Overview and Changes to the Guidance for Industry: Topical Dermatologic Corticosteroids – In Vivo Bioequivalence

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 1 :Noteworthy Guidance and Generic Approvals for Topical and Transdermal Products

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Learning Objectives

- Understand the revisions to the draft guidance for industry on topical dermatologic corticosteroids

- Able to identify and summarize the major changes to the pilot study and pivotal study criteria and designs

- Provide updates on the public comments received through FDA's docket for the draft guidance

Guidance History

1992 Interim Guidance: Topical Corticosteroids: In vivo Bioequivalence and In Vitro Release Methods	Recommended dermato-pharmacokinetic (skin stripping) and in vitro release studies
1995 Draft Guidance: Topical Dermatologic Corticosteroids: In vivo Bioequivalence	Recommended pharmacodynamic approach (vasoconstrictor assay): pilot dose duration-response study and pivotal bioequivalence study
2022 Draft Guidance: Topical Dermatologic Corticosteroids: In vivo Bioequivalence	Expanded the proposed methodology, including model selection and model optimization for the pilot dose duration-response study and clarified the study design and method qualification

Overview of the Revised Guidance (2022)

- Provide recommendation for potential ANDA applicants using pharmacodynamic (PD) approach to assess the bioequivalence (BE) of topical dermatologic corticosteroids
- Using skin blanching to assess BE of topical corticosteroids
- Measure the PD effect as a function of time
- Recommend two in vivo vasoconstrictor studies

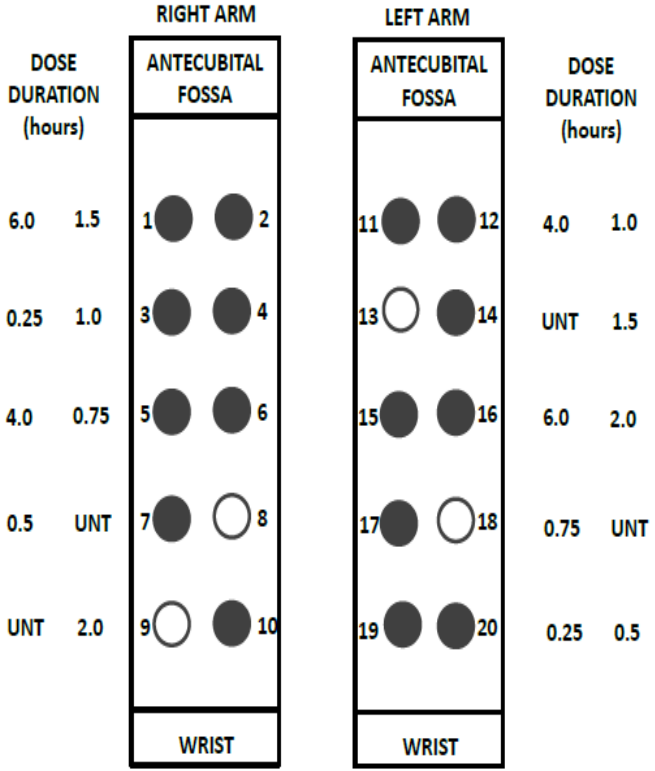
Pilot (Dose Duration-Response) Study: Determine ED50

- ✓ Reference standard only
- ✓ Apply for 7-9 durations
- ✓ Smaller subject numbers (20 - 24)
- ✓ Analysis of all completed subjects

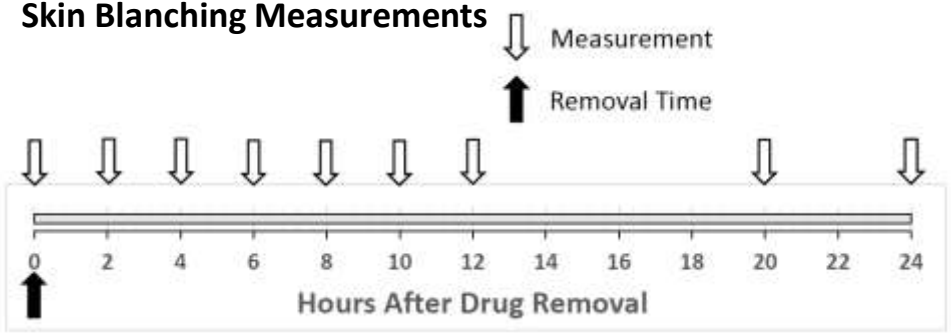
Pivotal BE Study

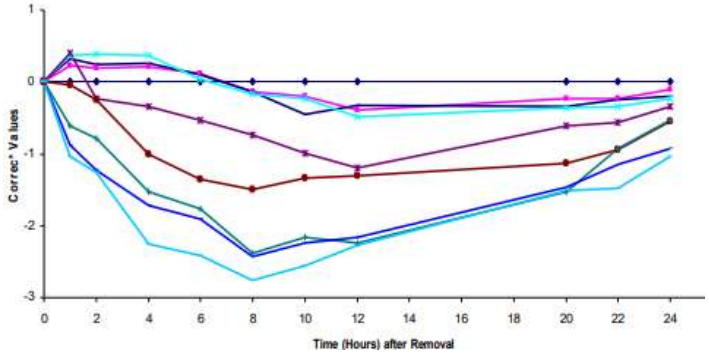
- ✓ Reference standard and test
- ✓ Apply for 3 durations only
- ✓ Larger number of subjects (40 or more detectors)
- ✓ Analysis on sub group of participants (detectors)

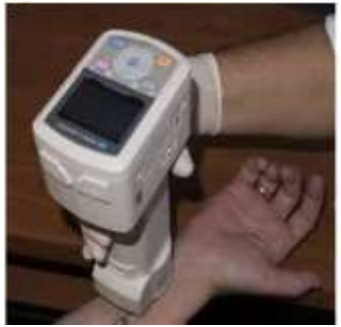
Example of the Skin Blanching Study Design for the Pilot Study



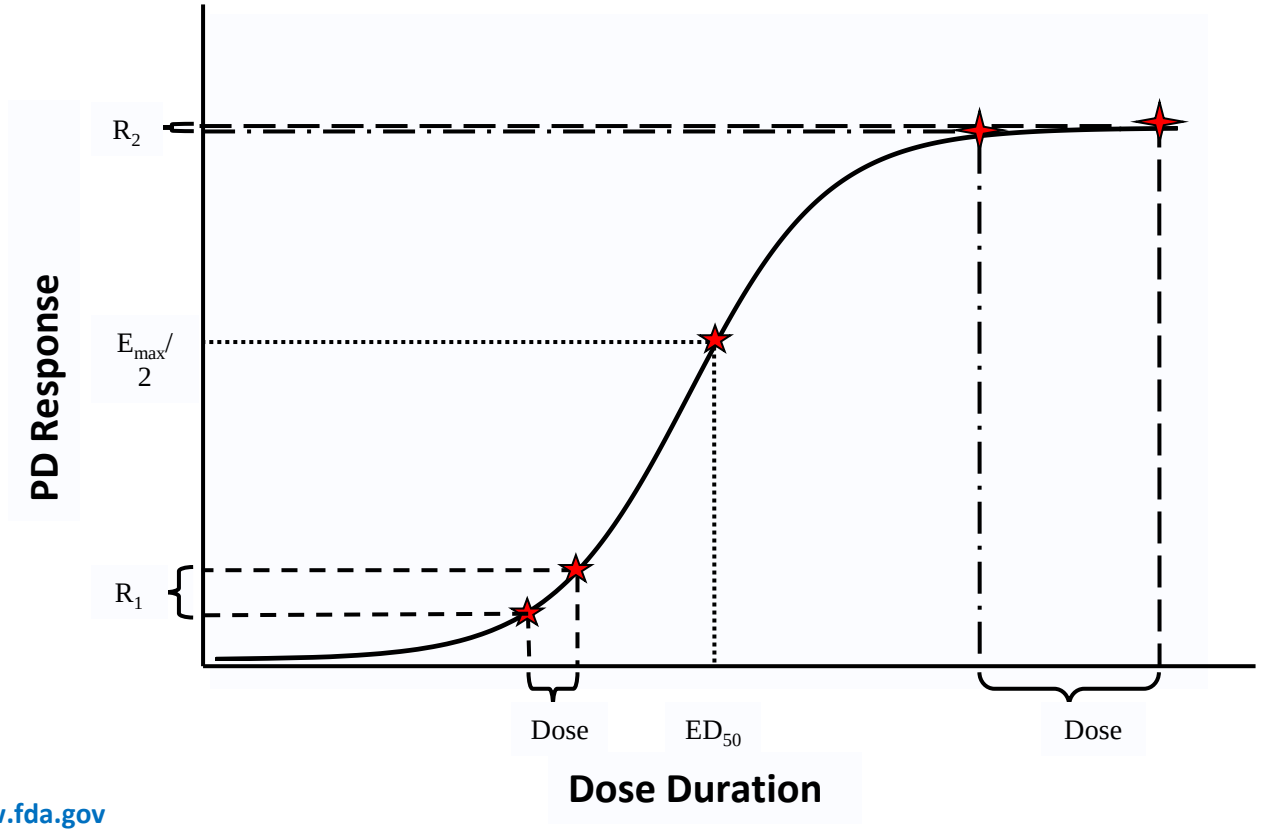
Skin Blanching Measurements







Selection of the Optimal Dose Duration and Detectors for the Pivotal Study



$D1 = ½ * ED_{50}$

$D2 = 2 * ED_{50}$

Subjects for the pivotal study should be a 'PD' detector with D2/D1 ratio of AUEC values ≥ 1.25 for simple Emax model

Summary of Major Changes to Topical Corticosteroid Guidance (2022)

Major Additions: Background

Addition	Rationale
Introduced Reference Standard (RS) in the pilot and pivotal studies	The RS selected by FDA is the specific drug product that the ANDA applicant must use in a conducting any in vivo BE testing required to support approval of its ANDA, the RS, selected by FDA, is ordinarily the reference listed drug (RLD)
Added in vitro characterization-based approach	If the proposed generic formulation contains no difference in inactive ingredients or in other aspects of the formulation relative to the RLD
Added model selection and model optimization for the pilot study	Ensure that the appropriate ED50 estimation is used in the pivotal study

Major Changes: Methods of Application and Removal - AUEC Starting Time and Method of Application

- Provided clarity on AUEC0-24hr starting time for the staggered application with synchronized removal method

	1995 Guidance	Revised 2022 Guidance
Compute AUEC0-24hr	"0" is defined as 0 min after drug removal	"0" is defined as within 15 mins after drug removal

- ✓ No true "0-hr" reading from time of drug product removal
- ✓ Stabilization period is required for the skin to normalize before the first Chromameter reading.

- Removed synchronized application with staggered removal from the guidance

Major Changes: PD Vasoconstrictor Studies - Dose Duration Response Model for Pilot Study

- Recommend the non-linear mixed effect modeling for ED50 determination including Model optimization:
  - E_{max} model selection
  - Estimation methods comparison
  - Model parameter selection
  - Error models selection
  - Initial estimates procedure
- Removed naïve pooled data method to determine the population ED50
- Removed P-Pharm and Simed program in the guidance

Major Changes: Pivotal Study

- Evaluable subjects (e.g., minimum value of the ratio should be 1.25 and both mean AUEC values at D_1 and D_2 are negative) added if simple Emax model is used

- Allowed to use the different ratio for selection evaluable subjects with justification depending on the selected dose duration-response model

- Specified the minimum # of each treatment per arm

	1995 Guidance	Revised 2022 Guidance
Dose durations and control sites on Each Arm	T, R and control: two sites per arm **D1, and D2: one site per arm**	T, R, control, **D1 and D2**: **two sites** per arm

For example: high variability of D1 value was observed.

ID#	RD1	RD2	D2/D1	LD1	LD2	D2/D1	D1	D2	D2/D1
1	10.96	-6.33	-0.58	-11.16	-4.54	0.41	-0.1	-5.44	54.4
2	10.88	-12.02	-1.10	-12.20	-12.38	1.01	-0.66	-12.2	18.48

Added a New Section: Vasoconstrictor Method Qualification

Chromameter qualification: The variability (% CV) for the intra-chromameter and the inter-chromameter measurements should be not more than 15%

Operator qualification: The variability (% CV) for the intra-operator and the inter-operator measurements should be not more than 15%

Updated eCTD Summary Tables

- **Updated eCTD Summary Tables:**

  - 2 (chromameter validation ad operator validation)

  - Removes skin site validation and intra-subject and inter-site validation
    - ✓Skin tone can vary within a subject and between subjects
    - ✓The site validation can only document the variation of measurements within a subject at different measurement sites and the variation of measurements between subjects

- **Link to Revised eCTD Summary Tables**: https://www.fda.gov/media/87599/download

Major Changes: Appendix

- Added example for skin blanching study design for pilot (dose-duration response) study
- Added calculation of AUEC for pilot and pivotal studies
- Added Emax models for pilot study
- Updated analysis of data for pivotal study
- Removed synchronized application with staggered removal schematic

Summary of Major Changes

- Introduced reference standard in the pilot (dose-duration response) and pivotal studies
- Added in vitro characterization-based approach
- Expanded recommendation on model optimization on pilot (dose-duration response) study
- Added a new section on vasoconstrictor method qualification
- Clarified recommendations on computing AUEC and number of replicate for each dose duration on each arm
- Added three new appendices (Appendix II: example for skin blanching study design for pilot dose-duration response study; Appendix III: Calculation of AUEC; Appendix III: Emax Model)
- Removed synchronized application with staggered method

Topic Areas with Questions and Comments Received From FDA Public Docket (FDA-2022-D-2170)

Seven public comments were received through the docket

- Clarify “study subject” in vasoconstrictor method qualification
- Clarify randomization of dose-duration skin sites
- SAS code for ED50 estimation for pilot dose duration-response study

Questions and Comments Received From FDA Public Docket (FDA-2022-D-2170)

- When referring to “study subject” under chromameter qualification and operator qualification section in the draft guidance, does this just mean an individual who would qualify for the study based on the inclusion and exclusion criteria? Can these measures be performed on clinic staff who meet criteria?

- Could the FDA provide the SAS code that they are using to do the nonlinear mixed effect modeling for ED50 estimation in the pilot dose duration-response study?

FDA is reviewing the comments and will publish a revised or finalized guidance in the future.

Summary and Recommendations

- The revised guidance is a crucial resource for ANDA applicants employing a pharmacodynamic approach to assess BE for topical dermatologic corticosteroids

- Applicants can submit questions via controlled correspondences (CCs) or to request a product development meeting for relevant complex products if need FDA's input before the study

- FDA provides multiple communication channels (such as CCs, product-development meetings and post-complete response meetings) at different stages to address industry's questions for generic drug development and regulatory approval

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Challenge Question #1

Only ‘detectors’ should be included in the pivotal study for bioequivalence evaluation.

A. False

B. True

Challenge Question #2

Which statement is true?

A. Only the reference standard is recommended to be used in the pilot (dose-duration vasoconstrictor response) study.

B. Both the reference standard and test product are recommended to be used in the pilot (dose-duration vasoconstrictor response) study.

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