Overview of Reserve Samples

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Outline

- US FDA regulations on reserve sample requirement for bioavailability (BA) and bioequivalence (BE) study
  - *in vivo* BA/BE study: Case #1
  - *in vivo* BA/BE study conducted under a Bio-IND: Cases #2
- Good documentation practices during BA/BE study conduct
  - Case #3

Background

Code of Federal Regulations (CFR) Title 21 Food and Drugs

- PART 320 – Bioavailability (BA) and Bioequivalence (BE) Requirements
  - Sec. 320.38 Retention of bioavailability samples
  - Sec. 320.63 Retention of bioequivalence samples

Regulations for reserve sample requirement

320.38 Retention of bioavailability samples

- *"(a) The applicant of an application or supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioavailability testing was performed under contract,* ***the contract research organization*** *shall retain an appropriately identified reserve sample of the drug product for which the applicant is seeking approval (test article) and of the reference standard used to perform an in vivo bioavailability study in accordance with and for the studies described in paragraph (b) of this section that is representative of each sample of the test article and reference standard provided by the applicant for the testing.*

Regulations for reserve sample requirement for BA and BE study

320.63 Retention of bioequivalence samples

- *"The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if bioequivalence testing was performed under contract,* ***the contract research organization*** *shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of the abbreviated application or supplemental application. The applicant or contract research organization shall retain the reserve samples in accordance with, and for the period specified in, § 320.38 and shall release the reserve samples to FDA upon request in accordance with § 320.38."*

Regulations for reserve sample requirement for BA and BE study conducted under a Bio-IND

CFR Title 21 Food and Drugs

PART 320 – Bioavailability (BA) and Bioequivalence (BE) Requirements

- Sec. 320.31 Applicability of requirements regarding an “Investigational New Drug Application.”
  - (a) Any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an "Investigational New Drug Application" (IND) if:
    (1) The test product contains a new chemical entity as defined in § 314.108(a) of this chapter; or
    (2) The study involves a radioactively labeled drug product; or
    (3) The study involves a cytotoxic drug product.

Regulations for reserve sample requirement for BA and BE study conducted under a Bio-IND

CFR Title 21 Food and Drugs

PART 312 – Investigational New Drug (IND) Application

- Sec. 312.57 Recordkeeping and record retention
  - *(d) **A sponsor** shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, § 320.38 or § 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in § 320.38.*
- *Sec. 312.52 Transfer of obligations to a contract research organization*
  - *(a) **A sponsor** may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization.*

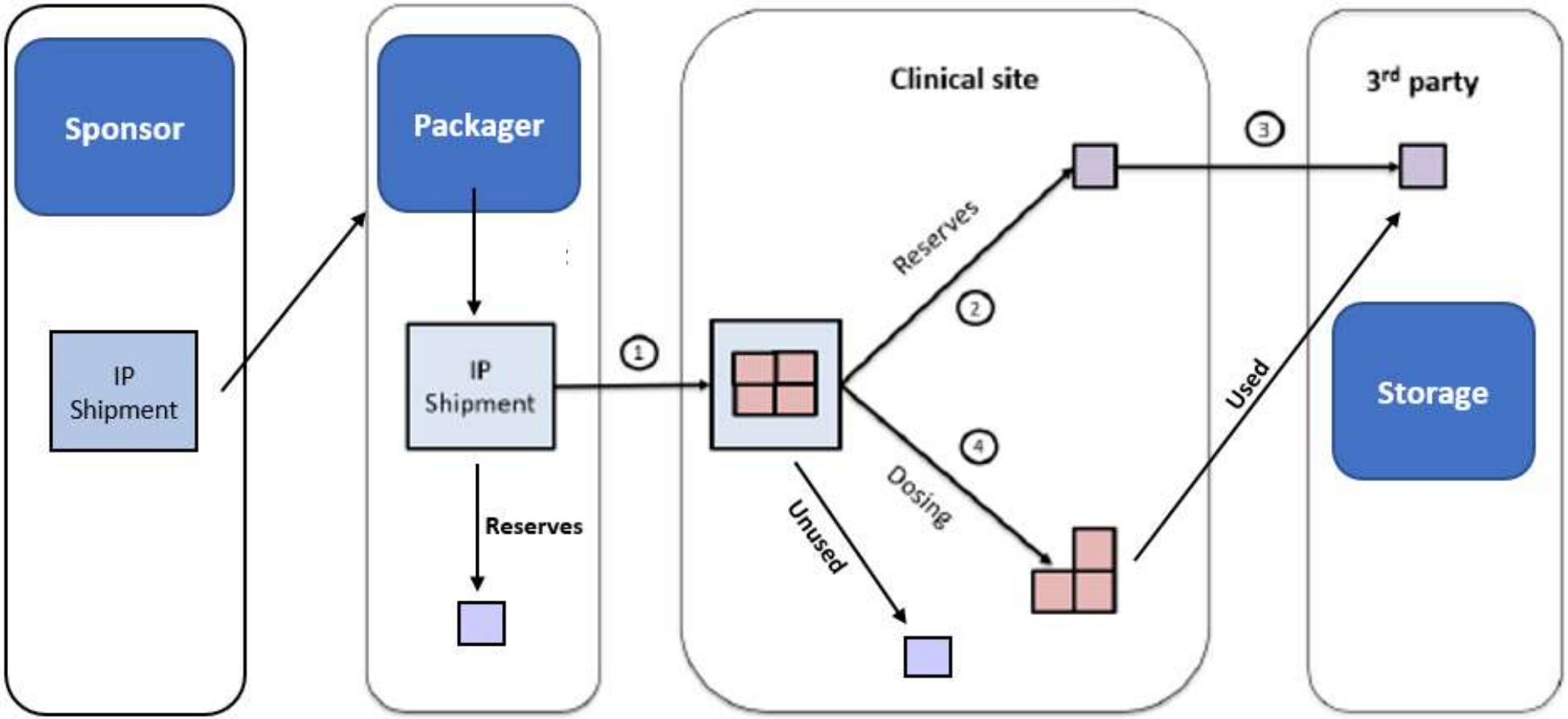
Case #1

- A BE study submitted under 505(j) to support an Abbreviated New Drug Application (ANDA)

- BE reserve sample retention requirement (320.38 & 320.63):
  - *"… the **contract research organization** shall retain reserve samples of any test article and reference standard used in conducting an in vivo… bioequivalence study."*
  - *"Each reserve sample shall be adequately identified so that the reserve sample can be positively identified as having come from the same sample as used in the specific bioavailability study".*

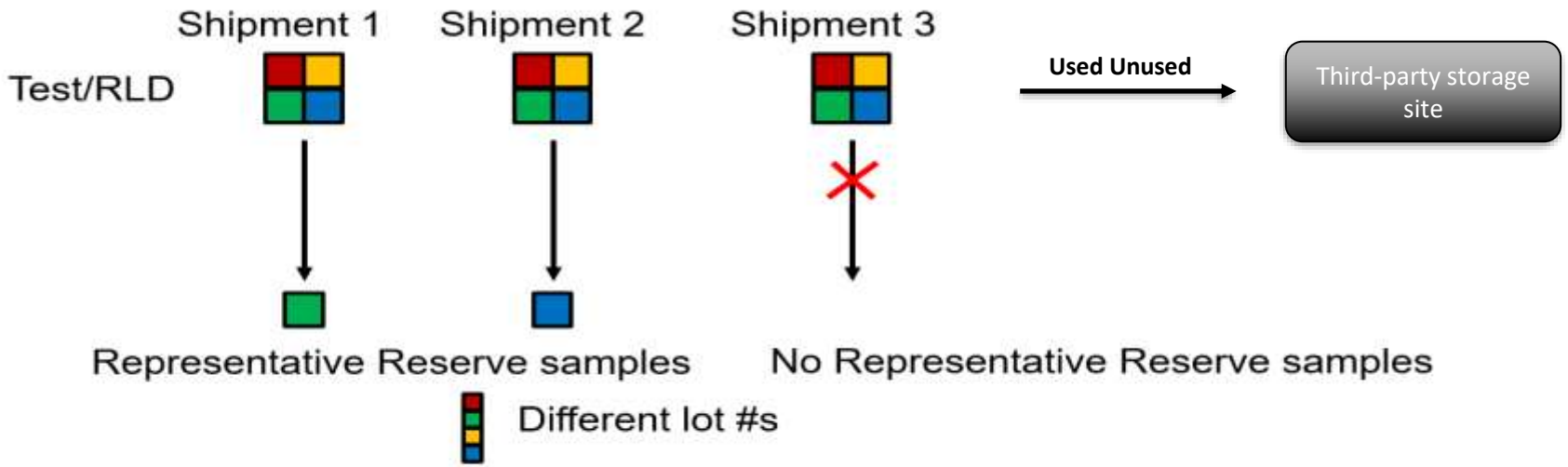
Case #1

- **Key players in the investigational products (IP) handling**



Case #1

- FDA conducted inspection of the clinical site.
- **Outcomes:** Objectionable findings were observed. Specifically,
  - The reserve samples were not retained from all shipments provided for testing in the study.
  - The clinical site indicated that the sponsor instructed them to retain reserve samples from Shipments #1 and #2 only, but not from Shipment #3.
  - After study completion, the clinical site shipped the reserve samples, used and unused IPs to a third-party storage site.



- **Representative reserve samples have to be retained from all shipments of drug products received by the testing site**

Case #1

Evaluation:

- Because the clinical site did not retain reserve samples for reference and test product from Shipment #3, authenticity of the drug products used in part of the study that used drug products from the that shipment could not be verified.
- The clinical site shipped the used and unused IPs from Shipment #3 to a third-party storage site.
- The used and unused IPs from Shipment #3 were retrieved from the third-party storage site and became available for review and verification during the remote record review.
- The used and unused IPs from Shipment #3 were verified and were used to mitigate the impact of not retaining reserve sample from Shipment #3.

Case #2

- A pivotal in vivo BE study with PK endpoint submitted under 505 (b)(2) to support a New Drug Application (NDA) application.
- The BE study had an associated Bio-IND.

- BE reserve sample retention requirement: (21 CFR 312.57, 21 CFR 320.38 and 320.63)
  - *"**A sponsor** shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, § 320.38 or § 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in § 320.38.*
  - ***A sponsor** may transfer responsibility for any or all of the obligations … to a contract research organization."*

Case #2 What is Bio-IND?

Bio-INDs are investigational new drug applications (INDs) submitted for bioavailability (BA) or bioequivalence (BE) studies under **21 CFR 320.31**. The Bio-IND is required by regulations in specific instances to ensure that proposed drug products are safe for use in human test subjects and do not expose them to undue risk.

21 CFR 320.31(a) states that any sponsor planning to conduct an in vivo BA or BE study in humans should submit a Bio-IND if:

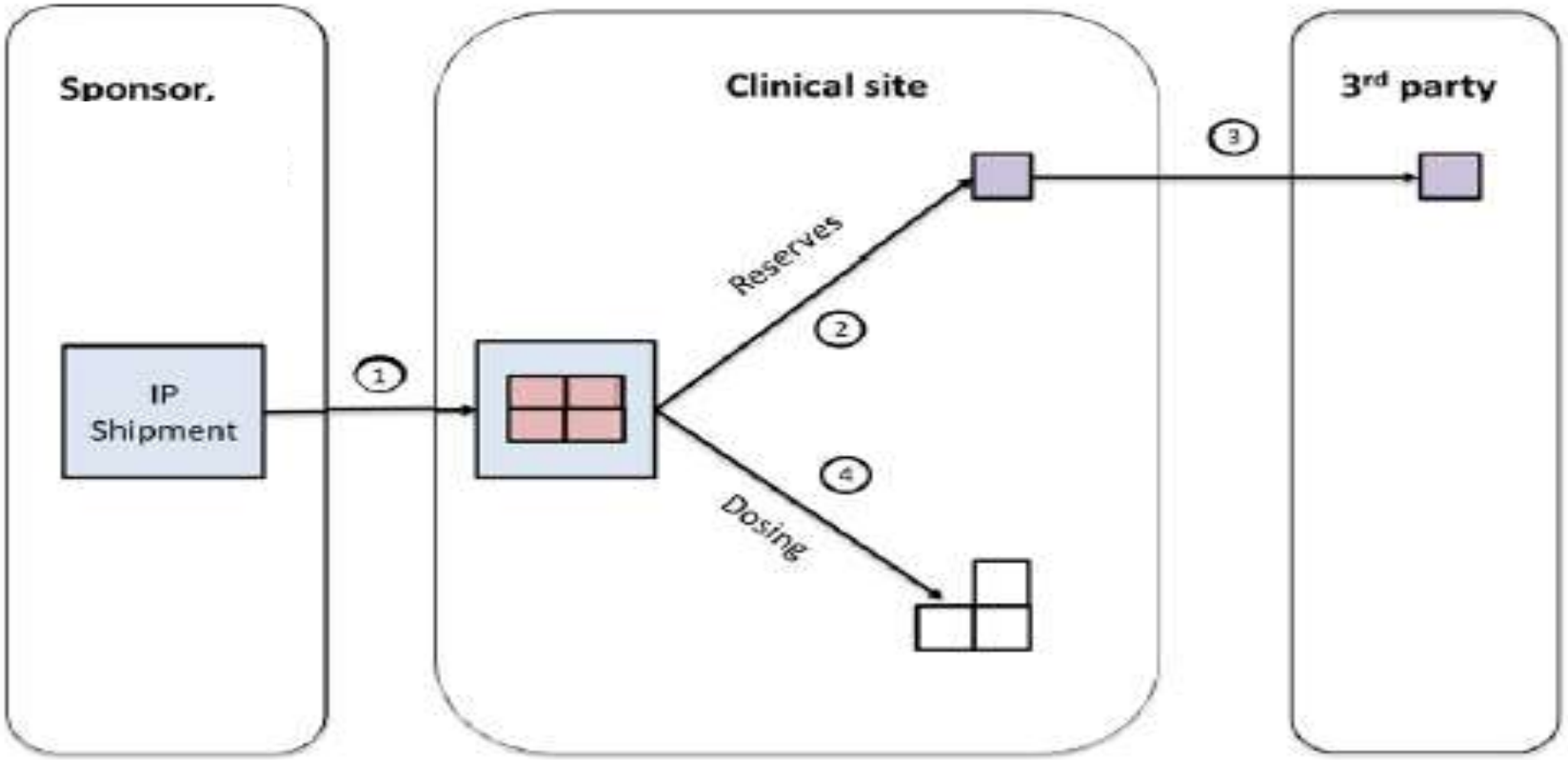
1) The study involves a radioactively labelled drug product, or
2) The study involves a cytotoxic drug.

Case #2

- The BE study had an associated Bio-IND.

- BE reserve sample retention requirement: (21 CFR 312.57, 21 CFR 320.38 and 320.63)
  - *"**A sponsor** shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, § 320.38 or § 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in § 320.38.*
  - ***A sponsor** may transfer responsibility for any or all of the obligations … to a contract research organization."*

Case #2



- Responsible for retaining reserve samples of any test article and reference standard used in conducting an in vivo BE study.
- The sponsor may transfer the responsibility to a CRO.

Delegated by the sponsor to be responsible for selecting reserve samples of the IPs used in the study.

Delegated by the sponsor to be responsible for retaining reserve samples of the IPs used in the study.

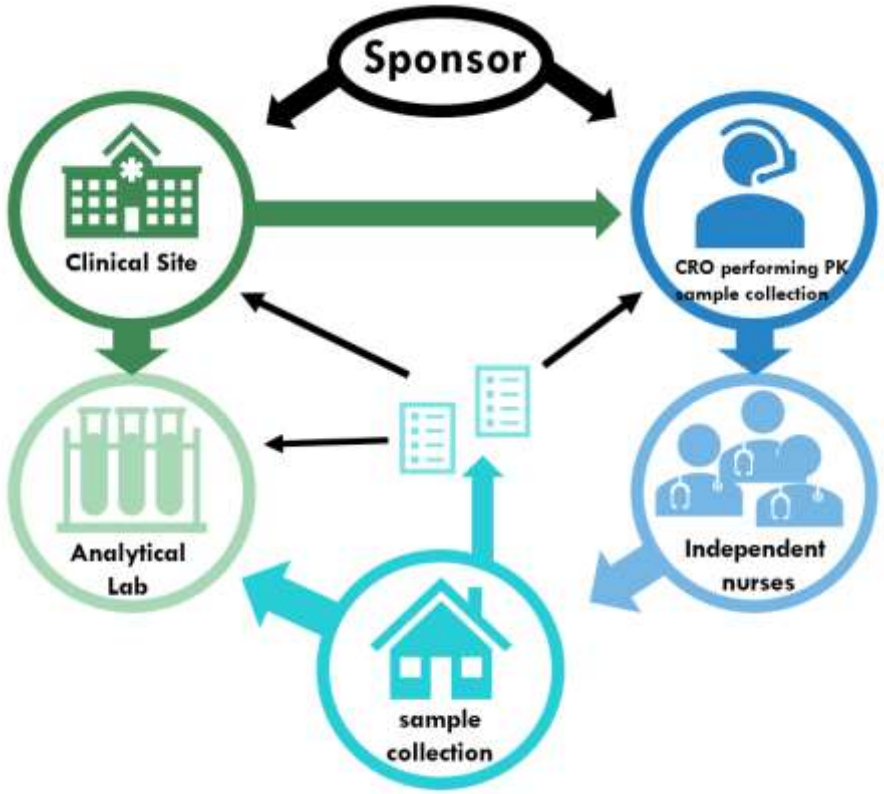
Case #2

- **Inspection outcomes**:
  - The clinical site selected the reserve samples and shipped them to the independent third-party storage facility.

- **Evaluation:**
  - Per the study protocol, reserve retention samples of each study drug were maintained by the sponsor's designee. The sponsor transferred the responsibility of selecting reserve samples to the clinical sites and the responsibility of retaining reserve samples to a third-party storage facility.
  - After completion of the study, each participating clinical site shipped the retention samples to the third-party storage facility as specified by the sponsor using a carrier that maintained proper temperature storage conditions for the duration of the shipment.
  - FDA Investigators verified the reserve samples retrieved from the third-party storage facility during the inspection.
  - This case met the regulatory requirements per 21 CFR 312.57 (d). Therefore, there was no regulatory violation.

Case #3

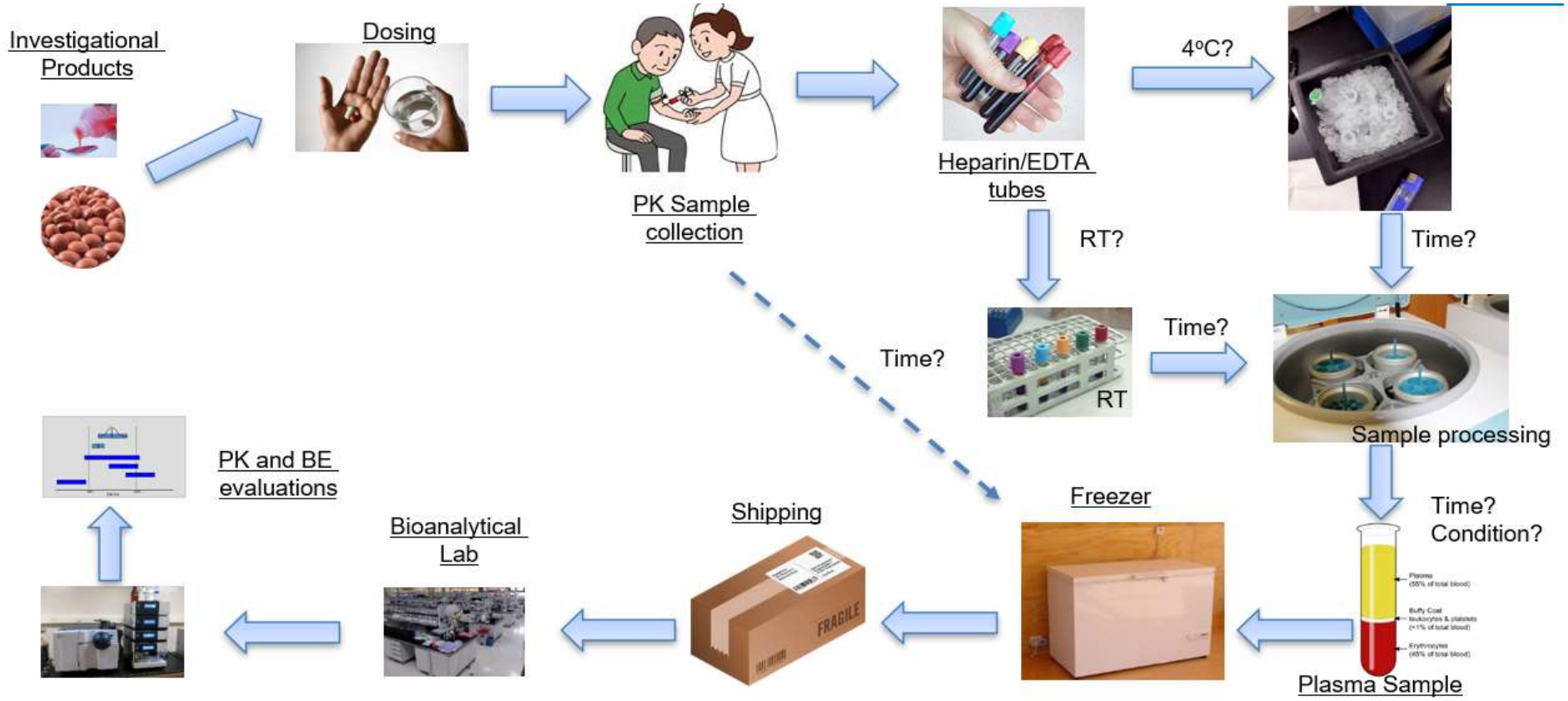
- An in vivo BA study with PK endpoint submitted under 505(b)(2) to support an NDA.
- The sponsor used a CRO to handle PK sample collection and processing at extended timepoints after dosing.



Case #3

- **Outcomes:** Objectionable findings were observed.

  Specifically, documentation for study subject PK sample collection and/or processing at certain timepoints were missing or inconsistent.



Case #3

Evaluation:

- Without the adequate and accurate documentation, it was impossible to reconstruct the conditions those subject samples underwent during collection and processing.

- We concluded that some concentration data of the affected subject samples are not reliable based on the available information provided by the clinical sites and the CRO responsible for PK sample collection

Concluding Remarks

- Become familiar with the relevant US FDA regulations on reserve sample requirements for BA and BE studies.
  - *in vivo* BA/BE study
  - *in vivo* BA/BE study conducted under a Bio-IND

- Understand the importance of good documentation practices during BA/BE study conduct and the potential impact on study data integrity.

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