U.S. FOOD & DRUG ADMINISTRATION

Filing and Refuse to Receive (RTR)

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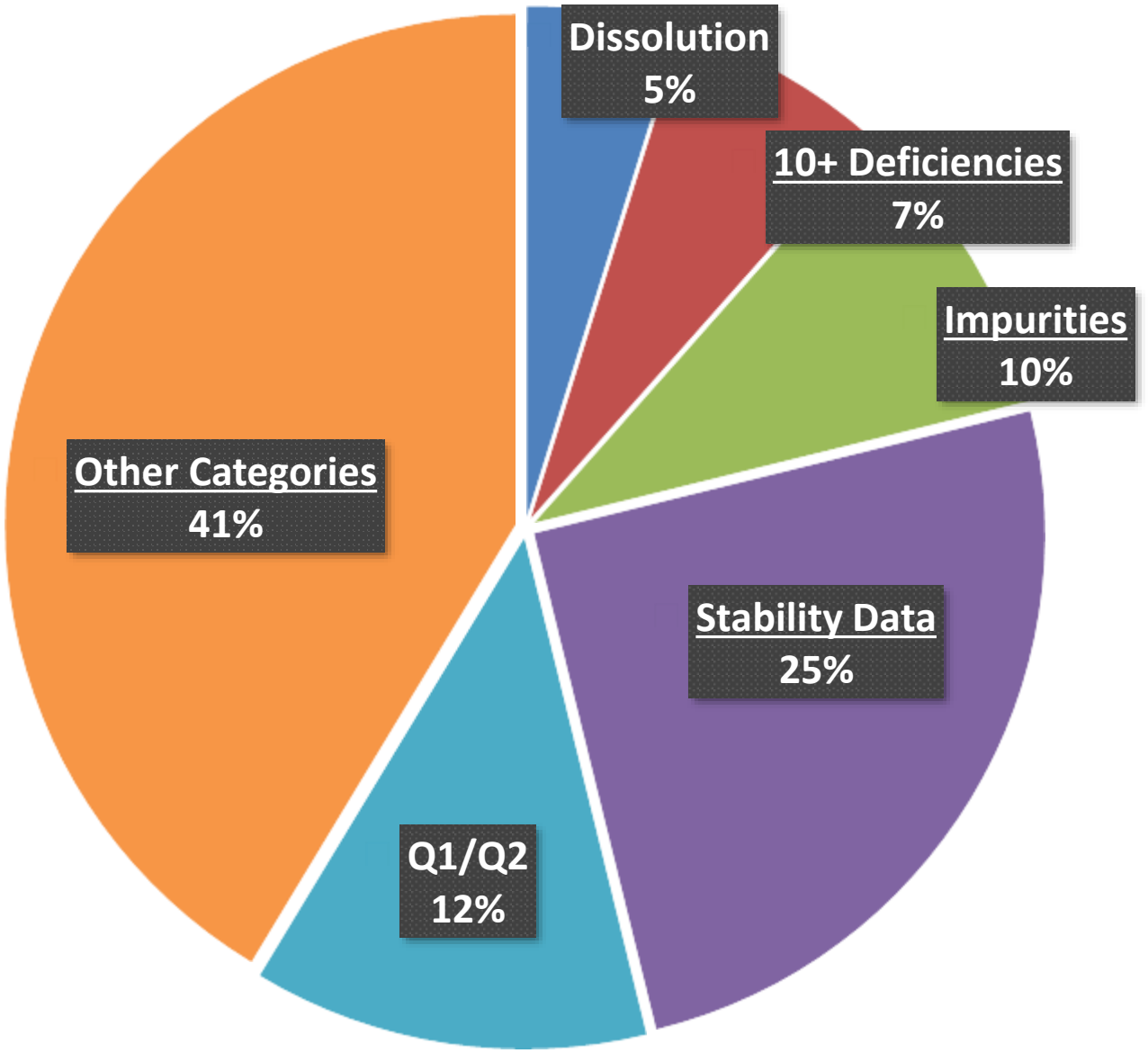
Discussion Overview

- Deficiency Metrics
- Major and Minor Deficiencies:
  - Module 1
  - Module 2
  - Module 3
  - Module 5
- Case Study

RTR Statistics

	FY 2016 (Oct. 2015 – Sept. 2016)	FY 2017 (Oct. 2016 – Sept. 2017)	FY 2018 (Oct. 2017 – Sept. 2018)
Total ANDAs Submitted	855	1320	1057
Total ANDAs RTR'ed	216 (25.26%)	168 (12.73%)	83 (7.85%)

Major Deficiencies (FY 2018)



Other RTR Categories

- Incomplete Type II DMF CA
- Inadequate Packaging
- Incomplete/Failed BE Studies
- Lack of Master Batch Records

Module 1

- Minor Deficiencies
  - Incomplete Form FDA 356h
  - Basis of Submission (Module 1.12.11)
  - Labeling (Module 1.14)
- Major Deficiencies
  - Unsigned Form FDA 356h
  - Omitted Form FDA 356h

Module 1 Deficiencies

- Form FDA 356h
  - **Field 9:** Is the drug product subject to a USP monograph?
  - **Field 11:** Should list the full chemical name
  - **Field 20:** Patent certification is inconsistent with the patent certification in Module 1.3.5.2
  - **Field 28:** Establishment information does not marry up with the establishment information in Modules 3.2.S and 3.2.P
  - **Field 29:** Typo of DMF# or did not list all DMFs referenced in Module 1.4.2

Module 1 Deficiencies

- Module 1.12.11
  - Basis for Submission 21 CFR §314.94(a)(3)
    - Failing to provide the appropriate Basis of Submission
      - Designate Reference Listed Drug (RLD) and Reference Standard (RS) (if applicable) currently listed in the *Orange Book*
    - ANDA Suitability Petition required?
      - Docket number
      - FDA's correspondence approving the petition

Module 1 Deficiencies

- Module 1.14
  - Labeling
    - eCTD: Legibility of draft and RLD container labels
    - Failing to provide the proposed container and carton labels for each strength and each packaging configuration (container size) (Module 1.14.1.1)
    - Failing to provide the RLD container and carton label for each strength (Module 1.14.3.3)

Module 2

- Minor Deficiency
  - Provide separate PDF and Word documents
- Major Deficiency
  - Inadequate dissolution
    - 12 units
    - Test media
    - ½ tablet (Modified-release Products)

Module 2 Deficiencies

- Module 2.7
  - Summary Data Tables in module 2.7
  - Provide the Certificate of Analysis for each strength of the RLD
  - **Table 10:** Long-term storage stability (LTSS) information
    - Exact location of the LTSS study reports and data
      - Provide working hyperlinks to the respective information

Module 2 Deficiency

- Dissolution Studies
  - **Table 5:** Summary of in-vitro dissolution
    - Not conducted on 12 units
    - Not conducted on all strengths (test vs. RLD)
    - Not conducted in all test media

Module 3

- Minor Deficiencies
  - Formatting of Justification Tables
  - Regional Batch Information
- Major Deficiencies
  - Q1/Q2
  - Justification of Impurities
  - Stability Data

Module 3 Deficiencies

- Modules 3.2.S.4.5 and 3.2.P.5.6
  - Justification of Specifications Tables
    - Follow recommended format for tables
    - Provide separate tables for:
      - Specified Identified
      - Specified Unidentified
      - Unspecified Impurities

Module 3 Deficiencies

- Module 3.2.R
  - Regional Information
    - Batch reconciliation and label reconciliation
      - Executed Batch Reconciliation tables should include **theoretical, actual, and packaged yield**
      - Yield should also be **expressed in dosage or product units** (e.g., number of tablets and bottles, number of vials, etc.)

Module 3 Deficiencies

- Not Q1/Q2 to RLD
  - Parenteral, ophthalmic, and otic solutions must be Q1/Q2 to the RLD
    - Qualitative
      - Changes to exception excipients are permitted*
      - Before submitting an ANDA, an applicant can submit a controlled correspondence
    - Quantitative

* Refer to (21 CFR 314.94(a)(9)(iii)) and (21 CFR 314.94(a)(9)(iv))

Module 3 Deficiencies

- Justification of Impurities
  - Justification for impurities (specified identified or specified unidentified) where proposed Acceptance Criteria (AC)% exceed regulatory Qualification (QT) or Identification Threshold (IT)%, respectively
    - Provide supporting data and information
  - Proposed AC% should not exceed regulatory IT% for Unspecified Impurities

Module 3 Deficiencies

- Stability Data
  - **Two** API lots for each strength
  - Minimum of **three** test batches of each strength
  - **Six** months' (180 days) worth of data with **three** time points
    - Accelerated and Long Term stability studies
    - Intermediate studies for all three batches of the specific strength if accelerated stability study shows significant change or failure of any attribute
  - Orientation of stability studies
    - Worst case and also non-worst case orientation
  - Verify **all** stability start and pull dates

Module 5

- Minor Deficiencies
  - Data Tabulation Dataset
  - eCTD

Module 5 Deficiencies

- Module 5.3.1.2
  - "Data Tabulation Dataset SDTM"
    - Pharmacokinetic ("PP") and concentration ("PC") data
    - SAS (.XPT) format

Module 5 Deficiencies

- Module 5.3.1.2 and module 5.3.1.4
  - eCTD
    - Descriptive Leaf titles
    - Bookmarks for any file with 5 or more pages
    - Bookmarks match table of content

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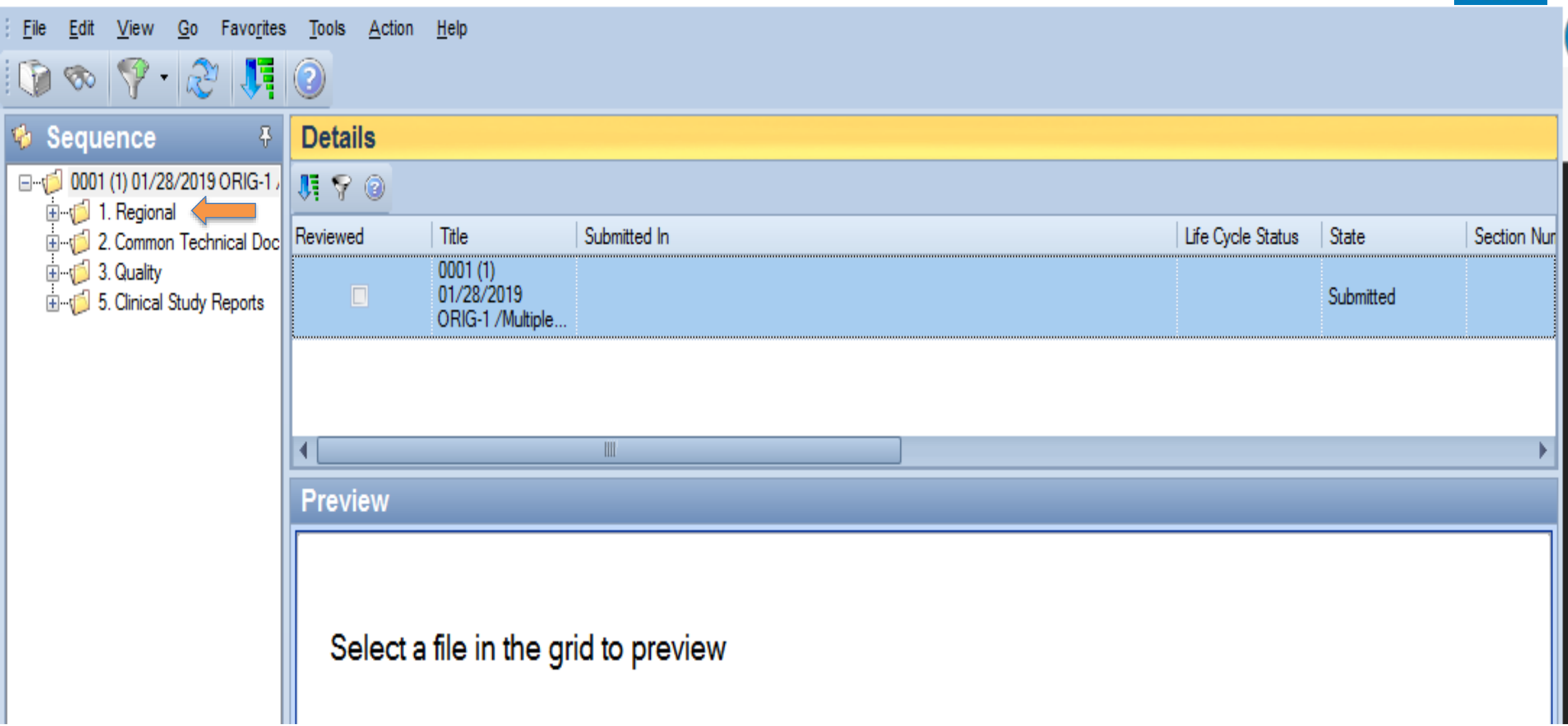
Case Study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1. Regional
2. Common Technical Doc
3. Quality
5. Clinical Study Reports
Details
Reviewed
Title
Submitted In
Life Cycle Status
State
Section Nur
0001 (1)
01/28/2019
ORIG-1 /Multiple...
Submitted
Preview
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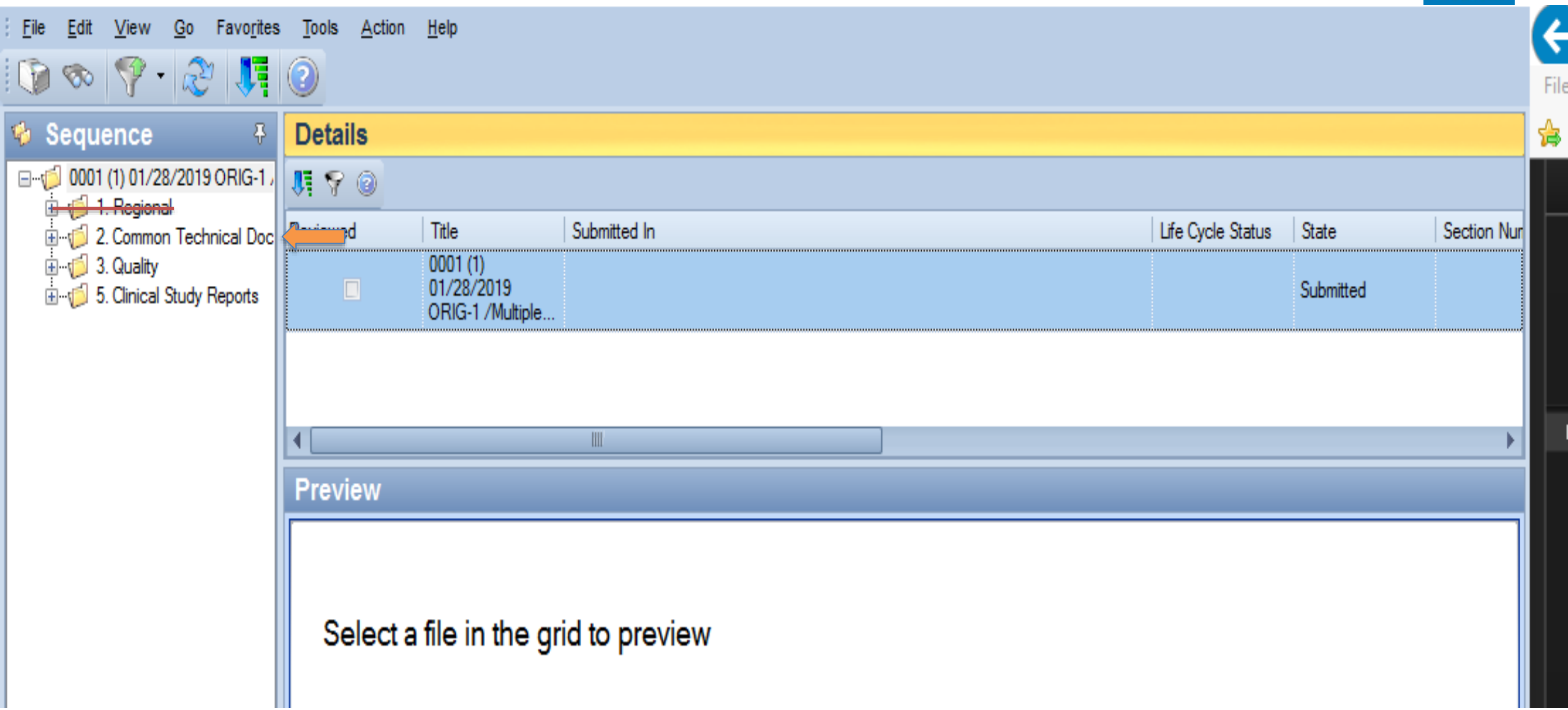
Module 1.12.11

Basis for Submission	
Reference Listed Drug #	NDA # 123456 ✓
Reference Listed Drug	Captain America Steroids (Super Soldier Serum) ✓
Reference Standard Drug #	N/A ✓
Reference Standard Drug	N/A ✓
Dosage Form	Injection
Strength(s)	10 mg/mL ✓
Applicant	The Avengers ✓
ANDA Suitability Petition Required?	Yes ✓
Docket Number	
Letter of Approval	
ANDA Citizen's Petition Required?	No ✓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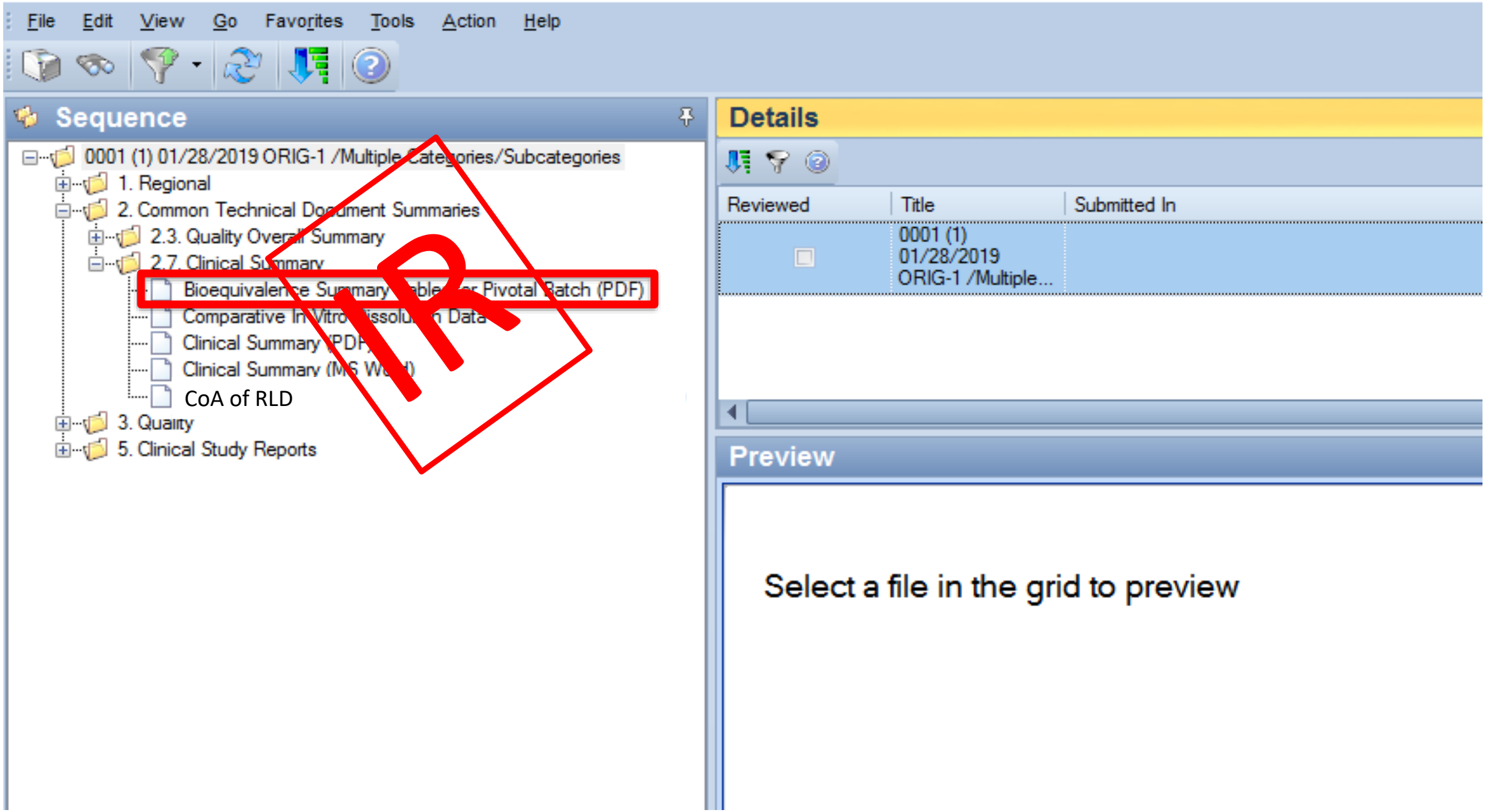
Module 2.7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1. Regional
2. Common Technical Document Summaries
2.3. Quality Overall Summary
2.7. Clinical Summary
Bioequivalence Summary Table for Pivotal Batch (PDF)
Comparative In Vitro Dissolution Data
Clinical Summary (PDF)
Clinical Summary (MS Word)
CoA of RLD
3. Quality
5. Clinical Study Reports
IR
Details
Reviewed
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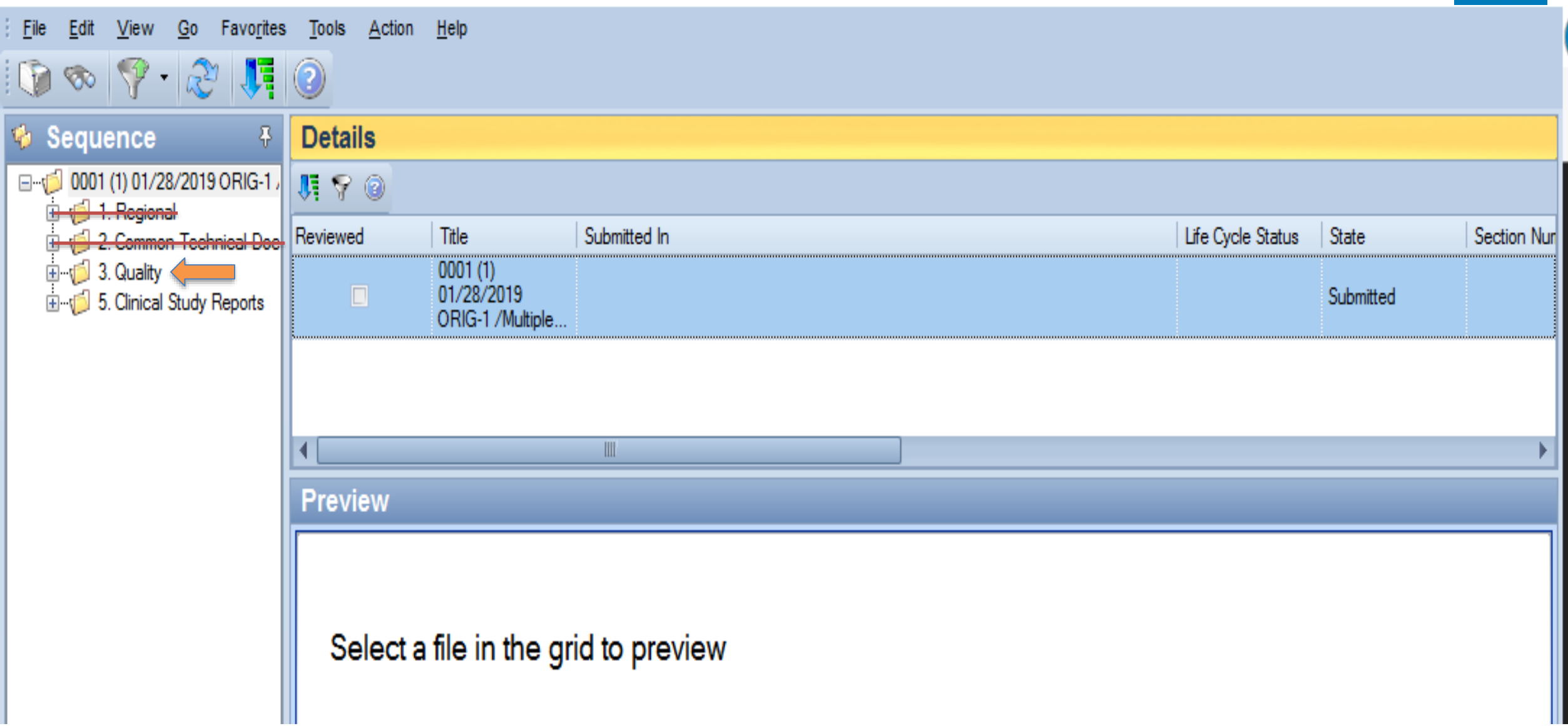
Table 10

Study Number	Super Soldier Serum			
Study Title	An open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over single-dose oral bioequivalence study of **Captain America Steroids** designed to test if the injection can transform a Steve Rogers into a fighting machine with no sense of fear. Subject will be in a fasting state.			
Study Type	☑In Vivo BE	☐In Vitro BE	☐ Permeability	☐Other
Submission Location: **Study Report**	**Study Report**			
	Appendix 1			
Validation Report **Bio analytical Report**	**Bioanalytical Report**			
Clinical Site **(Name, Address, Phone #, Fax #)**	Black Site X			
Principal Clinical Investigator **(Name, Email)**	Dr. Abraham Erskine			
Dosing Dates	1941			
Analytical Site **(Name, Address, Phone #, Fax #)**	Classi			
Principal Analytical Investigator **(Name, Email)**	Nick			
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)**	30 days			
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp ºC)	60 days			
LTSS Data Location	Module 5			

IR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Module 3.2.P.5.6

- Justification Tables

Unspecified Impurities

MDD	IT (%)	Regulatory IT Threshold	Proposed AC(%)	Not Acceptable if proposed AC (%) > Regulatory IT Threshold (%)
600 mg	2.00%	2%	Not more than 2 %	N/A
300 mg	3.00%	2%		
450 mg	1.00%	1%	2%	Per USP Monograph Specification

RTR

Template

IR

Unspecified Impurities: Acceptance criteria for these impurities should not be more than regulatory IT.

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)*	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)

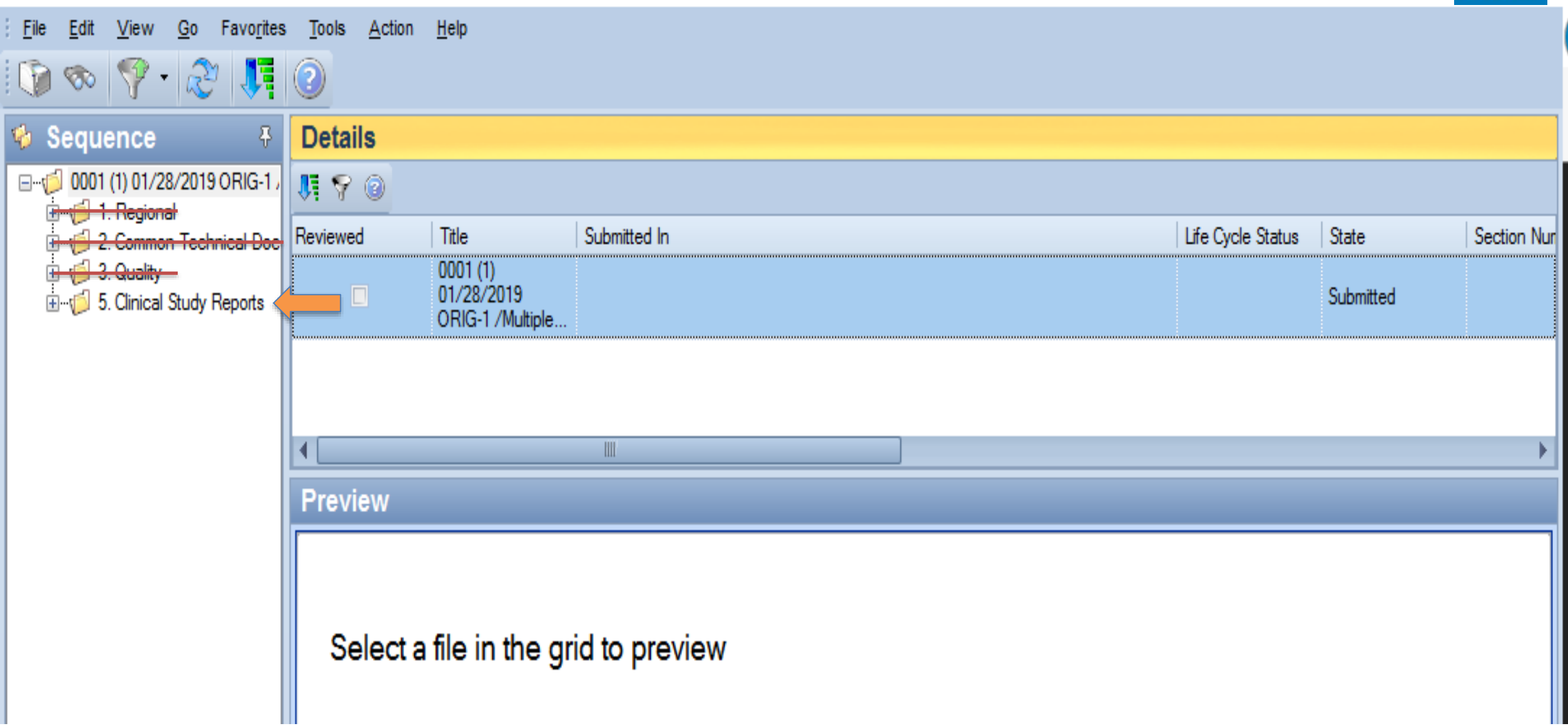
*Based on lower intake of impurity from IT (%) or IT (wt). If IT (TDI) is lower express as %.

Module 3.2.P.8

- Stability Data
  - Justification
    - (*Applicant*) have provided 3 months of accelerated and 9 months of both Intermediate and long term data in the submission of this ANDA. Our accelerated study experienced significant change, so intermediate stability data was generated for all batches.

Stability Protocol			
	Accelerated Condition 40°± 2°C / 75 ± 5%RH	Intermediate Condition 30°C±2°C/75%±5% RH	Long term Condition 25°± 2°C / 60 ± 5%RH
3M	✓	✓	✓
6M	✓	✓	✓
9M	✓	✓	✓
6M		✓	✓
9M		✓	✓

RTR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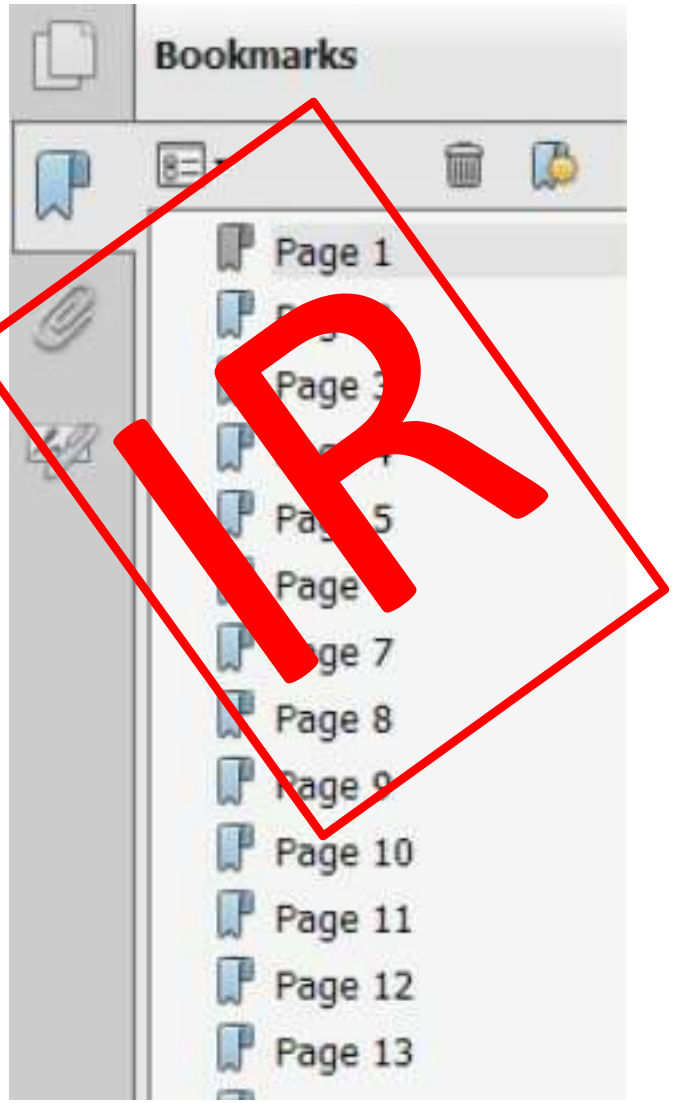
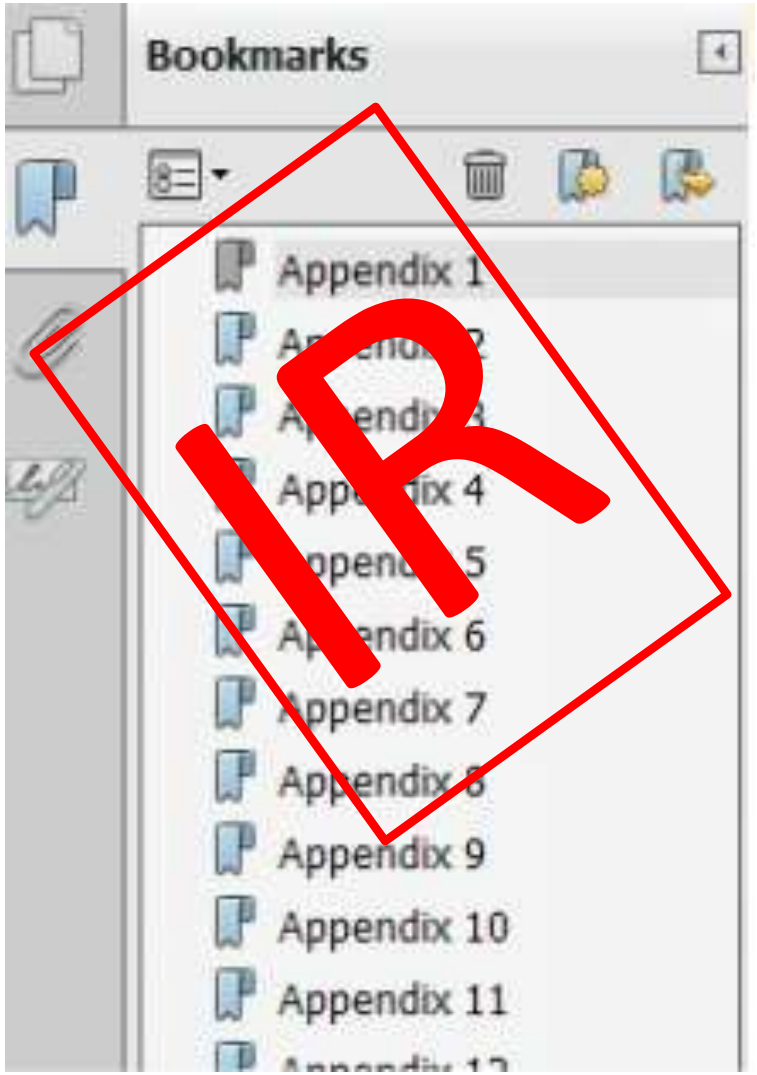
Module 5.3.1.4

File 1



File 2



Resources for Filing

- Guidance for Industry ANDA Submissions — Content and Format of Abbreviated New Drug Applications (Sept 2018)
- Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards (Revision 2, Dec. 2016)
- Guidance for Industry ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits (Aug. 2016)
- Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products Questions and Answers (May 2014)
- Draft Guidance for Industry Controlled Correspondence Related to Generic Drug Development (November 2017)
- MAPP 5200.14 Filing Review of Abbreviated New Drug Applications

Contact

Controlled Correspondence:

genericdrugs@fda.hhs.gov

ANDA Filing Status:

ANDAFiling@fda.hhs.gov

DFR Rescission Requests or RTR questions:

DFRSupervisor@fda.hhs.gov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