



U.S. Food and Drug Administration

Generic Drug User Fee Amendments of 2012

Optimizing your eCTD ANDA

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eCTD v3 History

- Developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
 - Step 4 agreement reached in 2003
- FDA published regional technical specifications and began receiving pilot submissions in 2003
- As of January 1, 2008, eCTD v3 has been the preferred format for electronic regulatory submissions to FDA

eCTD v3 History (2)

- At CDER, the eCTD format can be used (and is preferred) for ANDA, BLA, Drug Master File, IND, and NDA applications
- The eCTD format has many advantages, including the ability to “life cycle” documents
- The us-regional.xml and index.xml file published with your eCTD ANDA provide an electronic table of contents

eCTD Requirements

- eCTD format **will be required** for submissions to CDER, including ANDAs submitted to OGD
 - *Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
- In addition: GDUFA review metric goals only apply to submissions made electronically, following the eCTD format in effect at the date of submission
 - *Generic Drug User Fee Act Program Performance Goals and Procedures*

eCTD Timeline

- eCTD will be required after the finalization of the *Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
 - NDAs, BLAs, ANDAs: 24 months after finalization
 - INDs: 36 months after finalization

Getting Started

- Guidance Documents
 - *Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
 - *Draft Guidance for Industry: ANDA Submissions — Refuse-to-Receive Standards*
- Technical Specifications
 - *ANDA FILING CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION*
- CDER eCTD Webpage
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

General Considerations

- Publishing Tools
- Conversion from paper or non-eCTD electronic
 - Generally do not resubmit any previously submitted information
 - Use m1.4.4 to provide a PDF of the ANDA's paper TOC or other cross reference information
 - Contact esub@fda.hhs.gov if you have questions

Document Creation

- *FDA PORTABLE DOCUMENT FORMAT (PDF) SPECIFICATIONS*
 - PDF Version: 1.4 – 1.7
 - Standard Fonts
 - Page Sizes and Margins
 - Scanned Documents
 - Bookmarks
 - Document Table of Contents (TOCs)
- Ensure that PDF documents submitted meet all FDA Specifications

eCTD Samples

- Optional, but recommended step
- Sample submissions are tests only and not shared with review teams
 - You may use either real or “dummy” documents
- Contact esub@fda.hhs.gov for a sample application number and detailed submission instructions
- Must be sent on physical media (CD/DVD) and can take up to 30 days for review and feedback
 - Plan ahead and submit a sample early!

The Electronic Submissions Gateway (ESG)

- FDA's preferred method of transmission
- Requires a personal digital certificate
- Requires registration, load testing, and a guidance compliant test submission before receiving a production account
 - A guidance compliant test submission is only evaluated for technical acceptance, not for content like an eCTD Sample
- All eCTD submissions to OGD should be sent to the Center "CDER" with the submission type "eCTD"
- **Preparation/Registration/Policy Questions**
Email: esgprep@fda.hhs.gov
- **For Technical Issues with Submissions**
Email: ESGHelpDesk@fda.hhs.gov

eCTD Validation

- Use an eCTD Validator to identify structural problems with your submission BEFORE sending it to FDA
 - Do not ignore errors
 - High errors will result in the rejection of your submission – lost time and \$
- Current eCTD Validation Specifications are available on the CDER eCTD Webpage
 - The specifications include corrective actions but you can contact esub@fda.hhs.gov for personalized assistance

CDER eCTD Processing

Steps to follow for the fastest receipt by OGD

- Use the ESG
- Use only FDA fillable forms (not scanned forms)
- Use digital signatures
- Ensure that your forms and cover letter match in terms of application type and number (mistakes will cause a delay in processing)

CDER eCTD Processing (2)

- Common issues that prevent automated processing
 - Unable to extract information from PDF form
 - Missing FDA fillable form
 - Spaces and special characters not permitted in folder names
 - 4 digit sequence number folder should be the highest folder
 - Mismatched application number between us-regional.xml and form
 - Mismatched application type between us-regional.xml and form
 - e-CTD submission sent as wrong type (non-eCTD selected in Web Trader)

Rejections

- Submissions that are technically deficient or otherwise can not be processed
 - Can not determine the correct application number/type
 - High validation errors
 - Duplicate eCTD sequence numbers
 - Submitted to the wrong Center
 - Non-allowed file types
 - .zip
 - .exe

OGD Filing Review

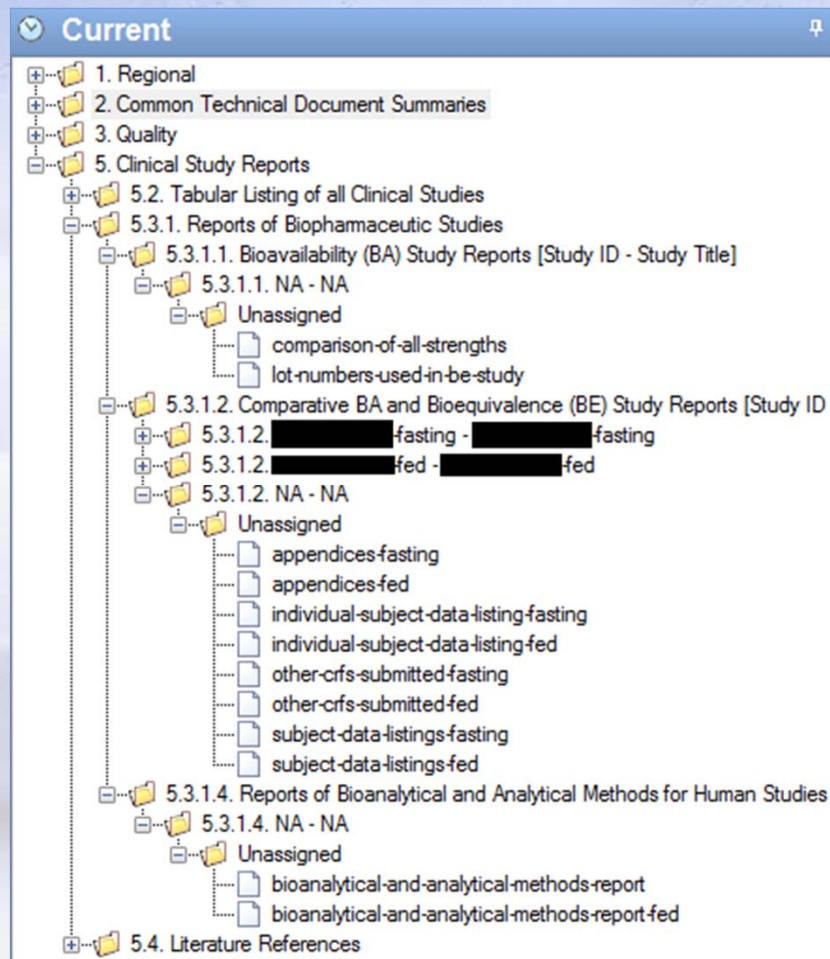
- GDUFA Obligations Met?
- Required content present to begin review?
- Content in its correct eCTD location?
 - Study Tagging Files (STFs) used correctly in module 5
 - Document consolidated into a single 3.2.P section
- Documents reviewable?
 - Fonts
 - Navigation (TOCs and Bookmarks)

Most Common eCTD ANDA Errors

- **Study Tagging File (STF) Errors**
 - STFs are required for all files in section 5.3.1.x
 - STFs are not required for 5.2 Tabular Listings and 5.4 Literature references, these are submitted as single separate files without an STF

Not good!

“NA – NA” and “unassigned” folders resulting from files not tagged in STFs



- **Study Tagging File (STF) Errors**

- Confusion about which “file-tag” to use for some items required by the ANDA checklist, e.g. formulation data in 5.3.1.1
 - Assign a unique study id and study title in the STF for each set of documents
 - For the file-tag, you can use ‘study-report-body’
 - Ensure that you use a concise and descriptive leaf title to describe the actual contents of the individual files for the reviewer **(leaf title and file name are different)**

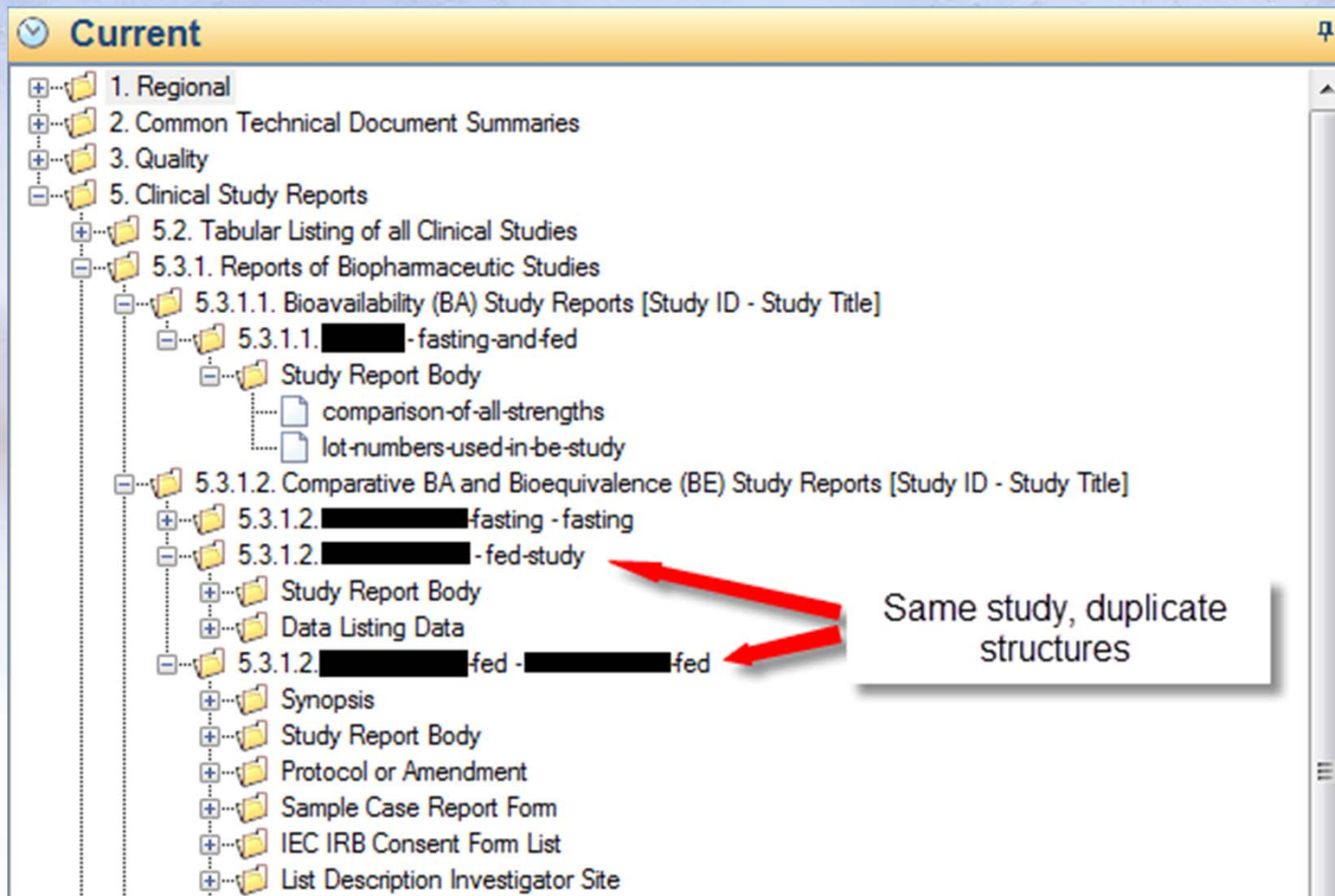
Good!

Unique study IDs and descriptive study titles; all files tagged in an STF

Current

- 1. Regional
- 2. Common Technical Document Summaries
- 3. Quality
- 5. Clinical Study Reports
 - 5.2. Tabular Listing of all Clinical Studies
 - 5.3.1. Reports of Biopharmaceutic Studies
 - 5.3.1.2. Comparative BA and Bioequivalence (BE) Study Reports [Study ID - Study Title]
 - 5.3.1.2. [REDACTED] - Single Dose, Reference Replicate Crossover Comparative Bioavailability Study of [REDACTED] 20 mg Delayed-Release Tablets in Healthy Male and Female Volunteers Fasting State
 - 5.3.1.2. [REDACTED] - Single Dose, Reference Replicate Crossover Comparative Bioavailability Study of [REDACTED] 20 mg Delayed-Release Tablets in Healthy Male and Female Volunteers Fed State
 - 5.3.1.3. In vitro - In vivo Correlation Study Reports [Study ID - Study Title]
 - 5.3.1.3. 0000 - In vitro-In vivo Correlation Study Reports
 - Study Report Body

Be careful with study id and study title metadata! Even the smallest discrepancy will cause files to be displayed separately in our viewer (e.g. addition or removal of a hyphen or space)



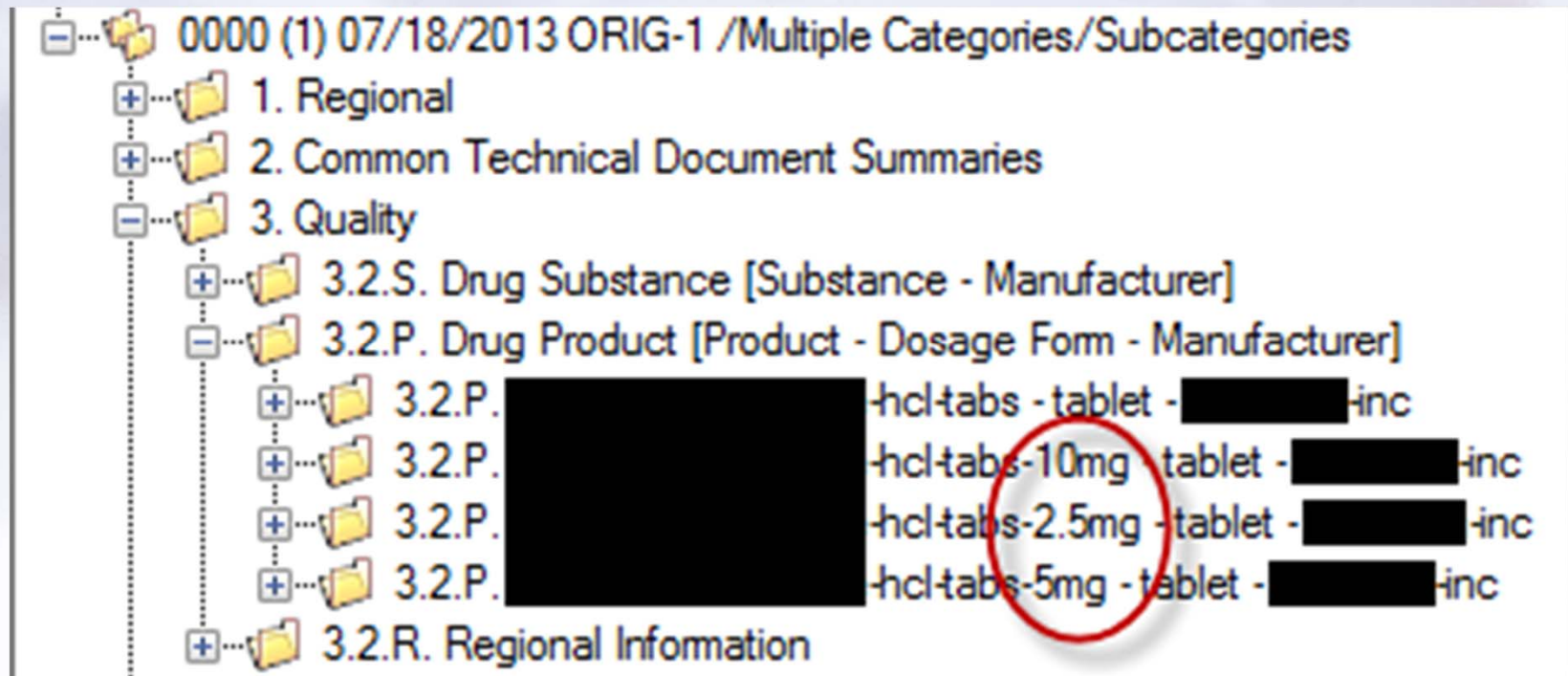
Same study, duplicate structures

- **Multiple 3.2.P Sections**

- In general, when a single application for multiple strengths can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one Drug Product section, with information for each of the product presentations and manufacturing schemes provided in the Appendices and Regional Information sections, as warranted.
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073285.pdf>

- **Multiple 3.2.P Sections**

- Do not submit different metadata creating different 3.2.P sections for different strengths of the same product!
- Submit this information in a single section and use clear and concise leaf titles to indicate documents that only apply to a certain strength



- **PDF Errors**

- **Most errors could be avoided by following the PDF Specifications**
- Create text-based PDFs from source documents
 - Avoid scanning documents or embedding scanned documents
 - Use validated OCR if you must scan a document
- Use only standard fonts
- Fully embed all non-standard fonts if used

- **PDF Errors**

- Initial View Settings

- Set the Navigation Tab to open to “Bookmarks Panel and Page.” If there are no bookmarks, set the Navigation Tab to “Page Only.” Page Layout and Magnification should be set to “Default.”

- Navigation

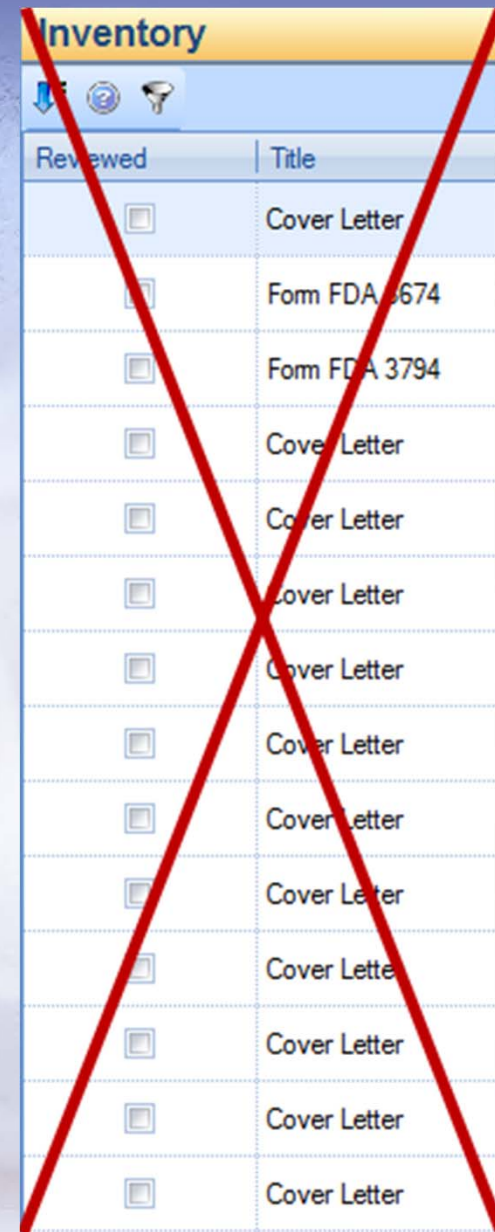
- Provide bookmarks and a hyperlinked TOC
 - Use hypertext links throughout the body of the document to link to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page as the narrative text

- **Leaf Titles**

- A leaf title is the display name given to a document and will be shown to the reviewer
 - A reviewer never sees the file/folder names in the file structure
- Leaf titles should not include file extensions, e.g. appendix1.pdf
- Leaf titles should not include hyphens or underscores, e.g. field-copy-certification.pdf
- Leaf titles should not include the eCTD section number, e.g. 1.3.2.field-copy-certification.pdf

- **Leaf Title**

- **Remember that the eCTD application is a “living” dossier and contains the history of all your submissions!**
- For example, the leaf title for a cover letter should also include the date (e.g., 2012-12-31) and eCTD sequence number.
- If documents of the same type are being provided in different file formats, a file format (e.g., “MS Word”) should be included at the end of the leaf title.



Reviewed	Title
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Form FDA 3674
<input type="checkbox"/>	Form FDA 3794
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter
<input type="checkbox"/>	Cover Letter

How Do I Get Help?

- **Contact CDER's Electronic Document Management Solutions Team!**
 - esub@fda.hhs.gov
 - Support is available before, during, and after submission
- **CDER eCTD Webpage (guidances and specifications)**
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
- **OGD ANDA Webpage**
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm>



Thank You!

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301-796-0597

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