

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

Jia Jian (JJ) Shen, Project Management Officer  
Division Data Management Services and  
Solutions Office of Business Informatics

Derek S. Smith, Ph.D., Branch Chief  
Office of Process and Facilities

April 11-12, 2018

# 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](mailto:esub@fda.hhs.gov) or CBER at [esubprep@fda.hhs.gov](mailto: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:

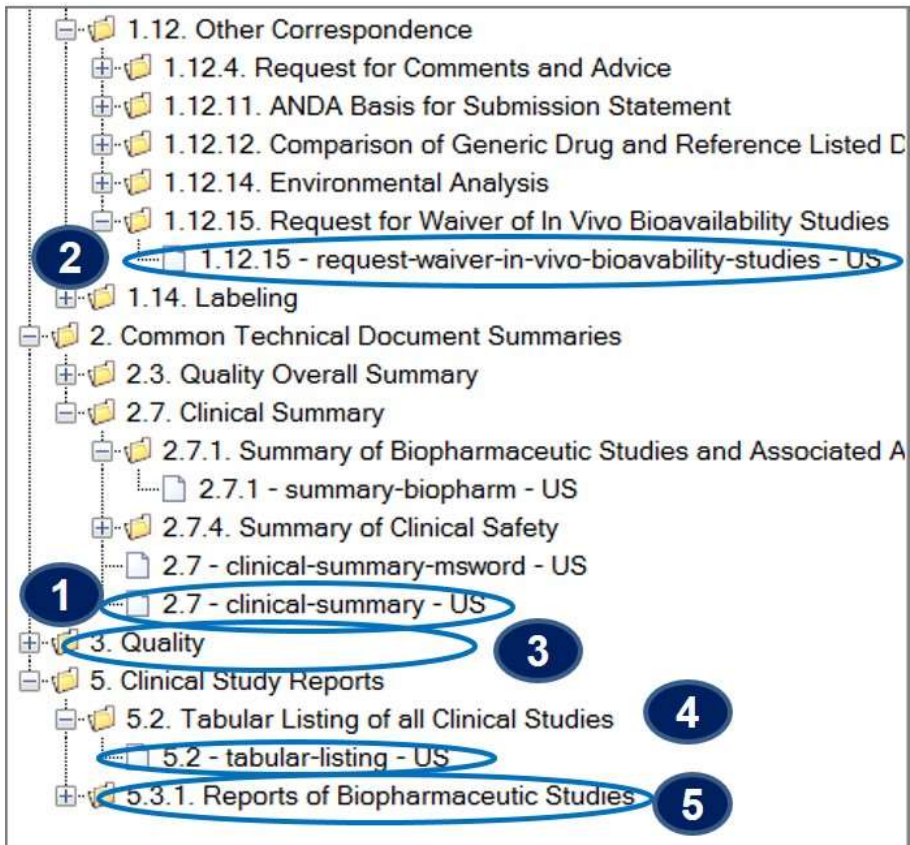
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm>

## 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 is 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- BE Site not listed on correct table:** 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   |                | Test |
| Table 6.1 Study Information -   |                | Test |
| Protocol/Phase:   |                |      |
| 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.) |                |      |
| Analytical Method Description   | Not Applicable |      |
| Analytical Equipment Used (e.g., name, model, etc.)                                 | Not Applicable |      |

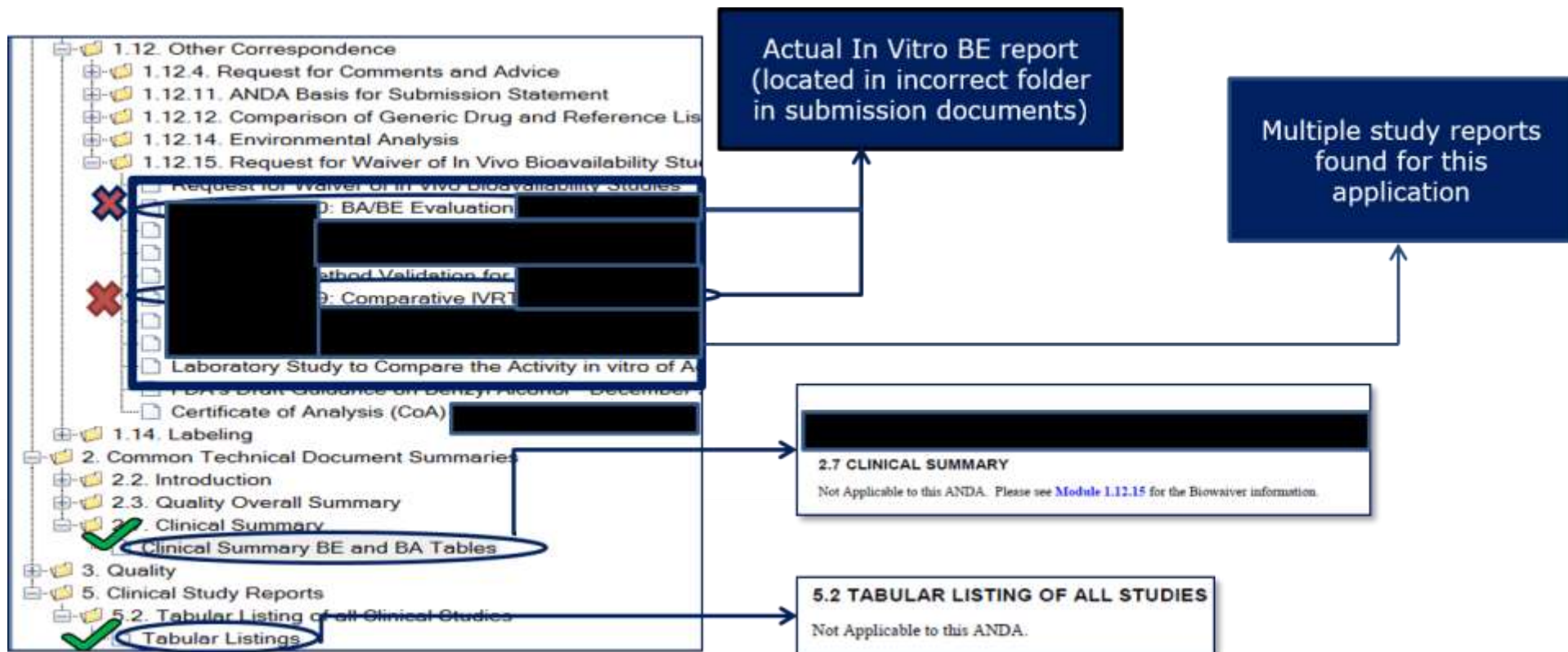
In Vitro BE site listed in Table 6 which is an unusual location for site.



## Challenges associated with BE Site Capture

**Challenge 2- BE Site Not listed in correct location:** 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: BE Study listed without an address**: 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.

|                                      |             |                                |
|--------------------------------------|-------------|--------------------------------|
| <div>PHARMACEUTICALS,<br/>INC.</div> | <div></div> | REPORT#:<br><div>7.01.01</div> |
|--------------------------------------|-------------|--------------------------------|

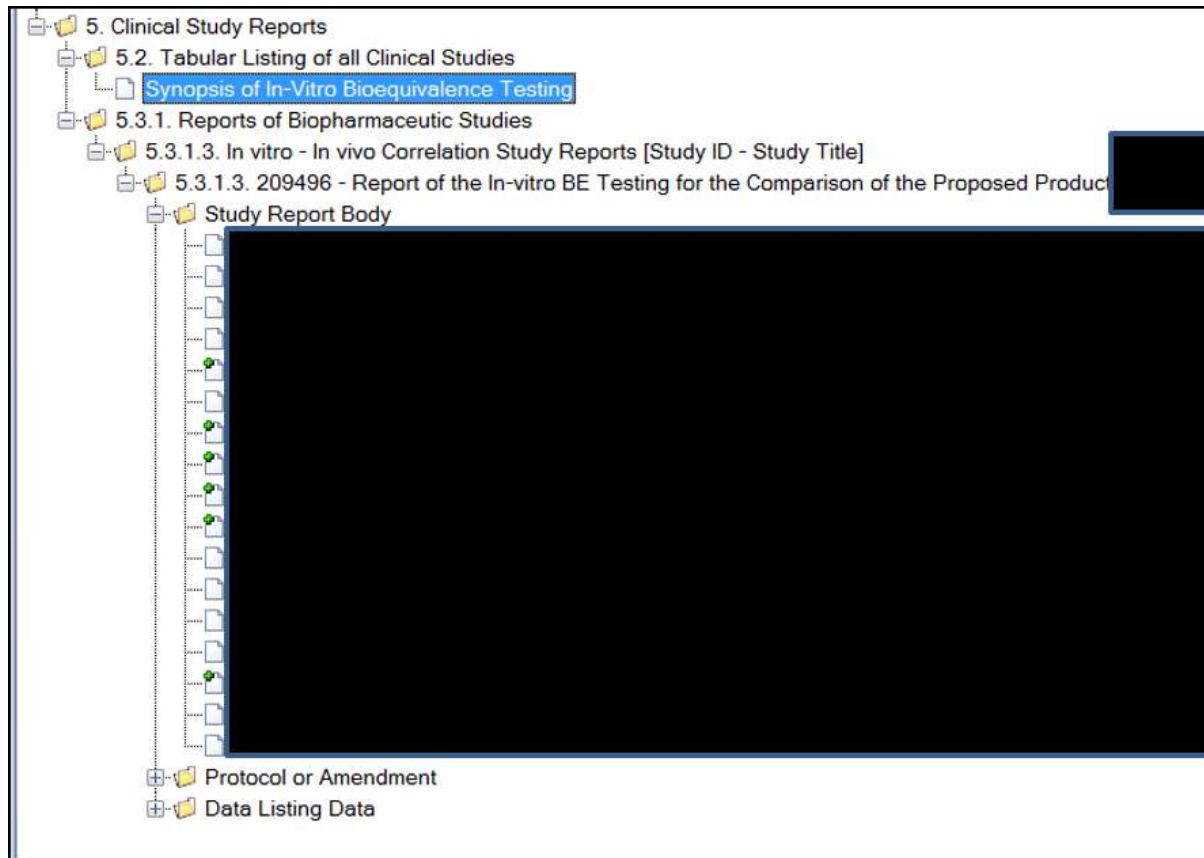
| Test Item             | Investigator | Title | Company / Department |
|-----------------------|--------------|-------|----------------------|
|                       |              |       |                      |
| In-vitro Release Test |              |       | Research             |
|                       |              |       | Research             |
|                       |              |       | Research             |

Note from reviewers, remember to add the name of the Investigators and study conduct dates.

No address listed in the documentation

## Challenges associated with BE Site Capture

**Challenge 4: Multiple study reports with sites that may/may not be inspected:** 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<sup>9</sup>

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

[ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

The screenshot displays the FDA website's 'Drugs' section, specifically the 'Electronic Common Technical Document (eCTD)' page. The header includes the FDA logo and navigation links for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. A search bar is located in the top right corner. The main content area is titled 'Electronic Common Technical Document (eCTD)' and includes a sidebar with links to 'Electronic Submissions to CDER', 'CDER Data Standards Program', 'Data Standards in the Drug Lifecycle', 'Electronic Common Technical Document (eCTD)', 'Electronic Regulatory Submissions and Review Helpful Links', 'Electronic Submissions Presentations', 'Study Data for Submission to CDER and CBER', 'Source Data Capture from Electronic Health Records (EHRs)', and 'Data Standards Manual (monographs)'. The main text explains that the eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). It also lists 'Important Dates' for submissions to CDER and CBER, including May 5, 2017, for New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs), and May 5, 2018, for Commercial Investigational New Drug Applications (INDs) and Master Files. A 'Quick Links' section on the right provides links to eCTD Guidance, eCTD Submission Standards, FDA Data Standards Catalog, eCTD Technical Conformance Guide, Drug Master Files (DMFs), and Technical Rejection Criteria for Study Data. A 'Notices' section at the bottom right lists updates such as 'FDA Extends Compliance Date for Submitting DMFs in eCTD format' and 'Third Acknowledgement for Successful eCTD Submissions (May 2016)'.

**U.S. FOOD & DRUG ADMINISTRATION**

Home > Drugs > Development & Approval Process (Drugs) > Forms & Submission Requirements > Electronic Submissions to CDER

### Electronic Common Technical Document (eCTD)

The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

**Important Dates**

After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that do not use eCTD will not be filed or received.

- **May 5, 2017:** New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs), must be submitted using eCTD format.
- **May 5, 2018:** Commercial Investigational New Drug Applications (INDs) and Master Files must be submitted using eCTD format.
- Please refer to the [eCTD Guidance](#) for the complete

**Quick Links**

- [eCTD Guidance \(PDF - 11 KB\)](#)
- [eCTD Submission Standards \(PDF - 91KB\)](#)
- [FDA Data Standards Catalog](#)
- [eCTD Technical Conformance Guide \(PDF - 303KB\)](#)
- [Drug Master Files \(DMFs\)](#)
- [Technical Rejection Criteria for Study Data \(PDF - 921 KB\)](#) **NEW**

**Notices**

- [FDA Extends Compliance Date for Submitting DMFs in eCTD format](#) **NEW**
- [Third Acknowledgement for Successful eCTD Submissions \(May 2016\)](#)
- [Past Notices](#)

## 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