Challenges & Expectations for BE Site and Manufacturing Facility Information in Applications

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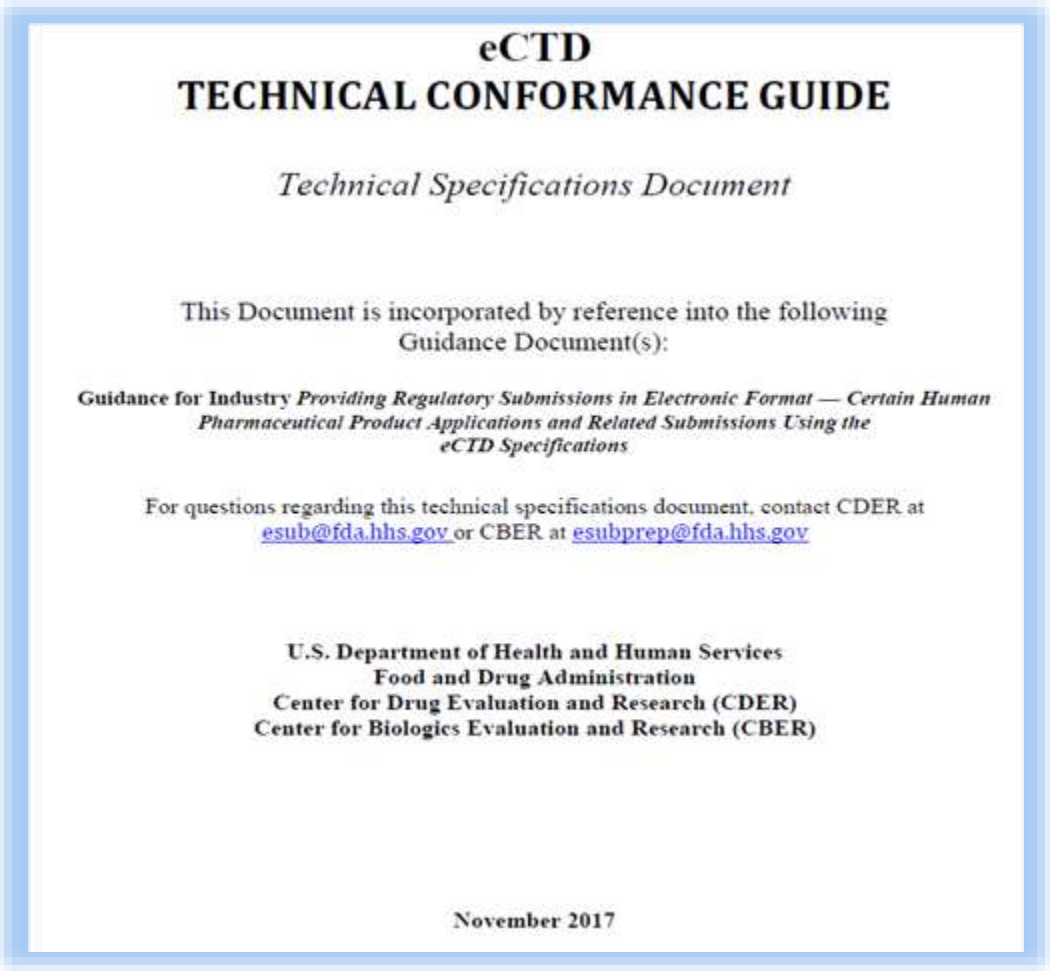
eCTD Technical Guidance on Bioequivalence Site Information



eCTD
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

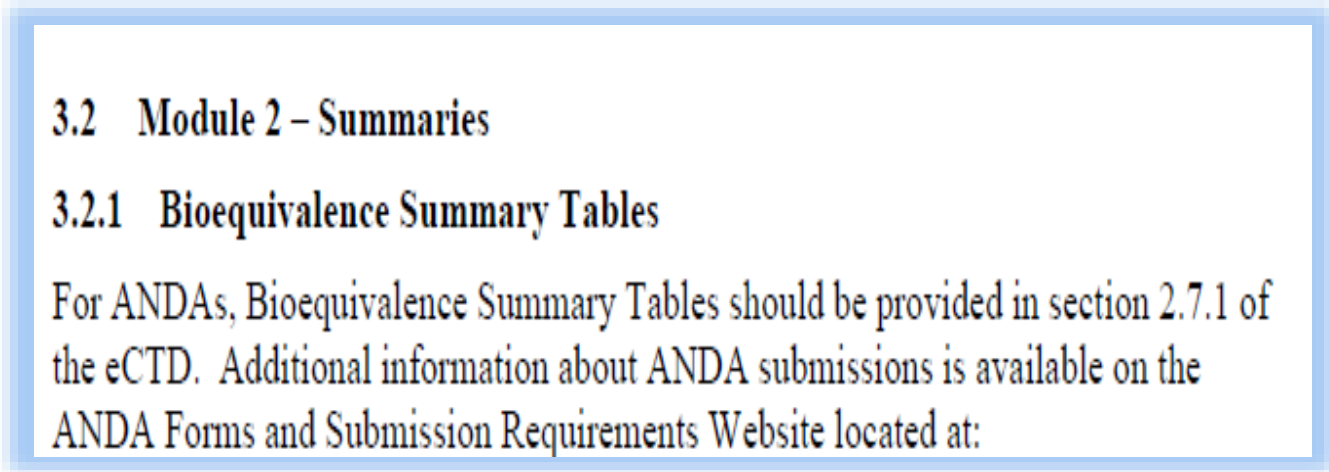
This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry ***Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications***

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2017



3.2 Module 2 – Summaries

3.2.1 Bioequivalence Summary Tables

For ANDAs, Bioequivalence Summary Tables should be provided in section 2.7.1 of the eCTD. Additional information about ANDA submissions is available on the ANDA Forms and Submission Requirements Website located at:

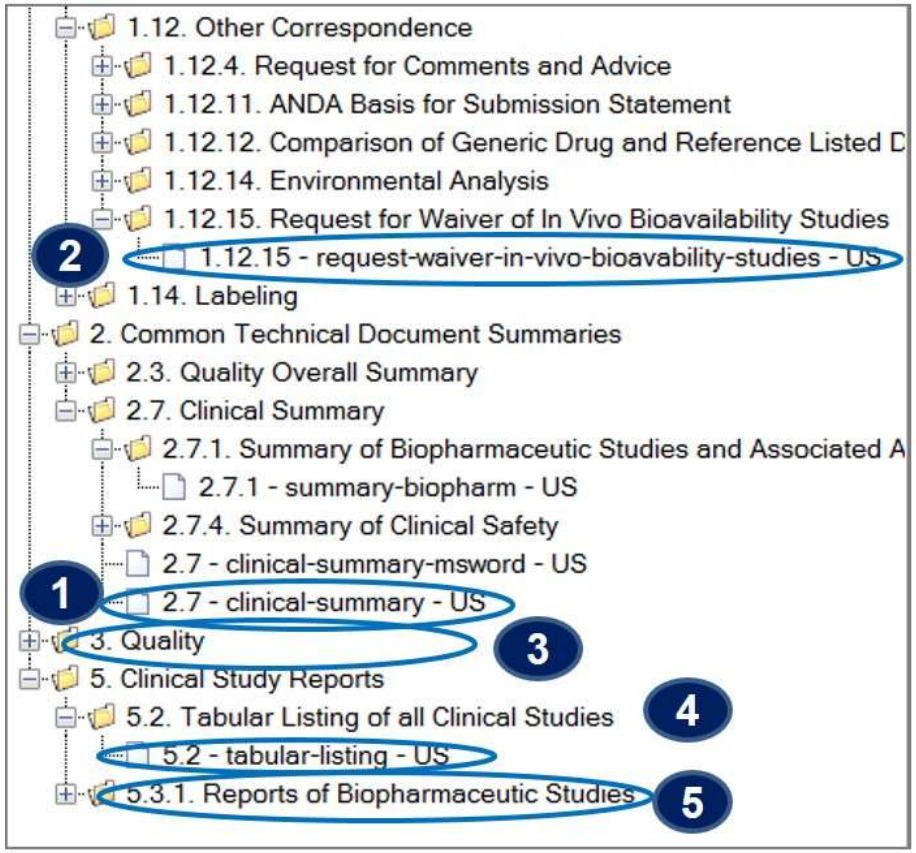
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm

Current Guidance

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf

IN VITRO BE Site Capture Process

From the submissions that FDA Received, BE site information are often not submitted in section 2.7.1. FDA has to retrieve BE Site information from multiple places in the submission. When Site Information are buried in various Modules.



Place 1	**Clinical Summary document in provided in Table 1 under Module 2.7.1.**
Place 2	**No sites mentioned in Table 10 but a bio-waiver included in Module 1.12.15, retrieve "In Vitro BE" site if any**
Place 3	**Bioequivalence site presented in Module 3 Tabular Listing**
Place 4	**Bioequivalence site presented in Module 5 Tabular Listing**
Place 5	**If an "In Vitro BE" study is identified, the analyst needs to look within Module 5 clinical reports to locate the actual "In Vitro BE" site. There is no standard section within the report that has the study details. In order to locate the In Vitro BE study, the analyst may need to perform a word search.**

Challenges associated with BE Site Capture

Challenge 1- <u>BE Site not listed on correct table</u>: On ANDA **2AAAAA (example 1)**, the in vitro BE site was mentioned in module 2 under table 6.1, please note there is no table 10 within module 2. Site is listed on an unusual table within module 2.

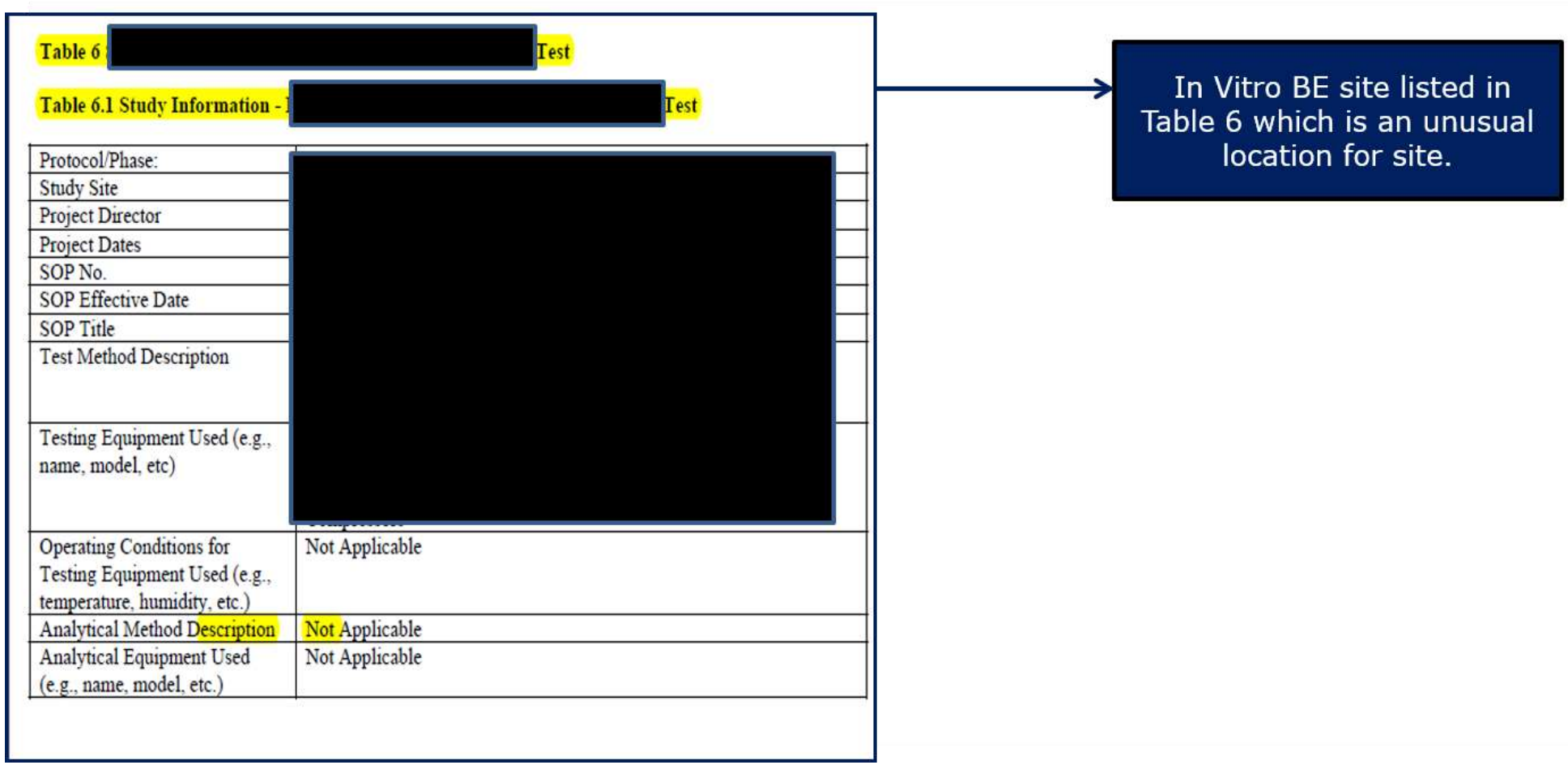


Table 6 [redacted] Test

Table 6.1 Study Information - [redacted] Test

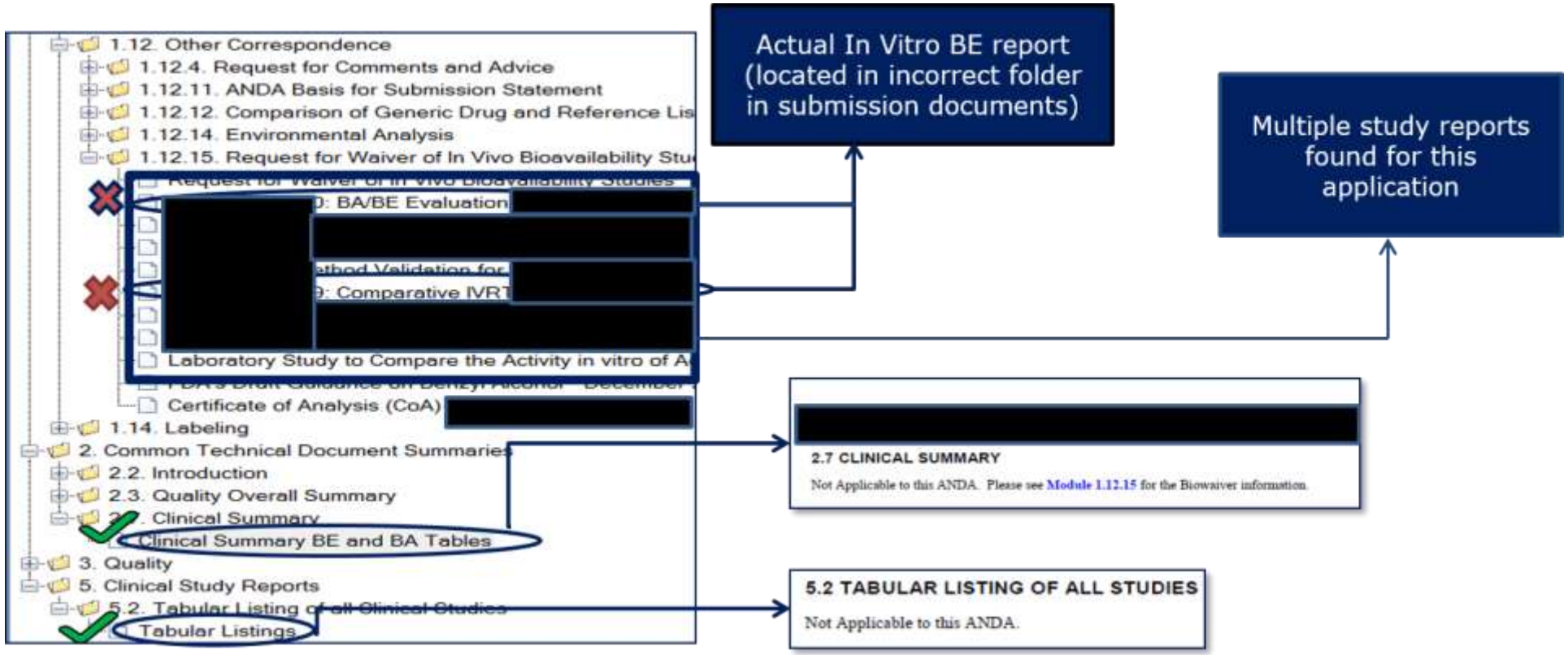
Protocol/Phase:	[redacted]
Study Site	
Project Director	
Project Dates	
SOP No.	
SOP Effective Date	
SOP Title	
Test Method Description	
Testing Equipment Used (e.g., name, model, etc)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc.)	Not Applicable
Analytical Method Description	Not Applicable
Analytical Equipment Used (e.g., name, model, etc.)	Not Applicable

In Vitro BE site listed in Table 6 which is an unusual location for site.

Challenges associated with BE Site Capture

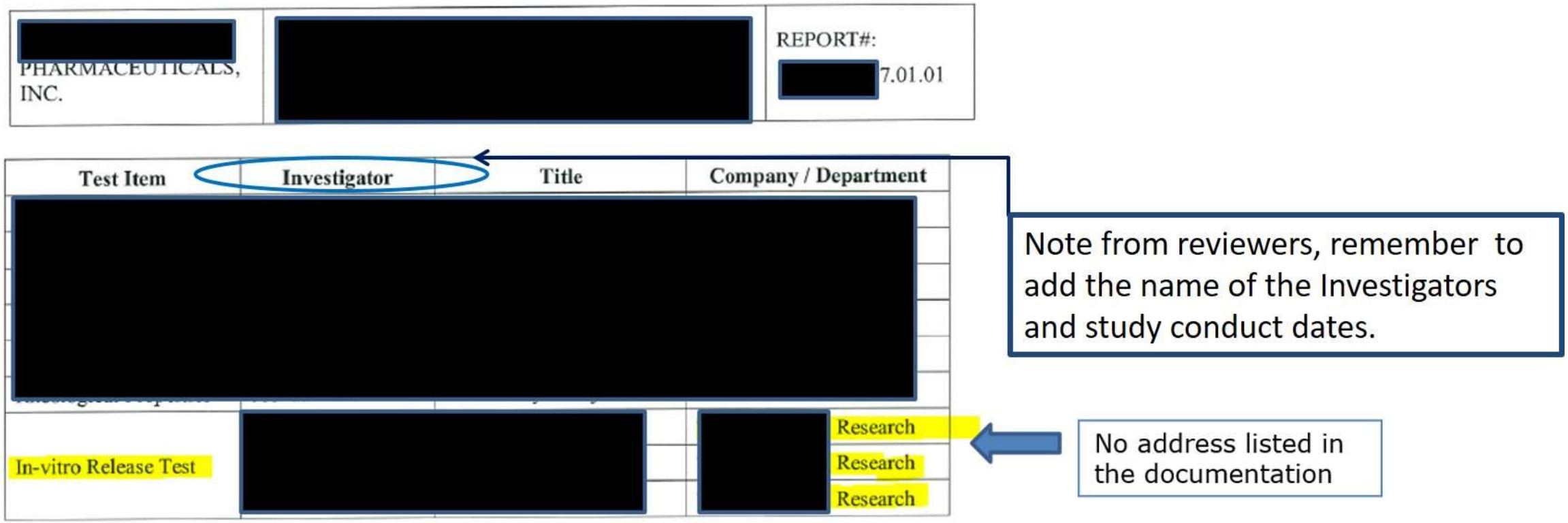
Challenge 2- <u>BE Site Not listed in correct location</u>: In Vitro BE sites are usually not centralized in a particular location, and can be difficult to locate within multiple documents and in different Modules.

➢ANDA **2BBBBB (example 2),** the In Vitro BE site was located in Module 1 rather than in Module 2, Table 10. Also with multiple reports to review with potential In Vitro BE studies.



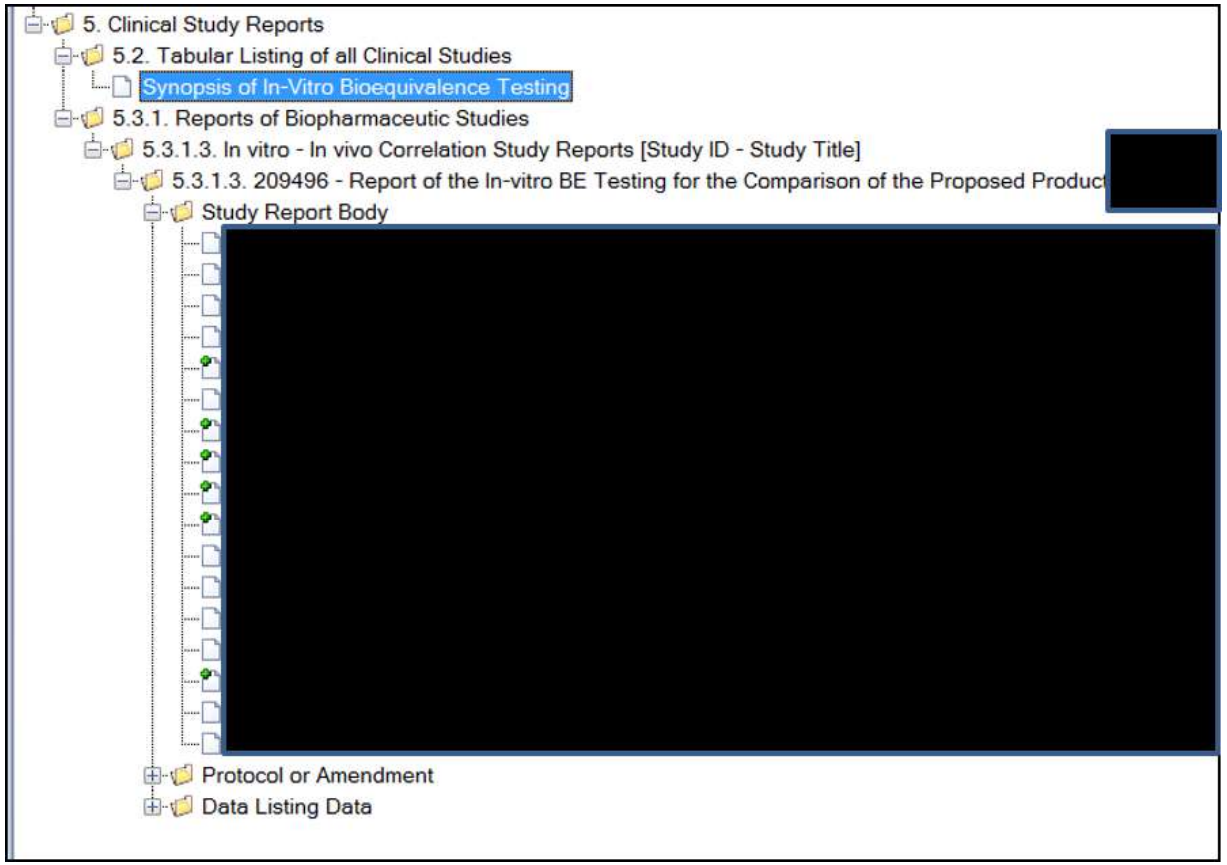
Challenges associated with BE Site Capture

Challenge 3: <u>BE Study listed without an address</u> : On **ANDA 2CCCCC (example 3)**, the In Vitro BE site is listed within the study report. The proposed site is listed at the top of each page, along with the Study Title Report #. It also lists that the In Vitro Test was performed by ABC Pharmaceuticals scientists but does not include the site address. The difficulty is identifying the location in which the study took place for ABC Pharmaceuticals.



Challenges associated with BE Site Capture

Challenge 4: <u>Multiple study reports with sites that may/may not be inspected:</u> Module 5 can hold multiple documents which could hold multiple In Vitro BE Studies. The challenge identifying which documents include the bioequivalence site that require review. An example can be seen on ANDA 2DDDDD.



Challenges In Summary

- Key components of BE site information is missing (name & address)
- BE sites appear in various formats (Tables, Study Reports, etc.)
- BE sites not consistently placed in the correct location of the eCTD submission
- **Implication:** Potential delayed issuance of an action letter due to misplaced or missing BE sites and/or relevant information.

Table 10 Study information

Table 10 Study Information[9]

Study Number				
Study Title				
Study Type	☐ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	location, ex: 5.3.1.2 location, ex: 5.3.1.2 location, ex: 5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax#)				
Principal Clinical Investigator (Name, Email)				
Analytical Site (Name, Address, Phone #, Fax#)				
Principal Analytical Investigator (Name, Email)				
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**				
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Analyte 1: Analyte 2: (if applicable) Note: The LTSS should be conducted at the upper limit of the storage temperature range.			
LTSS Data Location	Specify the exact location of the LTSS study reports and data, including Module, Section, Subsection, and page(s). Provide hyperlink(s) to the locations as appropriate.			

Please table 10 in the module 2.7.1.

create the separate table for each bioequivalence study

Model Bioequivalence Data

Summary Tables

Technical Specifications Document

For questions regarding this technical specifications document, contact the Office of Generic Drugs at genericdrugs@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Generic Drugs

February 2017

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf

ANDA Sponsors, we need your help…

To improve the access to quality data.

- Submit a complete list of **all** BE sites on Table 10 – Study Information
- Place BE Summary Tables in section 2.7.1 of the eCTD

Additional information about the ANDA submissions is available on the ANDA Forms and Submission Requirements Web page located at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm

Additional Resources

http://www.fda.gov/ectd

CDER submissions, contact:
EDATA@fda.hhs.gov
ESUB@fda.hhs.gov

Challenges to Manufacturing Facility Capture

- Accuracy of manufacturing facility information
  - Facility identifying information should be most current per Agency records
    - Use previous Establishment Inspection Report
    - Notify Office of Regulatory Affairs of changes ASAP
- Extraneous facilities listed in Form FDA 356h
  - Follow FORM FDA 356h SUPPLEMENT (9/17) instructions
  - Field 27 - all manufacturing, packaging, and control sites for both drug substance and drug product
  - Include facilities not meeting criteria for Form FDA 356h in Module 3

Commonly Observed Manufacturing Facility Omissions

- Bioequivalence, bioavailability, and stability batch manufacturing, packaging, and testing facilities *(not proposed for commercial manufacturing)*
  - Form FDA 356h Instructions do not specify
  - Refer to 21 CFR 314.94(a)(9) and 21 CFR 314.50 (d)(1)(ii)(b)
  - Recommended best practices
    - Include in appropriate section of Module 3
    - Notate the facility is not proposed for commercial manufacturing

Commonly Observed Manufacturing Facility Omissions

- Drug Master File Manufacturing and Testing Facilities
  - Form FDA 356h Instructions state include *all*
  - What does *all* mean?
    - Not just the final DMF manufacturing facility
    - Critical intermediate manufacturing facilities
    - Any sterilization, micronization, or release/stability testing facilities
  - Specify any special sourcing in both ANDA and DMF
    - DMF may list multiple final manufacturing facilities
    - ANDA may only source from certain facilities
    - Recommend using LOA

Closing Thoughts on Manufacturing Facilities

- Submitting accurate information in appropriate sections facilitates efficient quality assessment
- Consider impact of missing facilities on GDUFA dates
  - See – Draft Guidance for Industry: ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA
- Consider impact of changes to facilities
  - Do not forget 21 CFR 314.94(a)(9) and 21 CFR 314.50 (d)(1)(ii)(b)
  - See - Guidance for Industry: Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs
- For combination products, same submission expectations apply to the device manufacturing facilities