Inspecting BA/BE Clinical Studies

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SBIA OSIS Workshop
July 19 - 20, 2022

Disclaimer

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Outline

- Objectives of Compliance Program (CP) - 7348.003
- Scope of Compliance Program (CP) - 7348.003
- Documentation expectation under Compliance Program (CP) - 7348.003
- Summary

Objectives of CP - 7348.003

- To ensure the protection of the rights, safety, and welfare of human subjects participating in drug studies
- To ensure the quality and integrity of clinical, analytical, and statistical data from BA/BE studies
- To ensure compliance with applicable FDA regulations and to identify significant deviations

The scope of CP - 7348.003

This Compliance Program (CP) outlines **procedures** for FDA investigators who inspect domestic or international sites to ensure that the clinical portions of in vivo bioavailability (BA) and bioequivalence (BE) studies, including studies with pharmacokinetic (PK), pharmacodynamic (PD), or clinical endpoints (CE) submitted to the Center for Drug Evaluation and Research (CDER), are conducted in a manner that ensures subject safety and data integrity, and to document study conduct in accordance with applicable regulations.

Clinical portions of in vivo BA/BE studies under CP - 7348.003:

Study Types

- Studies with pharmacokinetic (PK) endpoints
- Studies with pharmacodynamic (PD) endpoints
- Studies with clinical endpoints (CE) (Covered by Dr. Xikui Chen)

Regulated Industry under CP - 7348.003:

Clinical Sites

Clinical sites may include:

- Contract research organizations (CROs)
- Part of a pharmaceutical company
- Other institutions such as hospitals or universities or individual doctor's office (CI)

*Clinical and analytical portions of BA/BE studies may be conducted at the same site or different sites

Possible BA/BE clinical inspections under CP - 7348.003

- OSIS monitors incoming drug applications to identify sites for surveillance inspections.
- Requests from CDER offices that review drug applications
- Directed inspections may also originate from complainants and whistleblowers (self-identified or anonymously) from the public and private sectors.

To evaluate the overall quality of subject safety and data integrity under 7348.003

The minimum 11 components to be included are:

1. Organization
2. Study Administration and Responsibility
3. Subjects' Records and Documentation
4. Test Article Accountability and Disposition
5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis
6. Randomization
7. Blinding Codes
8. Reserve Samples (Covered by Dr. Li-Hong Yeh)
9. Review of Electronic Data
10. International Inspections of Clinical BA/BE Study Sites
11. Reporting

Inspectional component -

Randomization Schedule (1)

- The randomization schedule is used in a clinical trial **to assign subjects randomly to one of the treatment regimens studied in the trial**

- Generated during the study design phase to **reduce any possible biases** that may arise in the trials. Randomization schedule applies to both open-label and blinded clinical trials.

Inspectional component -

Randomization Schedule (2)

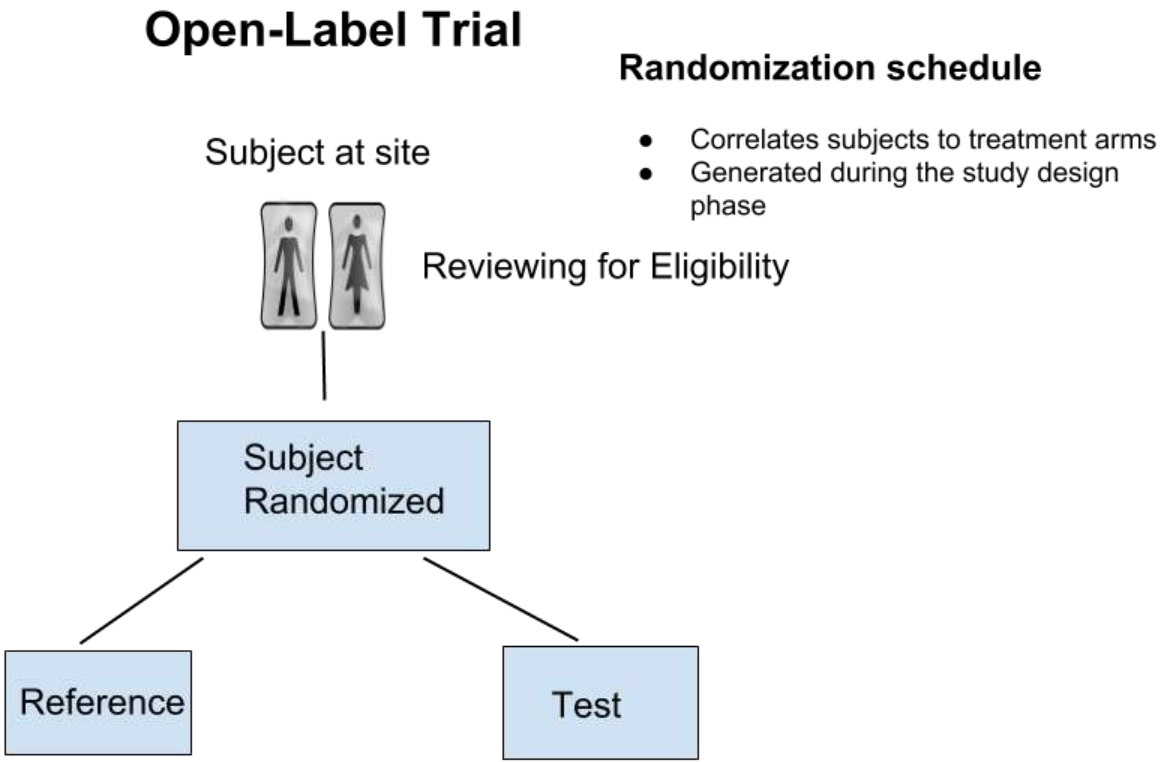
- **Open-label trials** - A type of study in which both the health providers and the subjects are aware of the drug or treatment being given

- **Blinded clinical trials** - A type of study in which the subjects (single-blinded) or the subjects and their doctors (double-blinded) do not know which drug or treatment is being given

Inspectional component -

Randomization Schedule (3)

Open-Label Trial



Inspectional component -

Randomization Schedule (4)

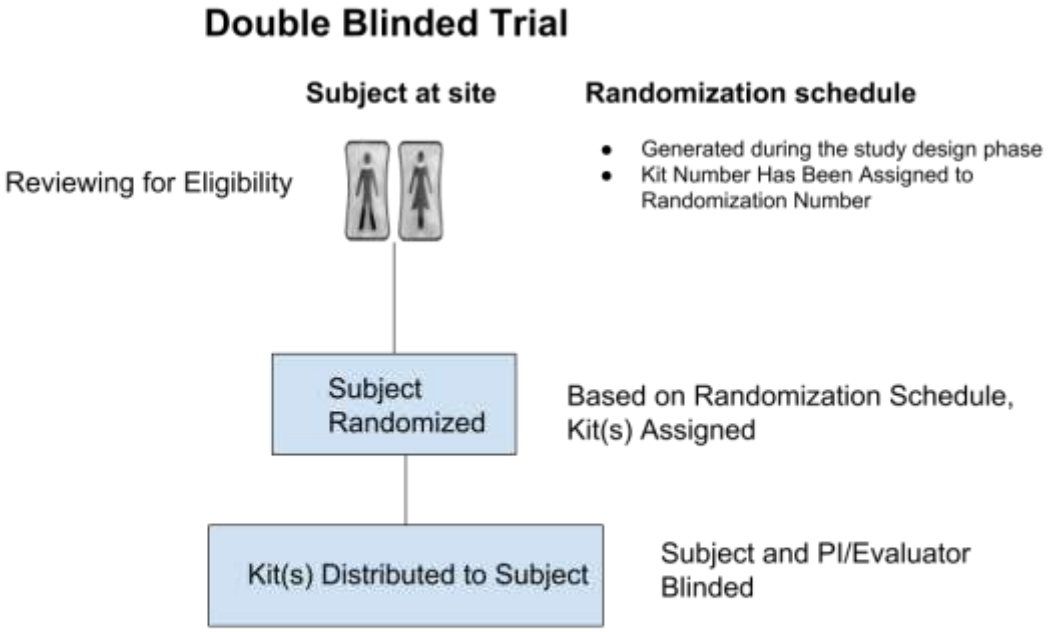
Open-Label Trial

Sequence 1: TR Sequence 2: RT ; Seed No.: 00614

SUBJECT ID	seq	PERIOD 1	PERIOD 2
1	2	R	T
2	1	T	R
3	1	T	R
4	2	R	T
5	2	R	T
6	1	T	R
7	2	R	T
8	1	T	R
9	1	T	R
10	1	T	R
11	2	R	T
12	2	R	T

Inspectional component -

Randomization Schedule (5)



Inspectional component -

Randomization Schedule (6)

Double Blinded Trial

Block Number	Kit Number	Treatment Arm Sequence Number	Treatment Name	Sequence Number
2093	69460	3	C	3279
2094	46556	1	B	3280
2094	30441	2	A	3281
2094	74712	3	C	3282
2095	38193	1	C	3283
2095	71518	2	B	3284
2095	47359	3	A	3285
2096	57078	1	C	3286
2096	32952	2	B	3287
2096	12276	3	A	3288
2097	70069	1	A	3289
2097	65382	2	B	3290
2097	86297	3	C	3291
2098	80723	1	A	3292
2098	19029	2	C	3293
2098	64257	3	B	3294
2099	41689	1	A	3295
2099	81076	2	B	3296
2099	74743	3	C	3297
2100	34736	1	A	3298
2100	17393	2	C	3299
2100	88434	3	B	3300

Inspectional component -

Randomization Schedule (7)

Double Blinded Trial

Compare the randomization schedule submitted to FDA with the randomization schedule maintained on site.

- **Paper based document** when the clinical site received the schedule and who has access to it

- **Application software**: Request a printout randomization schedule from software. If any different, request to access audit trails to trace these changes and evaluate the justifications. If no access to audit trails, request the printout randomization schedule dated on the study initiation date and dated on database lock date, and evaluate the changes and justifications

Inspectional component -
Randomization Schedule (8)

- **Interactive Web Response Systems (IWRS) / Interactive Voice Response Systems (IVRS)** are the technologies that clinical research sites use to enroll subjects into clinical trials, randomize subjects, and manage study drug supplies

- **IVRS/IWRS** can be accessed via telephone or web, and is more user friendly and easy to access from anywhere in the world through telephones or web

- The two technologies (IWRS/IVRS) fall under the umbrella term **Interactive Response Technology (IRT)**

Inspectional component -

Blinding Codes (1)

Blinding codes are used to track drug products – test, reference, or placebo (when applicable) that are given to each study subject without revealing the product identity to the subject, and/or the study personnel.

- Two parts, tear-off “scratch-off” labels that are attached to Kits containing the drug products
- Sealed “code-break” envelopes that are included with each shipment of drug product sent to clinical sites to be maintained at the clinical site for use by FDA
- An electronic version maintained in the software

Inspectional component -

Blinding Codes (2)

- **Accessing** the blinding codes

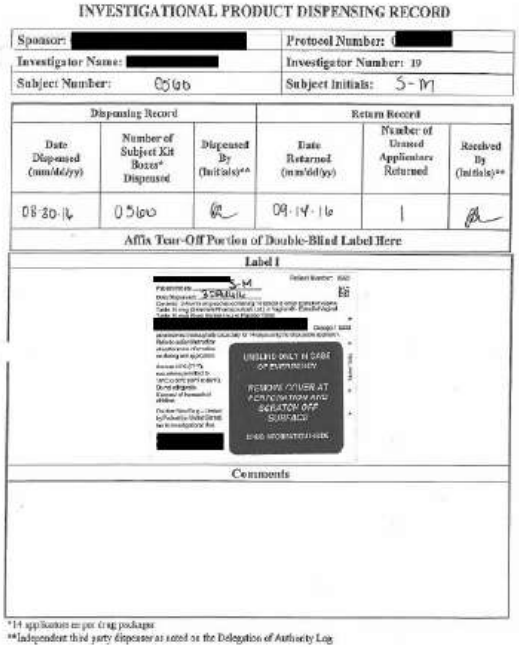
  - ✓ Determine how and when blinding codes were provided to the clinical site
  - ✓ Document whether the blinding codes remained at the clinical site throughout the duration of the study
  - ✓ Evaluate the access to, handling of, and storage of the blinding codes during the conduct of the study and after study completion

- **Breaking** the blinding codes during the inspection (performed by FDA Investigator) and emergency situation by clinical site personnel during the trial

Inspectional component -

Blinding Codes (3)

Examples of scratch off labels



INVESTIGATIONAL PRODUCT DISPENSING RECORD

Sponsor: [redacted]	Protocol Number: [redacted]
Investigator Name: [redacted]	Investigator Number: 19
Subject Number: 0560	Subject Initials: S-M

Dispensing Record			Return Record		
Date Dispensed (mm/dd/yy)	Number of Subject Kit Boxes* Dispensed	Dispensed By (Initials)**	Date Returned (mm/dd/yy)	Number of Unused Applicators Returned	Received By (Initials)**
08-30-16	0560	[redacted]	09-14-16	1	[redacted]

Affix Tear-Off Portion of Double-Blind Label Here

Label 1

[redacted] S-M [redacted] 560 [redacted]

UNBLIND ONLY IN CASE OF EMERGENCY

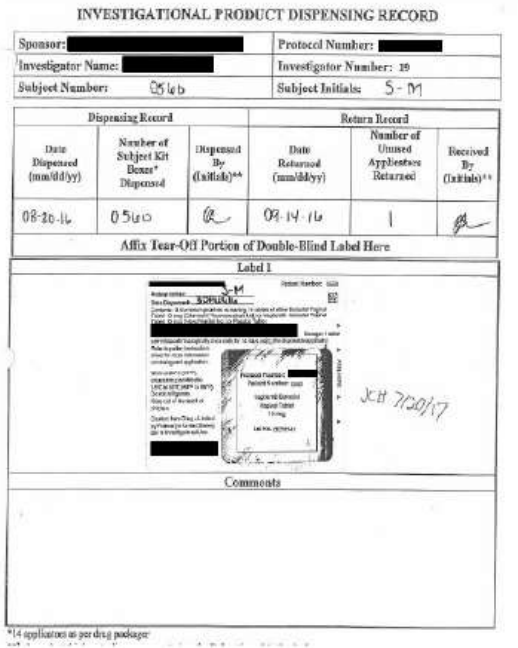
REMOVE COVER AT PERFORATION AND SCRATCH OFF SURFACE

[redacted]

Comments

*14 applicators as per drug packages

**Independent third party dispenser as noted on the Delegation of Authority Log



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Label 1

S-M [redacted] 560 [redacted]

[redacted]

JCH 7/20/17

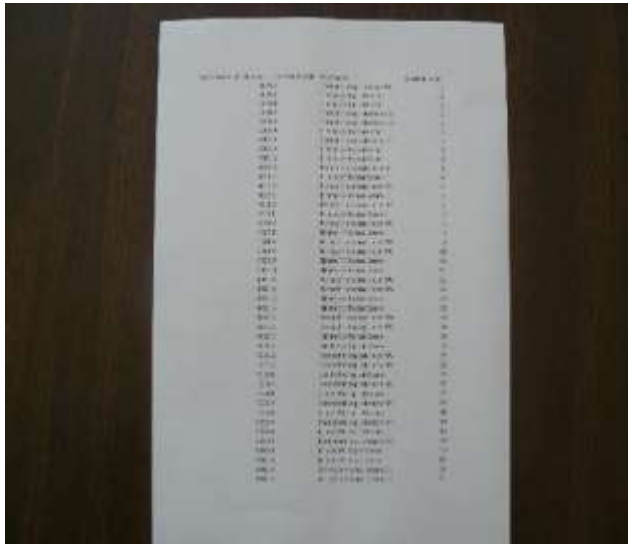
Comments

*14 applicators as per drug packages

Inspectional component -

Blinding Codes (4)

Example of sealed envelope



Inspectional component -

Blinding Codes (5)

Example of blinding codes from IVRS/IWRS

REC_NUM	KIT_NUM	TMT	TMT_TX
1	20678	1	[redacted]001 100/50 µg A
2	10691	1	[redacted]001 100/50 µg A
3	27385	1	[redacted]001 100/50 µg A
4	15597	1	[redacted]001 100/50 µg A
5	26174	1	[redacted]001 100/50 µg A
6	21278	1	[redacted]001 100/50 µg A
7	25533	1	[redacted]001 100/50 µg A
8	19919	1	[redacted]001 100/50 µg A
9	26808	1	[redacted]001 100/50 µg A
10	27462	1	[redacted]001 100/50 µg A

- The list of blinding codes was generated during the study design phase
- Investigational products (IPs) were packaged by packager based on the blinding codes and randomization schedule
- Unblind the blinding codes by clinical site personnel when there are safety reasons via IVRS/IWRS system

Inspectional component -

Blinding Codes (6)

Steps to track that the IPs were blinded per protocol when using IWRS/IVRS

- When were the blinding codes generated?
- Who generated the blinding codes?
- Who has accessed the blinding codes before uploading to IWRS/IVRS? (packager? Others…?)
- When were the blinding codes uploaded into IVRS/IWRS?
- Determine whether audit trail features were enabled after uploading the blinding codes.

Summary

- CP-7348.003 outlines the basic elements to be examined during the BA/BE clinical inspections
- Documentation of study related activities is critical during conduct of clinical BA/BE studies

Acknowledgements

Dr. Xikui Chen

Dr. Michael F. Skelly

Dr. Kimberly A. Benson

Dr. Seongeun (Julia) Cho

Dr. Douglas Pham

OSIS Management

Challenge Question #1

Which of the following records would be audited or reviewed during a clinical inspection for in vivo BA/BE studies?

A. Inclusion/exclusion criteria of subjects

B. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis

C. Informed consent documents

D. randomization scheme

E. All of the above

Challenge Question #2

True or False?

For closed studies, the ORA investigator must unblind the blinding code to assure that study subjects received the assigned treatment that was reported to FDA in the study report. However, ORA investigators usually do not unblind ongoing studies if there is no safety concern.

A. True

B. False

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