Application Submission and Filing Review Process

Ethan Chen, Director
Division of Data Management Services and Solutions
FDA/CDER Office of Business Informatics

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Agenda

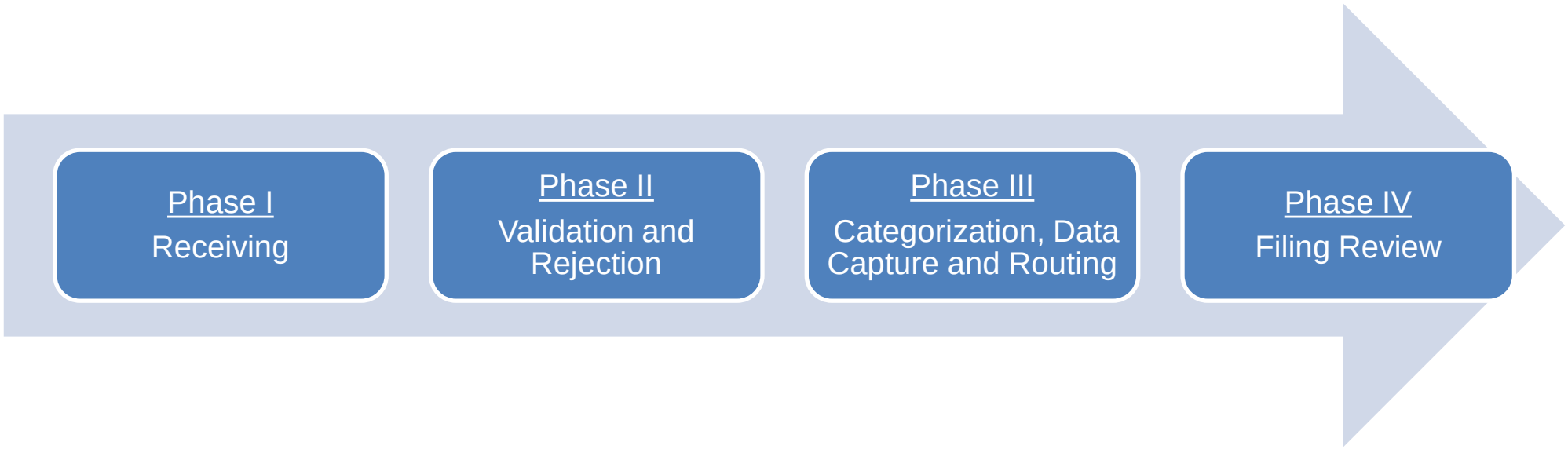
- **Application Submission and Filing Review Functional Process**
  - Receiving
  - Validation
  - Categorization, Data Capture and Routing
  - Filing Review
- **Key Takeaways**

Background

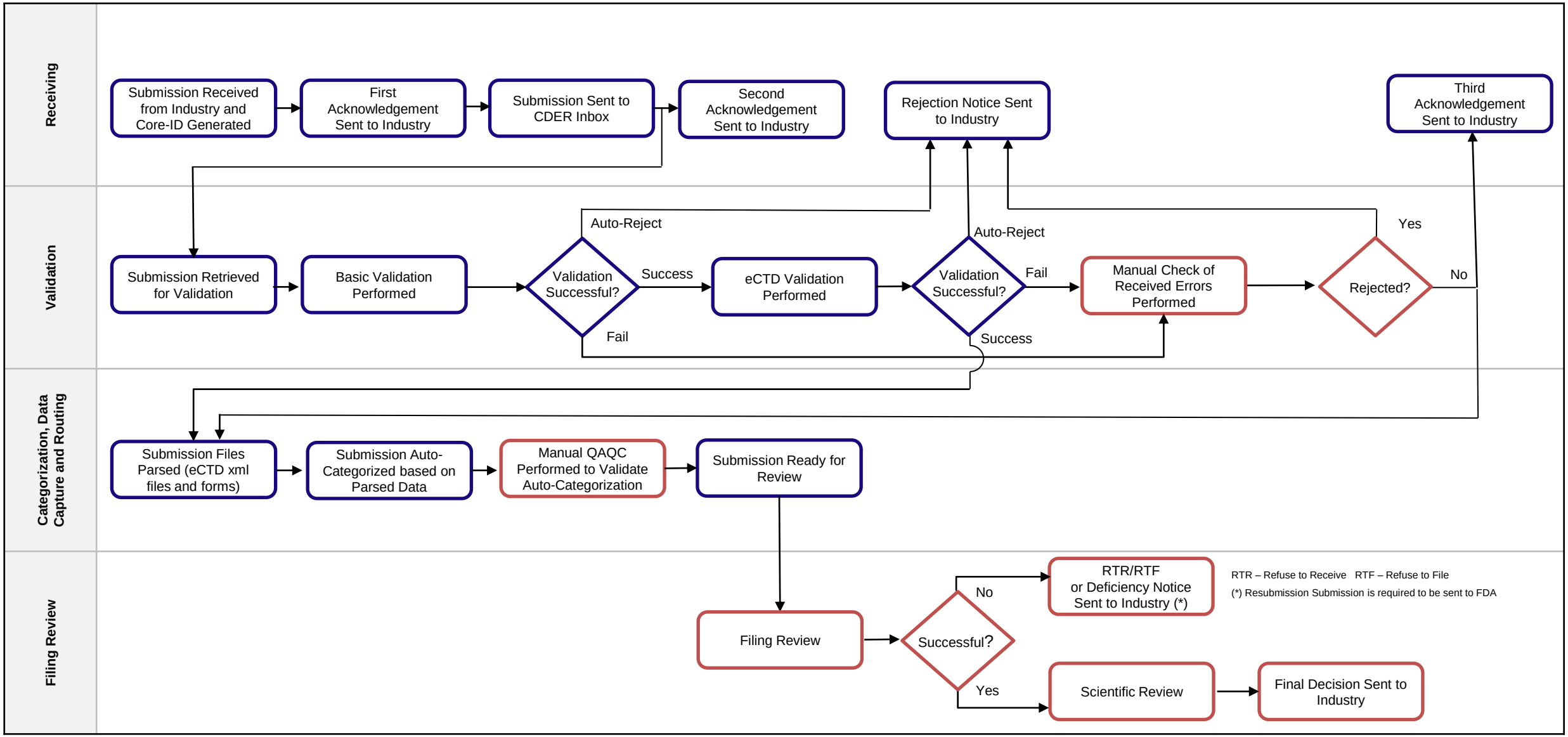
- **Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog**
- **FDA currently enforces**
  - eCTD Standard for NDA, BLA, ANDA submissions – May 5, 2017
  - eCTD Standard for Commercial IND, DMF Type II, IV and V submissions – May 5, 2018
  - Technical Rejection Criteria for Study Data since September 15, 2021
- **In 2022, FDA received 248,000 eCTD submissions for above application types, with 99.7% conformance rate to the eCTD standard.**

Application Submission and Filing Review Process – High Level

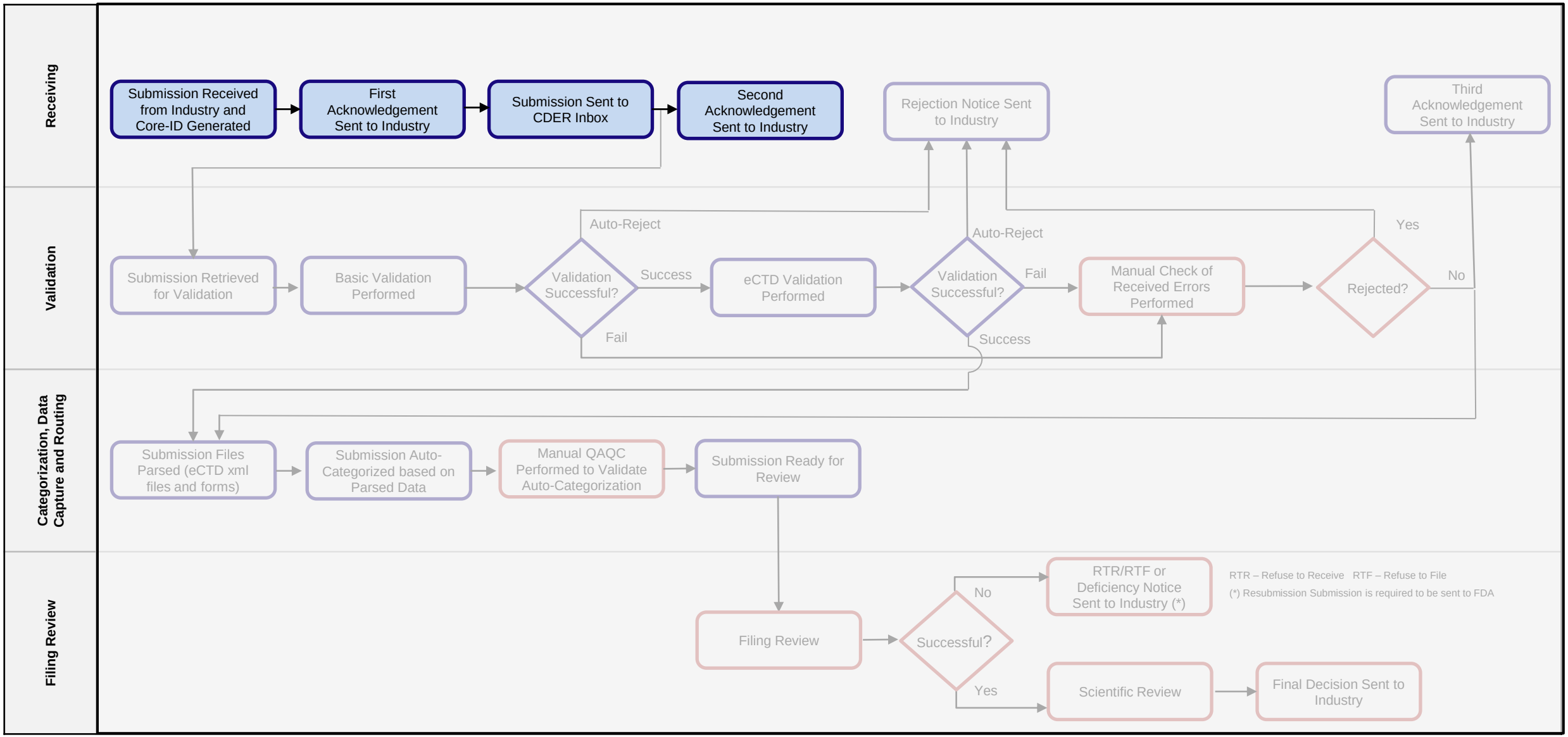
FDA Application Submission and Filing Review Process include the following four main phases:



Application Submission and Filing Review Process Diagram



Application Submission and Filing Review Functional Process – Receiving



Application Submission and Filing Review Process Diagram – Receiving

Submit eCTD via ESG

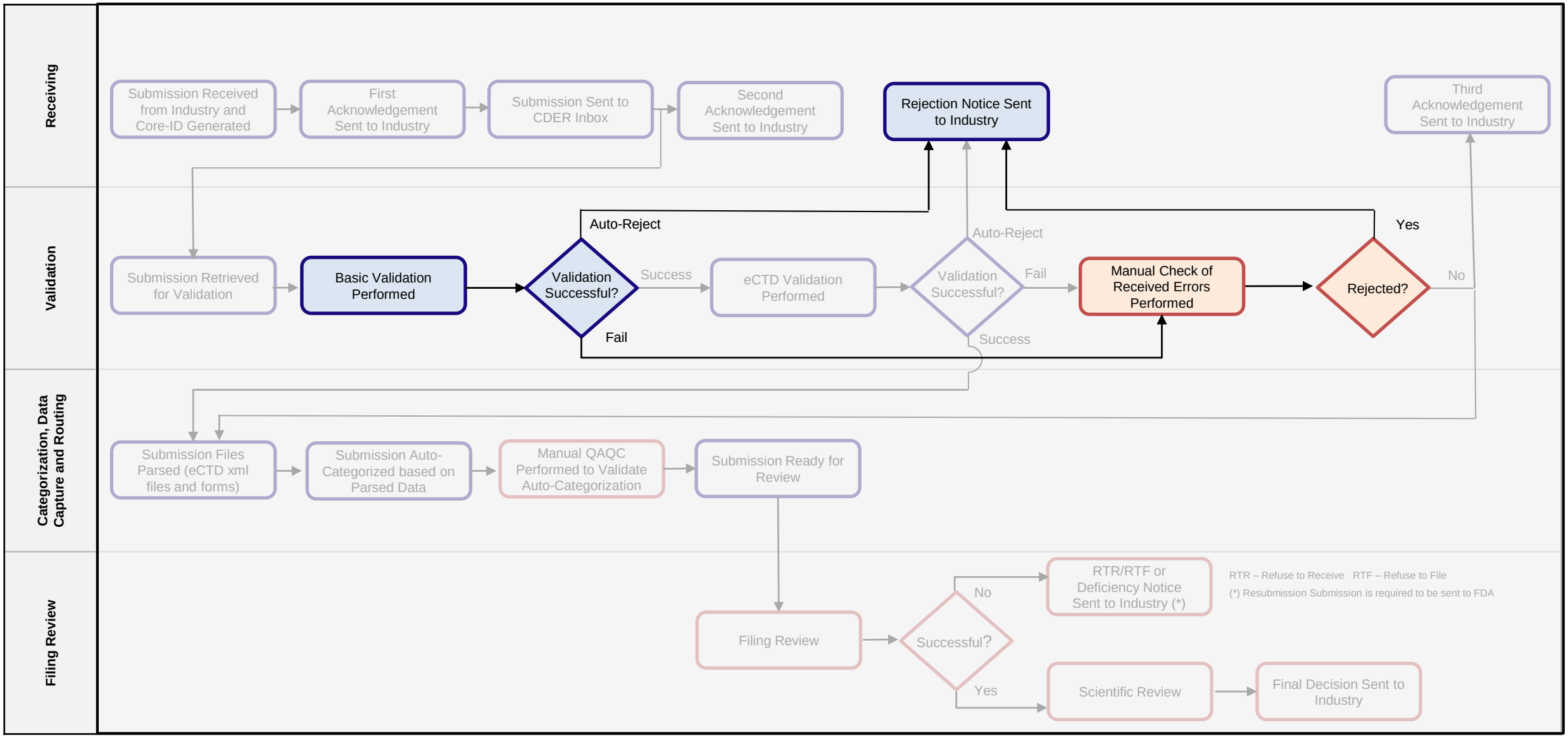
- Once the transmission to the ESG is completed, FDA issues First Acknowledgement to the Sponsor
- After the submission is delivered to CDER, ESG sends the Second Acknowledgment to the Sponsor.
- FDA Receipt Date is determined by the Guidance to Industry: Providing Regulatory Submissions in Electronic Format--Receipt Date. FDA Receipt Date is determined* by the Second Acknowledgement.

* For ANDA and Type II Drug Master File, the First Filer status is determined based on the date of submission as identified in the First Acknowledgement.

Second Acknowledgement Example:

```
Center for Drug Evaluation and Research (CDER)
U.S.Food and Drug Administration

SUBJECT:ACKNOWLEDGEMENT OF SUBMISSION RECEIPT
SENT FROM:FDA ELECTRONIC SUBMISSIONS GATEWAY (ESG)
PRODUCTION

Account Name:                                    Inc - GP
MessageId: <171786                                -NJPRI-20013>
CoreId: ci1649184                                 0@fdslv08799_te2

File Count: 11
Directory Count: 10

DateTime Receipt Generated: 04-05-2022, 14:54:02
Time Zone: Eastern

The date and time stamp contained in this message indicates when the ESG
delivered your submission to CDER for processing. Once your submission has
passed validation and been successfully processed, you will receive a final
acknowledgement.Submissions that cannot be processed are subject to
rejection.

Your official receipt date is calculated in accordance with the following
final Guidance for Industry :
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/
Guidances/UCM072385.pdf
```

Application Submission and Filing Review Functional Process – Validation (Basic)



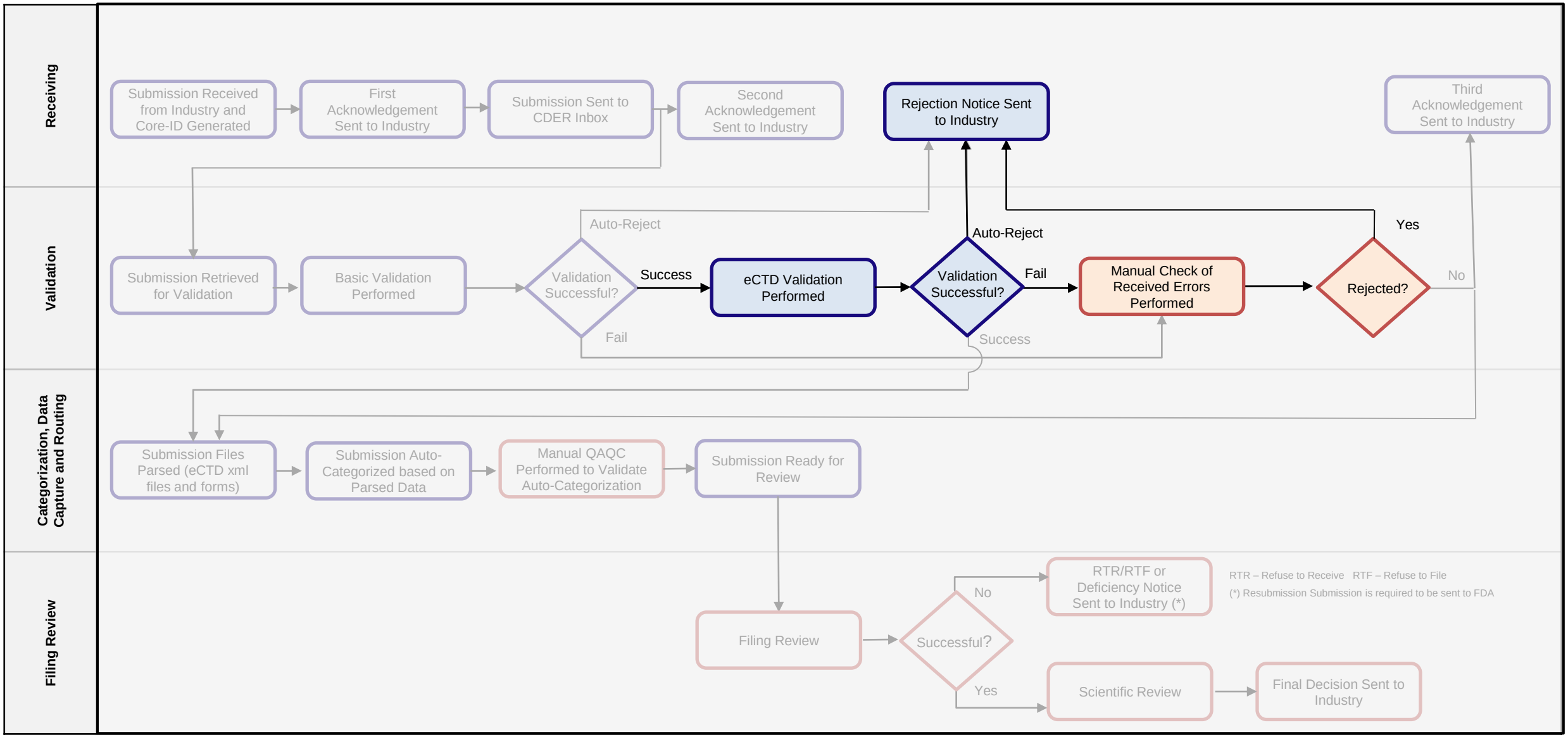
Application Submission and Filing Review Functional Process – Validation (Basic)

Basic check of incoming submissions is performed prior to eCTD validation.

Number of Rejection (FY2022)	Top Errors that result in auto-rejection of a submission
2815	Duplicate eCTD sequence
690	A submission contains only a single file
536	Backbone files are not provided in an eCTD submission

Number of Submissions (FY2022)	Top high basic errors that are subject to manual review and possible rejection
186	eCTD Sequence Number in a us-regional file does not match an eCTD Sequence number in the folder name
131	Application Type/Number does not exist in the FDA systems

Application Submission and Filing Review Functional Process – Validation (eCTD)



Application Submission and Filing Review Process – Validation (eCTD)

eCTD validation is performed against Specifications for eCTD Validation Criteria

Number of Rejection (FY2022)*	Top eCTD Errors that result in auto-rejection	eCTD Error Code
337	All submitted files are not referenced in the backbone files	Error Code 1306
269	Submission file(s) are referenced in the backbone files, but they are not provided within a submission	Error Code 1323
246	An unsupported DTD version is used in us-regional.xml	Error Code 1463
198	ts.xpt with information on the study start data for each study is not present	Error Code 1734
164	All files provided in a study section must be referenced by an STF file	Error Code 1789
Number of Submissions (FY2022)	**Top high eCTD errors that are subject to manual review and possible rejection**	**eCTD Error Code**
276	A submission type is invalid for an application type	Error Code 2034
141	A submission sub-type is invalid for submission type or/and application type	Error Code 2022

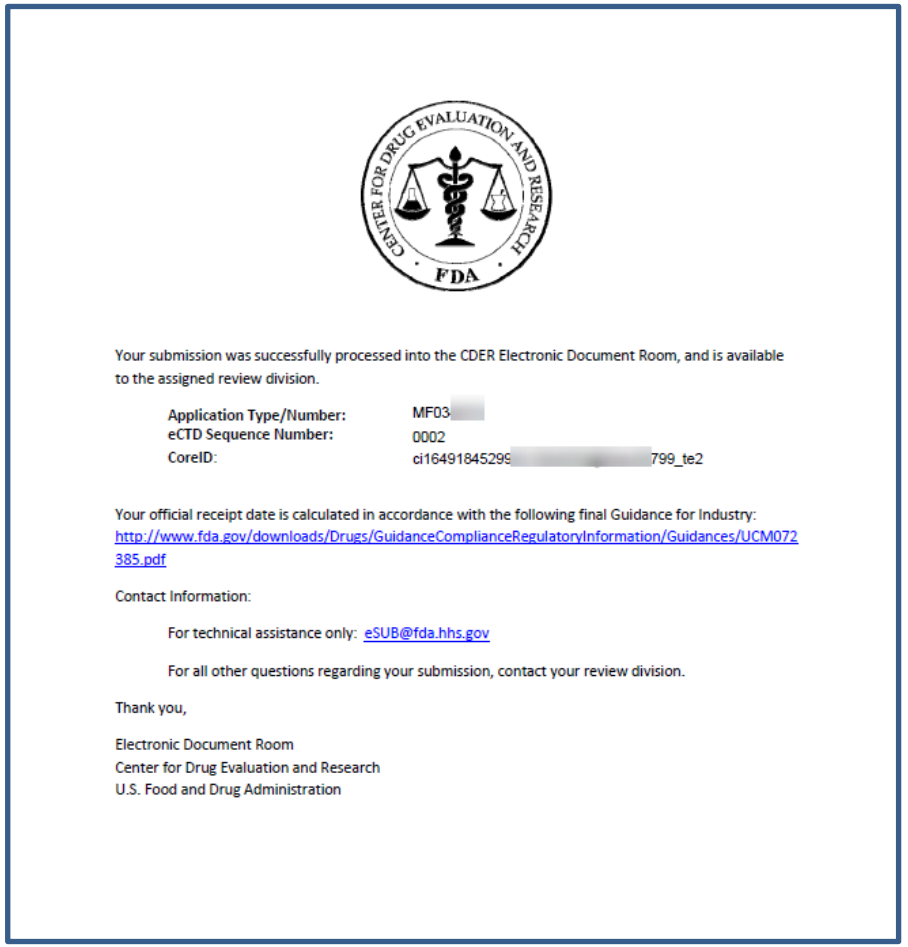
* In 2022, FDA rejects less than 2% of all eCTD submissions.

Application Submission and Filing Review Process – Validation

FDA will send the 3rd Acknowledgement to the Sponsor once the incoming submission passed eCTD Validation

- The submission will be passed to document room for further Categorization, Data Capture and Routing process.

Third Acknowledgement Example:



CENTER FOR DRUG EVALUATION AND RESEARCH · FDA ·

Your submission was successfully processed into the CDER Electronic Document Room, and is available to the assigned review division.

Application Type/Number:	MF03
eCTD Sequence Number:	0002
CoreID:	ci16491845299 799_te2

Your official receipt date is calculated in accordance with the following final Guidance for Industry:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072385.pdf

Contact Information:

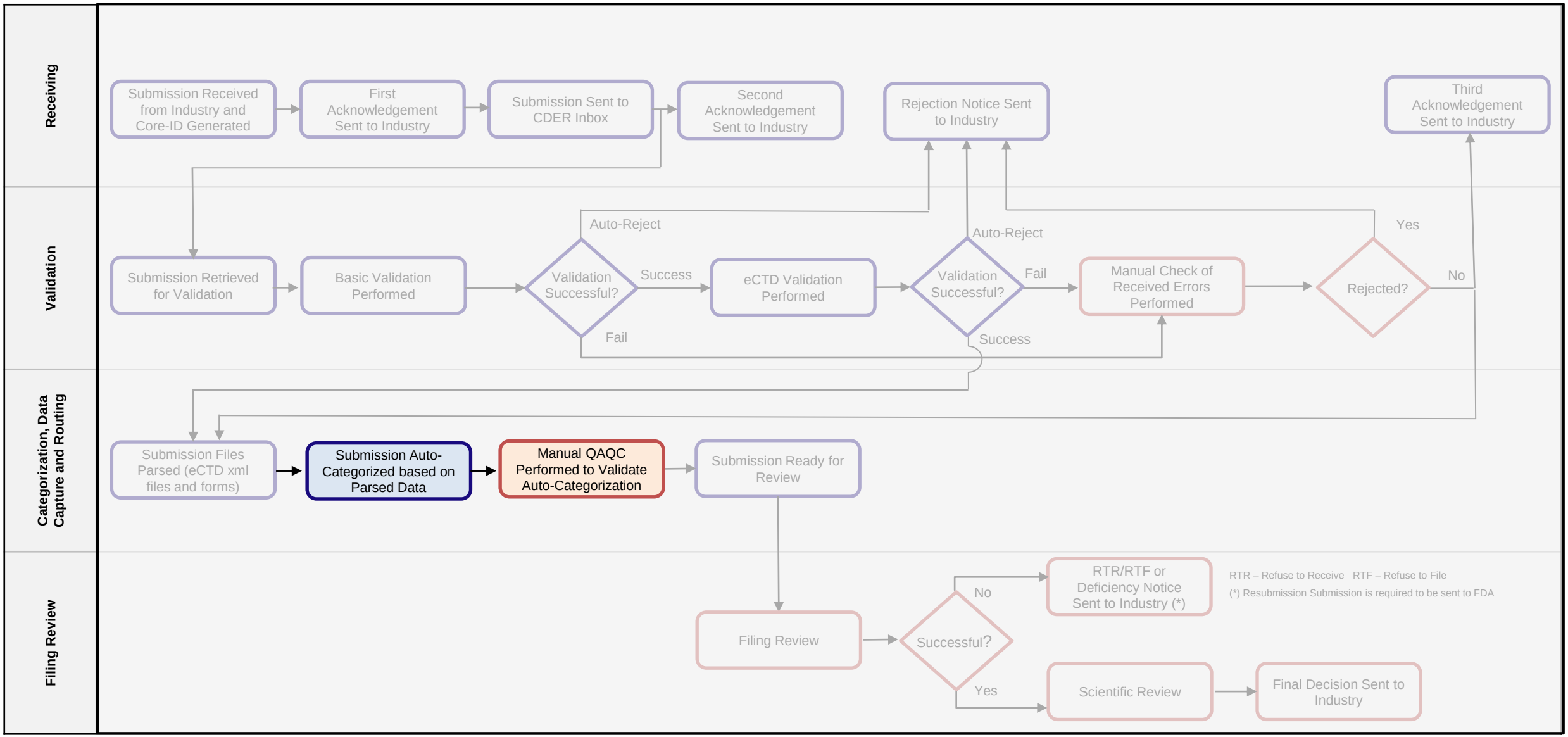
For technical assistance only: eSUB@fda.hhs.gov

For all other questions regarding your submission, contact your review division.

Thank you,

Electronic Document Room
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Application Submission and Filing Review Functional Process
Categorization, Data Capture and Routing



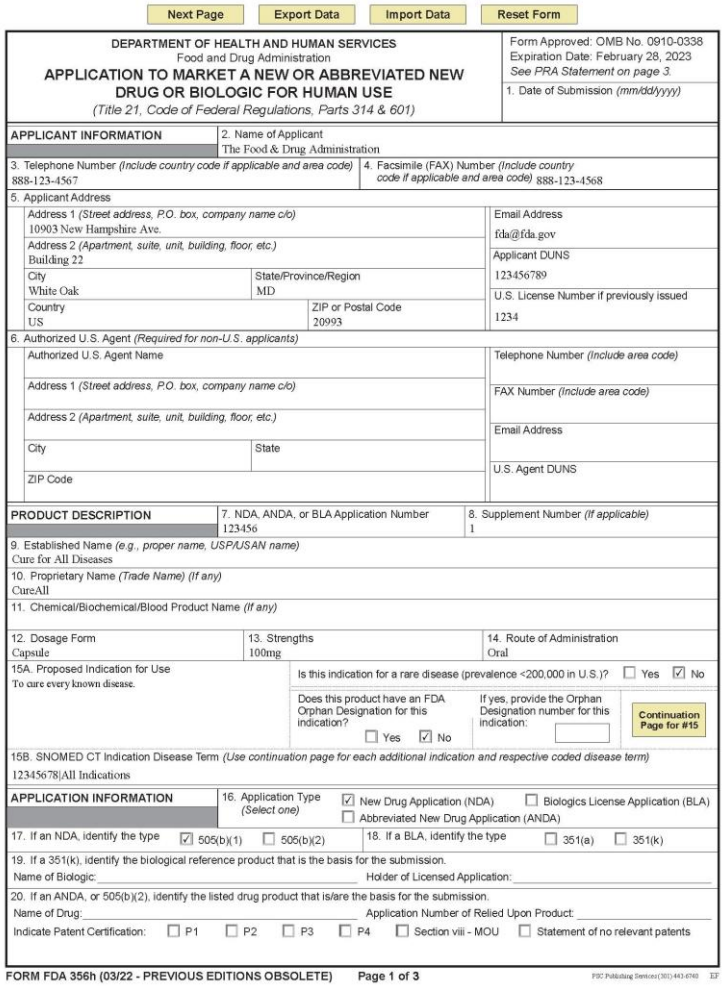
Application Submission and Filing Review Process
Categorization, Data Capture and Routing

FDA Document Room and Data Service team need to capture the meta data from the incoming submissions:

- Data from the Cover Letter
- Submission Meta Data*
  - ❑ Applicant
  - ❑ Product
  - ❑ Indication
  - ❑ Establishment
  - ❑ Submission Type
  - ❑ Supplement Category

* Submission Meta Data are located on 1571 Form for INDs and 356h Form for NDAs, BLAs, and ANDAs

Sample 356h form:



Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: February 28, 2023
See PRA Statement on page 3.

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant: The Food & Drug Administration

3. Telephone Number *(Include country code if applicable and area code)*: 888-123-4567

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*: 888-123-4568

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*: 10903 New Hampshire Ave.
Address 2 *(Apartment, suite, unit, building, floor, etc.)*: Building 22
City: White Oak
State/Province/Region: MD
Country: US
ZIP or Postal Code: 20993
Email Address: fda@fda.gov
Applicant DUNS: 123456789
U.S. License Number if previously issued: 1234

6. Authorized U.S. Agent *(Required for non-U.S. applicants)*

Authorized U.S. Agent Name
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City
State
ZIP Code
Telephone Number *(Include area code)*
FAX Number *(Include area code)*
Email Address
U.S. Agent DUNS

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number: 123456

8. Supplement Number *(If applicable)*: 1

9. Established Name *(e.g., proper name, USP/USAN name)*: Cure for All Diseases

10. Proprietary Name *(Trade Name) (If any)*: CureAll

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form: Capsule
13. Strengths: 100mg
14. Route of Administration: Oral

15A. Proposed Indication for Use: To cure every known disease.

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☑ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☑ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #15

15B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*: 12345678|All Indications

APPLICATION INFORMATION

16. Application Type *(Select one)*: ☑ New Drug Application (NDA) ☐ Biologics License Application (BLA) ☐ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type: ☑ 505(b)(1) ☐ 505(b)(2)

18. If a BLA, identify the type: ☐ 351(a) ☐ 351(k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.
Name of Biologic: _____ Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is/are the basis for the submission.
Name of Drug: _____ Application Number of Relied Upon Product: _____
Indicate Patent Certification: ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

FORM FDA 356h (03/22 - PREVIOUS EDITIONS OBSOLETE) Page 1 of 3

Application Submission and Filing Review Process – Routing Automation

The FDA has been working on expediating initiation of the submission review process by automating the submission categorization process.

When data is submitted correctly in eCTD backbone files (e.g., us-regional.xml file) and regulatory form (e.g., Form 356h), submission can be efficiently routed to the assigned review division and/or reviewer(s)

However, data issues with eCTD submissions can prevent the FDA from implementing the fully automated submission categorization process

- **Data discrepancy** between the backbone files and FDA regulatory forms
- Under utilization of existing **eCTD headings and attributes**
- Not identifying **grouped submissions in eCTD backbone**
- **Placement of submission files** in eCTD modules/sections not relevant to file contents

Application Submission and Filing Review Process
Sample Error Prevents Automation

Can you guess the correct regulatory activity in this submission?

us-regional.xml (DTD V2.01)

```
<application-information application-type=[redacted]>
  <submission submission-type="amendment">
    <sequence-number>[redacted]</sequence-number>
    <related-sequence-number>[redacted]</related-sequence-number>
  </submission>
</application-information>
```

Indicating "Amendment"

Form 356h

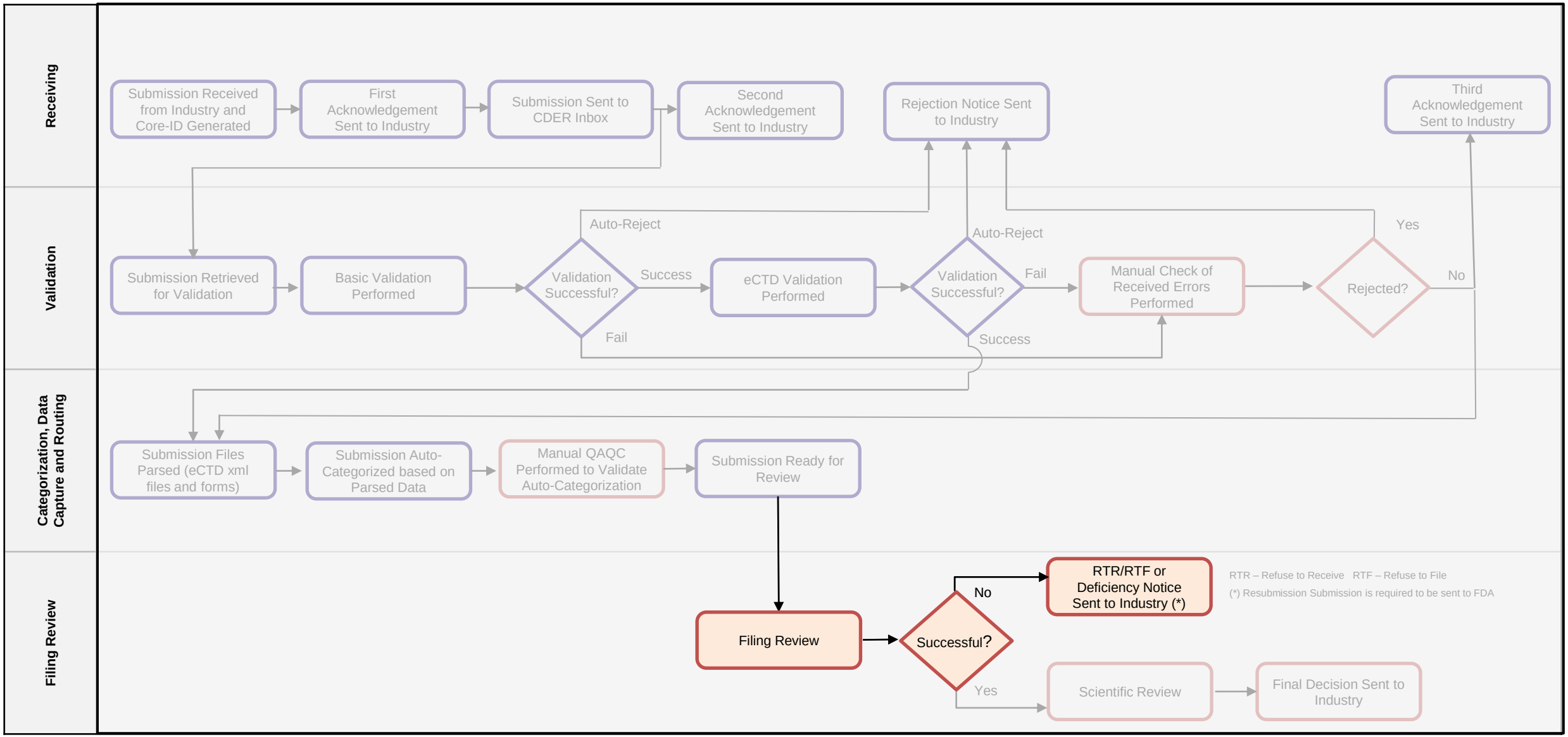
Indicating "Initial Submission"

21. Submission *(See instructions)*	☑ Original	☐ Labeling Supplement	☐ CMC Supplement	☐ Efficacy Supplement	☐ Annual Report	
☐ Product Correspondence	☐ REMS Supplement	☐ Postmarketing Requirements or Commitments	☐ Periodic Safety Report			
☐ Request for Proprietary Name Review	☐ Other *(Specify)*: _____					
22. Submission Sub-Type	☐ Presubmission	☐ Amendment	23. If a supplement, identify the appropriate category.	☐ CBE	☐ Prior Approval (PA)	
	☑ Initial Submission	☐ Resubmission		☐ CBE-30		

This submission was an amendment containing patent information.

The appropriate "Submission Sub-Type" on Form 356h should have been "Amendment"

Application Submission and Filing Review Functional Process – Filing Review



Application Submission and Filing Review Process – Filing Review

During the Filing Review, the FDA reviewers check if there are any major submission deficiencies that would not permit timely, efficient, and complete review by all relevant review division disciplines.

If such deficiencies exist, a submission is:

- **Refuse to Receive (RTR)** for ANDA applications
- **Refuse to File (RTF)** for BLA and NDA applications
- **Deficiency Notice***

* In some cases, Review Office may send a deficiency notice to the applicant about the missing piece and give the applicant an opportunity to submit the missing material to avoid RTR/RTF.

Application Submission and Filing Review Process – Filing Review

Examples of ANDA deficiencies that result in Refuse to Receive (RTR):

- Submission format and organization
- Non-payment of GDUFA user fee obligations
- Missing sterility assurance data
- Product quality deficiencies (e.g., inactive ingredient limits, incomplete stability studies, not qualitatively and quantitatively the same with respect to certain dosage forms)
- Bioequivalence and clinical deficiencies (e.g., failed in-vivo BE studies, incomplete dissolution data)

Guidance and regulations:

- ANDA Submissions - Refuse-to-Receive Standards: Questions and Answers Guidance for Industry | FDA
- ANDA Submissions -- Refuse-to-Receive Standards Rev.2 | FDA

Application Submission and Filing Review Process – Filing Review

Examples of NBA/BLA deficiencies that result in Refuse to File (RTF):

- Materially lacking or inadequately organized submissions
- Supporting information included in the submission is inadequate for one or more requested indications
- Relies on a single adequate and well-controlled trial where the need for more than one trial to demonstrate effectiveness has been identified, without adequate justification
- Failure to submit an assessment of studies related to the potential abuse of a drug where applicable
- Required content is not submitted in the format specified by FDA (i.e., electronically)

Guidance and regulations:

- (DRAFT) Refuse to File: NDA and BLA Submissions to CDER Guidance for Industry | FDA

Key Takeaways

Key takeaways from today's topics

- Incoming submission needs to go thought receiving, validation, categorization/data capturing/routing, and filing review phases before it can be reviewed.
- FDA performs basic and eCTD validation for an incoming submission and sends acknowledgements to sponsor if a submission is successfully processed or failed.
- Critical submission meta data are being captured automatically to support validation, categorization and routing.
- Data quality is important for efficient submission processing and routing; issues with a submission may not be discovered during the Validation process (after the successful 3rd ack); Filing issues are communicated via deficiency notices and/or RTR/RTF
- CDER is building more advanced analytics capability, extracting and leveraging both structured and unstructured data from sponsor submissions, to improve its data-driven decision-making regulatory review process.

Acknowledgments

The author would like to thank Ela Dybala, Jonathan Resnick, JJ Shen, and other FDA staff for their time and effort in helping collect and analyze data and information as presented in this paper.

DIA