



Bioequivalence Discussion Topics: All Bioequivalence Studies Rule Specific Products Guidance Process

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The following presentation reflects the opinions of the author and does not necessarily represent the official position of the US-FDA

Outline

- The All-Bioequivalence (BE) Studies Rule
 - History
 - Implementation
 - Statistics on data submitted under the rule
- Overview of how BE Recommendations for Specific Products are developed at the Office of Generic Drugs (OGD)



History of the All-BE Studies Rule

All BE studies rule: history

- 2000 – issue discussed before FDA’s Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee
- 2003 – proposed rule posted in Federal Register (FR)
- 2009 – final rule posted in FR
- 2009 – draft companion Guidance for Industry posted
- 2011 – final companion Guidance posted



Implementation of the All-BE Studies Rule

All BE Studies Rule: associated regulations

- Became effective July 2009
- Codified under FDA's regulations
 - 21 CFR 314.94
 - 21 CFR 314.96
 - 21 CFR 320.1
 - 21 CFR 320.21
 - Requires ANDA applicants to submit data from all BE studies conducted on a drug product formulation submitted for approval

All BE Studies Rule: companion guidance

- Describes types of ANDA submissions covered by the All BE Studies Rule
- Recommends a format for summary reports of BE studies
- Explains types of formulations that the Agency considers to be the “same” as that submitted for approval

Types of BE study submissions covered by All BE Studies Rule

- Should submit a complete report for each BE study on which the applicant relies for approval
- Should submit a complete or summary report for all additional BE studies conducted on the same formulation of the drug product contained in
 - ANDAs
 - ANDA amendments
 - ANDA supplements requiring BE studies
 - ANDAs submitted under a suitability petition
 - ANDA annual reports

Same drug product formulation

- The formulation of the drug product submitted for approval
- Any formulations that
 - Have minor differences in composition or method of manufacture from the formulation submitted for approval
 - But similar enough to be relevant to the FDA's determination of BE
- Examples on how to apply are given in the guidance

“Same” formulation

IR products and non-release controlling excipients in MR products

- Difference in ingredient intended to affect color or flavor
- Different approved printing ink ingredient
- Difference in excipient technical grade, specification
- Difference in drug substance or excipient particle size
- Minor differences in excipient amounts; table in Guidance provides clarification

“Same” formulation

if differences \leq percentages shown below
IR and MR non-release controlling excipients

Excipient	Difference (\leq) in Excipient Wts Between Two Formulations
Filler	10
Starch	6
Other disintegrant	2
Binder	3
Ca or Mg stearate	0.5
Other lubricant	2
Talc	2
Other glidant	0.2
Film coat	2
Cumulative total of all differences	10

NOT the “same” formulation IR products and non-release controlling excipients in MR products

- Addition or deletion of an excipient
- Difference in excipient weight between two formulations exceeds the percentages specified in the Guidance
- Cumulative total of all excipient weight differences > 10%

“Same” formulation release-controlling excipients in MR products

- Difference in excipient technical grade, specification
- Difference in drug substance or excipient particle size
- Difference in the amount of release-controlling excipient(s) $\leq 10\%$

NOT the “same” formulation release-controlling excipients in MR products

- Addition or deletion of an excipient
- Difference in the amount of release-controlling excipient(s) > 10%

Calculating % differences in excipients between formulations

- Compare experimental (new) formulation versus to-be-marketed (TBM) formulation submitted for approval
- Expressed as the difference in excipient weight between the two formulations

$$100^* \frac{\text{amt in new formulation} - \text{amt in TBM formulation}}{\text{amt in TBM formulation}}$$

- e.g., if new contains 105 mg filler and TBM contains 100 mg filler, this is a 5% difference

Submitting data

- Should submit a summary report for all pilot, non-pivotal, and failing BE studies on the “same” formulation as that submitted for the ANDA
 - Model Summary Tables are posted on FDA’s website
- OGD sends a deficiency letter if summary tables do not follow the format on website
- Also acceptable to submit complete report

Submitting data on studies that fail to meet BE limits

- For an acceptable BE study, the 90% CI of the geometric mean test/reference ratios for AUC and C_{max} should fall within limits of 80-125%
- For each study that fails to meet BE limits, should provide valid explanation of why this is the case
- OGD may send a deficiency if the explanation is missing or inadequate

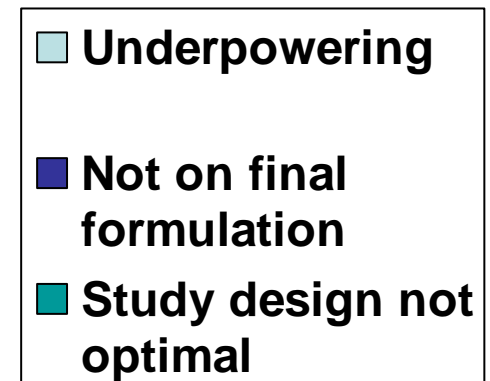
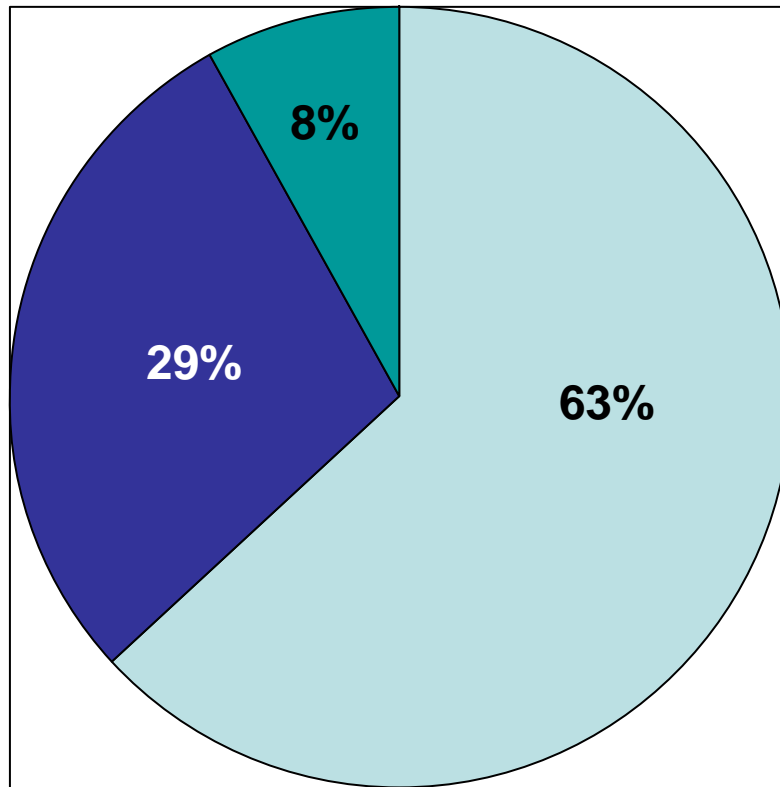


***Statistics on failed BE study
data submitted since the All BE
Studies Rule became effective***

Receipt of failed BE studies for review since July of 2009

Description	Number
No. of BE submissions surveyed	50
Total no. of BE studies reviewed	199
Total no. of failed BE studies reviewed	88
No. of failed BE studies per submission	1 to 6

Information about 88 failed BE studies reviewed from 2009-present





BE Recommendations for Specific Products

Developing specific products BE recommendations guidance



OGD receives letter requesting BE requirements or protocol for a BE study on a specific drug product



OGD assigns to a reviewer



Reviewer researches drug PK, PD, safety, dosing regimen, biopharmaceutics



A written BE review supports each Guidance



Each Guidance is linked to the appropriate NDA, and posted on FDA's website

Additional features of BE guidance development at OGD

- BE reviewers collaborate with
 - OGD clinicians on safety issues; and
 - Office of New Drugs or Office of Clinical Pharmacology on complex products.
- Guidances are posted in draft for comment
- Postings announced in FR
- Comments from industry are received and responded to before finalizing guidances
- 882 guidances now posted

Additional features of BE guidance development at OGD

- Queue time for response to written correspondence from industry is 6-12 months
- Reviewer pool from
 - DB Control Team
 - OGD Science Team, or
 - Occasionally DB reviewers as routine work
- DB Control Team led by CDR Yi Zhang and Kim Raines, Ph.D.
 - 2 reviewers rotate into team each month
 - Overseen by Drs. Conner and Davit

Drugs

Bioequivalence Recommendations for Specific Products

- [Guidance for Industry: Bioequivalence Recommendations for Specific Products \(PDF - 81KB\)](#)¹ (Issued June 2010)
- [Dissolutions Methods Database](#)²

"Please submit comments for any of the guidances posted in the Bioequivalence Recommendations for Specific Products website to the Division of Dockets Management (DDM) under Docket FDA-2007-D-0369-0015. For electronic comments refer to the website <http://www.regulations.gov>³ OR you can mail your written comments to DDM (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Please contact the Regulations.gov HelpDesk at 1-877-378-5475 (toll free) for assistance regarding submissions."

Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient [Total count 882]
A⁴ B⁵ C⁶ D⁷ E⁸ F⁹ G¹⁰ H¹¹ I¹² J¹³ K¹⁴ L¹⁵ M¹⁶ N¹⁷ O¹⁸ P¹⁹ Q²⁰ R²¹ S²² T²³ U²⁴ V²⁵ W²⁶ X²⁷ Y²⁸ Z²⁹

Newly Added Recommendations - September 2011 (5 New; 3 Revision) updated 9/29/2011

Active Ingredient (link to Specific Guidance)	Type	Route of Administration	Dosage Form	RLD Application Number (link to Orange Book)	Date Recommended
Cholestyramine (PDF - 168KB) ²⁷	Draft	Oral	Powder	16640 ²⁸ 19669 ²⁹	9/2011
Clindamycin HCL (PDF - 31KB) ³⁰	Draft	Oral	Capsule	50162 ³¹	9/2011
Dinoprostone (PDF - 159KB) ³²	Draft	Endocervical	Gel	19617 ³³	9/2011
Etravirine (PDF - 34KB) ³⁴	Draft	Oral	Tablet	22187 ³⁵	9/2011
Potassium Chloride (PDF - 34KB) ³⁶	Draft	Oral	Tablet, Extended Release	19439 ³⁷	9/2011

Revisions

Active Ingredient (link to Specific Guidance)	Type	Route of Administration	Dosage Form	RLD Application Number (link to Orange Book)	Date Recommended
Benzoyl Peroxide; Erythromycin (PDF - 209 KB) ³⁸ <i>Revised</i>	Draft	Topical	Gel	50557 ³⁹	9/2011
Benzoyl Peroxide; Erythromycin (PDF - 205KB) ⁴⁰ <i>Revised</i>	Draft	Topical	Gel Pouch	50769 ⁴¹	9/2011
Milnacipran HCL (PDF - 42KB) ⁴² <i>Revised</i>	Draft	Oral	Tablet	22256 ⁴³	9/2011

Links on this page:

1. [/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf](#)
2. [/Drugs/InformationOnDrugs/ucm135742.htm](#)
3. <http://www.regulations.gov>
4. [/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm](#)
5. [/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081288.htm](#)
6. [/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081292.htm](#)
7. [/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081317.htm](#)
8. [/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081318.htm](#)
9. [/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081320.htm](#)

Contains Nonbinding Recommendations

Draft Guidance on Clindamycin Hydrochloride

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

Active ingredient: Clindamycin Hydrochloride

Form/Route: Capsule/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
 Design: Single-dose, two-way crossover in-vivo
 Strength: 300 mg
 Subjects: Healthy males and nonpregnant females, general population.
 Additional Comments:

2. Type of study: Fed
 Design: Single-dose, two-way crossover in-vivo
 Strength: 300 mg
 Subjects: Healthy males and nonpregnant females, general population.
 Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

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

Bioequivalence Based on (90% CI): Clindamycin

Waiver request of in-vivo testing: 75 mg and 150 mg based on (i) acceptable bioequivalence studies on the 300 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.



Summary and conclusions

Summary and Conclusions

- FDA believes that evaluating failed BE studies will increase understanding of how changes in components, composition, and manufacturing methods may affect generic product formulation performance
- Via the Specific Products BE Recommendations Guidances, information on BE study requirements for over 800 potential generic drug products can be found in the public domain

References

- Model Bioequivalence Data Summary Tables,
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf>
- CDER Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134846.pdf>
- CDER Guidance for Industry: BE Recommendations for Specific Products,
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>



Thank you for your attention!