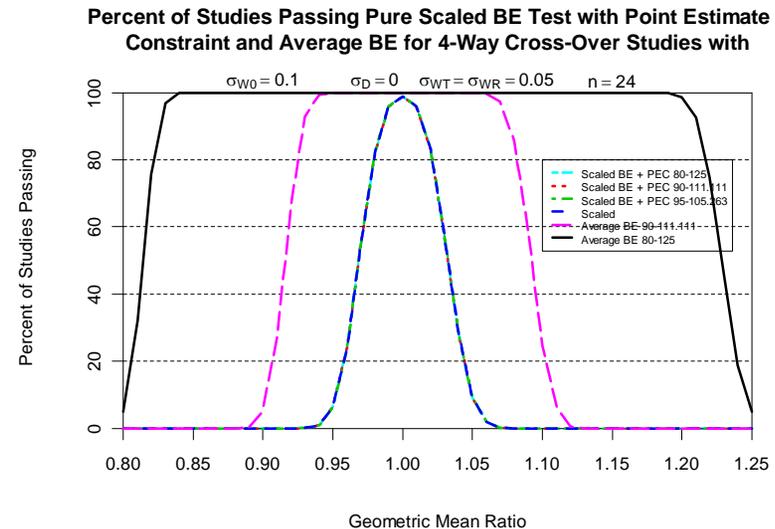
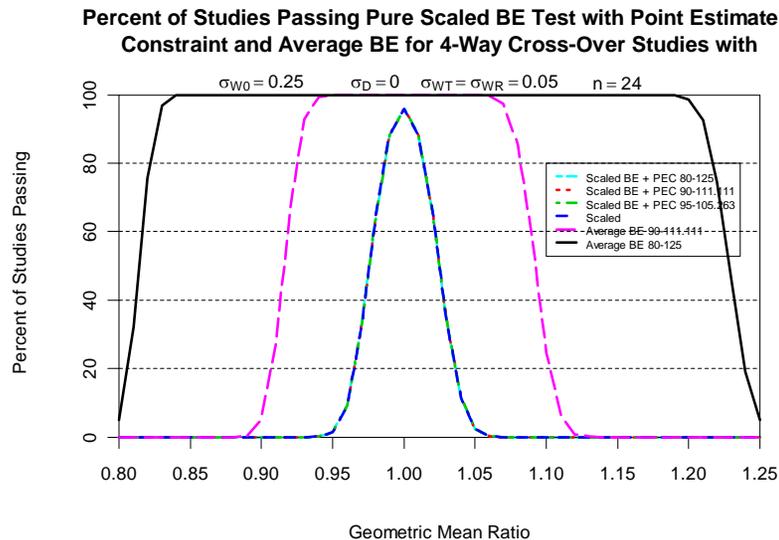
# Scaled Average BE (cont'd.)

implied BE limits for three cases  
Case 1=green Case 2=red Case 3=blue



# Scaled Average BE (cont'd.)

- It became apparent that Case 2 was too stringent
- Results for Case 1 and Case 3 were qualitatively similar. Case 1 is slightly more stringent than Case 3.





# Point Estimate Constraints

Point Estimate Constraints (PEC) considered

- 95-105.26%
- 90-111.11%
- 80-125%

For the range of variabilities considered, 80-125% had no effect (i.e. it wasn't any harder to pass with it than without it.)



# Experimental Designs

- To apply Scaled Average BE, at least the Reference product must be replicated. The classic two-period TR, RT design cannot be used
- Three-Period Crossover Design

	period		
	1	2	3
T	T	R	R
R	R	T	R
R	R	R	T



# Experimental Designs (cont'd.)

- Four-Period Crossover Design

period			
1	2	3	4
T	R	T	R
R	T	R	T

## Experimental Designs (cont'd.)

- Because both products are replicated in the four-period design, it is possible to make a statistical comparison of  $\sigma_{WT}$  and  $\sigma_{WR}$ . For this reason, attention was concentrated on this design.

There have been attempts to compare within-subject variances within the classic TR, RT two-period design (see, e.g., Guilbaud, 1993 *J. Amer. Stat. Assoc.*), but such a comparison may be confounded with other factors, and would not be expected to be as efficient as that available with the four-period fully replicated design.



## Regular Unscaled Average BE with Narrower Limits

- The Working Group also looked at regular average BE with BE limits of 90-111.11%.
- This approach could be implemented with the classic TR, RT crossover design. However, use of that design, as already discussed, would not permit efficient comparison of within-subject variances.



## Regular Unscaled Average BE with Narrower Limits (cont'd.)

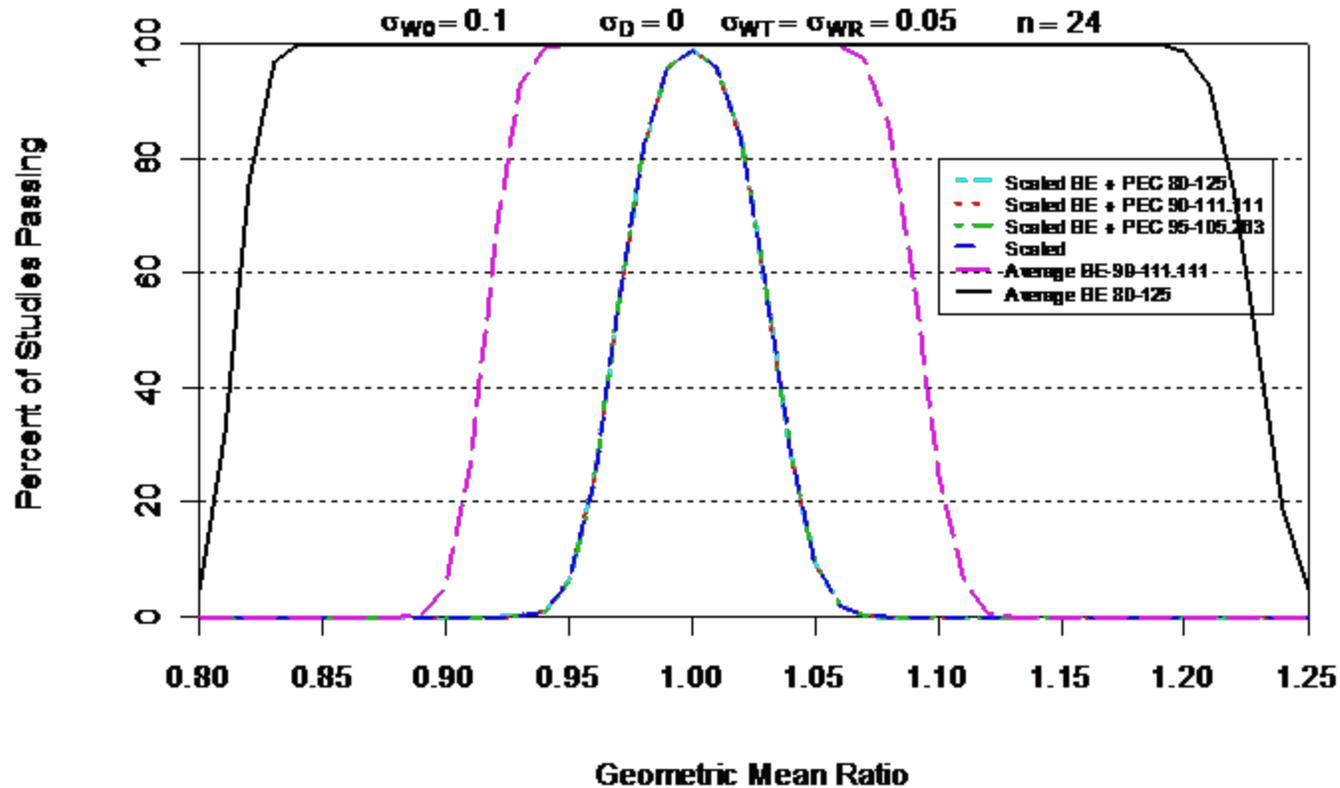
- One of the arguments for scaled average BE is that the level of variability may be indicative of the therapeutic ratio – if a drug is highly variable, it presumably has a wide therapeutic window. Conversely, if a drug shows low variability, the therapeutic window might be narrow.

Use of regular average BE with narrower limits takes no direct account of the amount of variability.



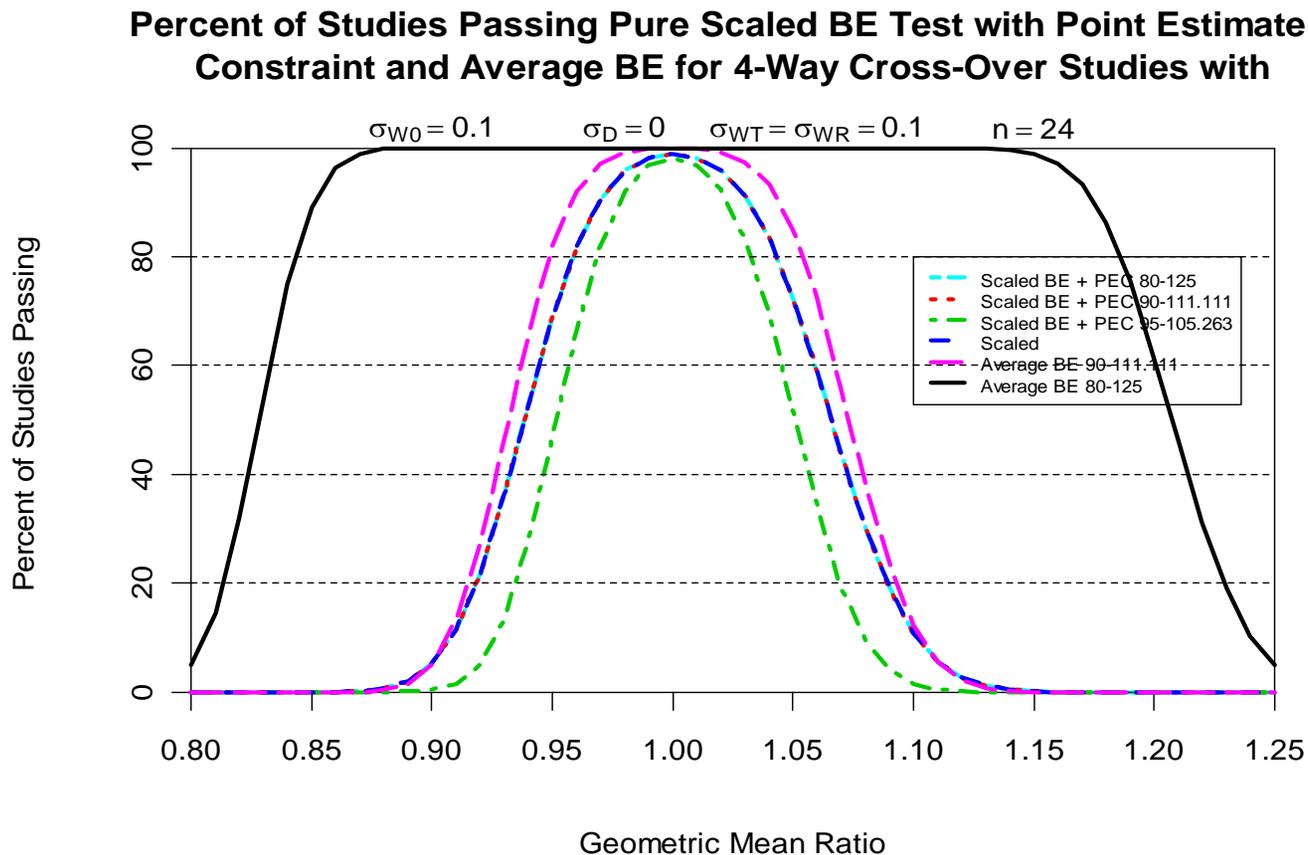
## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$

**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**



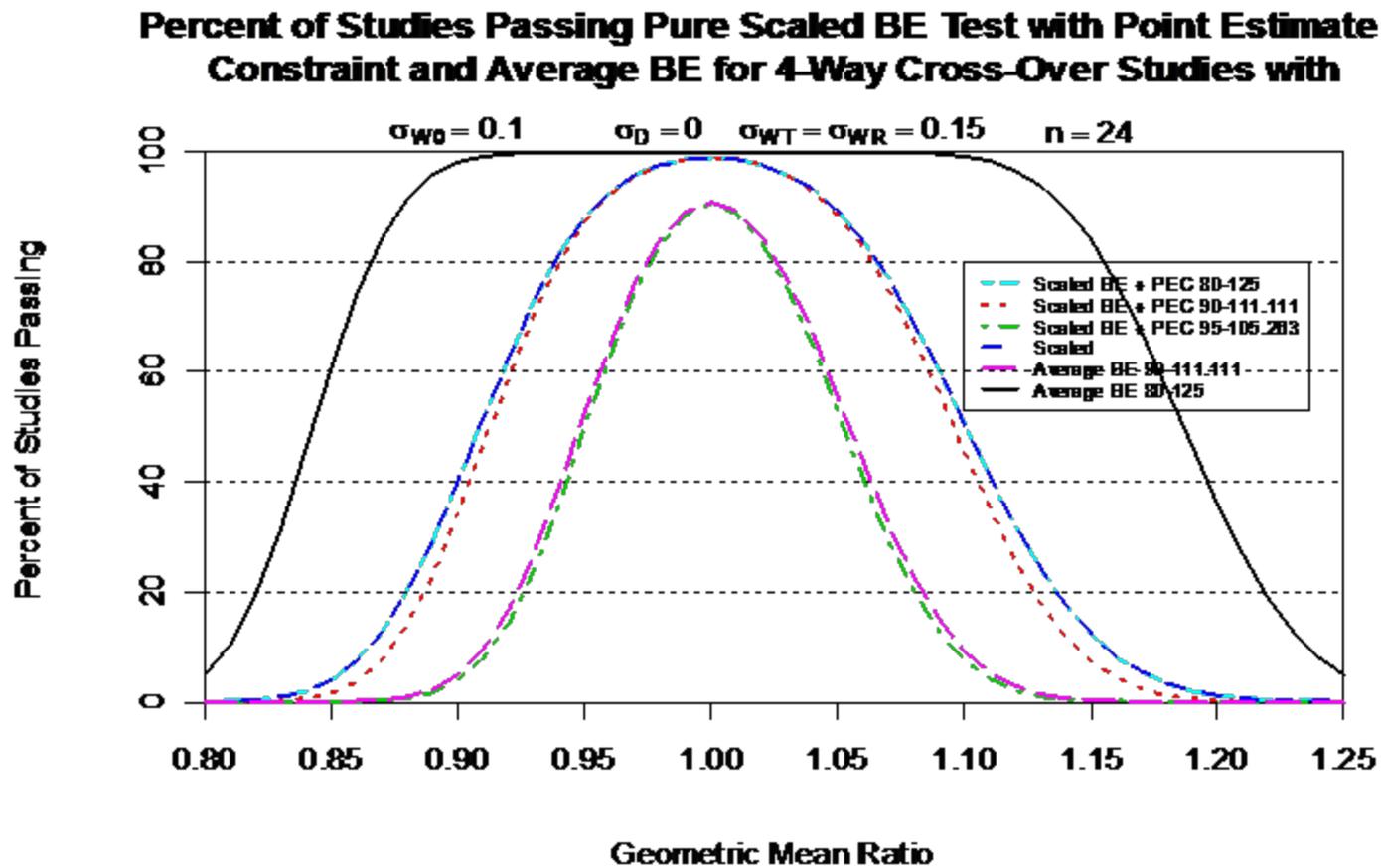


## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)



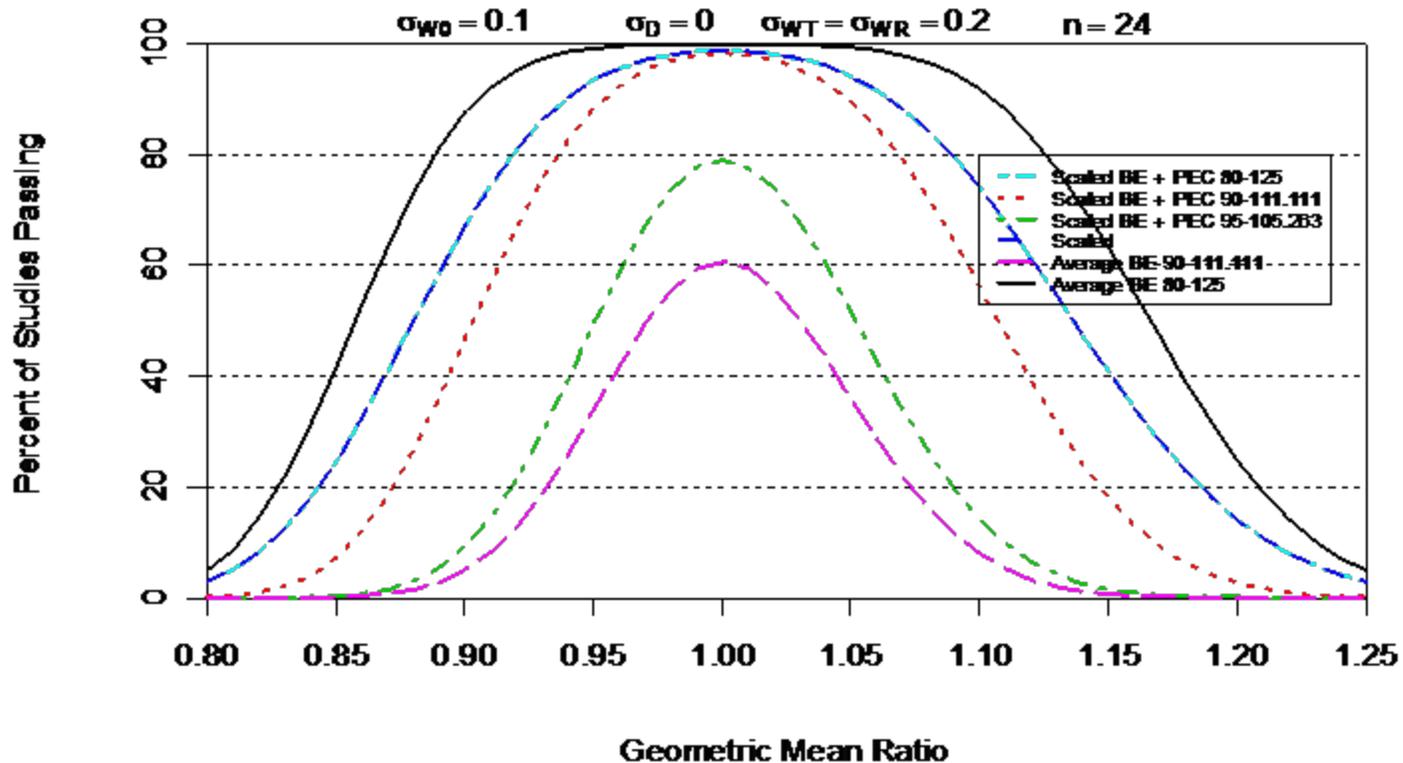


## Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)



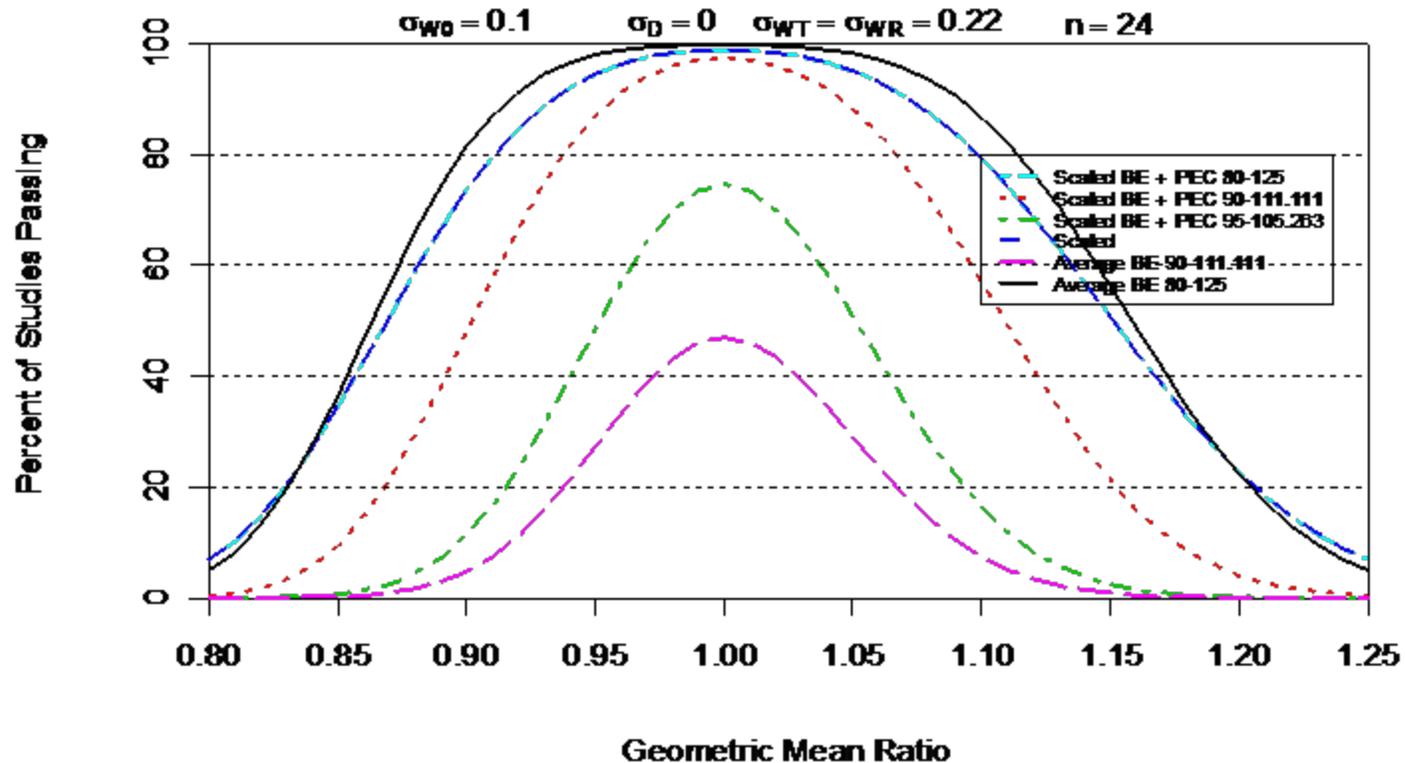
# Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**



# Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

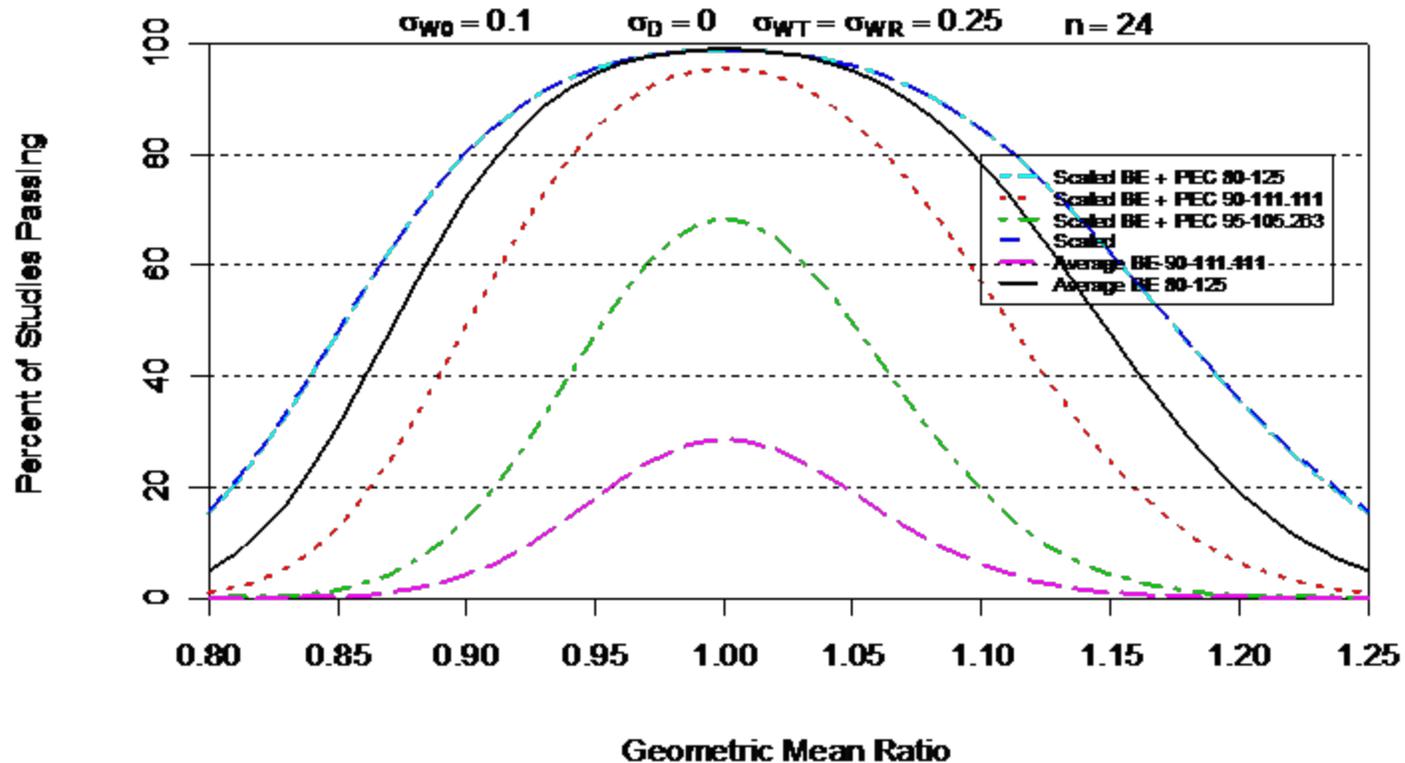
**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**





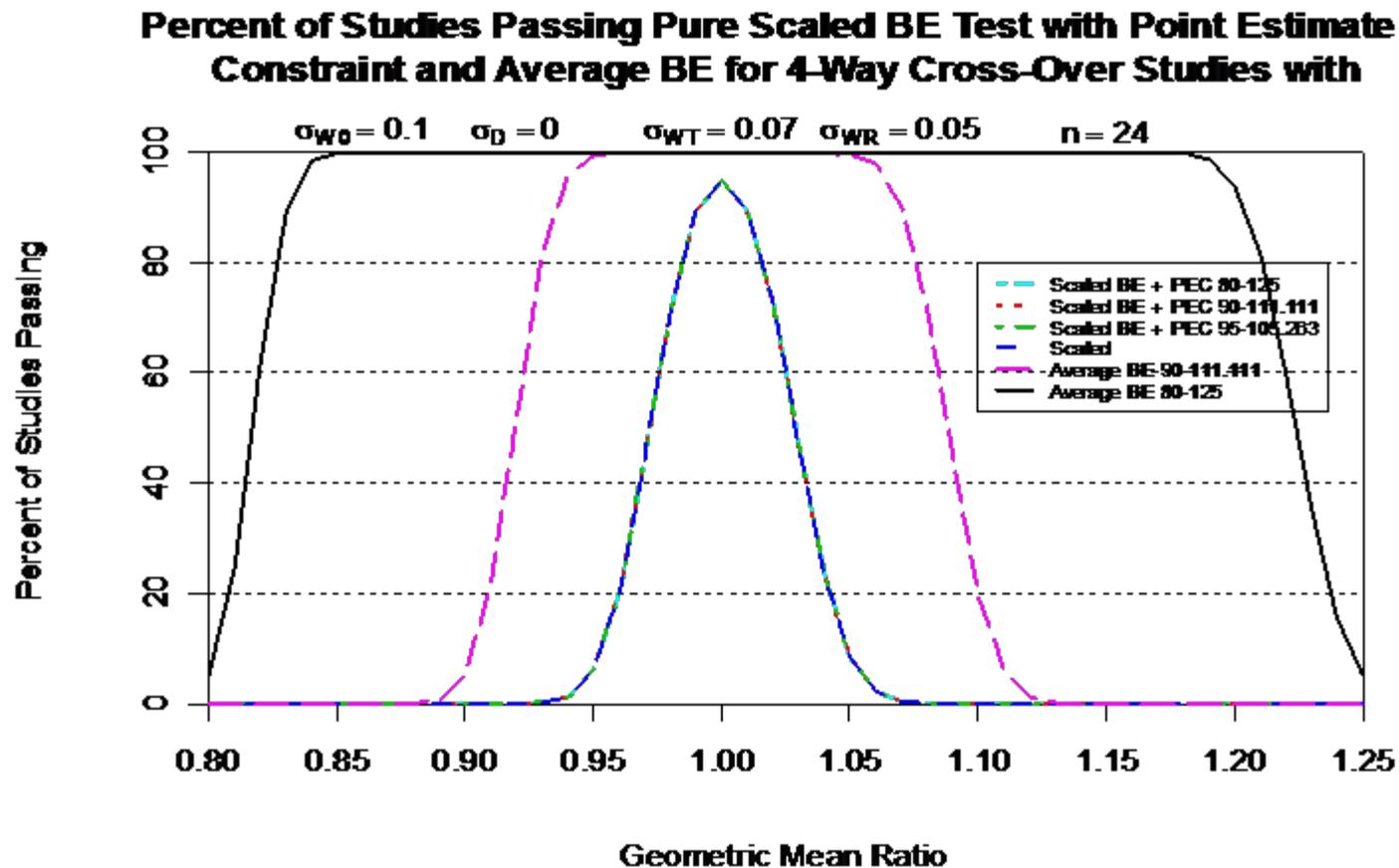
# Results for Case 3: $\sigma_{WT} = \sigma_{WR}$ , $n=24$ (cont'd.)

Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with



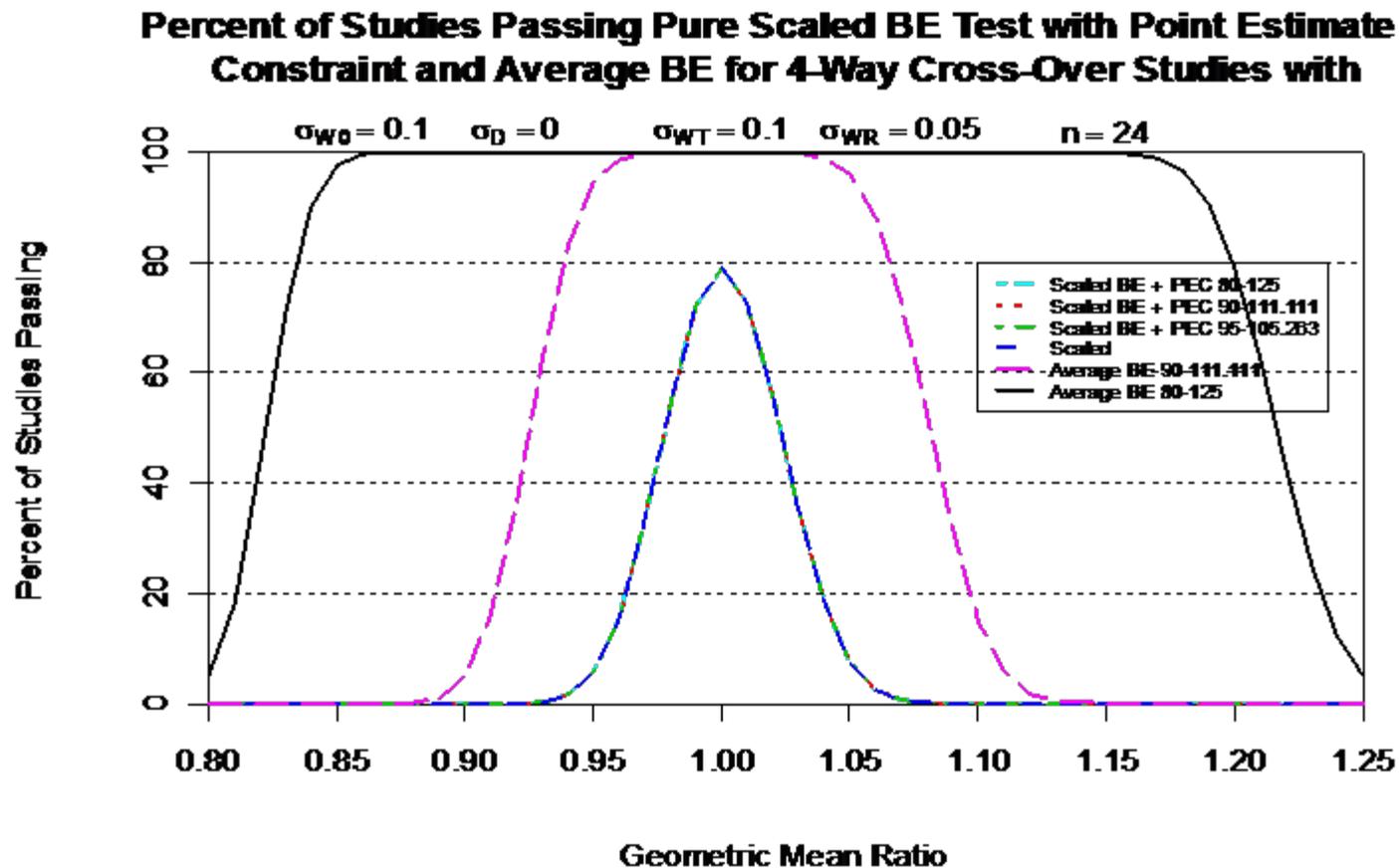


## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

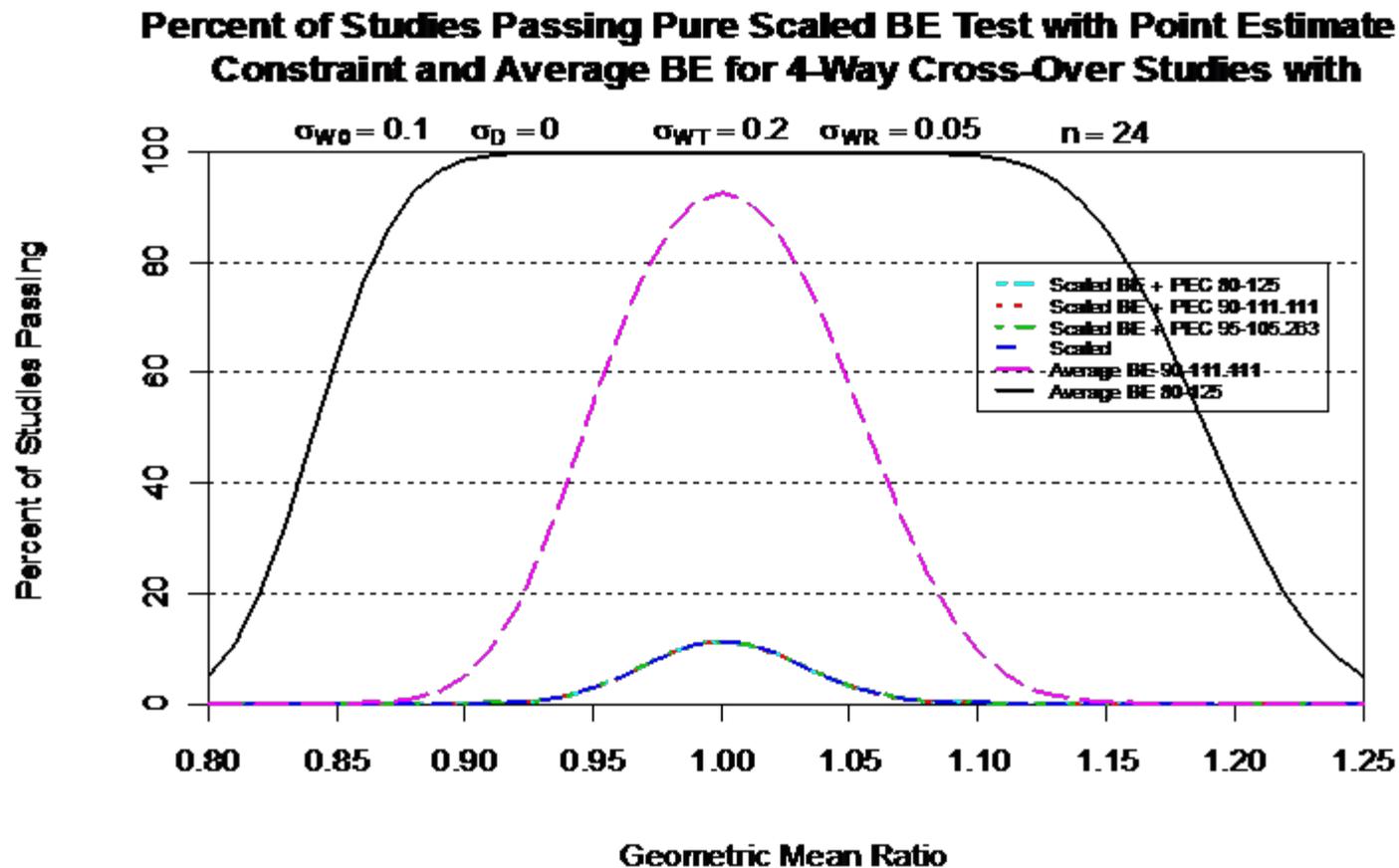




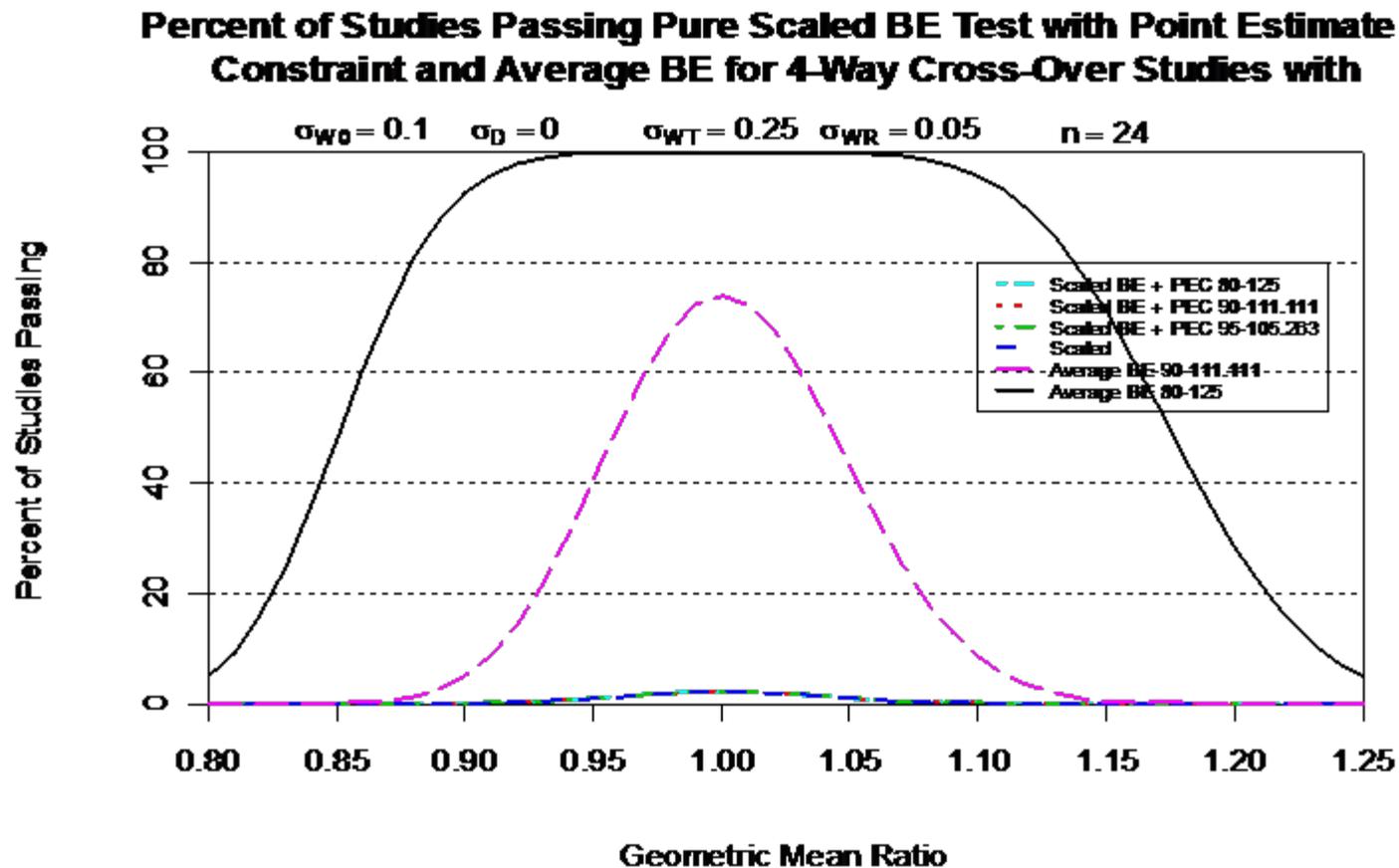
## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

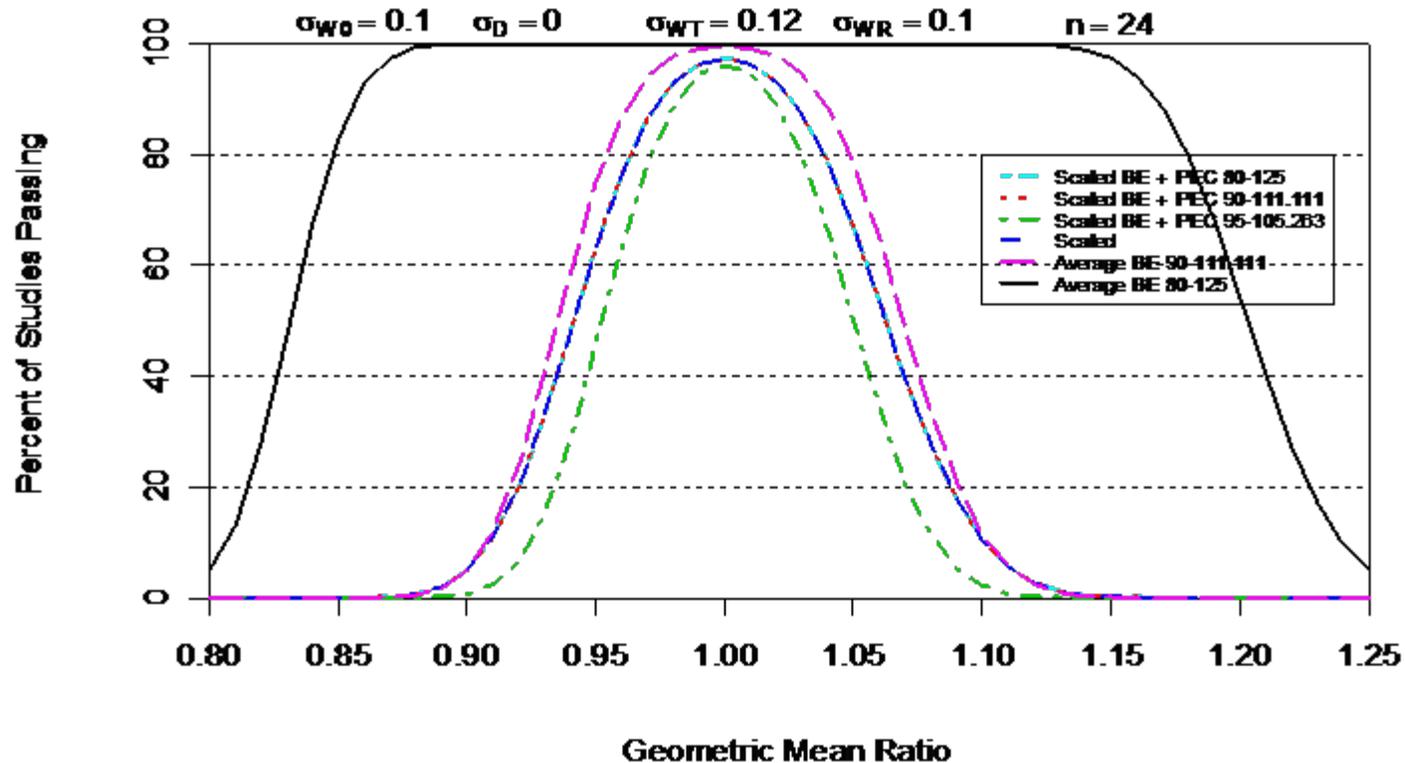


# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



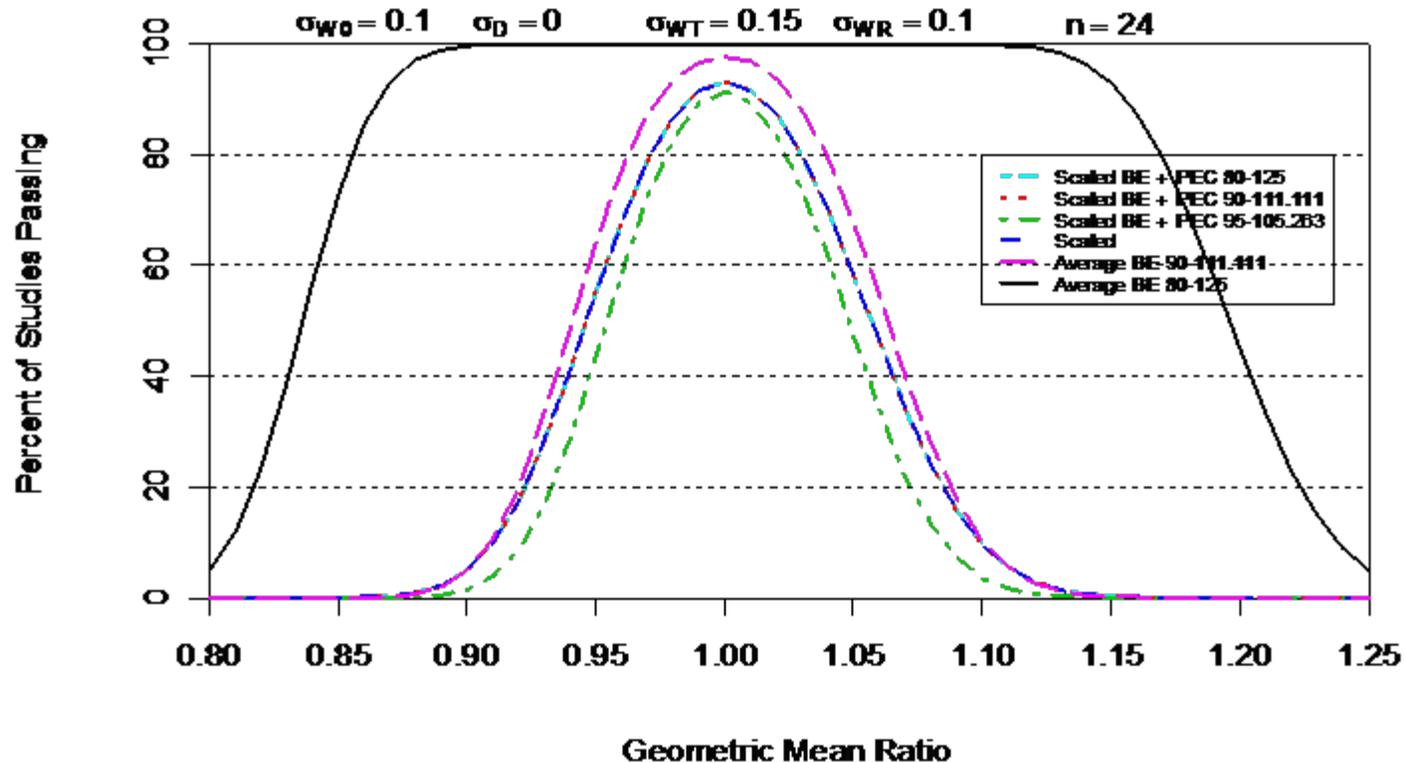
# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**



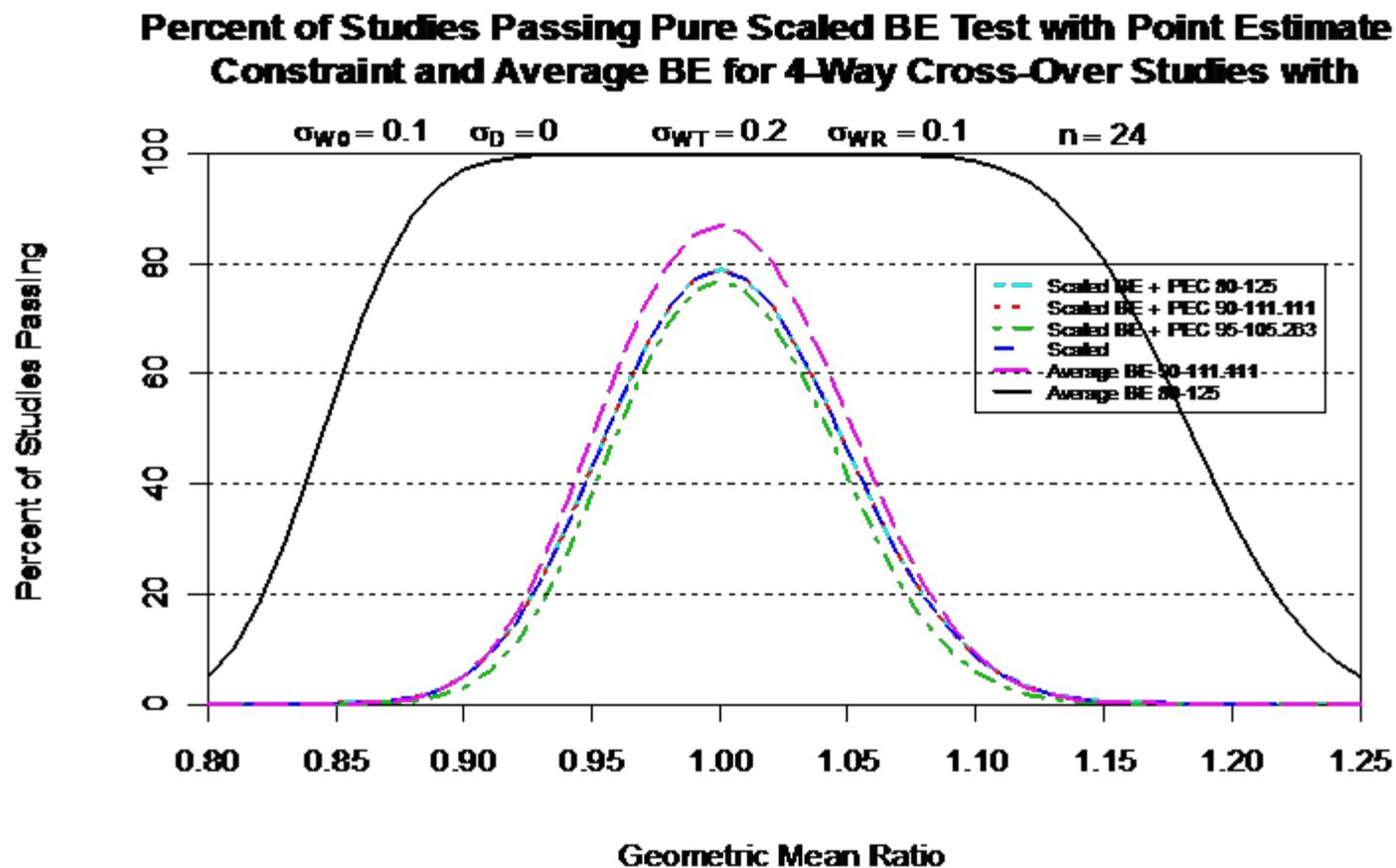
# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**



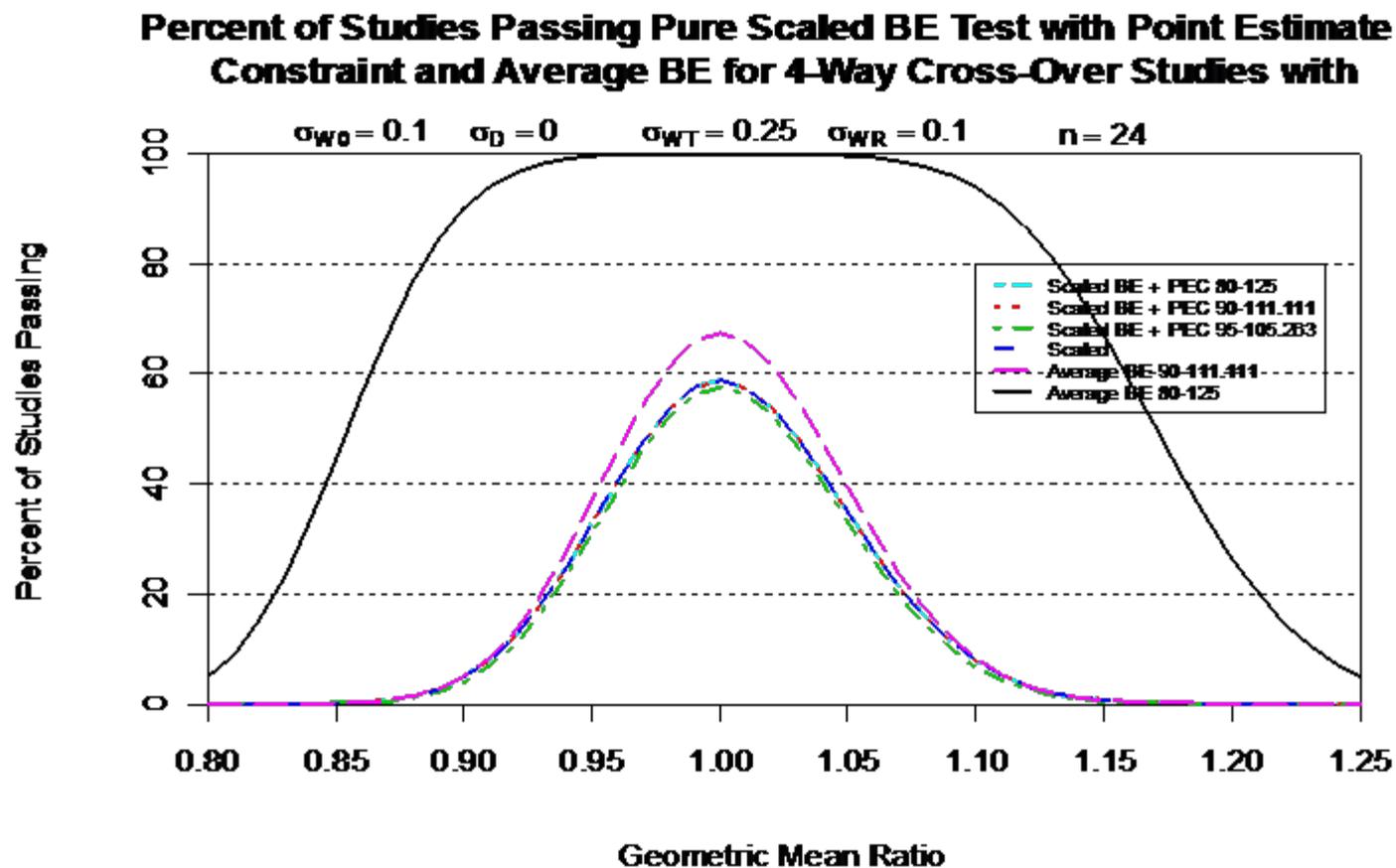


## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



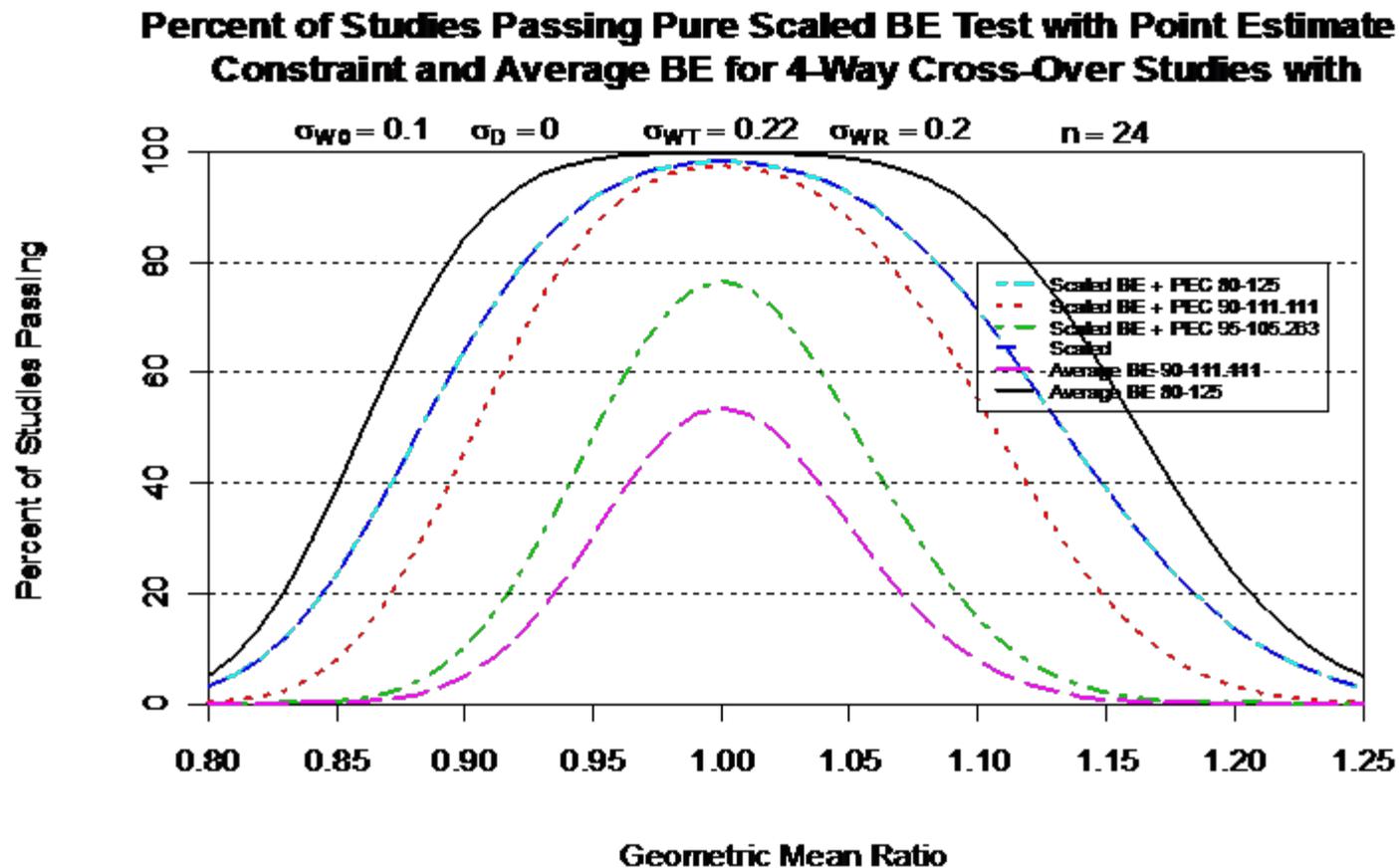


## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



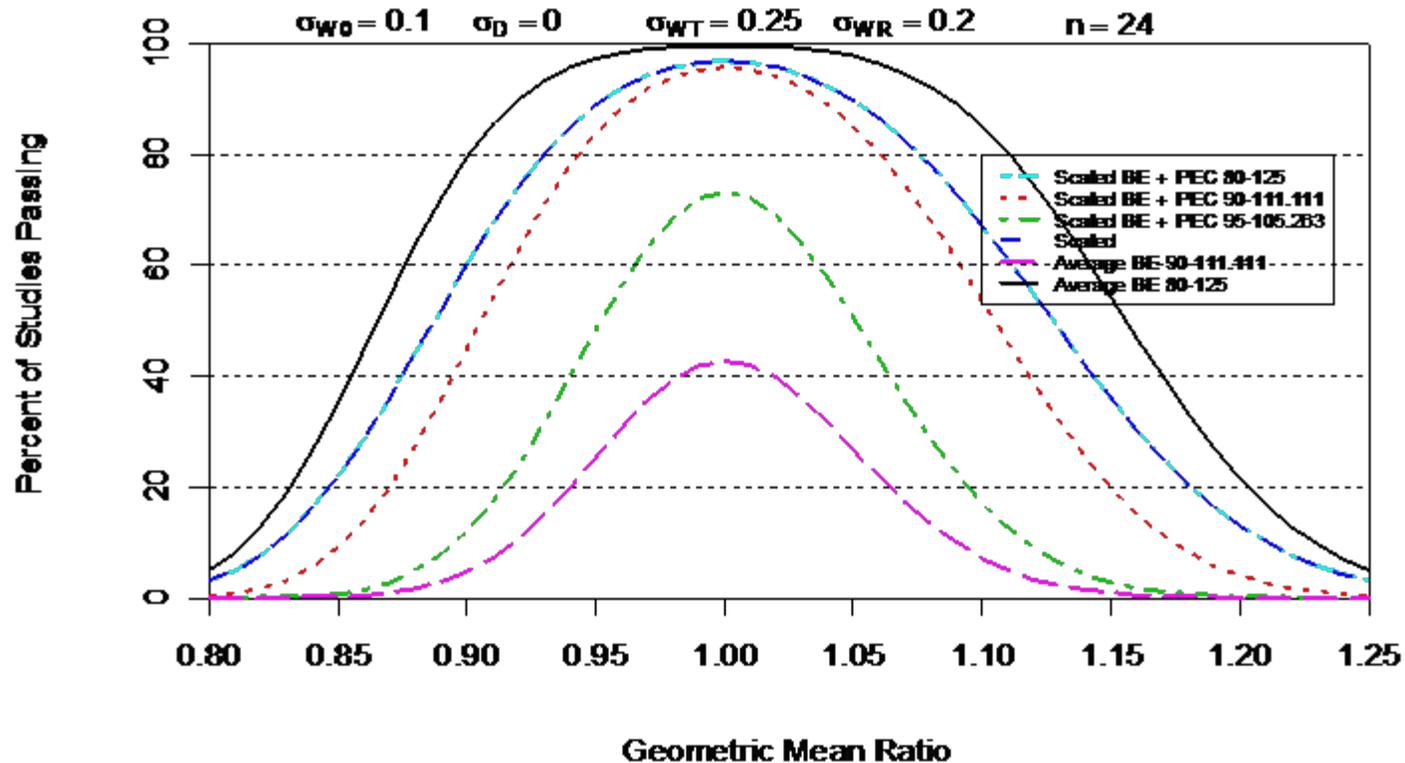


## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)



# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=24$ (cont'd.)

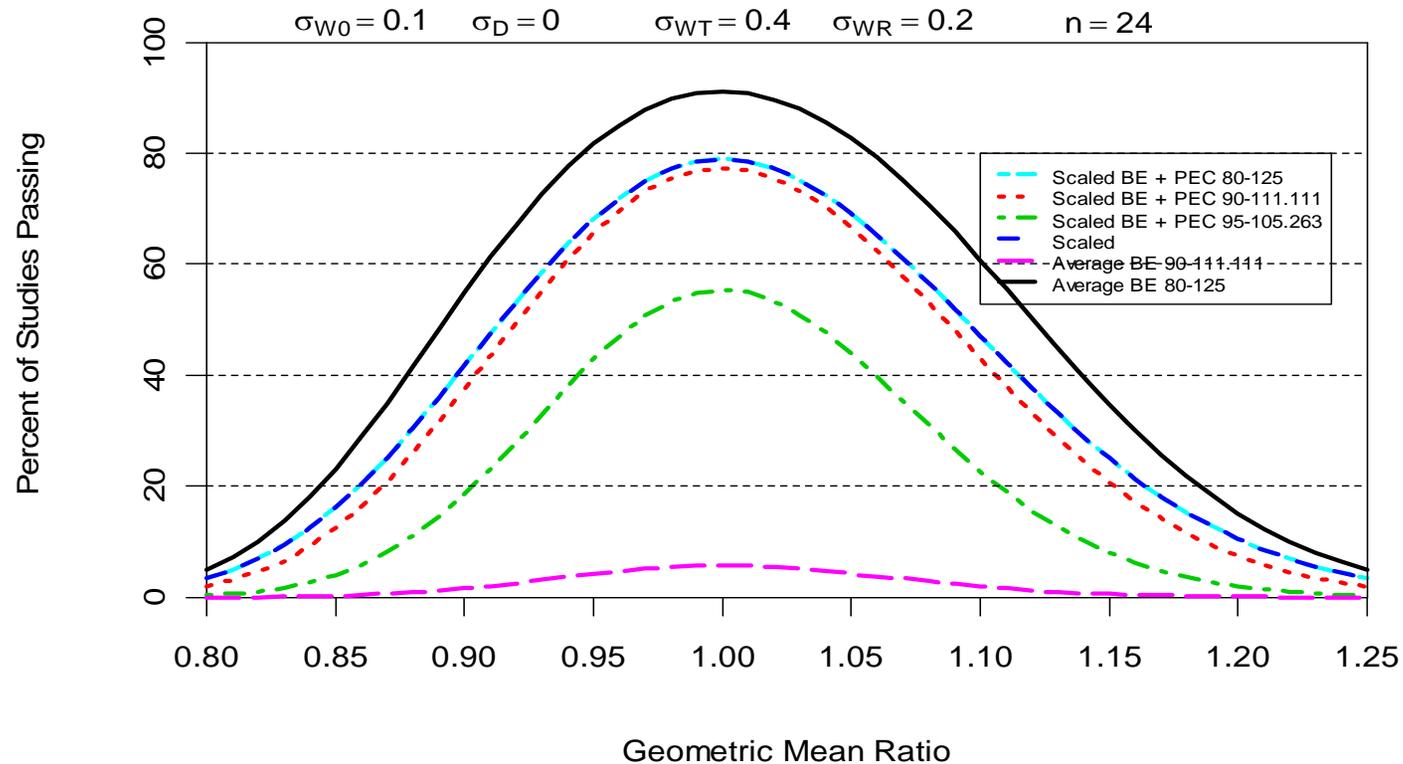
**Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with**





# Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , n=24 (cont'd.)

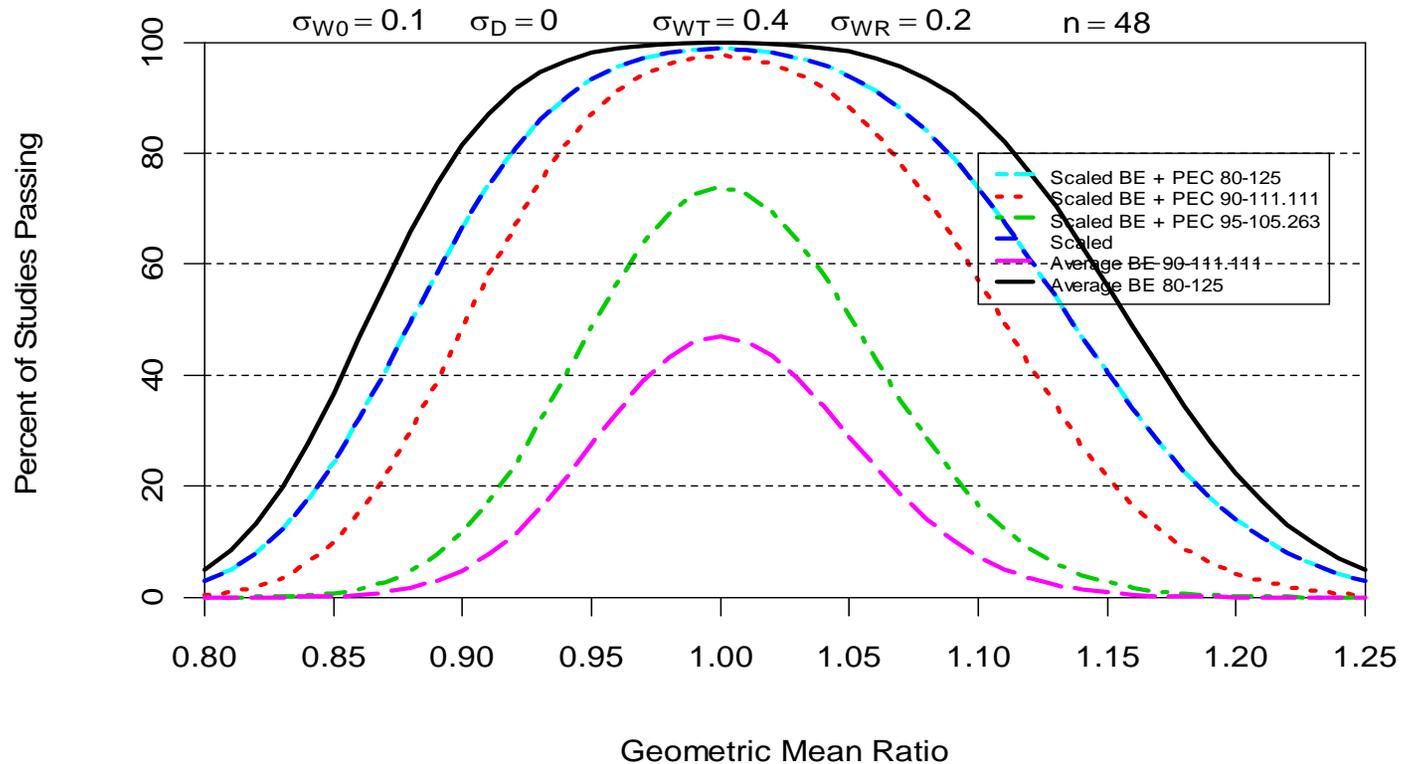
Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with





## Results for Case 3: $\sigma_{WT} > \sigma_{WR}$ , $n=48$

Percent of Studies Passing Pure Scaled BE Test with Point Estimate Constraint and Average BE for 4-Way Cross-Over Studies with



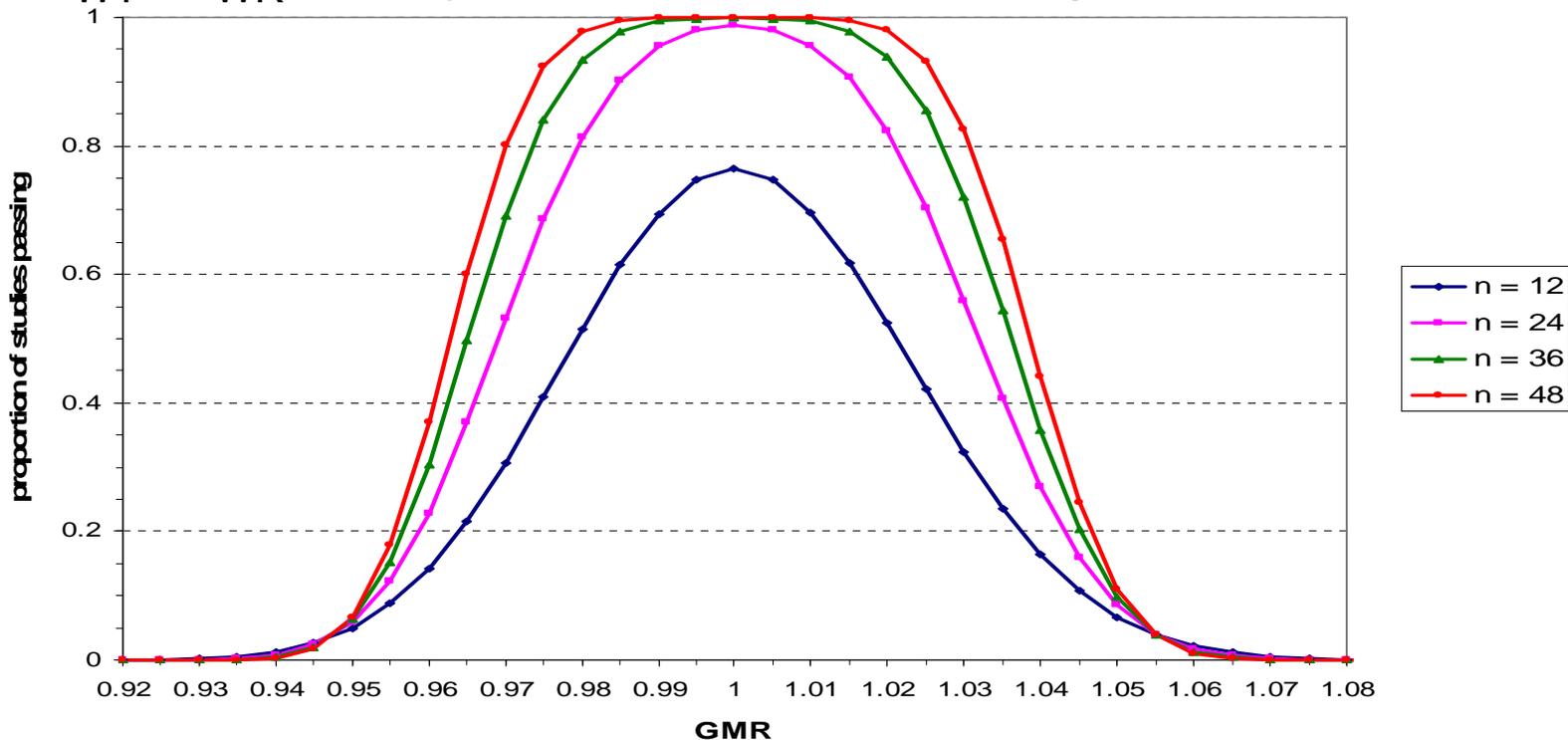


## Requiring the 90% Confidence Interval to Contain 1.0: Problematic

- Another proposal that has been considered is to require the usual 90% confidence interval for the GMR to contain the value 1.0.
- While I (DJS) understand the surface appeal of this requirement, it can have unintended consequences

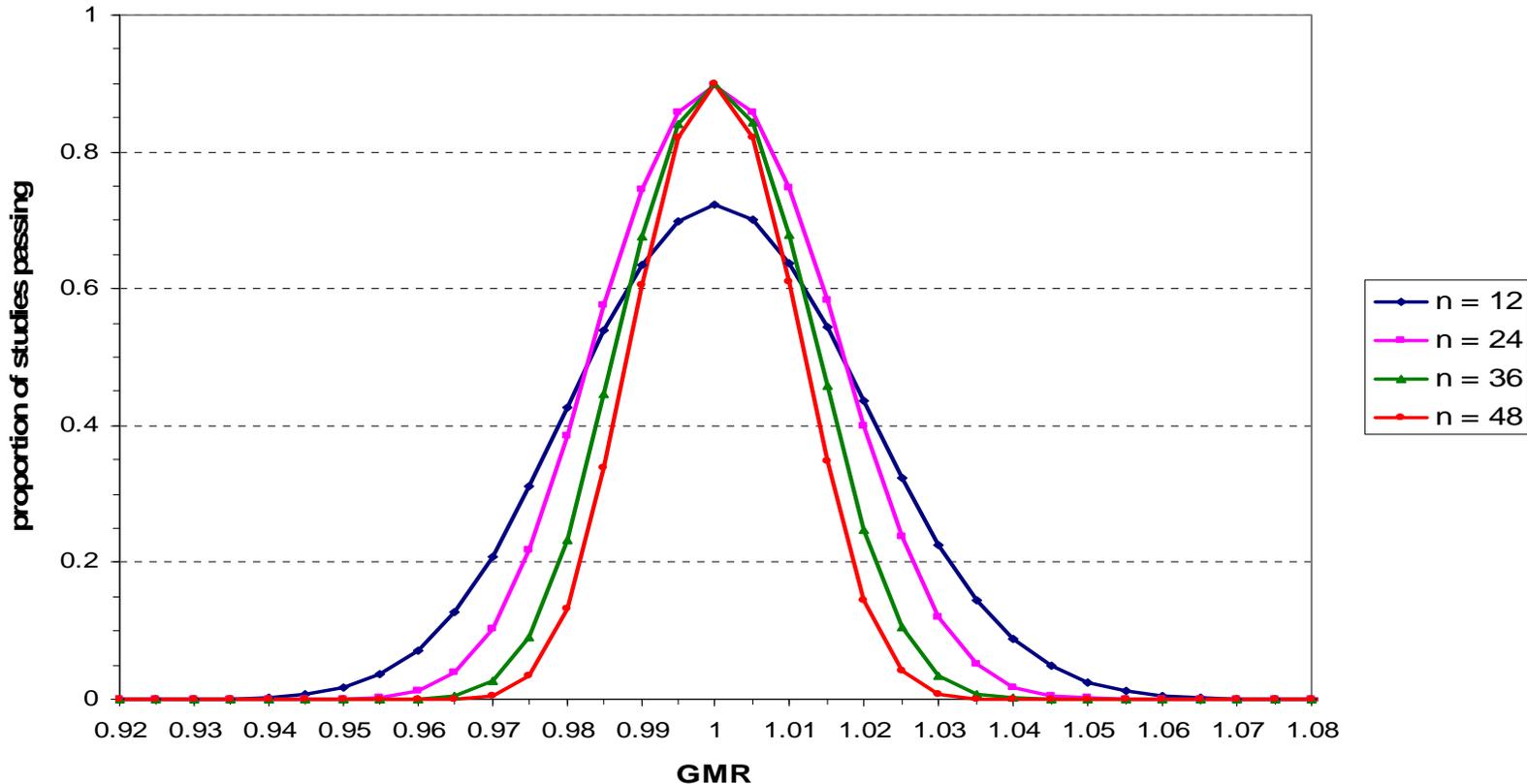
# Requiring the 90% Confidence Interval to Contain 1.0: Problematic (cont'd.)

- Here is an example of Scaled Average BE (Case 3,  $\sigma_{WT} = \sigma_{WR} = 0.05$ ) for four different sample sizes



# Requiring the 90% Confidence Interval to Contain 1.0: Problematic (cont'd.)

- Here is the same case, but with the added requirement that the 90% confidence interval contain 1.0



## Requiring the 90% Confidence Interval to Contain 1.0: Problematic (cont'd.)

- In this example, even for GMR very close to 1.0 (e.g. 0.98 – closer than required by potency testing), the higher the sample size, the **lower** the chance of passing the test. Generic product sponsors would have a *disincentive* to study more subjects.
- Also, even if the  $GMR = 1.0$ , no matter how great the sample size the chance of passing never exceeds 0.90, since there is always that 10% chance that the 90% confidence interval will not contain the true value of 1.0.
- In my (DJS) personal opinion, this requirement is a bad idea.

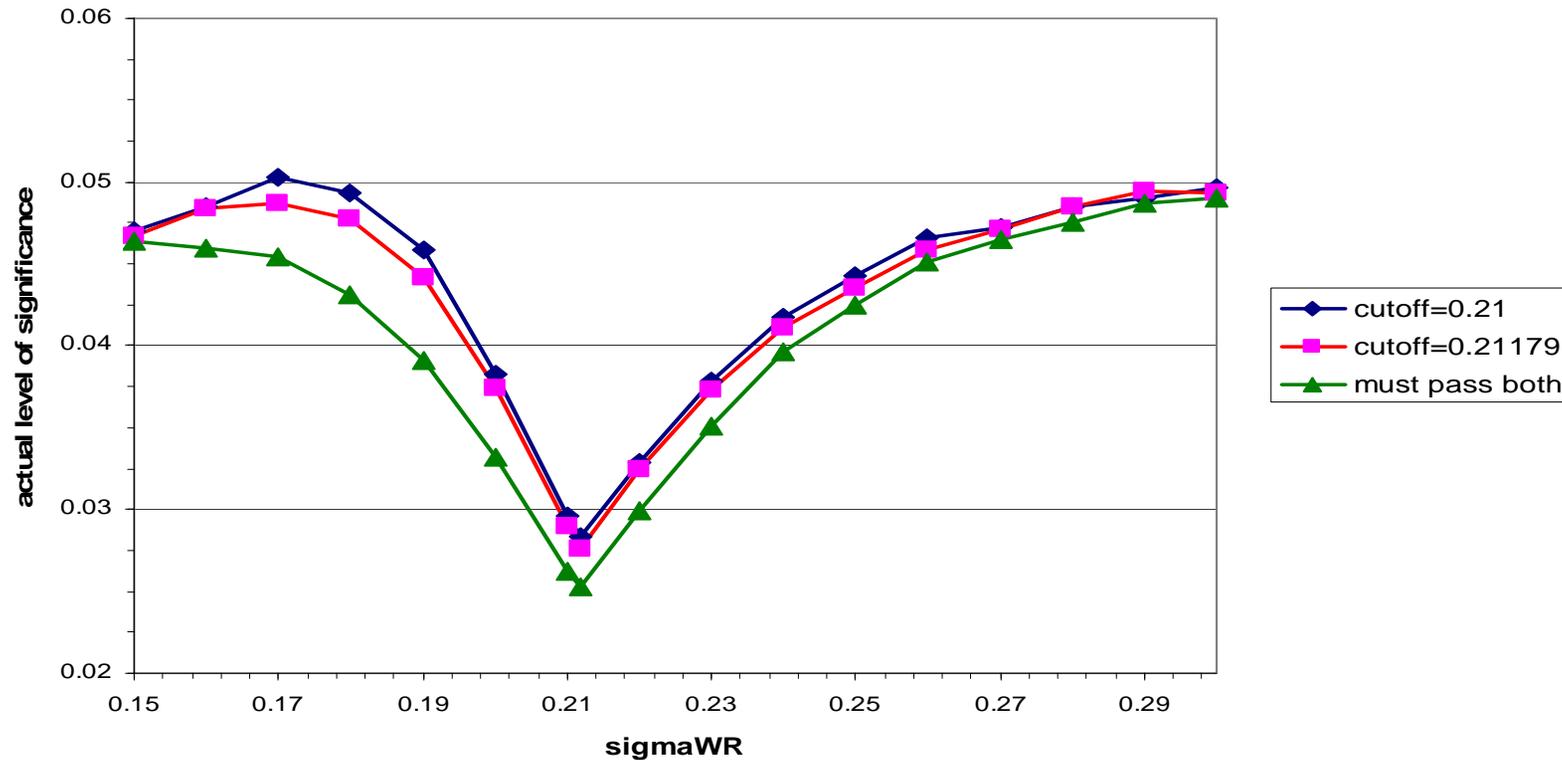
## Ensuring that the BE Limits are Never Wider than 80-125%

- One concern with Scaled Average BE is that the estimate of  $\sigma_{WR}$  from a particular study might be high, and we would be using BE limits wider than 80-125%.
- There are two ways to prevent this.
  - Establish a cutoff value on  $s_{WR}$ , the *estimate* of  $\sigma_{WR}$ , and switch to regular unscaled BE with limits of 80-125% for studies where  $s_{WR}$  exceeds the cutoff. For Case 3, a reasonable cutoff would be  $s_{WR} = 0.21179$ , or possibly 0.21.
  - Use “Must Pass Both” – require every study to pass the criteria we propose (e.g. scaled average BE, possibly with a PEC) and *also* pass regular unscaled BE with limits of 80-125%.



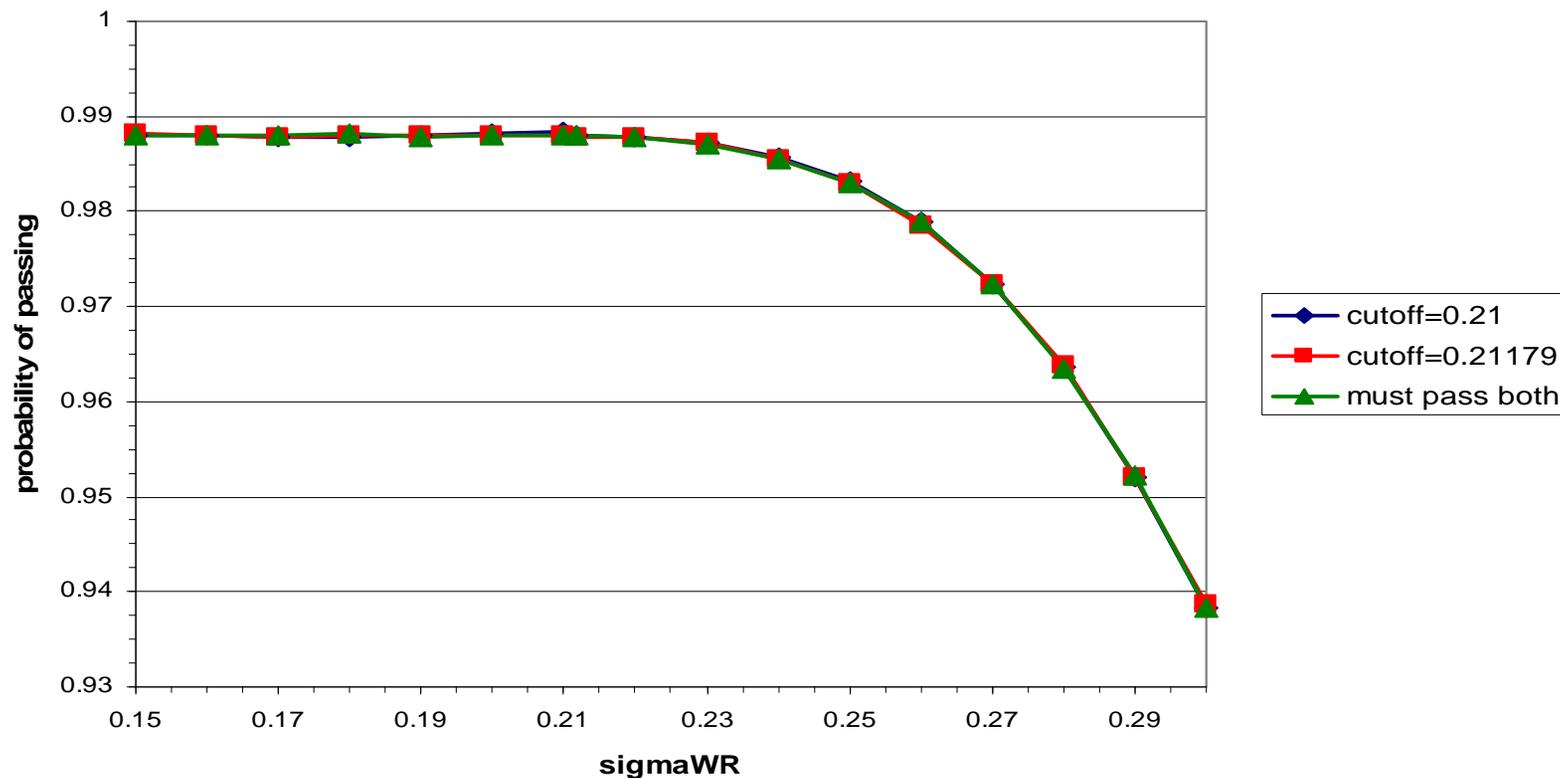
# Ensuring that the BE Limits are Never Wider than 80-125%

- Both of these methods preserve the actual level of significance at no more than 5%



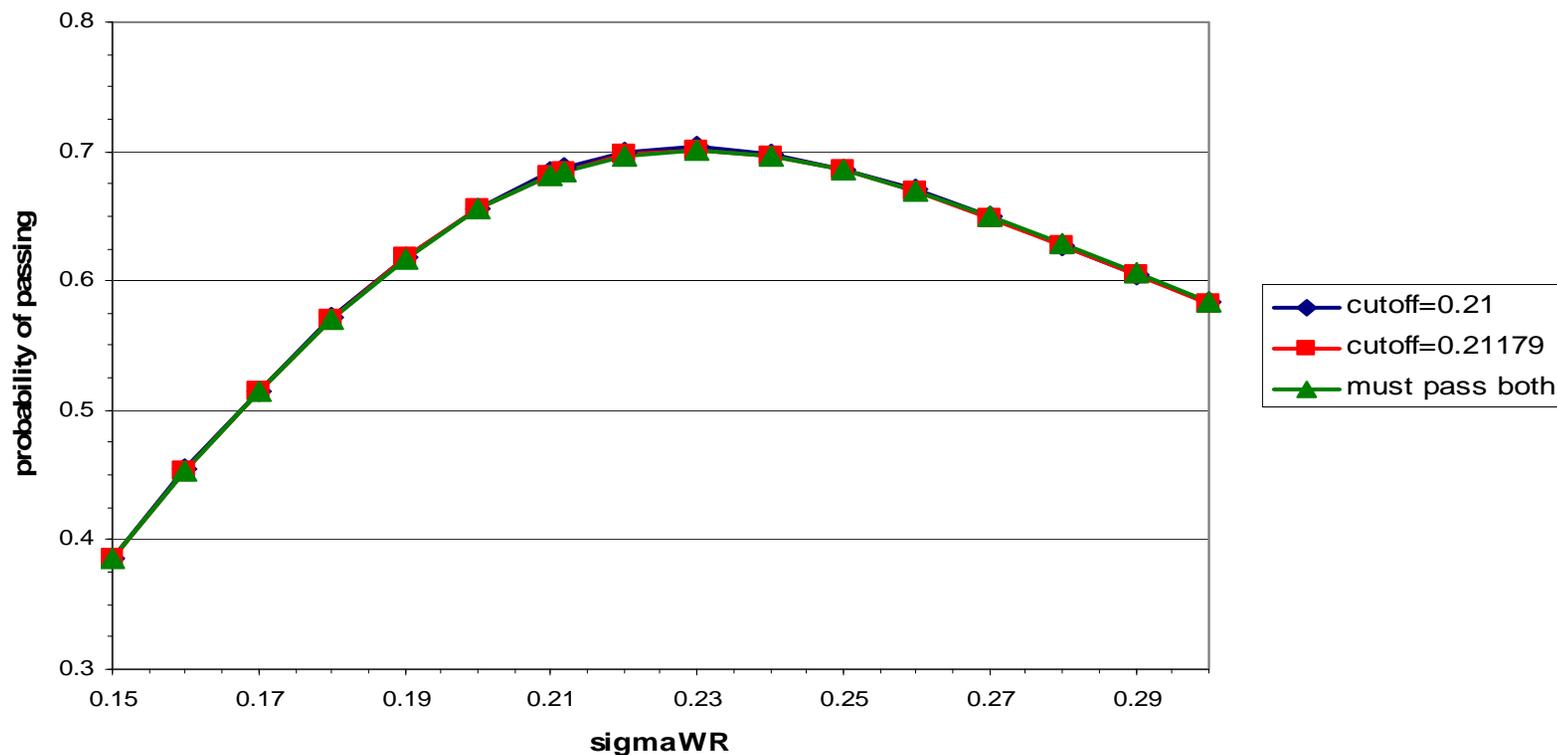
# Ensuring that the BE Limits are Never Wider than 80-125%

- When GMR = 1.0, there is almost no difference in power for the two approaches



# Ensuring that the BE Limits are Never Wider than 80-125%

- When  $GMR = 0.90$ , there is also almost no difference in power for the two approaches





# Pharmaceutical Quality of Narrow Therapeutic Index (NTI) Drug Products

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology  
July 26, 2011*

**Wenlei Jiang, Ph.D.**  
**Office of Generic Drugs**

# Background

- At the conclusion of the April 2010 ACPS meeting on NTI drugs, the committee voted 11-2 that the current bioequivalence standards are not sufficient for NTI drugs. 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)



# Objectives

- Evaluate pharmaceutical quality of approved NTI drug products
- Assess whether some pharmaceutical quality standards should be strengthened for NTI drug products

# NTI Pharmaceutical Quality Survey

- NTI product formulation design and manufacturing process
- NTI product specification tests, analytical methods and acceptance criteria (e.g. potency, dissolution, impurity)
- NTI product batch release and stability data
- Drug product recall data submitted to FDA (Jan 1<sup>st</sup>, 2000 - May 3<sup>rd</sup>, 2011)



## Selected Oral NTI Products for Survey

Drug Name	Currently Available Oral Dosage Forms	Earliest Year Approved
Carbamazepine	Tablet, Chewable tablet, Extended Release (ER) tablet, ER capsule, Suspension	1968
Digoxin	Elixir, Tablet	1997
Levothyroxine	Tablet, Capsule	2000
Phenytoin	ER capsule, Chewable tablet, Suspension	1976
Theophylline	Solution, ER tablet, Sustained release (SR) capsule	1990
Wafarin	Tablet	1954
Lithium	Tablet, Capsule, ER Tablet	1970

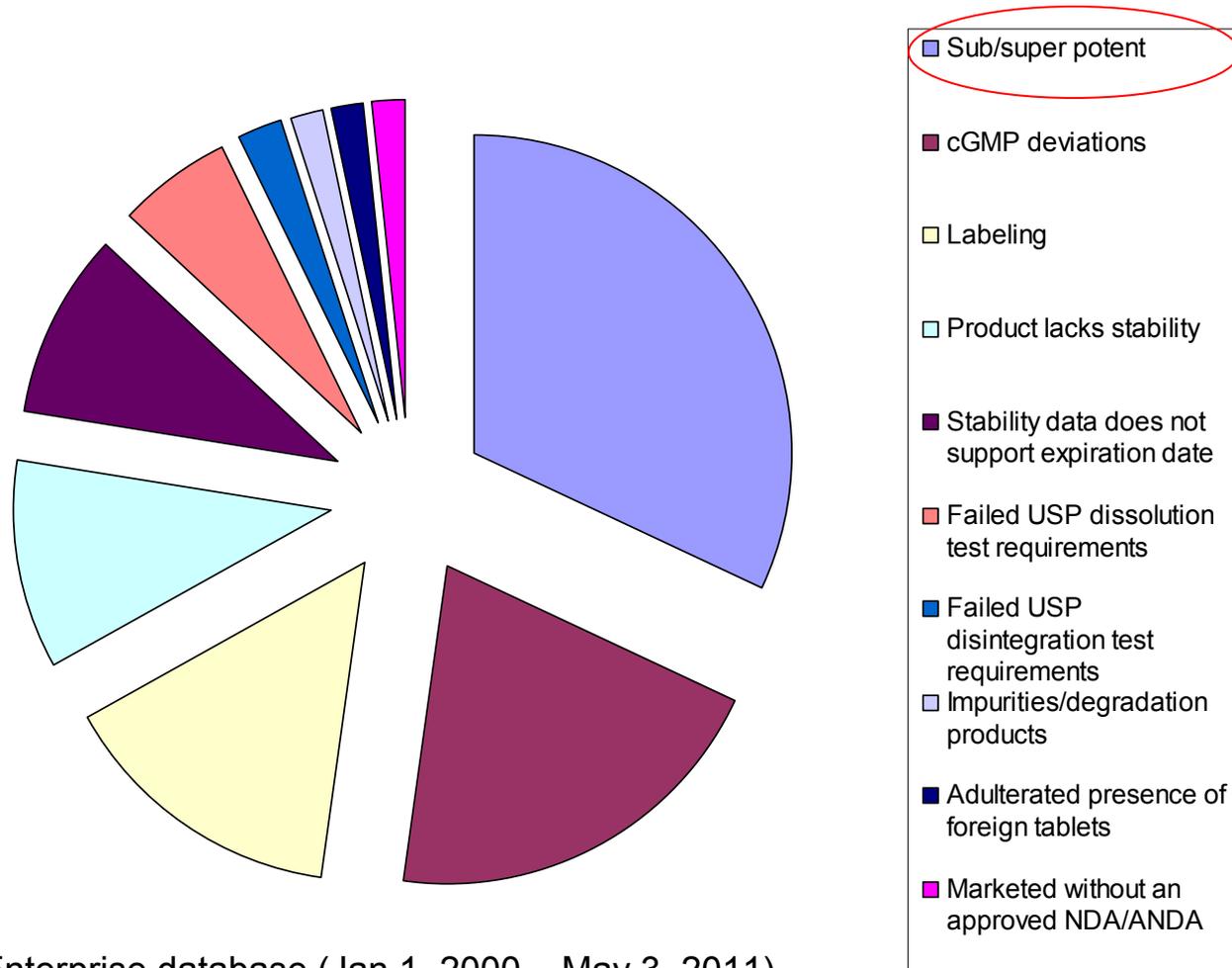
Over 80 approved and active applications

Not a comprehensive list of NTI drugs

# Quality Survey Observations

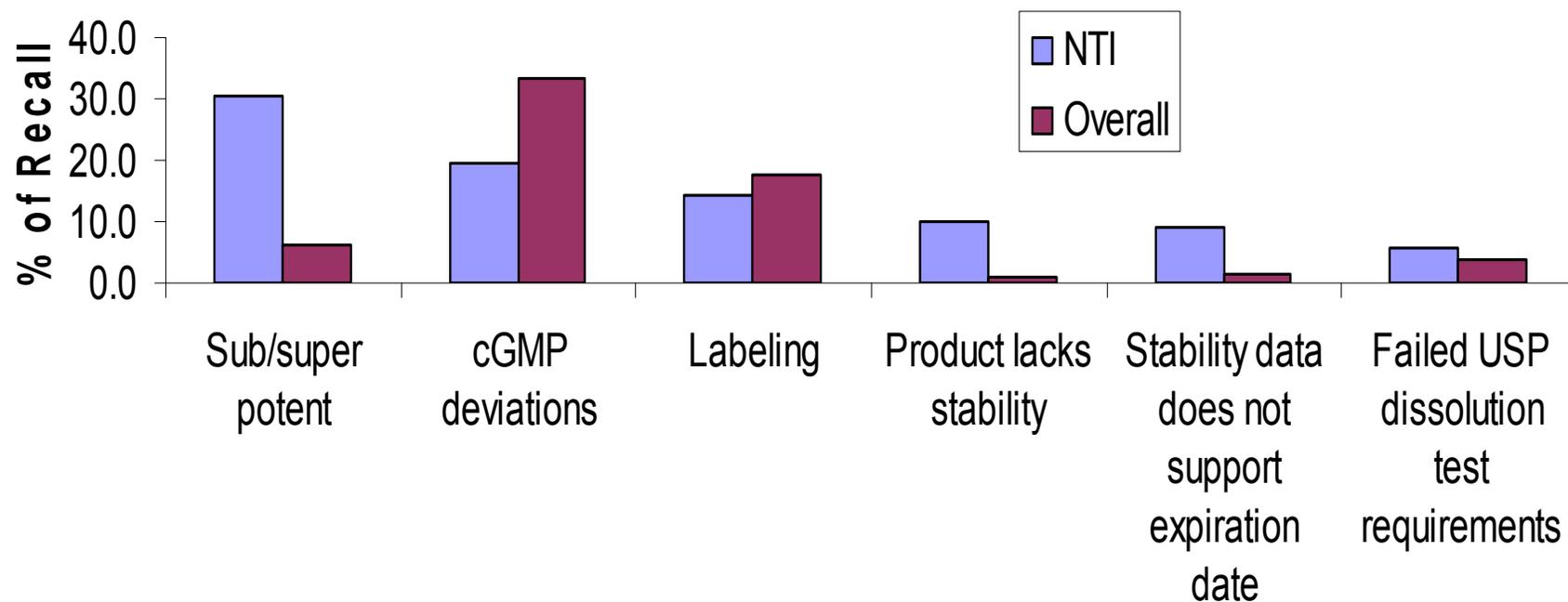
- Inactive ingredients
  - All below amounts in Inactive Ingredient Guide.
- Most surveyed NTI drug products are scored.
  - Dose strengths are as low as 0.013 mg. Some strengths are separated by  $\leq 10\%$  of drug dose.
- Manufacturing processes
  - Wet granulation process most common, followed by direct compression, and dry granulation.
- Comparable specification tests and acceptance criteria among ANDAs and NDAs
  - Assay
  - Dissolution
  - Impurities

# Top 10 Surveyed NTI Product Recall Categories Related to Pharmaceutical Quality



Data from Recall Enterprise database (Jan 1, 2000 – May 3, 2011)

## Major Recall Rates of Surveyed NTI Compared with Overall Drugs



# Potency

- Potency expressed as the quantity of active ingredient per dosage unit.

e.g., percent labeled claim (e.g., 96%), or amount of active ingredient per dosage unit (e.g., 24 mcg per tablet)

- Potency determined by assay (chromatographic, chemical determination or biological assay)

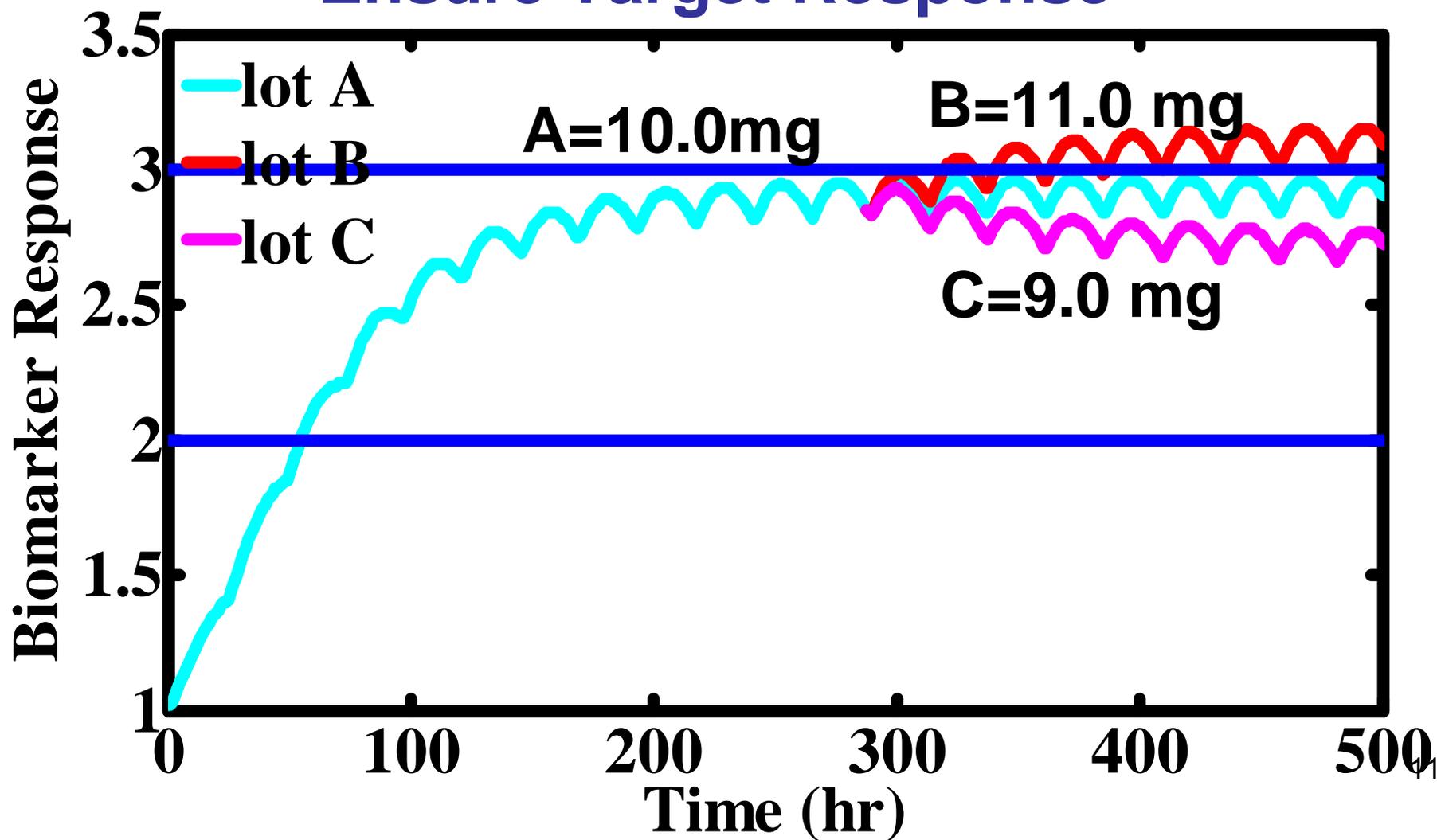


# Variable Pharmacopeia Assay Standards for NTI Drug Products

<b>Drug products</b>	<b>Assay USP limits</b>	<b>Assay BP limits</b>
NTI drug A Tablet	92.0-108.0%	95.0-105.0%
NTI drug A chewable tablet	93.0-108.0%	-
NTI drug A Extended release tablet	90.0-110.0%	-
NTI drug A Extended release capsule	90.0-110.0%	-
NTI drug A Suspension	90.0-110.0%	-



## Assay Limits 90.0-110.0% Insufficient to Ensure Target Response



## **Assay Limits 90.0-110.0% Insufficient for NTI Drugs with Close Dose Strengths**

- Tablet strengths are separated by  $\leq 10\%$  of drug dose.
- If a tablet loses 10% potency, its drug content will overlap with that of a tablet at the next lower dose strength.



# Tighter BE Limits Require Narrower Assay Limits

<b>Drugs</b>	<b>Assumption</b>	<b>BE limits</b>	<b>Assay limits</b>
Non-NTI	20% variation in pharmacokinetics (PK) won't lead to clinically relevant difference	90% CI 80-125%	90.0-110.0%
NTI	10% or lower variation in PK won't lead to clinically relevant difference	Tighter	Tighter



## Proposal to Tighten Assay Limits

For all NTI drug products, the assay limit is proposed to be:

95.0 -105.0%

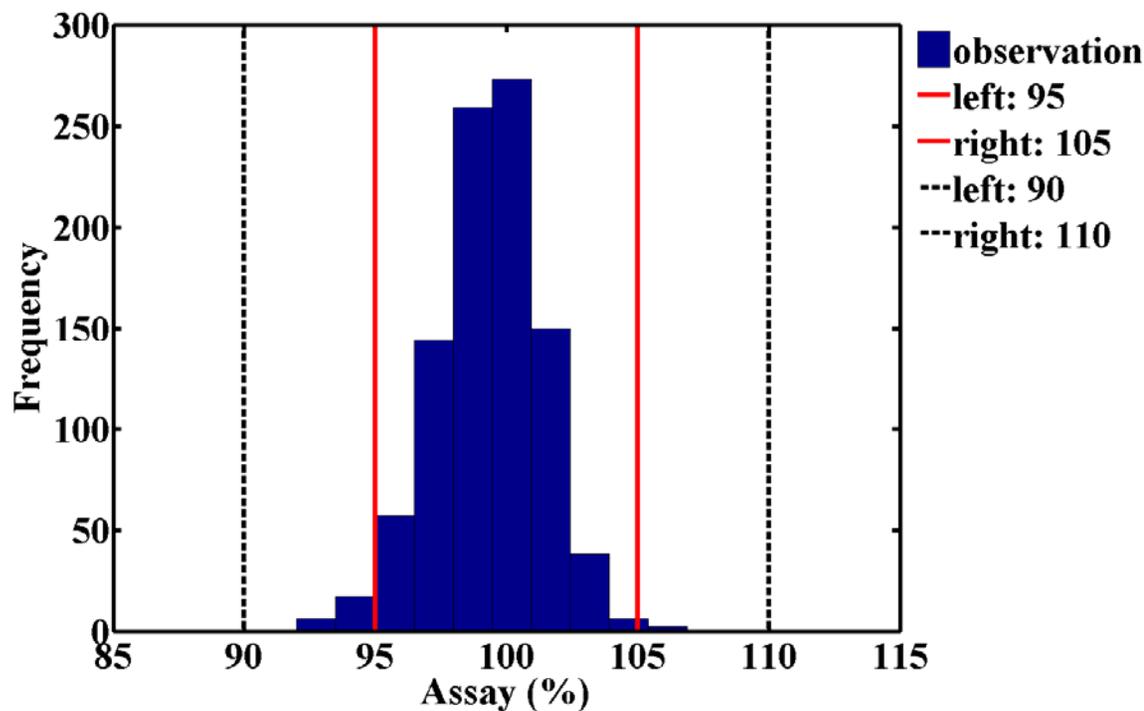
## Benefits of Tighter NTI Assay Limits

- Represent the expected clinical performance for NTI drugs
  - Small potency differences among lots, different manufacturers, and at different time during shelf life
- Consistent assay standards among different NTI drugs and dosage forms
- Prerequisite for meeting tighter bioequivalence limits

# NTI Product Quality Enhancement

- Tighter assay limits represent the expected clinical performance
- Testing against the tighter limits does not reduce the underlying variability
  - Potency failures will still be observed on stability and in market
- Quality by Design(QbD) approaches to reduce potency variability
  - Design formulation and manufacturing process
  - Monitor and update manufacturing process  
so that there is high probability to consistently provide the desired clinical performance

# Impact of Tighter Assay Limits on Approved NTIs



Average  $\pm$ SD: 99.3  $\pm$  2.2

## Conclusions

- Accurate drug dose is especially critical to NTI drug products. Drug potency issue is the No.1 reason for NTI drug product recall.
- Potential tightening of BE standards for NTI drugs necessitates tighter assay limits.
- Tightening NTI assay limits **and** utilizing QbD will have positive impacts on NTI drug product quality.



# Acknowledgements

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Kiet Nguyen

Bhawana Saluja

Feiyan Jin

Xinyuan Zhang

Lane Christensen

Robert Lionberger

Lawrence Yu



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

# **FDA Proposal for Bioequivalence of Generic Narrow Therapeutic Index Drugs**

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology*

*July 26, 2011*

**Barbara M. Davit, Ph.D., J.D., Acting Director  
Division of Bioequivalence 2, Office of Generic Drugs  
Center for Drug Evaluation and Research (CDER)  
United States Food and Drug Administration (US-FDA)**



# Outline

- Objectives of proposal
- Establishment of regulatory definition of narrow therapeutic index (NTI)
- Other regulatory agencies and NTI drugs
- Potency
- Study design
- Bioequivalence (BE) limits
- Summary and conclusions



***Objectives of proposing a new  
BE approach for generic narrow  
therapeutic index (NTI) drugs***



## Objectives of proposing a new BE approach for generic NTI drugs

- For NTI drugs, comparatively small differences in plasma concentrations may lead to serious therapeutic failures or adverse reactions
- Do we need to have a new BE approach that adds additional assurance of similarity of delivered doses and plasma concentrations following brand-generic or generic-generic switches?

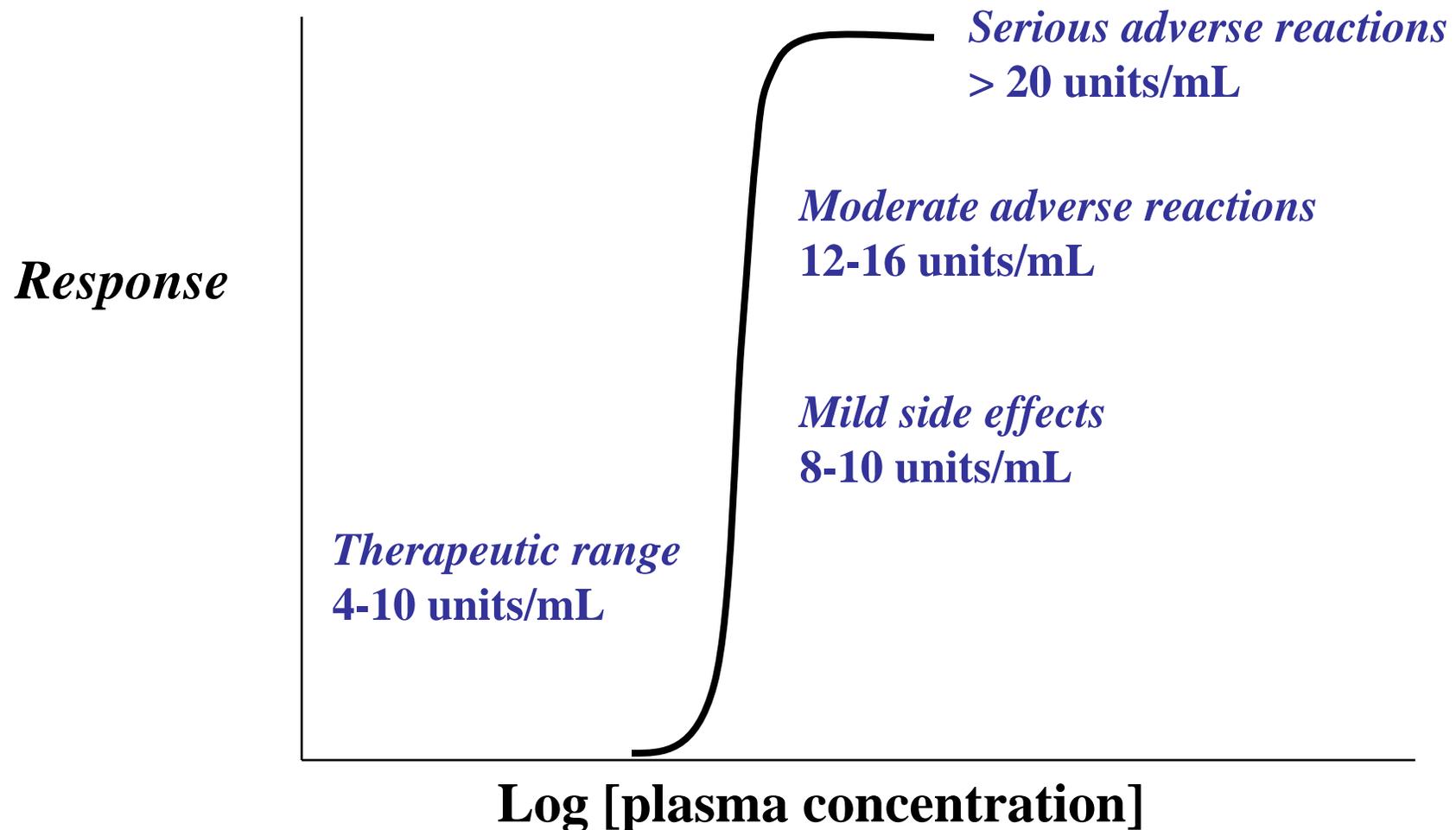


# ***Establishing a regulatory definition of NTI drugs***

## **Elements of proposed regulatory definition of NTI drugs**

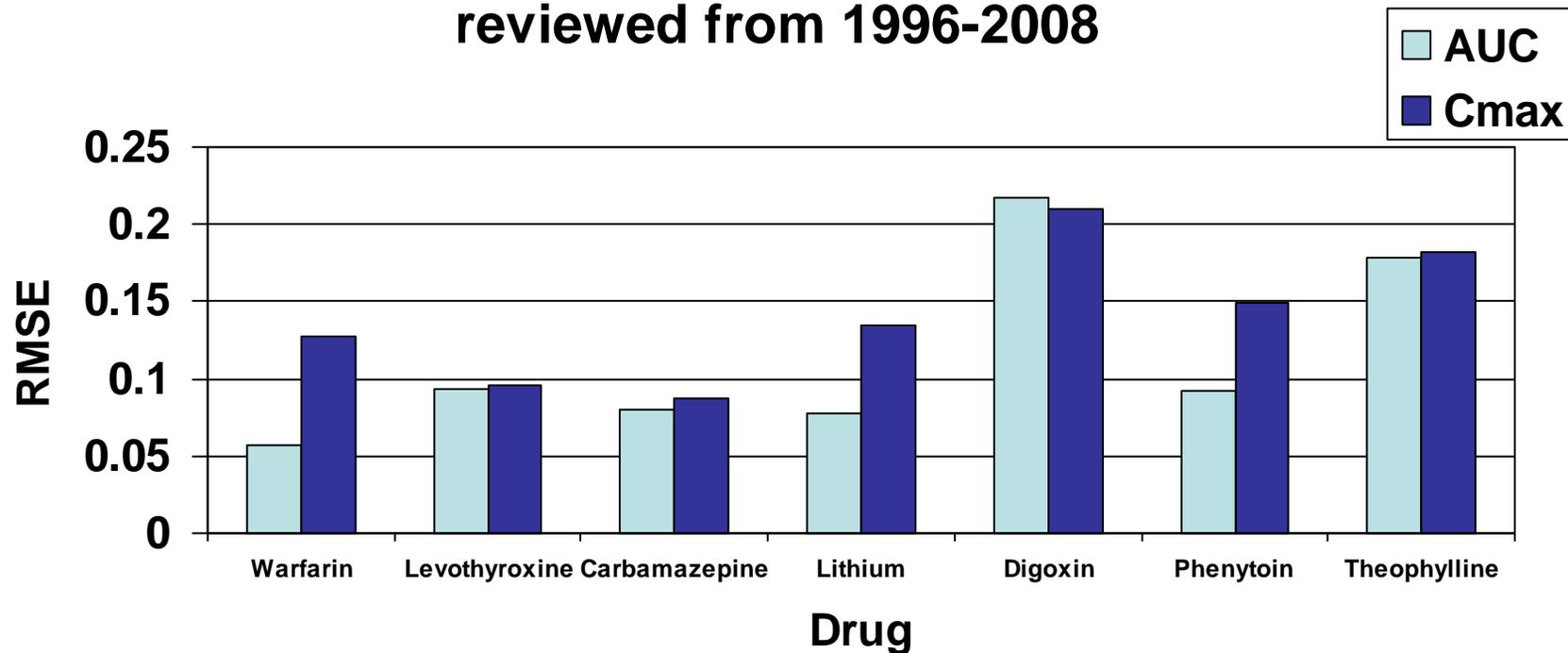
- Small differences in dose or plasma concentration may lead to serious therapeutic failures and/or adverse reactions;
- Serious events are persistent, irreversible, slowly reversible, and/or life-threatening;
- Steep dose-response curves;
- Subject to therapeutic drug monitoring;
- Small within-subject variability.

# NTI drugs have steep plasma concentration-response curves

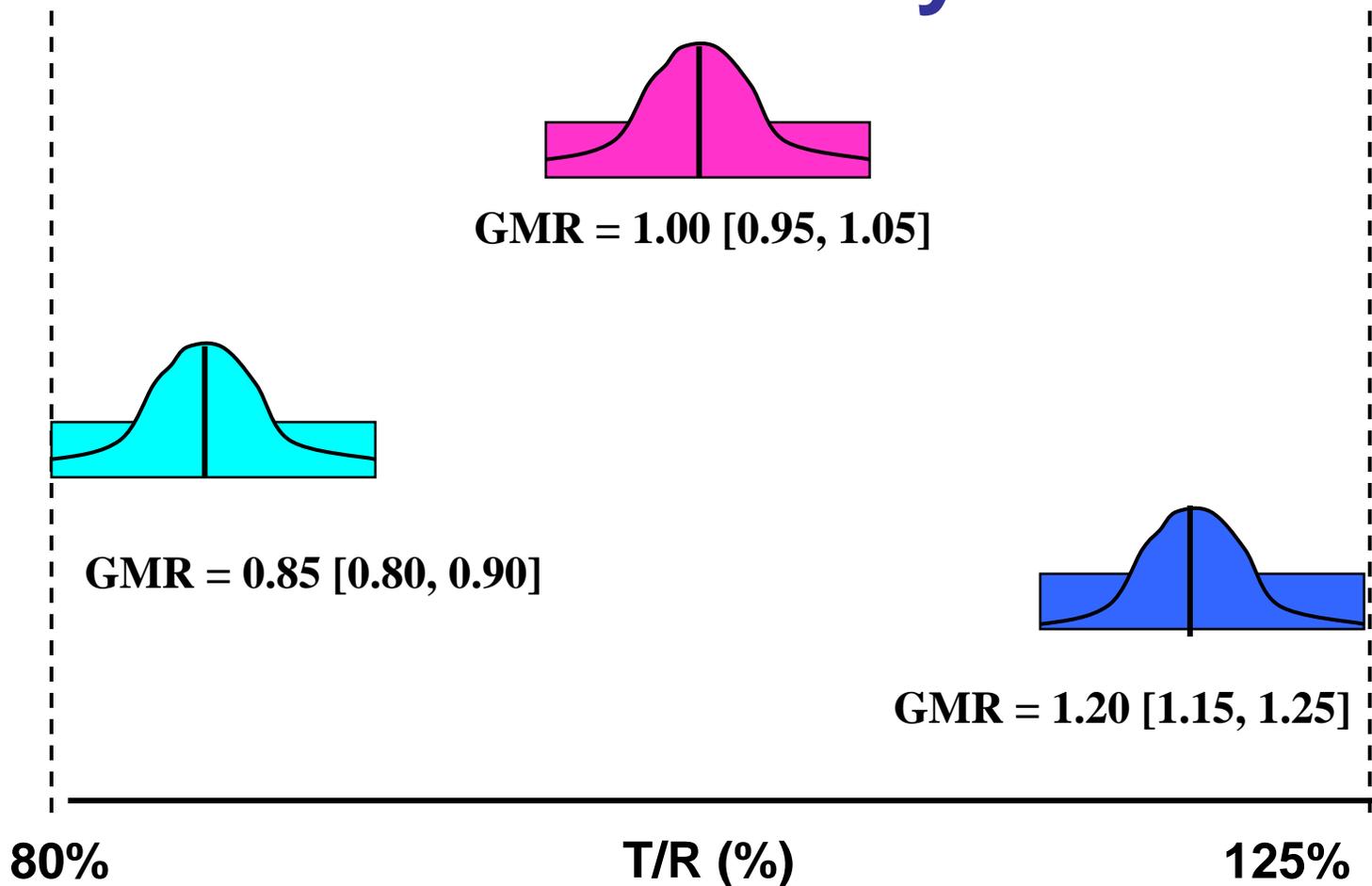


# NTI drugs generally have small within-subject variability

Average Root Mean Square Error values from 2-way BE studies of approved generic NTI drugs reviewed from 1996-2008



# Possible theoretical worst-case scenarios for BE study outcomes





***What do other regulatory agencies require in generic NTI drug submissions?***

## BE study acceptance criteria for generic NTI drugs

- European Union (EMA)
  - AUC: 90-111.11%
  - Cmax: 90-111.11% or 80-125%; case-by-case
- South Africa (MCC)
  - AUC and Cmax: 80-125%\*\*
  - Should not substitute generic NTI drugs unless patient adequately monitored during transition

\*\* For non-NTI drugs, BE limits for Cmax are 70-133%



## **BE study acceptance criteria for generic NTI drugs (cont'd)**

- Canada (Health Canada)
  - For “critical dose” drugs
  - AUC: 90-112%; C<sub>max</sub>: 80-125%
- Japan (NIHS) – AUC, C<sub>max</sub>: 80-125%
  - Compare in vitro dissolution profiles of lower strengths of test and reference products
  - If statistical tests show that test and reference dissolution profiles are not similar, then in vivo testing is necessary (no biowaiver)



# *Potency*



## 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



# ***Recommended BE study design for NTI drugs***



## 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***



## 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  $\leq 10\%$ , 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

# Reference-scaled ABE approach

- T and R are considered BE if

$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

- Where
  - $\mu_T$  and  $\mu_R$  are the means of the In-transformed pharmacokinetic (PK) endpoint;
  - $\sigma_{WR}$  is the within-subject standard deviation (SD) of the In-transformed PK endpoint of the reference

## Reference-scaled ABE (cont'd)

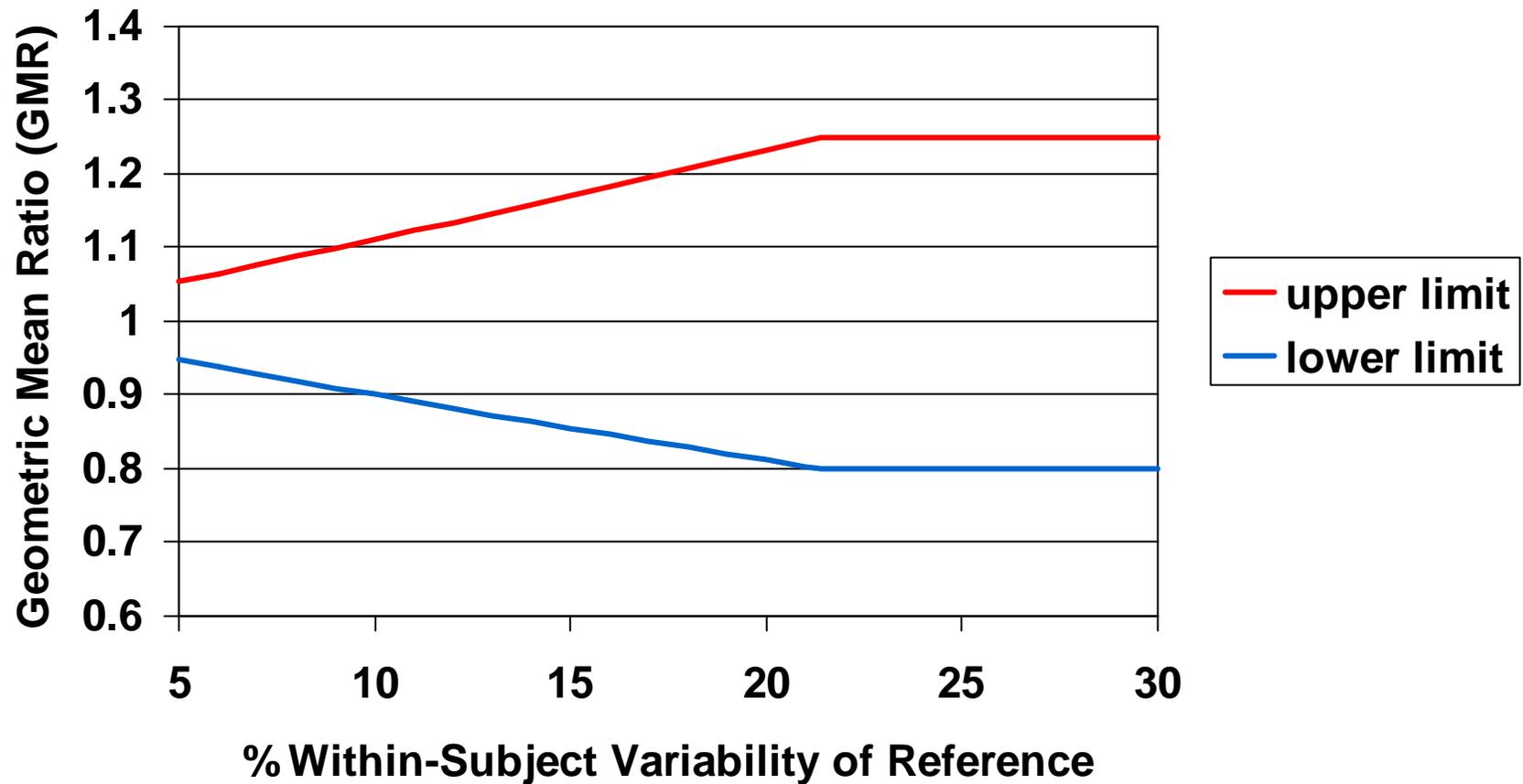
- The regulatory limit  $\theta$  is defined as

$$\theta \equiv \left( \frac{\ln(\Delta)}{\sigma_{W0}} \right)^2$$

- Where  $\sigma_{W0}$  is a regulatory constant
- $\Delta$  is the upper BE limit that applies when  $\sigma_{WR} = \sigma_{W0}$
- For NTI drugs, FDA proposes to set  $\sigma_{W0}$  as 0.10 and  $\Delta$  as 1.1111 (= 1.0/0.9)



## Implied BE limits on Geometric Mean (T/R) Ratios





# ***Summary and conclusions***



## Summary

- Applying a regulatory definition will permit classification of drugs which have a NTI
- Tightening potency specifications will reduce variation in delivered doses of NTI drugs upon brand-to-generic or generic-to-generic switches



## Summary (cont'd)

- Conducting 4-way fully replicated BE studies will permit comparison of test and reference AUC and C<sub>max</sub> variances to assure that these do not differ significantly
- Applying a reference-scaled ABE approach to analyze BE data from generic NTI drugs is more conservative and more appropriate to the PK characteristics of each NTI drug

## **Overall, we conclude that using the proposed approaches will:**

- Bring the US into harmony with other regulatory agencies who make special considerations for acceptance limits for BE studies of NTI drugs; and
- Improve public confidence in quality and switchability of generic formulations of NTI drugs.



## Acknowledgements

- Dale Conner
- Stella Grosser
- Wenlei Jiang
- Rob Lionberger
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- Patrick Nwakama
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- Don Schuirmann
- Sriram Subramaniam
- Lawrence Yu
- Xinyuan Zhang



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***Thank you for your attention!***



# Quality and Safety of Generic Drug Products

*Advisory Committee for Pharmaceutical  
Science  
and  
Clinical Pharmacology*

*July 26, 2011*

**Keith O. Webber, Ph.D.**  
**Deputy Director**  
**Office of Pharmaceutical Science**  
**Acting Director**  
**Office of Generic Drugs**  
**CDER, FDA**



# Generic Drugs

- >75% of prescriptions are filled with generics
- Cost savings is substantial (\$800M over last 10 yrs.)
- Cost differential and substitution at pharmacy limits patients' choices
- OGD serves to ensure that generic drugs are equivalent to their brand name counterparts.



# Regulations

- Generic drugs must be the same as the Reference Listed Drug
  - Active Ingredient
  - Dosage Form
  - Strength
  - Route of Administration
  - Conditions of Use
- Variances in formulation are allowable



# Quality-by-Design

- Global initiative
- Product designed with performance in mind
- Manufacturing process designed to ensure consistent product quality



# Safety Concerns

- Many safety concerns apply to brand product and generic versions
  - e.g., API – related adverse events
- Some are unique to formulation, product design, or manufacturing



# Safety Issues

- Swallowability
  - Size, Shape, Coating
- Medication errors
  - Inconsistent appearance
    - Inability to recognize dispensing errors



# Patient Compliance

- Discomfort with change
- Dissatisfaction with medicine due to:
  - Bad taste
  - Bad odor
  - Tactilely unpleasant (e.g., O.D.T)
  - Size too large



# Skepticism

- Doubts about performance due to concerns with appearance or other sensory characteristics.



# OPS Activities

- Monitoring Patient Complaints
- Post-marketing Surveillance
- Laboratory Research
- Developing Standards & Regulatory Policy



# Topics

- Clinical and Safety Perspective
  - **Laurie Muldowney, MD** (Medical Officer, OPS, CDER, FDA)
- Quality Perspective
  - **Vilayat Sayeed, Ph.D.** (Director, Division of Chemistry III, OGD)
- Research Activities
  - **Mansoor Khan, Ph.D.** (Director, Div. of Pharmaceutical Quality Research, Office of Testing and Research, OPS)
- Industry Perspective
  - **Gordon Johnson** (GPhA)



# Postmarketing Drug Safety: Considerations for ANDAs

*Advisory Committee for Pharmaceutical  
Science  
and  
Clinical Pharmacology  
July 26, 2011*

**Laurie Muldowney, MD  
OPS/CDER/FDA**



# Agenda

- Unique Safety Considerations for Generic Drugs
- Evolving OGD Postmarketing Process
- Clarifying Questions



# Background

- **FDAAA**
  - Increasing emphasis on postmarketing surveillance
  - Safety First Initiative
- **Generic skepticism**
  - Need for a process whereby we specifically evaluate generic drug products during the postmarketing period



# Public Skepticism about Generics

- Perception that generic products don't work as well as the brand products
  - Frequent perception that more expensive is better
  - Lack of understanding of the generic approval process
  - Historical
- Worsening symptoms after switch to therapeutically equivalent product often attributed to a faulty generic
- May be related in part to experiences with different generic drug characteristics
  - Different appearance from RLD and other generics

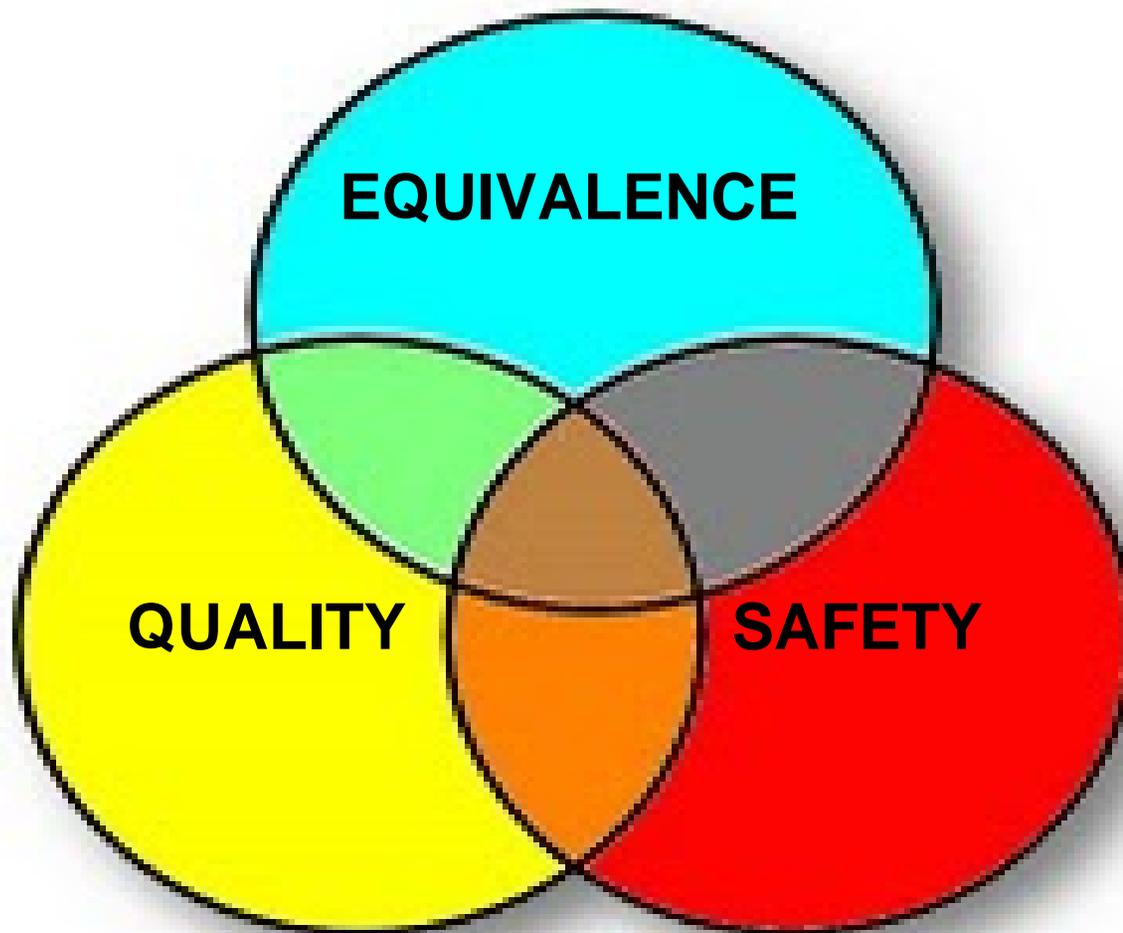


## Postmarketing Safety Considerations in ANDAs

- Unique needs and challenges for generic drug products
- Emphasis on manufacturer specific quality, safety, and equivalence issues
  - Formulation differences
  - Manufacturing process quality assurance
  - Bioequivalence questions
- Less focus on safety issues related to the active ingredient
  - OSE/OND focus
- Focus is not limited to serious, unlabeled adverse events



# Generic Drugs Postmarketing Surveillance





# Quality Issues and Complaints: Examples

## Patch won't stick





# Quality Issues and Complaints: Examples

## Syringe failures





# Quality Issues and Complaints: Examples

## Labeling problems: Missing lot and exp. date





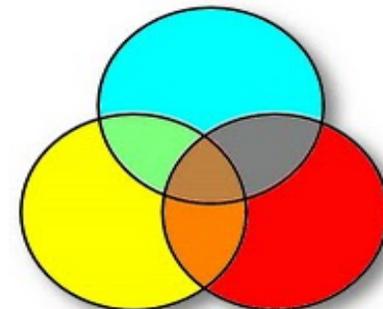
# Quality Issues and Complaints: Examples

**Many complaints about ODOR and TASTE!**



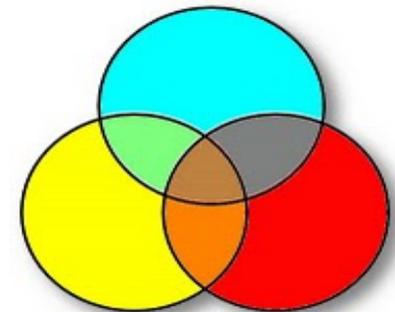
## Examples of Quality Issues that May Lead to Safety Issues

- A larger tablet may be more difficult to swallow
- A tablet that disintegrates quickly or sticks to a moist surface may be difficult to swallow
- A tablet coating may be needed to mask a bad taste or odor, to keep the tablet intact until it is swallowed, or to protect the esophagus from an irritating drug substance
- A transdermal patch that doesn't stick will not be effective



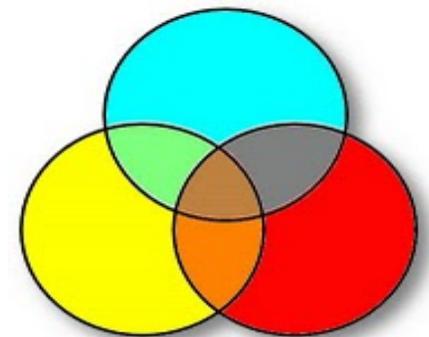
## Therapeutic Equivalence (TE)

- *Pharmaceutical equivalents*: contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration
- *Therapeutic equivalents*: pharmaceutical equivalents and **can be expected to have the same clinical effect and safety profile** when administered to patients under the conditions specified in the labeling.
- Therapeutically equivalent products must meet the following general criteria:
  - Approved as safe and effective;
  - Pharmaceutical equivalents;
  - Bioequivalent
  - Adequately labeled;
  - Manufactured in compliance with Current Good Manufacturing Practice regulations



# Therapeutic Inequivalence

- *“I switched to generic x and it didn’t work like the brand name product”*
  - TE products are expected to have the same clinical effect and safety profile
- Quality issues can affect equivalence
- Formulation differences? BE issues?
- Challenging to interpret
  - Anecdotal, low reporting rates
  - Generic skepticism
  - Nocebo effect, Weber effect
  - Poor quality of reports





## Goals of OGD Postmarketing Surveillance

1. Determine whether allowable differences between the generic product and the RLD have changed the safety or efficacy profile of the product
2. Ensure manufacturer specific quality assurance through collaboration with OC
3. Apply new understanding to future premarket reviews



# CURRENT OGD Postmarketing Surveillance Process

- **Postmarketing Surveillance Team**
  - Responsible for initial triage and tracking of potential safety issues
- **Bimonthly Postmarketing Surveillance Meetings**
  - Larger group including multiple CDER office representations
  - Responsible for initial assessment of potential safety signals and recommendations for further evaluation/action
- **Safety First Processes**
  - Utilize existing processes and procedures for tracking, evaluating, and communicating about potential safety issues



# OGD Postmarketing Surveillance Team

- Multidisciplinary team within OGD which addresses emerging safety and quality issues in OGD
- Focal point for information from various offices pertaining to safety issues which impact generic products
- Initiates evaluation and tracking of reports of inferior product quality, adverse events, and different therapeutic effect compared with RLD
- Works collaboratively with other CDER offices when potential issues are identified as requiring further investigation



# Data Sources/Signal Generation

- DQRS
  - Field Alert Reports (FARs)
  - Spontaneous MedWatch reports through DQRS:
    - Quality complaints (quality only issues and quality issues leading to adverse events)
    - Direct reports of unexpected therapeutic effects after switching
- AERS
- Spontaneous reports sent directly to OGD
- Published literature
- Consumer groups and other sources
- Future considerations/opportunities:
  - Data mining strategies
  - Distributed databases (e.g. Sentinel System)
  - Optimizing FAERS



## Evaluation/Management of Potential Signals

- Initial evaluation
  - Compare formulations/BE study results
  - AERS search
  - Manufacturing information
- Discuss at bimonthly postmarketing surveillance meeting
- Determine need for further evaluation



# Evaluation/Management of Potential Signals (continued)

- OTR studies
- Official consult to OSE for safety/drug utilization analysis
- Communication/exchange of information with firm
- Utilize existing processes created through Safety First
  - Create DARRTS Tracked Safety Issue (TSI)
  - Establish Safety Issue Team for significant safety issues
  - Issue Drug Safety Communications, as indicated
- Collaborative studies/postmarketing research with outside partners



## Possible Outcomes from Postmarket Reviews

- No action indicated
- Change in product rating (e.g. from AB to BX)
- Request reformulation
- Development of guidance or policy
- Product withdrawal from marketplace



# Ongoing Postmarketing Research: AEDs

- **Background:**
  - Agency receives occasional spontaneous AE reports of therapeutic inequivalence for antiepileptic drugs (AEDs)
  - Significant skepticism related to the therapeutic equivalence of these drug products
  - Several epilepsy organizations express concerns about the interchangeability of AEDs
- **Objective:**
  - Assess whether an FDA approved generic epilepsy drug is bioequivalent to the innovator product (and other relevant generics) in epilepsy patients under clinical use conditions



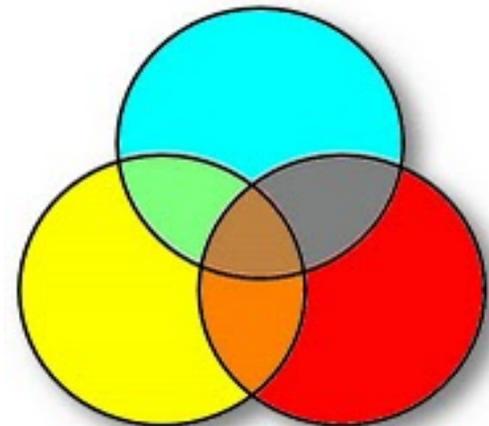
## Ongoing Postmarketing Research: AEDs (continued)

- Contract awarded to University of Maryland
  - Conduct a prospective, randomized, blinded, four period replicate crossover steady-state study to determine if generic lamotrigine 100 mg is bioequivalent to RLD in epilepsy patients
- Additional studies planned to compare BE with generic to generic switches

## *Orally Disintegrating Tablet*

Received reports that a specific manufacturer's orally disintegrating tablet had clogged and blocked oral syringes and feeding tubes, when the drug was administered as a suspension through these devices

- Collaborative evaluation
  - DQRS search, AERS search, search of periodic safety reports
  - OGD Science Team evaluation of formulation
  - OSE drug utilization information
  - OTR testing
  - OC facilitated meetings with manufacturer
- Created TSI (through OSE)
- Voluntary Market Withdrawal
- Communication with Stakeholders





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# Questions?



# Equivalence by Design - Consumer Concern

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology*

*July 26, 2011*

**Vilayat A. Sayeed, Ph.D.**  
**Director, Division of Chemistry III**  
**Office of Generic Drugs**



## ICH Q8(R2)- Quality by Design

- Systematic approach to development
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management
- Begins with predefined objectives



# Predefined Objectives

## Quality Target Product Profile

- Active Pharmaceutical Ingredient
- Product Strength
- Dosage Form
- Route of Administration
- Labeling (conditions of use)
- Performance
- Quality
- BA/BE



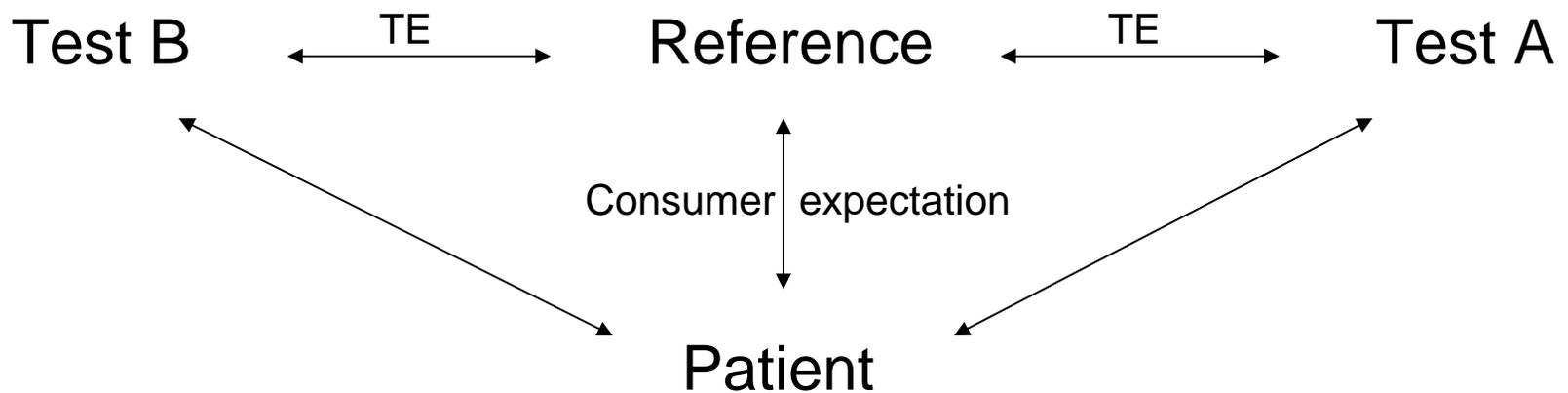
# **Predefined Objectives Overlooked**

## **Quality Target Product Profile Issues of Concern**

- Beads in capsule shell
- Tablet size, shape and color
- Tablet score - Ease of splitting
- Taste and odor masking and tablet dust (coated vs. uncoated)



## Why are these objectives critical?





# Predefined Objectives Overlooked

## Beads/Powder in capsule shell

- Reference has beads – Test has mini tablet
  - Published draft guidance (addresses condition of use concerns)
- Capsule products not covered by use condition
  - Include this in PD strategy to address consumer compliance



# Predefined Objectives Overlooked

## Tablet size, shape and color

- Test substantially larger than RLD for same strength
- Shape in combination with size can be an issue
  - A draft guidance will be issued soon
- Same size, shape and color for all strengths

# Predefined Objectives Overlooked

## Tablet Score – Ease of Splitting

- Uneven breaking
- Crumbles upon splitting
- Content distribution concerns (in-house data)
  - A draft guidance will be issued soon





# Predefined Objectives Overlooked

## Taste and odor masking and tablet dust

- Design and process difference
- Reference non-function coat, test uncoated



# Predefined Objectives Overlooked

## Office Focus

- Pay attention to physical and organoleptic properties of reference in test development
- Look from consumer perspective and potential for non-compliance



# Division of Product Quality Research (DPQR): Regulatory Research to Support the Office of Generic Drugs

*Advisory Committee for Pharmaceutical Science  
and  
Clinical Pharmacology*

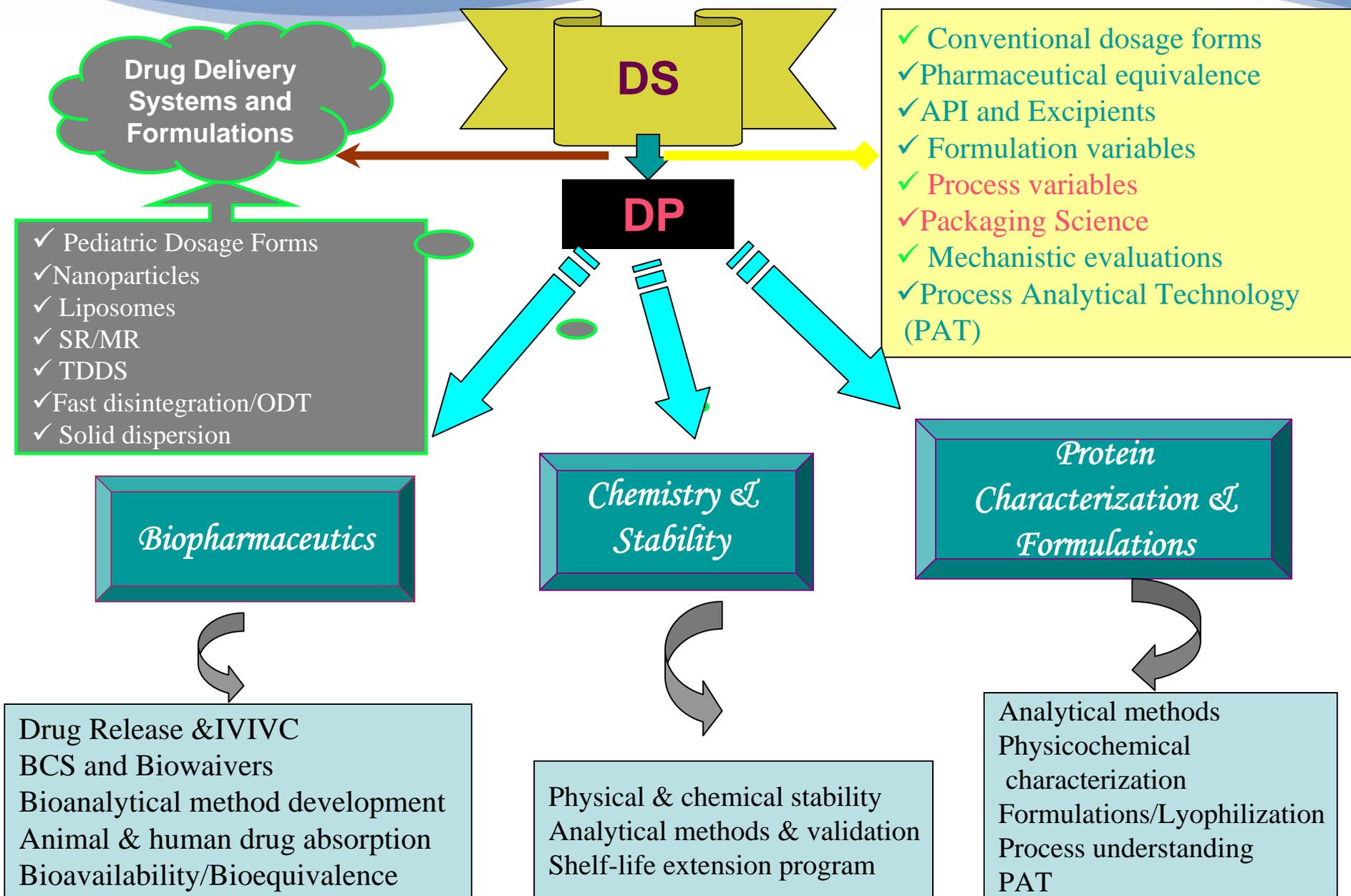
*July 26, 2011*

**Mansoor A. Khan, R.Ph., Ph.D.**  
**Director, OPS/OTR/DPQR**

# DPQR Research Programs..

Sept. 2010

www.fda.gov





# Stability Studies

- Applicant conducts systematic stability testing (21 CFR 211.166) according to a prescribed protocol
    - Select samples from representative batches
    - Store samples at defined storage conditions
    - Accelerated (40°C/75% relative humidity or RH)
      - Long-term (25°C/60% RH)
      - Intermediate (30°C/65% RH), if needed
- Pull samples at predetermined intervals



gabapentin recall

Search

SafeSearch strict

About 840,000 results (0.14 seconds)

Advanced search

- Everything
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- Videos
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White Oak, MD Change location

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Generic Firm Commences Gabapentin Recall Due to Excessive Impurities

Nov 16, 2007 ... Ranbaxy Pharmaceuticals initiated a voluntary Class III recall of 73 million gabapentin tablets because the allowed level of impurities in ... www.fdanews.com ... FDAnews Drug Daily Bulletin - Cached - Similar

India's Ranbaxy recalls gabapentin tablets in U.S. | Reuters

Nov 15, 2007 ... MUMBAI, Nov 16 (Reuters) - Indian drugmaker RanbaxyLaboratories Ltd is recalling some gabapentin tablets in the United States, ... www.reuters.com/article/.../ranbaxy-recall-idUSBOM996220071116 - Cached

Gabapentin 100 mg capsules (Neurontin) - Recall

Jan 8, 2008 ... Alert - Gabapentin 100 mg capsules (Neurontin) - Recall. healthcare.utah.edu/pharmacy/alerts/79.html - Cached - Similar

News : MHRA batch recall: Gabapentin 300mg capsules (Teva)

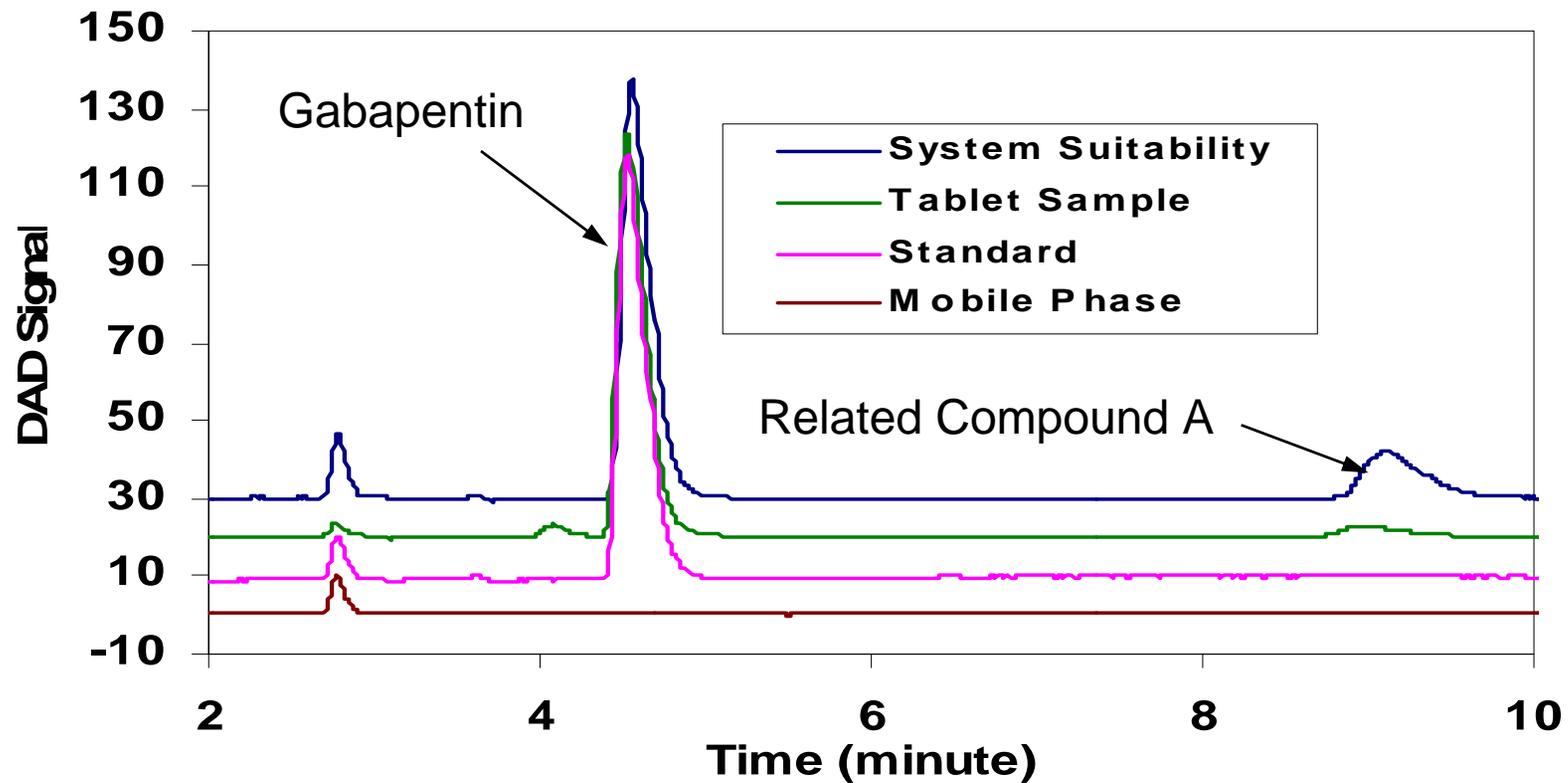
MHRA batch recall: Gabapentin 300mg capsules (Teva). 22nd December 2010. Teva UK Ltd are recalling all remaining stock of the following batches of ... www.palliatedrugs.com/.../mhra-batch-recall-gabapentin-300mg-capsules-teva-.html - Cached

Gabapentin recall - Epilepsy Forum

2 posts - 2 authors - Last post: Dec 29, 2007 Quote : Last month, Ranbaxy Pharmaceuticals announced a voluntary recall of 73 million tablets of its epilepsy and nerve pain drug, ... www.coping-with-epilepsy.com ... Peer Support > The Library - Cached

[News] Contamination Responsible for Topamax Recall - 1 post - Apr 19, 2011

# FDA Study on Gabapentin



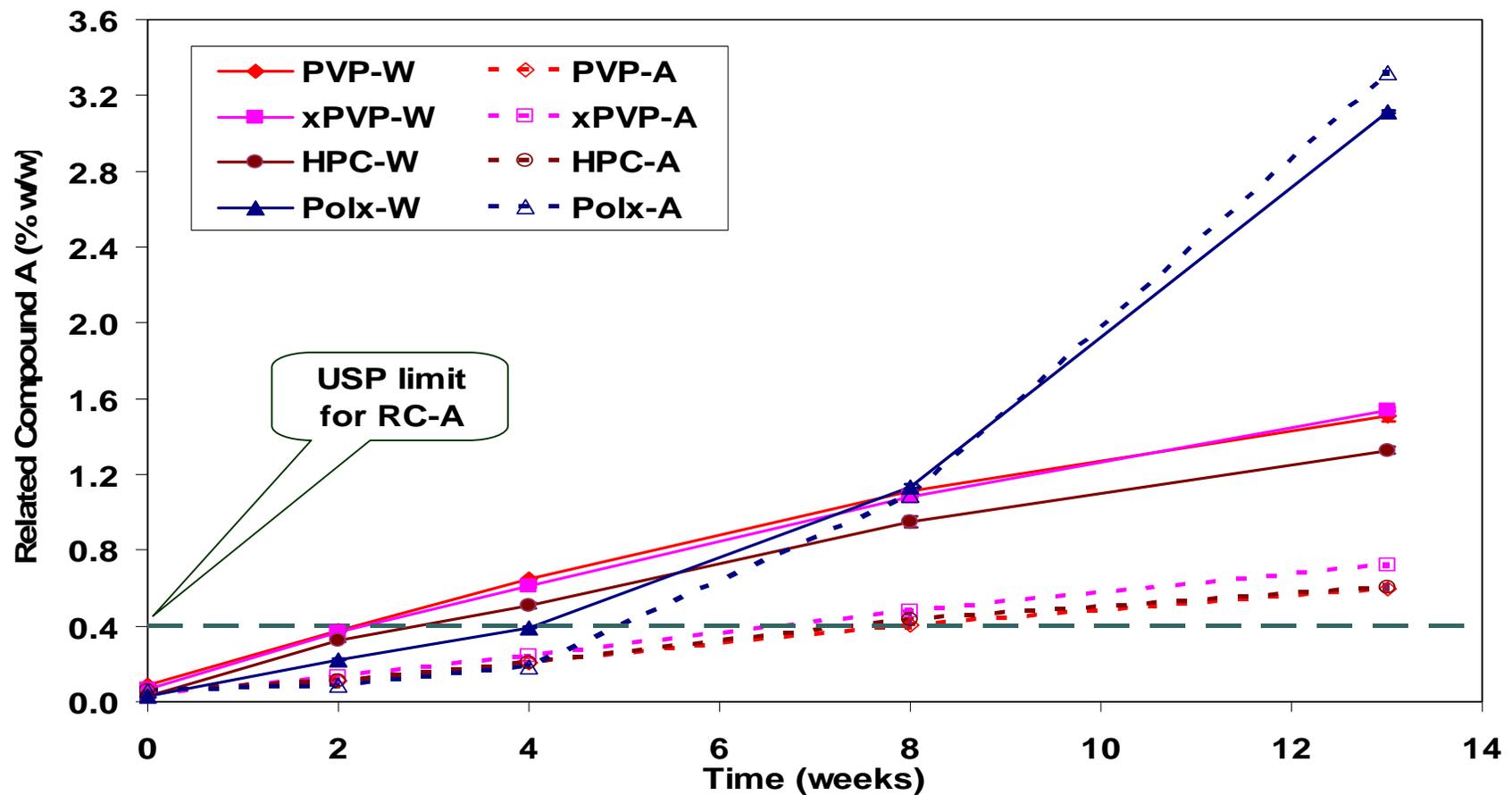
Int J Pharm. 2008 Feb 28;350(1-2):65-9

J Pharm Biomed Anal. 2008 Jan 7;46(1):181-6

J Pharm Biomed Anal. 2007 Apr 11;43(5):1647-53



## RC-A Formation in Tablets at 40 °C/75% RH





# Stability of Marketplace Generic Products

- Evaluated several products in the market as follows:
  - Determined products quality attributes such as assay/potency and dissolution with approved and validated methods.
  - About six months before the expiration date, the products were placed in stability chambers at 25°/60% RH and analyzed for assay/potency and dissolution for three months.
- Bioequivalence study with one product is in progress.



## Potency and Stability of Bupropion Tablets

Product	Bupropion Amount Found/Tablet (mg) ± SD (% Labeled Strength ± SD)			
	Time in chamber (months)			
	0	1	2	3
Product 1	300 ± 0.6 (100 ± 0.2)	298.0 ± 2.7 (99.37 ± 0.9)	302.0 ± 2.6 (100.7 ± 0.9))	300.4 ± 2.3 (100.1 ± 0.8)
Product 2	302 ± 0.2 (100.7 ± 0.1)	297.9 ± 3.3 (99.3 ± 1.1)	300.9 ± 3.7 (100.3 ± 1.2)	300.1 ± 0.8 (100.0 ± 0.3)
Product 3	304 ± 2.5 (101.3 ± 0.8)	301 ± 3.5 (100.3 ± 1.2)	298 ± 6.1 (99.3 ± 2.0)	298 ± 0.6 (99.3 ± 0.2)
Product 4	304 ± 1.1 (101.3 ± 0.4)	302 ± 3.9 (100.7 ± 1.3)	333 ± 1.7 (101.0 ± 0.6)	301 ± 0.4 (100.3 ± 0.1)

Impurities – None detectable



## Dissolution and Stability of Bupropion Tablets

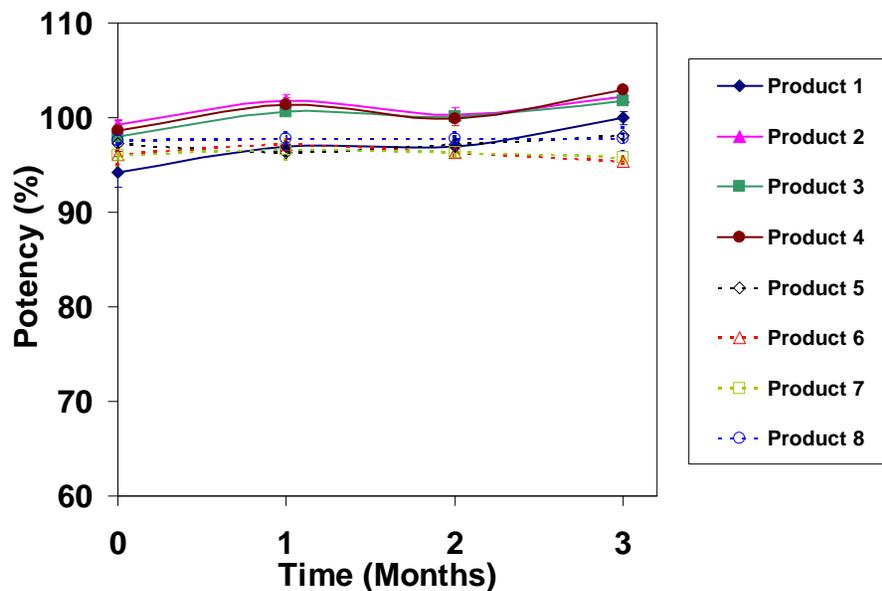
Product	Bupropion Amount Dissolved (%) $\pm$ SD at 16 hrs			
	Time in chamber (months)			
	0	1	2	3
Product 1	101.57 $\pm$ 2.79	101.81 $\pm$ 0.87	100.63 $\pm$ 1.27	102.04 $\pm$ 1.27
Product 2	97.82 $\pm$ 0.97	99.11 $\pm$ 1.02	99.81 $\pm$ 1.39	99.13 $\pm$ 0.85
Product 3	94.32 $\pm$ 3.25	93.97 $\pm$ 1.59	90.09 $\pm$ 1.36	94.32 $\pm$ 1.91
Product 4	101.56 $\pm$ 1.29	99.81 $\pm$ 0.43	96.29 $\pm$ 0.97	100.87 $\pm$ 1.81

USP Tolerance for Amount Dissolved (%) at 16 hrs is: NLT 80%

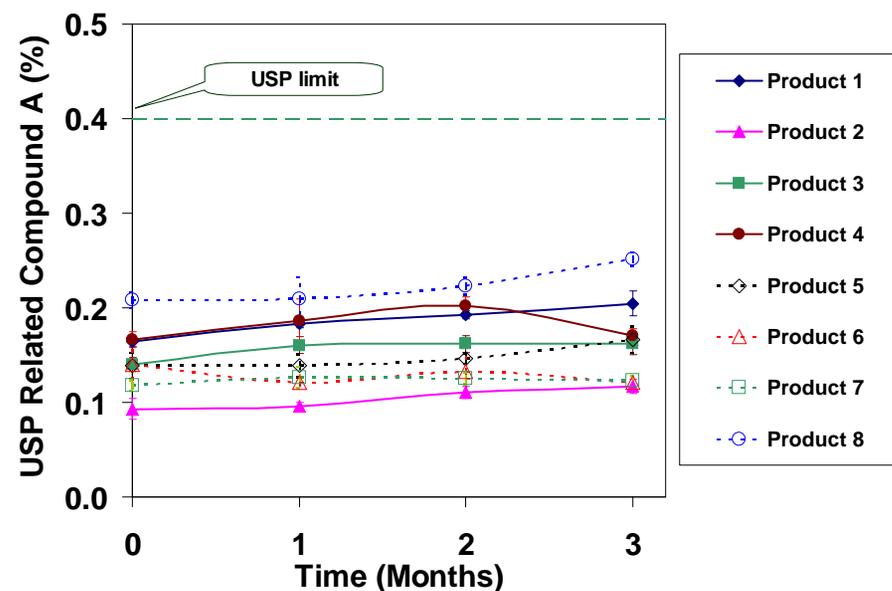


# Potency and Stability of Eight Gabapentin Tablet Drug Products

## Potency

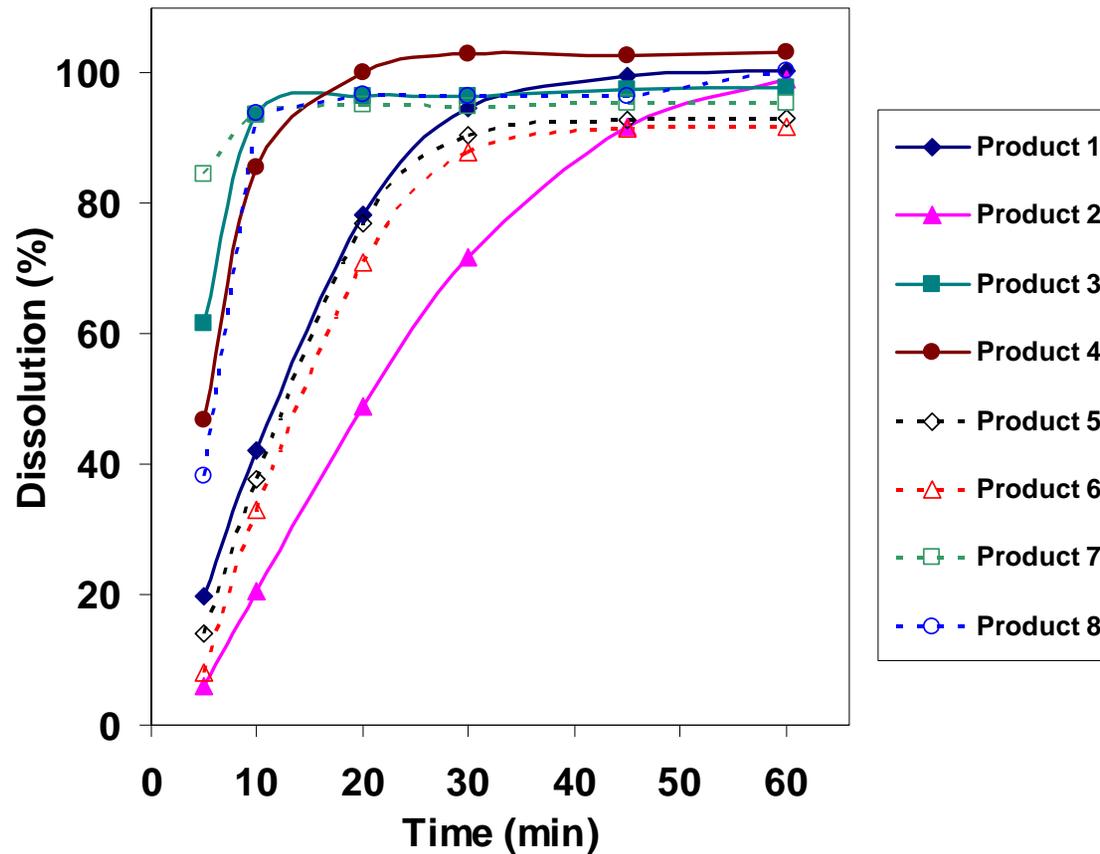


## Stability



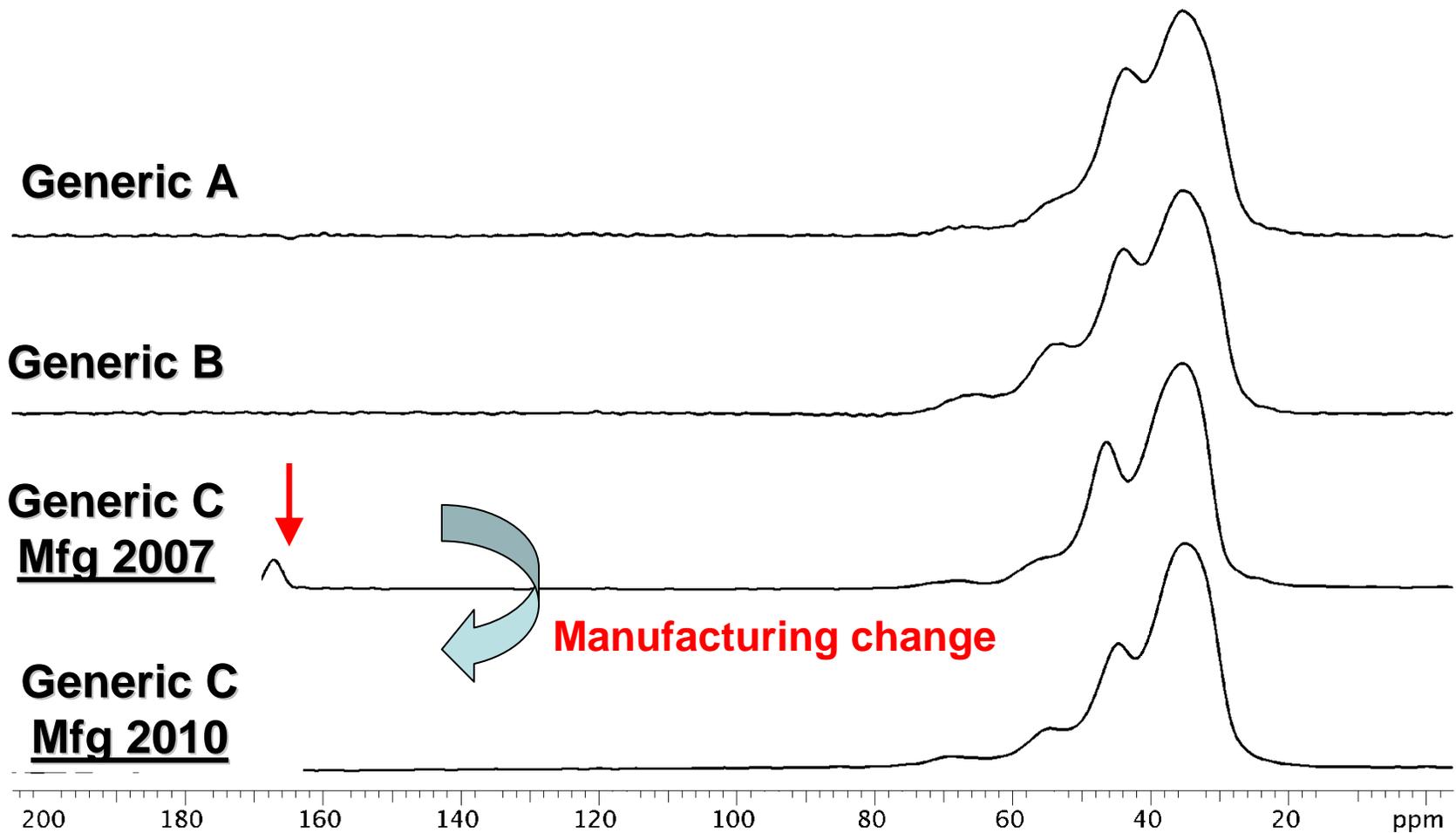
All samples met the compendial requirements when stored under ICH long-term storage conditions (25 °C/60% RH)

# Dissolution Profile of Eight Gabapentin Tablet Drug Products

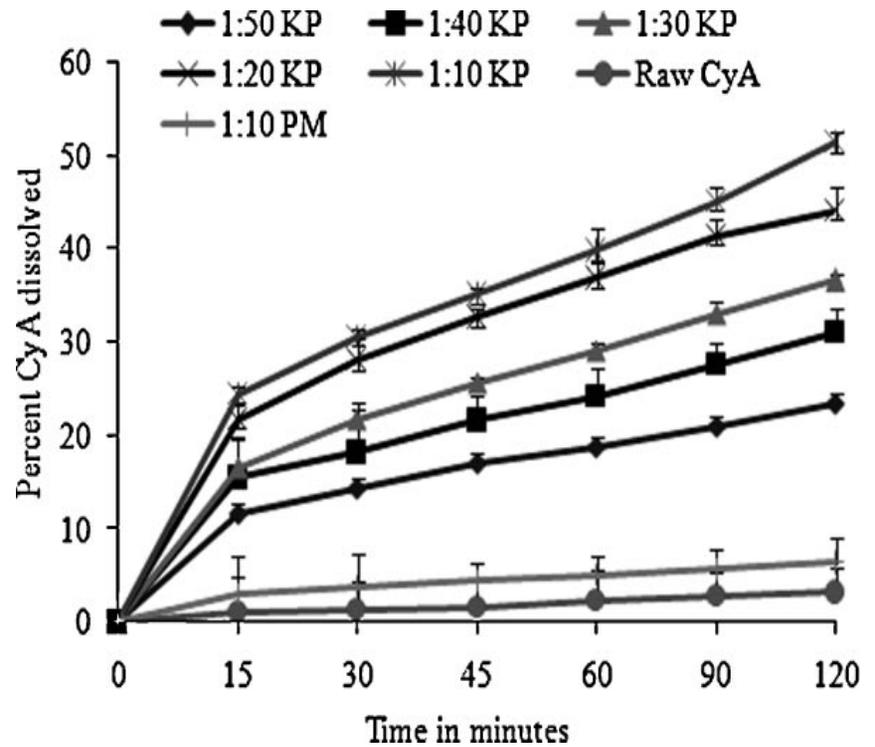
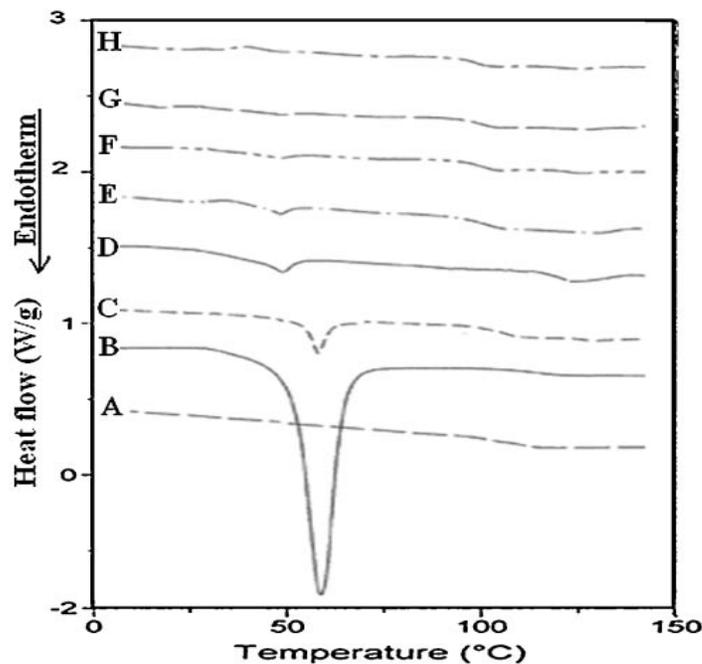


All samples met the compendial requirements of NLT 80% (Q) dissolution in 45 min

# Solid-State NMR Spectroscopy:

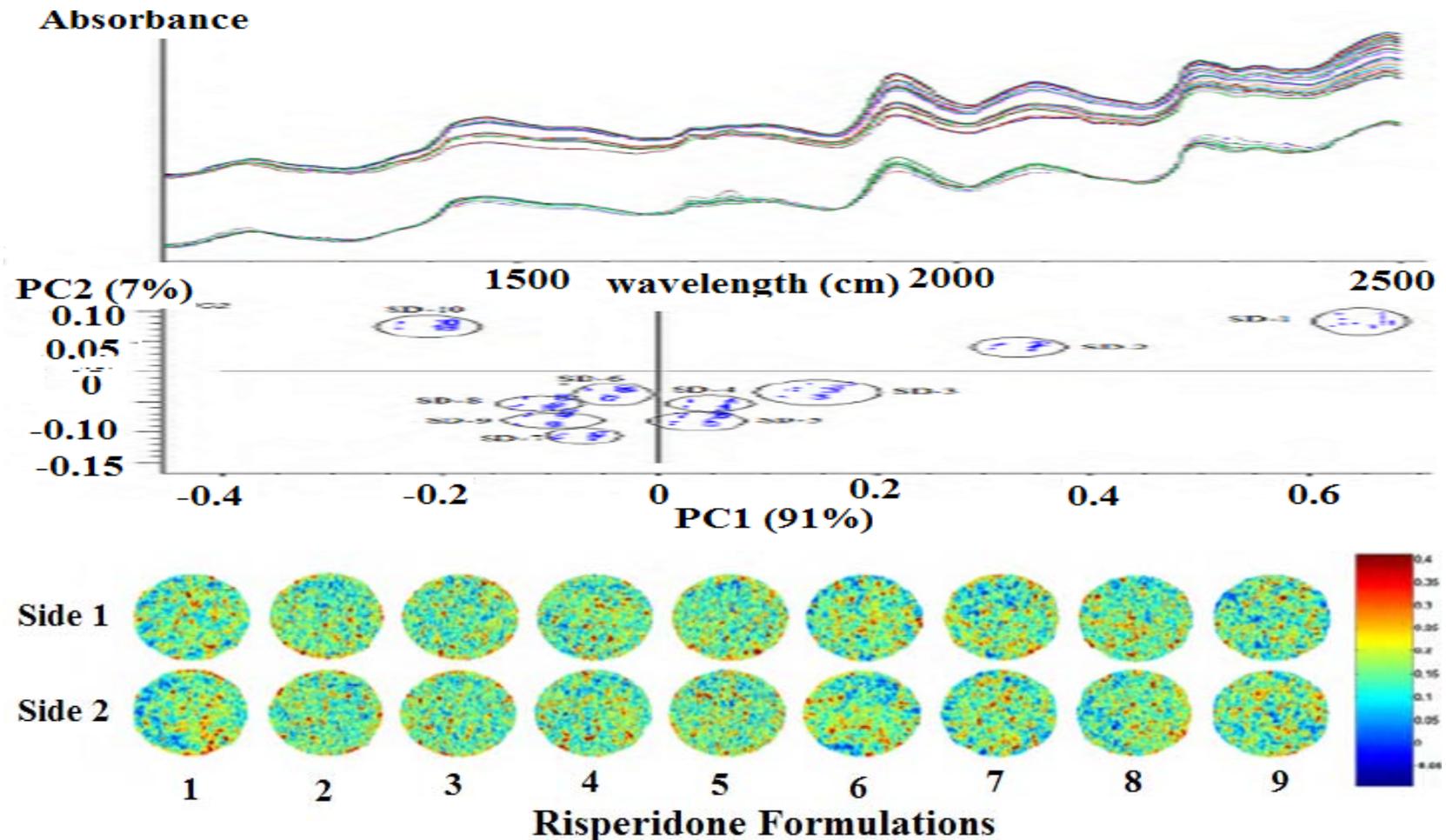


# DDS Team: DSC and Dissolution to Understand and Control Solid Dispersions



*J. Pharm., Sci., (2008), 97(12), 5328-5340*

## NIR and Chemical Imaging to Understand and Control Solid Dispersions



*Int. J. Pharm.* (2010), 400, 49-58.

# pK Changes with Crystallinity

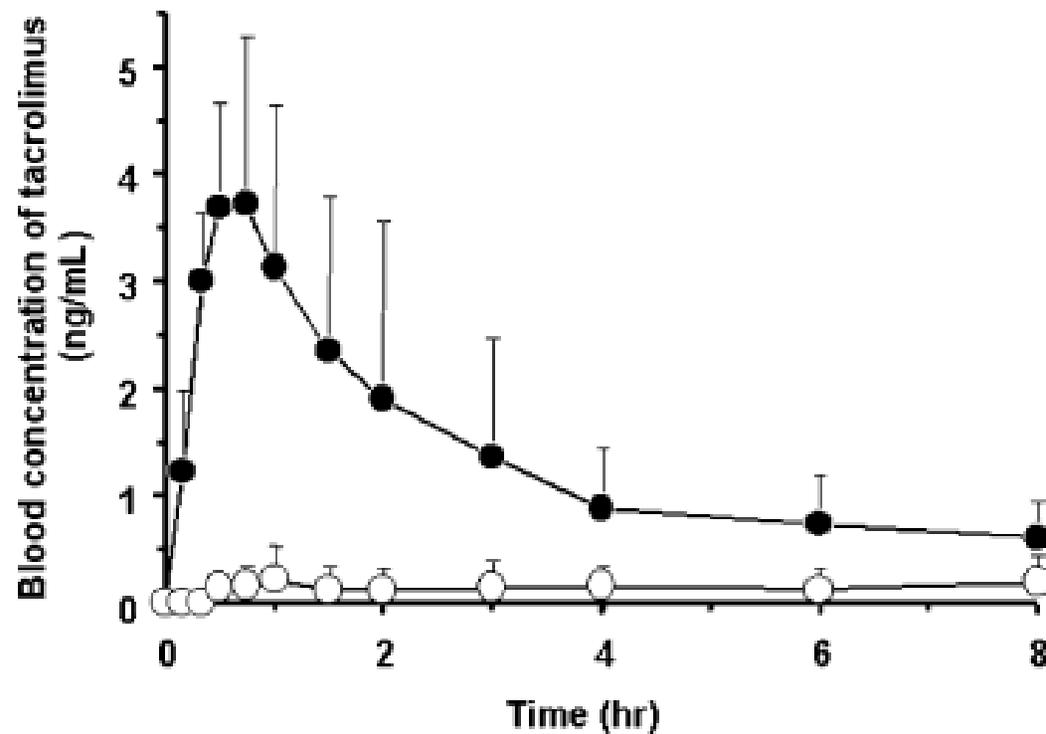


Fig. 5. Blood concentration of tacrolimus after oral administration of SDF with HPMC to beagle dogs. (●) SDF of tacrolimus with HPMC; (○) tacrolimus crystalline powders.



## How is Variability Explained by the Sponsor?

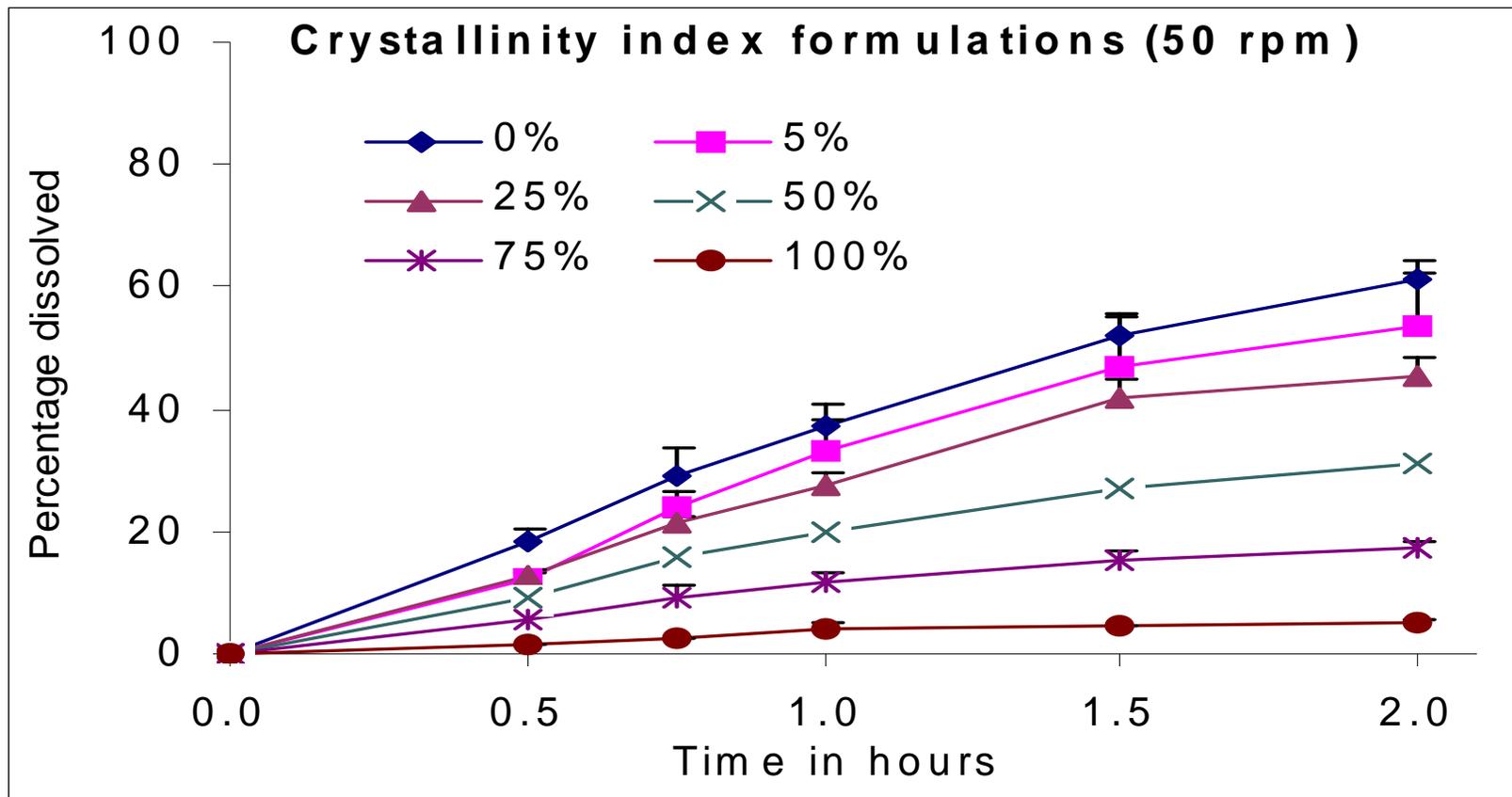
- Preparation method
- Drug: hypromellose ratio
- Additives and the order of addition
- Choice of solvent
- Residual solvent
- Storage condition



## Dissolution Methods in ANDA Submissions

<b>Product 1</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 2</b>	<b>0.01 m NaPO4 + 0.1% SDS</b>
<b>Product 3</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 4</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 5</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 6</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 7</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 8</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 9</b>	<b>0.005% HPC (pH 4.5)</b>
<b>Product 10</b>	<b>0.1% SLS in 0.1N HCl (pH 4.5)</b>

## Dissolution Data of Crystallinity Index Formulations at 50 rpm

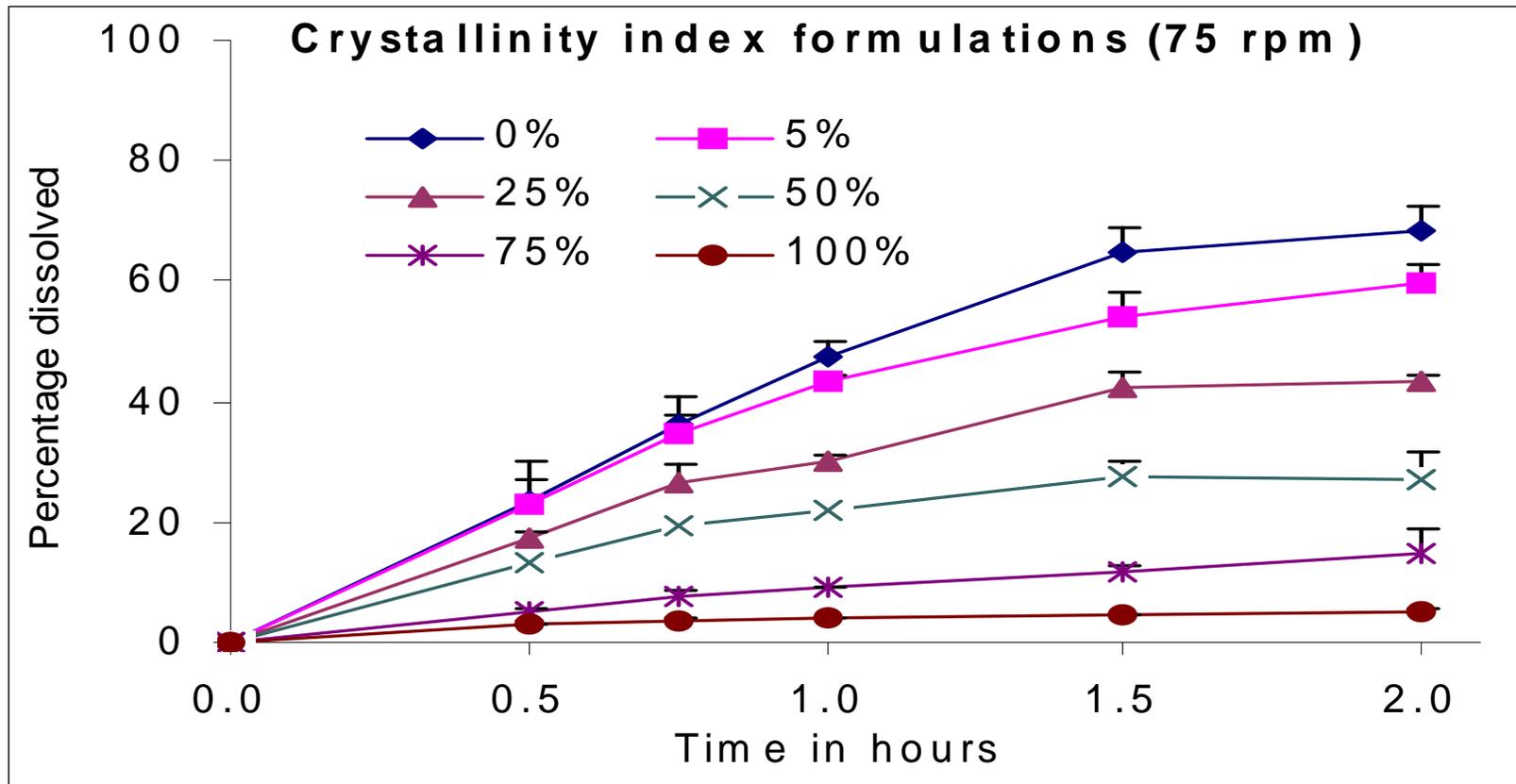


**FDA Dissolution method:**

900 mL 0.002% HPC pH 4.5 with H<sub>3</sub>PO<sub>4</sub>, 50 rpm, 37<sup>0</sup> C

Error bars are Std. Dev. values

## Dissolution Data of Crystallinity Index Formulations at 75 rpm

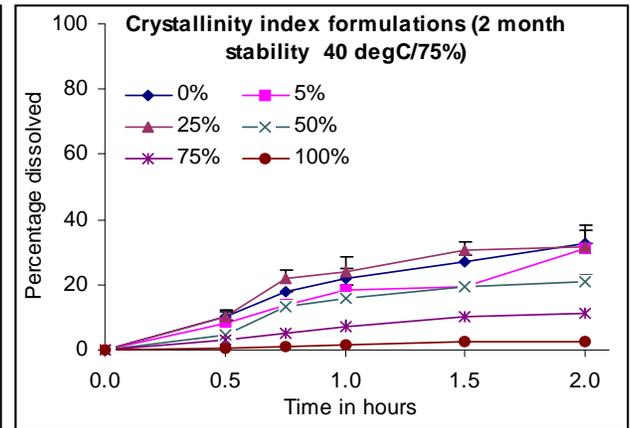
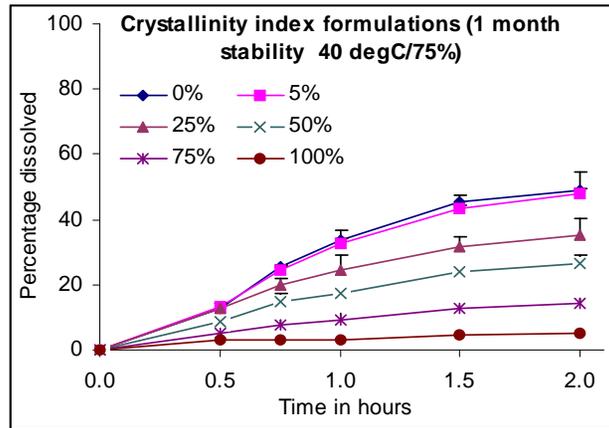
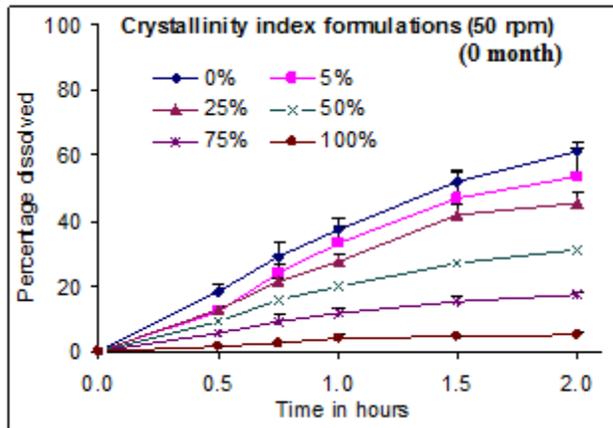


**FDA Dissolution method:**

900 mL 0.002% HPC pH 4.5 with H<sub>3</sub>PO<sub>4</sub>, 75 rpm, 37<sup>0</sup> C

Error bars are Std. Dev. values

# Dissolution Data of Crystallinity Index Formulations at 0, 1 and 2 Month Stability (40deg/75%)



**FDA Dissolution method:**

900 mL 0.002% HPC pH 4.5 with H3PO4

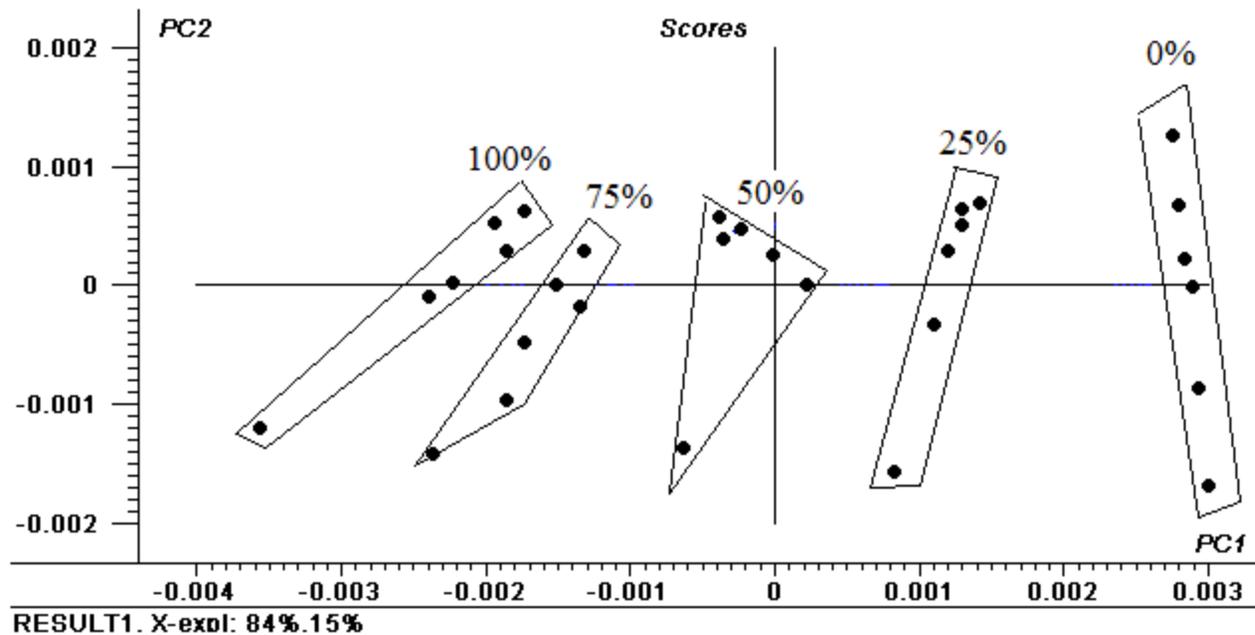
50 rpm and 75 rpm

37 degC

Apparatus II

Error bars are StDev values

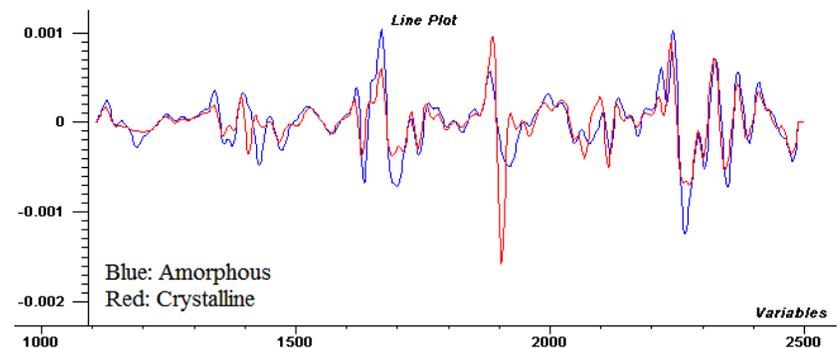
## PCA Analysis



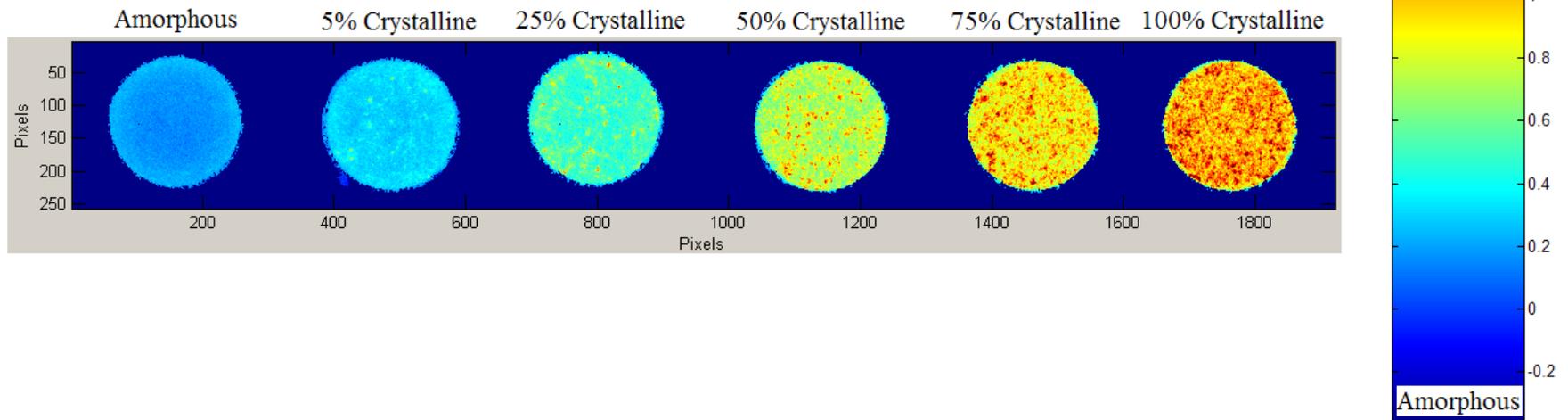
PCA analysis using full cross validation technique after processing the raw NIR data with third order polynomial Savitsky-Golay at 11 points smoothing

PC1 and PC2 explained 84% and 15% of the variability among the spectra

Formulations were clustered according to the degree of crystallinity for the loading vector of PC1

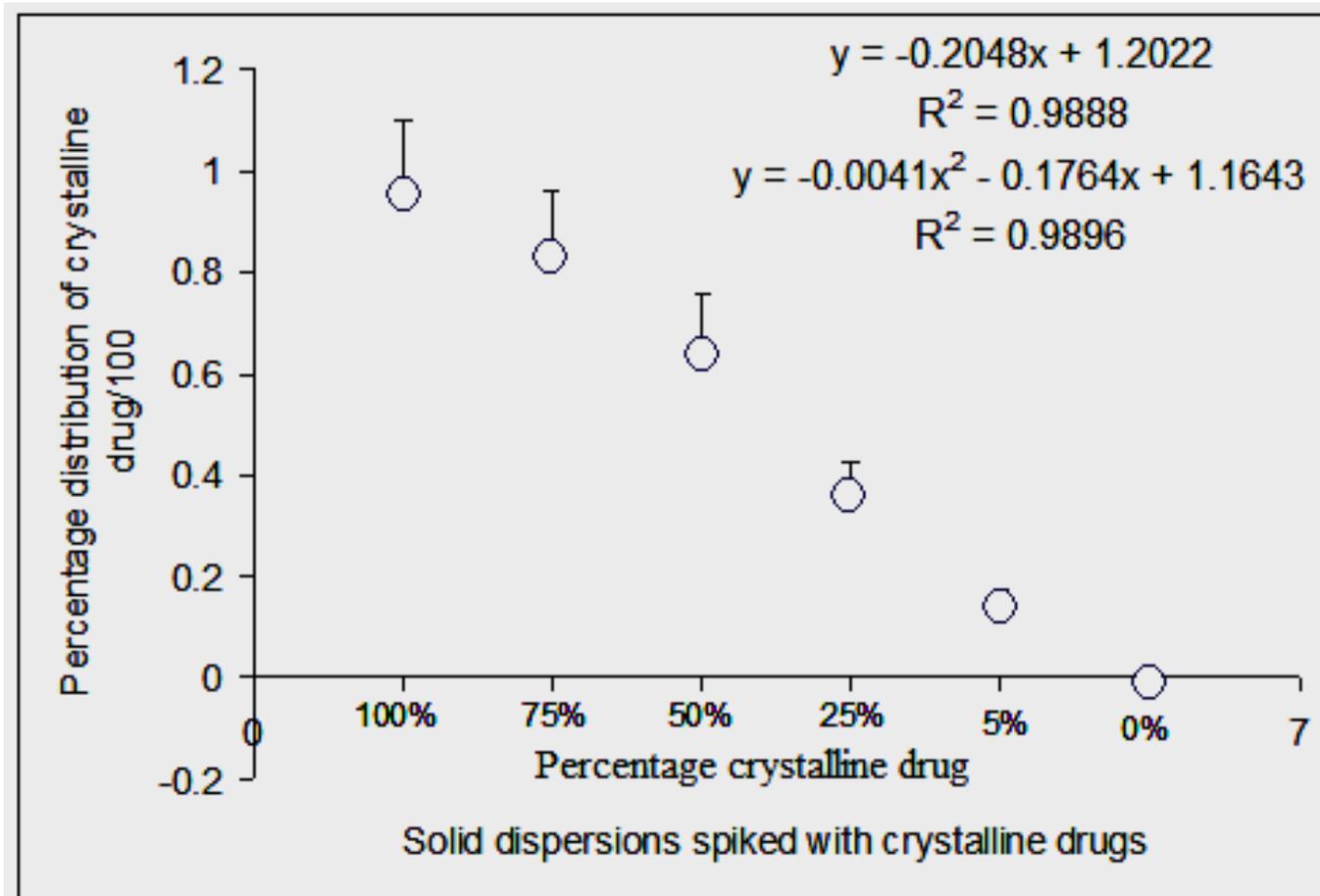


**Concatenated PLS second derivative images of tacrolimus solid dispersions (without excipients). Library was constructed using the amorphous and crystalline components.**

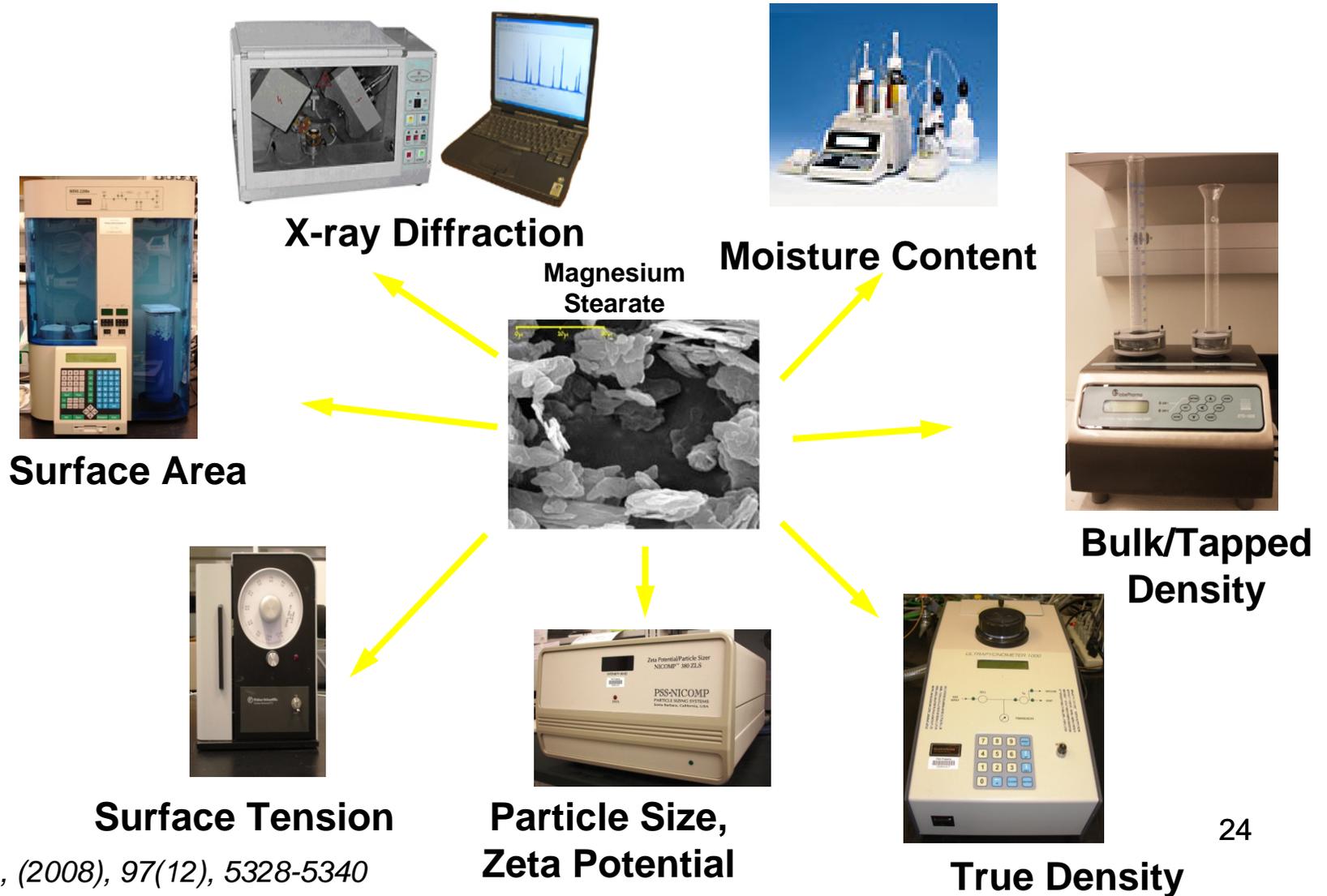




## NIR PLS Truncated PLS Images Statistics



# Mg.St. Bovine vs Plant Source: Raw Material Characterization



# Tablet Characterization



**Hardness  
Tester**

## Tablets



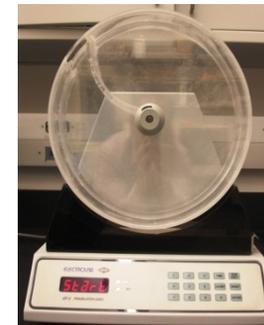
**Weight  
Measurement**



**Compression/  
Ejection Force Data**



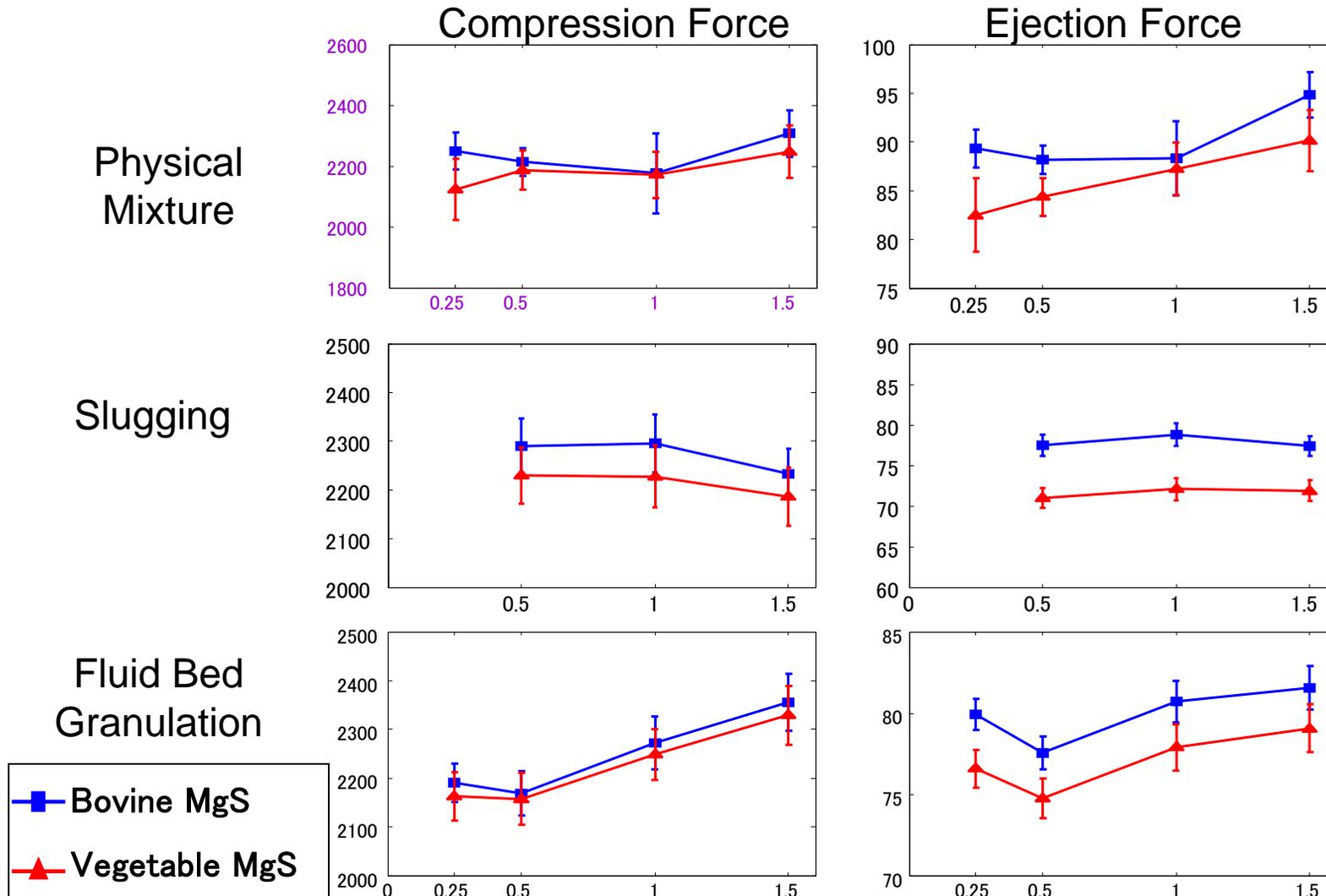
**Dissolution Testing**



**Friability Tester**



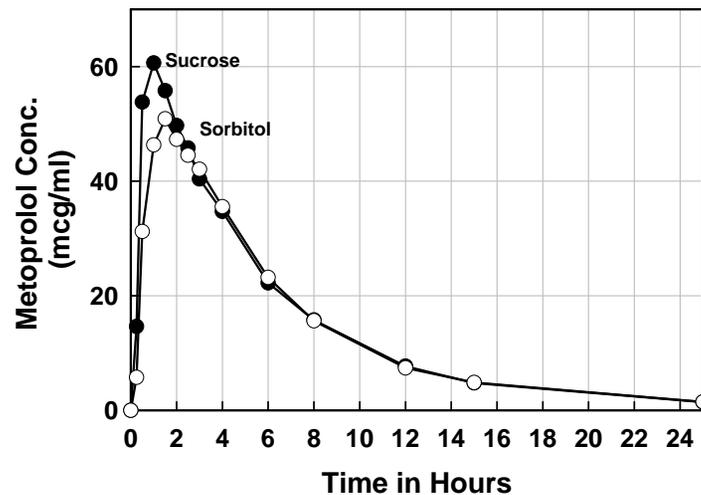
## Effects on Functionality - Compression / Ejection



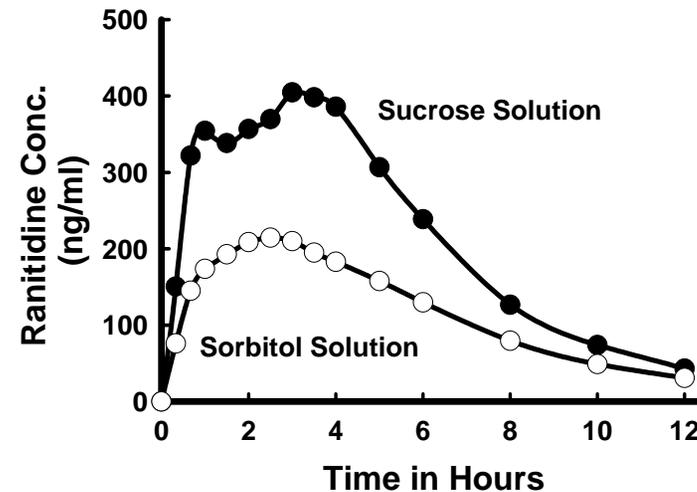
JPS, 2008, 97:5328-40 AAPSP PharmSciTech, 2009, 10:500-4

# Biopharmaceutics Team: BCS Guidance-Excipient Effect

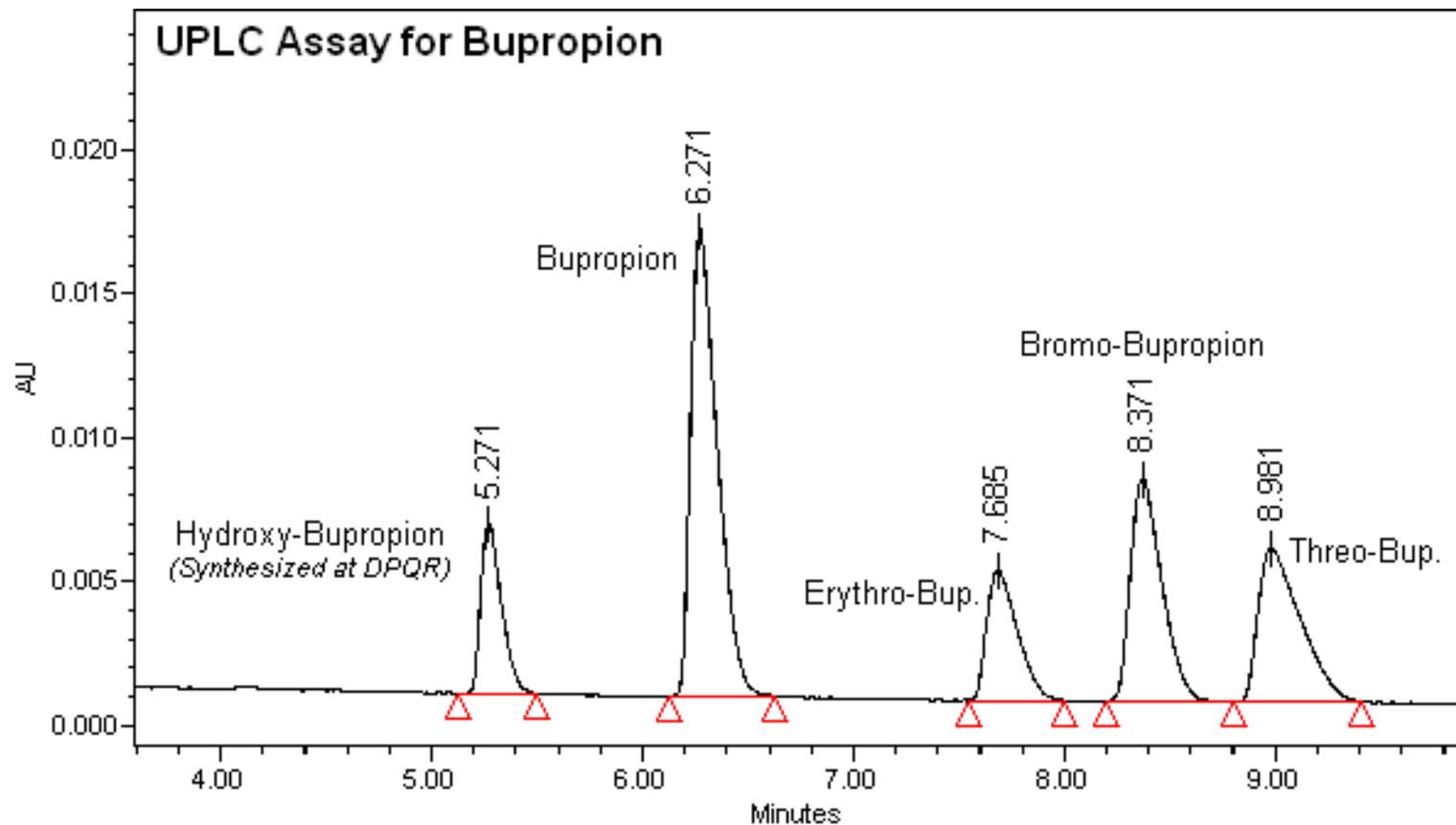
**BCS Class I-Drug**



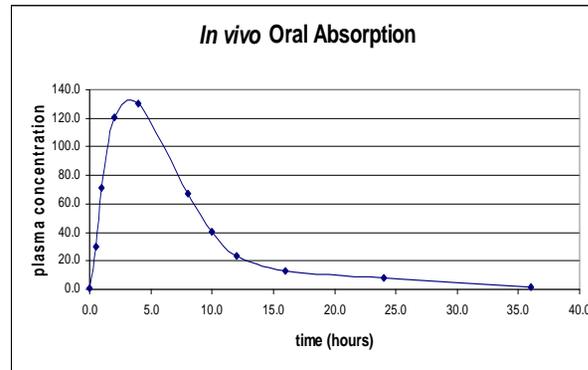
**BCS Class III-Drug**



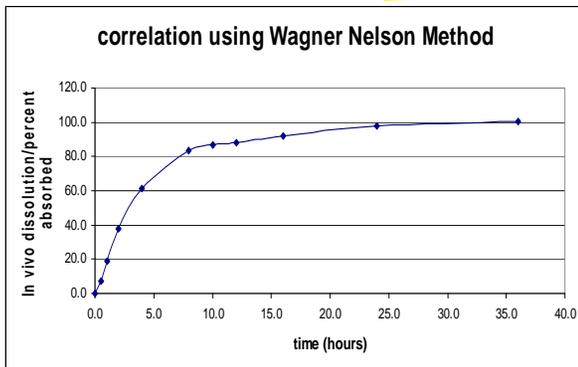
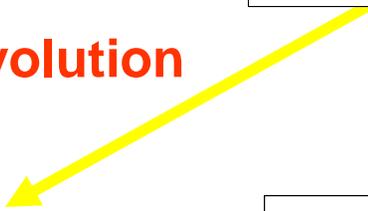
# Bupropion Bioequivalence Studies (ongoing)



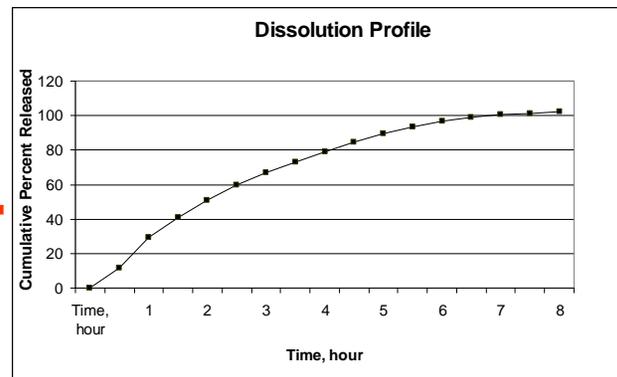
# Setting Dissolution Specifications?



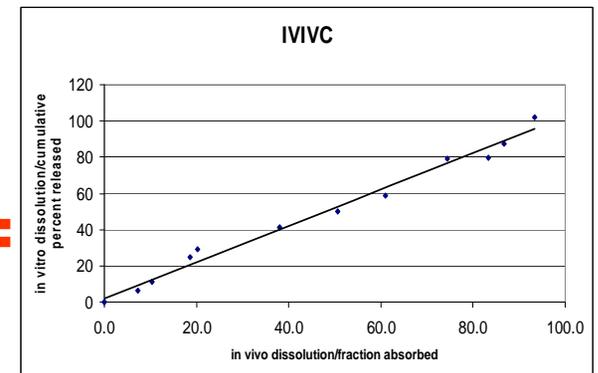
**Deconvolution**



+



=

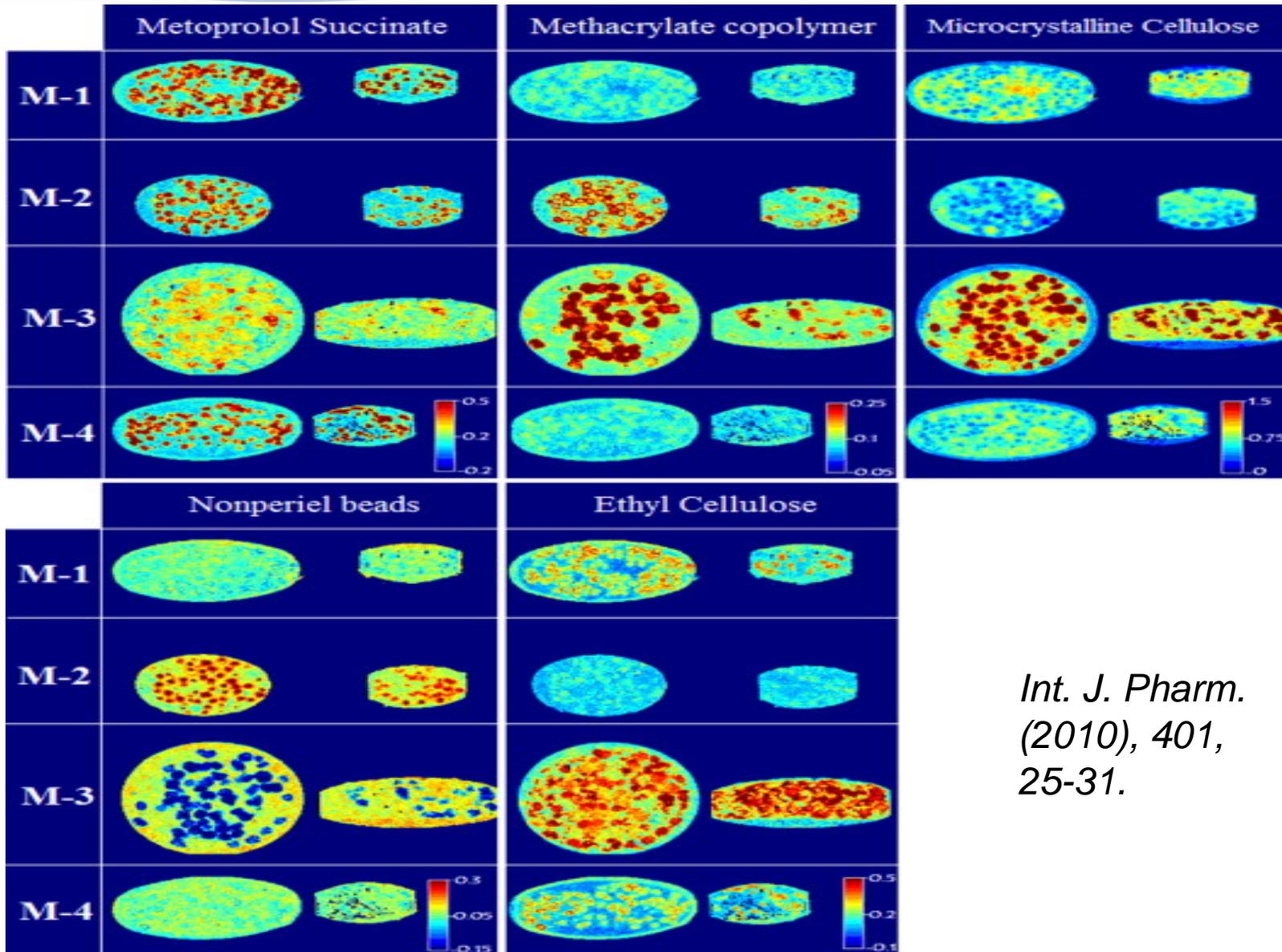




# Tablet Splitting - Influence of Tablet Splitter

600 mg gabapentin tablets from same bottle





*Int. J. Pharm.*  
(2010), 401,  
25-31.



# Conclusions

DPQR scientists continues to provide regulatory research support to the Office of Generic Drugs

# Acknowledgements

DPQR staff

OTR office support

Financial support from NIH, MCM, CP, OPS, OGD, OWH, ONDQA, OC, RSR

# **Impact of Formulation and Quality on Safety and Acceptance of Generic Drugs**

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

Gordon Johnston, R.Ph., M.S.

Generic Pharmaceutical Association

July 26, 2011

# Outline

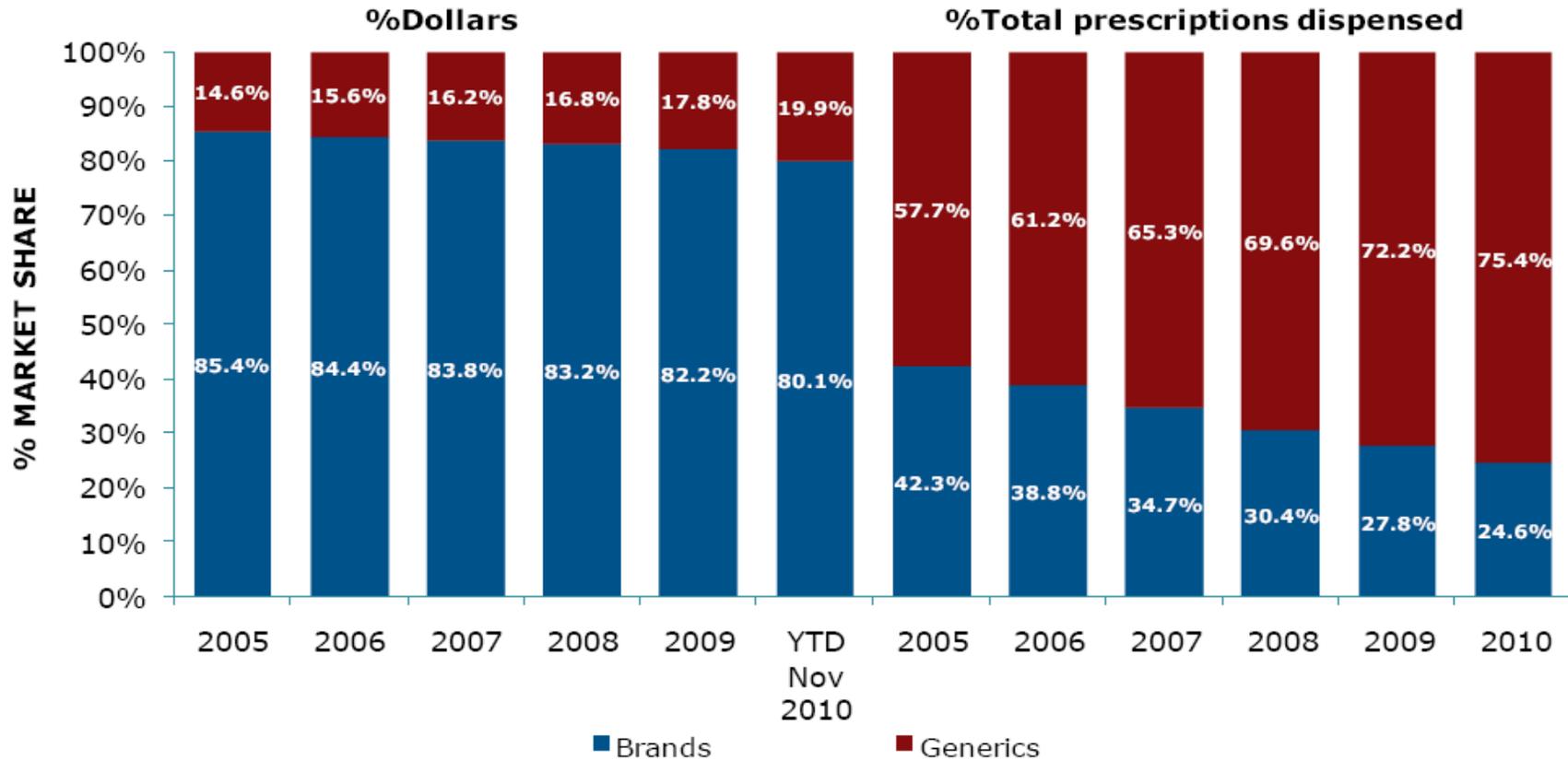
- Overview of generic drug quality standard
- Formulation considerations
- Quality by Design
- Literature
- Summary

# Why Are We Having This Dialogue?

- 27 history of generic drugs in the U.S.
- Anecdotal reports of quality concerns
- Misconceptions about quality standards and FDA requirements for generic drugs



# Sales and TRx share brands and generics

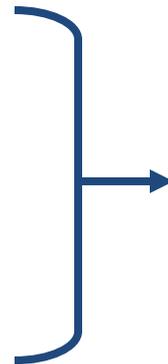


Source: IMS Health, National Sales Perspectives, Nov 2010, Branded generics disaggregated, Source: IMS Health, National Prescription Audit, Branded generics disaggregated, Dec 2010

# FDA Approval Criteria

## NDA vs. ANDA

- Chemistry
- Manufacturing
- Controls
- Labeling
- Testing
- Bioequivalence (Bioavailability)
- Animal Studies
- Clinical Trials



- Chemistry
- Manufacturing
- Controls
- Labeling
- Testing
- Bioequivalence

# Generic Drug Approval Requirements

- Same quality requirements
- Same manufacturing requirements
- Same labeling as brand product
- Same safety and efficacy, i.e., ***therapeutic equivalence***

# Generic Formulations

## Pharmaceutical Equivalence

- Same active ingredient
- Same strength
- Same dosage form
- Same route of administration
- Comparable labeling



## Bioequivalence

- In Vivo Studies
  - PK
  - PD
  - Clinical
- In vitro Studies



## Therapeutic Equivalence

**"A" Therapeutic Rating  
(A substitute)**

# Inactive Ingredients

- Generic formulations **MUST** use inactive ingredients previously approved in a drug product for the same route of administration
- Cannot exceed the quantities previously approved for same route of administration (based on single dose or total daily exposure)
- Meet compendial or other applicable standards of quality, purity, and identity

# Specifications

- Drug product specifications are based on established standards. Typically required to reflect the tightest standard based on:
  - Process capabilities
  - ICH
  - USP
  - Reference listed drug
- Specifications are set to assure quality throughout the shelf life of a product

# Quality Standards

- Product Quality Standards
  - USP
  - ICH
  - Reference listed drug
  - EP, JP
- All inactive and active ingredients must be national and/or international standards of quality

# Quality Standards

- Good Manufacturing Practices
  - Generic facilities are subject to FDA's requirements for good manufacturing practices
  - Inspected with the same frequency as brand facilities

# ANDA Review Process

- Generic drug review cadre represent a mix of highly trained experts
  - Chemists
  - Process engineers
  - Pharmacokineticists
  - Pharmacologists
  - Physicians
  - Pharmacists
- Same relevant training and expertise as New Drugs

# Post Approval Requirements

- FDA has a single, consistent standard for monitoring drug product quality after approval
- Generic manufacturers must review, test and report on drug product quality following the same regulations as brand products

# Quality by Design: A Transition in the Approach to Drug Product Development

# Quality by Design

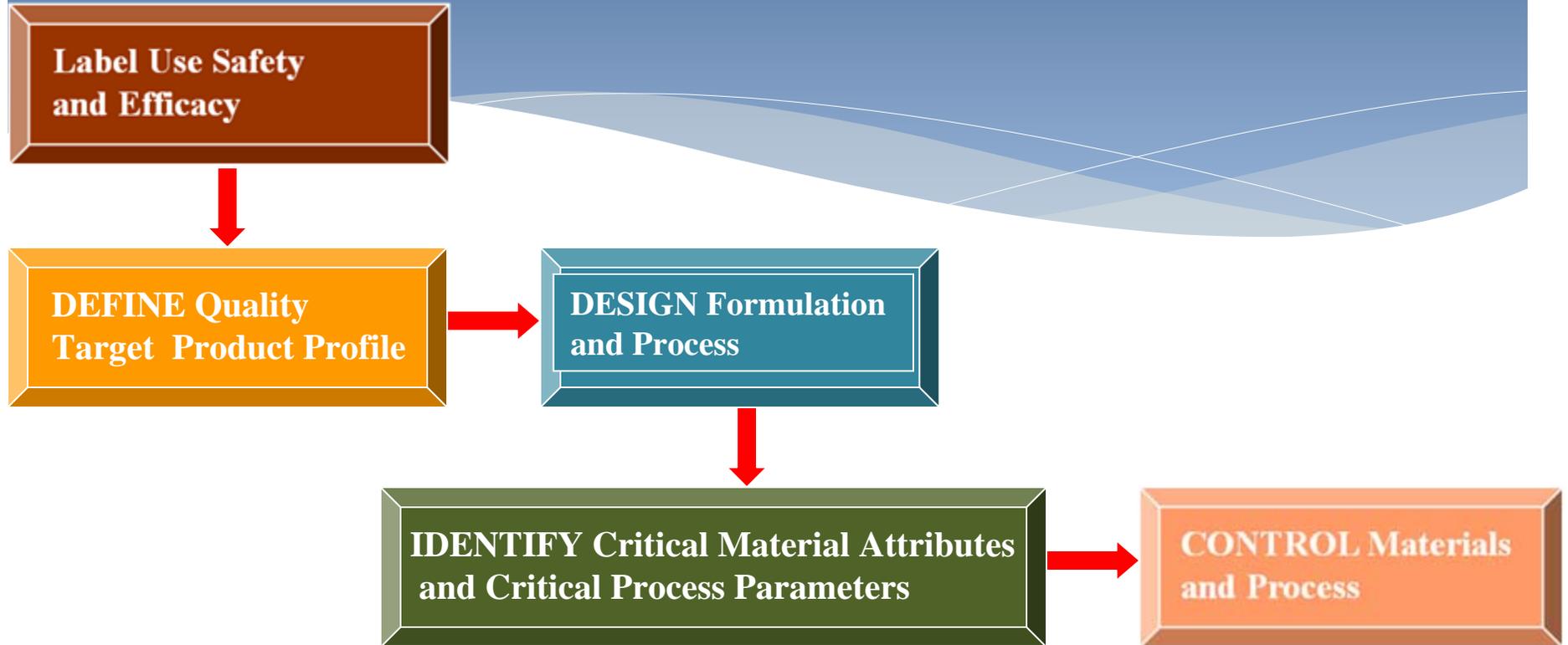
- \*A systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
- \* Industry has historically employed QbD principles
- \*FDA's QbD initiative represents an advancement in regulatory science to provide a more consistent and defined approach to formulation development

# An Integrated Approach to Product/Process Design

\*Helen Winkle- May 5, 2011



# Overview of QbD



**TARGET**

**DESIGN and  
UNDERSTANDING**

**IMPLEMENTATION**

*Yu. Pharm. Res.* 25:781-791 (2008)

# Goals of QbD\*

- Designing quality into all aspects of drug development
- Ensuring manufacturers are responsible for quality of products
- QbD is [in accordance with Q8(R)]:
  - Systematic approach to development
  - Begins with predefined objectives
  - Emphasizes product and process understanding and process control
  - Based on sound science and quality risk management
- Change in how FDA will look at applications - assessment focused on critical quality attributes (chemistry, pharmaceutical formulation, and manufacturing processes) as relate to product performance

\* H Winkle, FDA, May 5, 2011

# Required Elements of QbD for Generic Drugs

- Quality target product profile (QTPP)
  - Including critical quality attributes (CQAs) of the drug product
- Product design and understanding
  - Critical material attributes (CMAs) of the drug substance and excipients
- Process design and understanding
  - Critical process parameters (CPPs)
- Control strategy
  - How and why

# Factors that Impact Product Quality and Performance

- Formulation
- Quality of API and excipients
  - Impurities
  - Physical form
- Storage conditions

# Prior Knowledge

- Industry should be allowed to apply extensive commercial manufacturing experience
- Example: Injectable manufacturing plants utilize a fixed number of well understood terminal sterilization cycles
  - Adopting a suitable existing cycle is the appropriate application of prior knowledge
  - Utilizing existing cycles promotes plant efficiency
  - Re-inventing the wheel or proving the negative provides no value to manufacturer or consumer

# Questions Remain

- Adoption of QbD for active ingredient manufactures
- Use of prior knowledge
- Stability requirements at the time of filing
- Number of batches/size of batches at the time of filing
- How to address scientific disagreements

# QbD and the Manufacture of APIs

- Principles of QbD are not limited to FDF
- What are the agency's expectations for APIs?
  - Implementation timeline
  - Data requirements

# Quality Target Product Profile

- The development goal is to be interchangeable with the brand, i.e. generic
- Not the same as NCE product development
- A justification of therapeutic equivalence should be sufficient for most parameters

QTPP Element	Target	Justification
Dosage form	Tablet	Comparable size, differences in shape and color acceptable
Dosage design	IR tablet	Pharmaceutical equivalent to the brand
Route of Administration	Oral	Pharmaceutical equivalent to the brand
Dosage strength	20 mg	Pharmaceutical equivalent to the brand
Container/closure system	HDPE bottle and cap	Provide 24 month of shelf life
Pharmacokinetics	AUC and Tmax profile BE to brand	Obtain 'A' rating
Drug product quality		
	Physical Attributes	Meet compendial standards, ICH standards and quality parameters established by the brand
	Identification	
	Potency	
	Content uniformity	
	Impurities	
	Residual solvents	
	Dissolution	
	Microbial limits	
	Hardness	
	Friability	
Stability	24 RT temperature shelf life	Market demand upon commercialization

# Generic Drug Safety and Performance

# Ongoing FDA Support of Bioequivalence Standards

**Therapeutic Equivalence of Over-the-Counter Drugs**

**Therapeutic Equivalence Letter to FDA**

January 28, 1998

Dear Colleagues:

As you may be aware, certain individuals board of pharmacy, and drug utilization certain products may differ in the safety or raised by them is whether the safety of from a brand name product to an FDA comment on the safety of interested requests that you inform your staff.

For both brand name and generic products marketed in the U.S., most speed generic drug product, the FDA interchangeable with the brand name product. FDA approved product the health care provider. Both are some appropriate equivalent generic drug. **Therapeutic Equivalence**

In addition to tests per and that there are no documented could not be used. For example, you might drug to assess. In my pay close attention to the product for FDA we should be able to do this with the product might be.

**FROM THE FOOD AND DRUG ADMINISTRATION**

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

January 5, 2004

Dear Mr. Bradley:

This is in reply to your letter to Dr. Janet Wooster that asks for clarification regarding brand name /

The Food and Drug Administration (FDA) for gone through the approval process, brand name. However, as background, the eight manner described below. This information does not meet prior to approval.

- The basis for submitting a new drug application must be a previously approved drug. The generic product administration, dosage.
- The generic firm or brand name drug that the two products are interchangeable in the patient population.
- In addition to labeling, the generic firm must previously have marketed the drug in the United States.
- A generic manufacturer must have previously marketed the drug in the United States.
- The generic firm must have previously marketed the drug in the United States.

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

January 11, 2000

Dear Ms. Schaller:

This is in reply to your correspondence dated November 11, 1999, regarding a statement you submitted to the FDA regarding the safety of generic drugs. It was forwarded to the FDA for review.

The FDA has many years of experience in the review and equivalence of generic drugs. The FDA is to ensure that all drugs marketed in the U.S. are safe, effective, and of high quality. The FDA requires that the proposed generic product be equivalent to the brand name product in terms of safety, strength, quality, purity, and performance in both the rate and extent of absorption.

FDA considers an therapeutically equivalent (1) they are approved in the same dosage form and route of administration, (2) they are equivalent in strength, quality, purity, and performance, and (3) they are manufactured in accordance with Good Manufacturing Practices.

FDA considers drug products to be therapeutically equivalent if they have the same active ingredient, the same strength, the same dosage form, and the same route of administration. The FDA also considers drug products to be therapeutically equivalent if they have the same active ingredient, the same strength, the same dosage form, and the same route of administration, and the products are manufactured in accordance with Good Manufacturing Practices.

**U.S. FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**BIOTRANSFORMATION AND PHARMACOKINETICS**  
 (Composed with the American Pharmacists Association and the American Association of Clinical Pharmacologists)

MONDAY, MAY 21, 2000

The joint meeting was held at 8:30 a.m. in the Boardroom of the National Transportation Safety Board, 1200 Pennsylvania Avenue, N.W., Washington, D.C. Dr. David C. Goff, Director of the Center for Drug Evaluation and Research, and Dr. Paul W. Lehmann of Johns Hopkins University were the speakers.

**DAVID C. GOFF, M.D.**, Director, Division of Metabolic and Endocrine Drug Products, Division of Biopharmaceutics and Pharmacokinetics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

**PAUL W. LEHMANN, M.D.**, Johns Hopkins University School of Medicine, Division of Biopharmaceutics and Pharmacokinetics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

**NEAL P. GROSS**, Director, Division of Biopharmaceutics and Pharmacokinetics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

# Generic Drug Bioequivalence Studies

- 1997 study of 127 bioequivalence studies
  - Mean difference between brand and generic
    - AUC = 3.47%
    - Cmax = 4.29%
- 1984-1986 study of 224 bioequivalence studies
  - Mean difference between brand and generic
    - AUC = 3.5%
- 2009 study of 2,070 bioequivalence studies performed between 1996-2007
  - Mean difference between brand and generic
    - AUC = 2.3%

Original article

**Acute epilepsy exacerbations in patients switched between A-rated anti-epileptic drugs**

**Conclusions:**

After addressing potential confounders, no evidence that A-rated switching was associated with increased acute exacerbations of epilepsy was found. Study limitations include potentially incomplete identification of seizures, no information on indication for medication use, and limited information on duration and severity of disease. This study provides additional insight into the relationship between A-rated AED switching and acute exacerbations of epilepsy.



# Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

## A Systematic Review and Meta-analysis

**Conclusions** Whereas evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs, a substantial number of editorials counsel against the interchangeability of generic drugs.

*JAMA. 2008;300(21):2514-2526*

[www.jama.com](http://www.jama.com)

Original article

# Acute epilepsy exacerbations in patients switched between A-rated anti-epileptic drugs

**Conclusions:**

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## **Observational cohort study of switching warfarin sodium products in a managed care organization**

CLAUDIA N. SWENSON AND GRODZANA FUNDAK

“Conclusion... Use of a generic warfarin sodium product... in patients previously receiving the innovator product... did not change the International Normalized Ratios more than did continued use of the innovator product...”

## Seizure Outcomes Following the Use of Generic versus Brand-Name Antiepileptic Drugs

### A Systematic Review and Meta-Analysis

Aaron S. Kesselheim,<sup>1</sup> Margaret R. Stedman,<sup>1</sup> Ellen J. Bubrick,<sup>2</sup> Joshua J. Gagne,<sup>1</sup> Alexander S. Misono,<sup>1</sup> Joy L. Lee,<sup>1</sup> M. Alan Brookhart,<sup>3</sup> Jerry Avorn<sup>1</sup> and William H. Shrank<sup>1</sup>

### Conclusion

A systematic review and meta-analysis of trials comparing seizure outcomes from use of brand-name and generic AEDs shows no association between loss of seizure control and generic substitution for at least three types of AEDs. Observational study data suggest that brand-name-to-generic AED switching may be associated with 'switch-backs' and increased rates of health services utilization, but these studies are limited by unmeasured confounders and other factors in their design. Although physicians may want to consider more intensive monitoring of high-risk patients taking AEDs when any medication change occurs, in the absence of better data, there is little evidence-based rationale to challenge the implementation of generic substitution for AEDs in most cases.

Conclusion... there is little evidence based rationale to challenge the implementation of generic substitution for AEDs in most cases.”



Journal of the American Pharmacists Association

## Consumers' Views on Generic Medications

**Caroline A. Gaither, Duane M. Kirking, Frank J. Ascione, and Lynda S. Welage**

J Am Pharm Assoc 41(5):729-736, 2001. © 2001 American Pharmaceutical Association

**Conclusion:** More research is needed on consumers' decision-making processes and behaviors regarding generic medications. Mass education efforts, financial incentives, and greater communication among patients and health care professionals should continue to influence the use of generic medications.



## **Discontinuation Rates and Healthcare Costs in Patients Starting Brand and Generic Sertraline**

**Anna Vlahiotis, MA; Scott Devine, PhD, MPH; Jeff Eichholz, PharmD; Adam Kautzner, PharmD**

**Presented at the  
2010 Academy of Managed Care Pharmacy Educational Conference, October 15, 2010, Saint Louis, MO**

“Conclusions: The risk of discontinuation and the short-term healthcare costs were lower in patients starting generic sertraline compared with patients starting the branded



## **Discontinuation Rates and Healthcare Costs in Patients Starting Brand and Generic SSRIs and SNRIs**

**Anna Vlahiotis, MA; Scott Devine, MPH, PhD; Jeff Eichholz, PharmD; Adam Kautzner, PharmD**

**Presented at the  
2010 Academy of Managed Care Pharmacy Educational Conference, October 15, 2010, Saint Louis, MO**

“Conclusions: The risk of discontinuation was similar in patients starting either a branded or a generic SSRI/SNRI... The results of this study provide further evidence that the use of generic antidepressants as first-line agents in the treatment of some mental health disorders can be encouraged as an important pharmacy cost saving approach.”

# Summary

- The regulatory structure for generic drugs is designed to assure quality
- FDA scientists apply the same quality standards to brand and generic drugs
- Regulatory science advances/QbD the next step to underscore quality
- Long history of generic drug safety , therapeutic equivalence, patient acceptance