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Blinding during Bioequivalence Trials

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Outline

- Bioequivalence studies
- Blinding codes
- FDA inspections
- Case examples
- Closing remarks

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Bioequivalence

- 21 CFR 314.3
  - **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…

Bioequivalence (BE) Studies

- Pharmacokinetic Endpoint BE studies
  - Typically a single-dose, randomized, open-label study
  - BE is based on drug concentrations in biological samples collected at various time points before and after treatment
- Clinical Endpoint BE study
  - When a drug is not intended for systemic absorption, or measurement in the blood is not practical
  - BE is determined by evaluation of clinical efficacy

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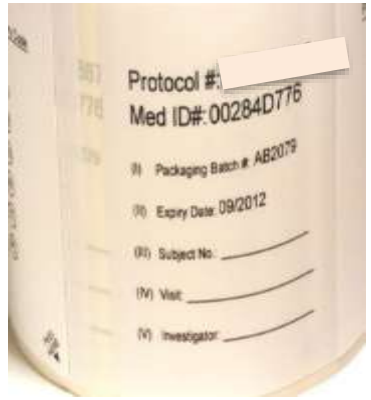
Clinical Endpoint BE Study

- Treatment IDs are typically unknown (blinded) to the investigator and study subjects
- Clinical sites receive drugs labeled with a randomization number or code



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Blinding Codes

- Blinding codes link the randomization number to treatment ID
- Examples include;
  - Tear-apart scratch-off label
  - Sealed envelope
  - Interactive voice/web response system (IVRS/IWRS)

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Blinding Codes

- Guidance for Industry: Handling and Retention of BA and BE Testing Samples (2004)
  - *For a blinded study, we recommend that the study sponsor and/or drug manufacturer provide to the testing facility a sealed code for use by FDA should it be necessary to break the code. The sealed code should be maintained at the testing facility.*
- Bioresearch Monitoring Compliance Program 7348.003 (2018)
  - Inspection Procedures

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FDA Inspections - Blinding

- Evaluate if appropriate individuals were blinded per protocol and they remained blinded throughout the study
- Review subjects' dosing records
- Unblind the treatment subjects received
- Verify if subjects' treatment IDs match with those in submissions
- If blinding codes were unsealed prior to the inspection, evaluate the justifications

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Case Example #1

- Multi-center, randomized, double-blind, pharmacodynamic study comparing innovator's inhalation product to a generic
- Three out of seven clinical sites were selected for inspection
- Dosing document – the site removed the blinded (masked) tear-off label from IP and placed it on a subject's drug dispensation record
- Sponsor's study monitor collected original dosing records and the clinical site only maintained photocopies
- During inspection, sponsor sent back the dosing records to the clinical site

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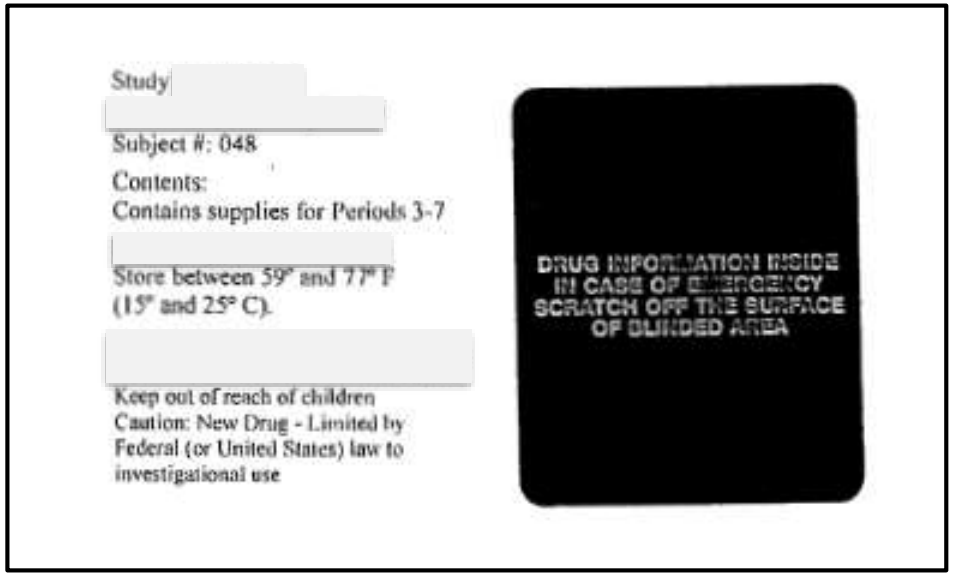
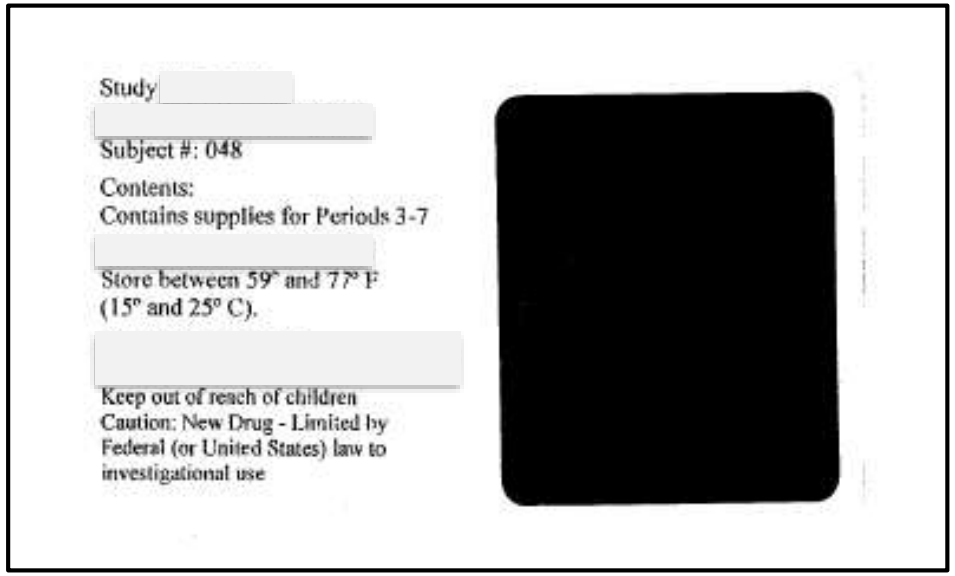
Dosing Records: Original vs. Copy

Photocopy retained at the site



Original returned from the sponsor



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Dosing Verification

- The sponsor could not locate original dosing records for 7 subjects for the study
- FDA recommends the sealed treatment codes be maintained at the testing facility*
- FDA investigator un-blinded the scratch-off label to verify if subjects received correct treatment
  - Discrepancies

*Guidance for Industry - Handling and Retention of BA and BE Testing Samples, May 2004

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Dosing Verification

- Treatment codes in the dosing records/study report did not match with those in the study protocol

	Treatment codes per dosing records	Treatment codes in the study protocol
A	Vehicle (Placebo)	Vehicle (Placebo)
B	Test, 90 mg	Reference, 90 mg
C	Reference, 90 mg	Reference, 180 mg
D	Test, 180 mg	Test, 90 mg
E	Reference, 180 mg	Test, 180 mg

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Dosing Records

- Discrepancies in treatment IDs between the returned dosing records and study protocol
  - Can we ensure who got what?
  - Sponsor collected original dosing records
- FDA's expectation is blinding codes remain at the clinical site throughout the duration of the study and until the FDA inspection

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Case Example #2

- Randomized, double-blind, parallel group study to determine the local equivalence of innovator's and generic oral inhalation products in adult asthma patients
- Interactive voice response system (IVRS) was used for randomization and treatment assignment

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Inspection Findings

- The clinical sites received a sealed envelop containing blinding codes after the study report was finalized
- During inspection, the site did not have access to the IVRS system
- FDA investigator was not able to access IVRS and the audit trail, thus unable to authenticate who got what

Additional Supporting Records

- Subject dispensing logs, including randomization number and kit number
- Material schedule listing kit numbers and drug IDs with an attributable time stamp
- By linking kit numbers in dispensing logs to those in the material schedule, subjects' treatment IDs were verified
- Treatment IDs consistent with the original randomization schedule

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Closing

- Approval of generic drugs is based on demonstration of BE
- Verification of who got what (T/R/P) is critical in determining BE and data integrity for BE studies

Protecting the blind and the appropriate handling of blinding codes help assuring the integrity of the study

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Thank you!

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