Filing Review Basics - Refuse to Receive

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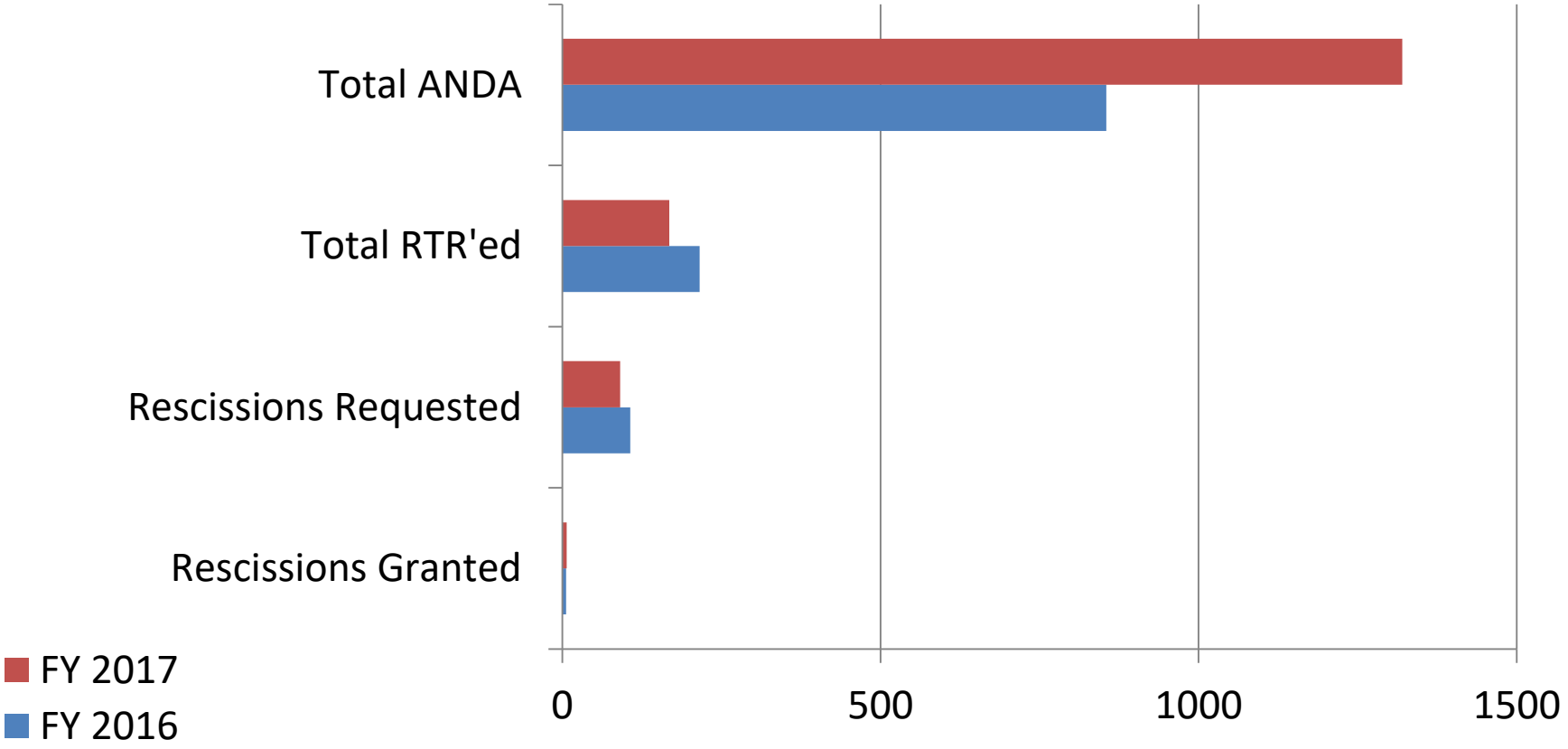
Discussion Overview

- Refuse-to-Receive (RTR) Statistics
- Common RTR Deficiencies
- Communications
- Resources

Division of Filing Refuse-to-Receive (RTR) Statistics

	FY 2016 (Oct. 2015- Sept. 2016)	FY 2017 (Oct. 2016- Sept. 2017)
Total ANDAs Submitted	855	1320
Total ANDAs RTR'ed	216 (25.26%)	168 (12.73%)
Total Rescission Requests Submitted	107	91
Total Rescission Requests Granted	6	7

View of FY 2016 and 2017 ANDA



Top RTR Deficiencies for FY 2017

- Stability (e.g., Lack of 2 API lots used and/or 3 test batches)
- Inadequate dissolution (including all applicable dissolution, e.g., half-tablet dissolution for functional scored, modified release products)
- Impurities
- Incomplete Response to Deficiencies (including eCTD deficiencies)
- Not Q1/Q2 to RLD
- Incomplete/Inadequate BE Study Data

Top RTR Deficiencies for FY 2017

- Stability (e.g., Lack of 2 API lots used and/or 3 test batches)
  - Two API lots for each strength not used
  - Minimum 3 test batches not submitted
  - Lack of 6 months and/or 3 time points for Accelerated and Long term study data
  - Accelerated stability studies stopped early

Top RTR Deficiencies for FY 2017

- Inadequate dissolution
  - Product specific guidance recommended dissolution studies
  - Half-tablet dissolution must be provided for functionally scored, modified-release products
  - Should perform minimum of 12 dosage-unit comparative dissolution for each strength of Test and RLD.

Top RTR Deficiencies for FY 2017

- Impurities
  - Lack of Justification for drug product and drug substance
  - Unspecified Impurities/degradation: AC % should not exceed the regulatory IT %.
  - Provide all supporting data and information to justify any above regulatory threshold limits

Top RTR Deficiencies for FY 2017

- Incomplete Response to Deficiencies
  - Response must be received within 7 calendar days
  - Documents must follow eCTD and PDF specifications
  - Check for completeness of all folders, subsections and leaflets
  - Ensure there are no duplicate files
  - Contact **CDER ESUB at** esub@fda.hhs.gov

Top RTR Deficiencies for FY 2017

- Incomplete/Inadequate BE Study Data
  - Failed to provide evidence of data for BE studies in Module 2.7.
  - Non-recommended BE study without justification

Top RTR Deficiencies for FY 2017

- Not Q1/Q2 to RLD
  - Parenteral, ophthalmic and otic solutions must be Q1/Q2 to the RLD
  - Specific changes from RLD drug product are permitted for exception excipients
  - Applicant must provide justification for all exception inactive ingredients changes
  - Check Product Specific Guidance for Q1/Q2 requirement
  - Before submitting ANDA, an applicant can submit controlled correspondence to request Q1/Q2 evaluation.

Rescission Requests

- Reconsideration requests should be submitted directly to the ANDA as an amendment

- Contact the DFR Rescission Request mailbox (DFRSupervisor@fda.hhs.gov) for any questions

Controlled Correspondence: Division of Filing Review

- Definition
- Types of Controlled Correspondence
- GDUFA II Commitment Letter

Standard Controlled Correspondence Definition

- Requesting information on a specific element of generic drug product development

- Post-approval submission requirements that are not covered by CDER post-approval changes guidance and are not specific to an ANDA

Complex Controlled Correspondence Definition

- Evaluation of Clinical Content
- Review of Bioequivalence (BE) protocols for drugs that reference listed drugs with risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU)
- Evaluation of alternative BE approaches within the same study type

Controlled Correspondence Expectations for GDUFA II

- Standard controlled correspondence: review and respond to 90% within 60 calendar days
- Complex controlled correspondence: review and respond to 90% within 120 calendar days
- If related to one or more pending CPs, the 60 or 120 days time period starts on the date FDA responds to the petition or last pending petition
- Review and respond to 90% of request for clarification of ambiguities within 14 calendar days

Use of Controlled Correspondence to Aid in Filing Review

- Request for Q1/Q2 Formulation Assessment
- Request Related to Inactive Ingredient Evaluation (IID evaluation)
- Filing Strategy Inquiries

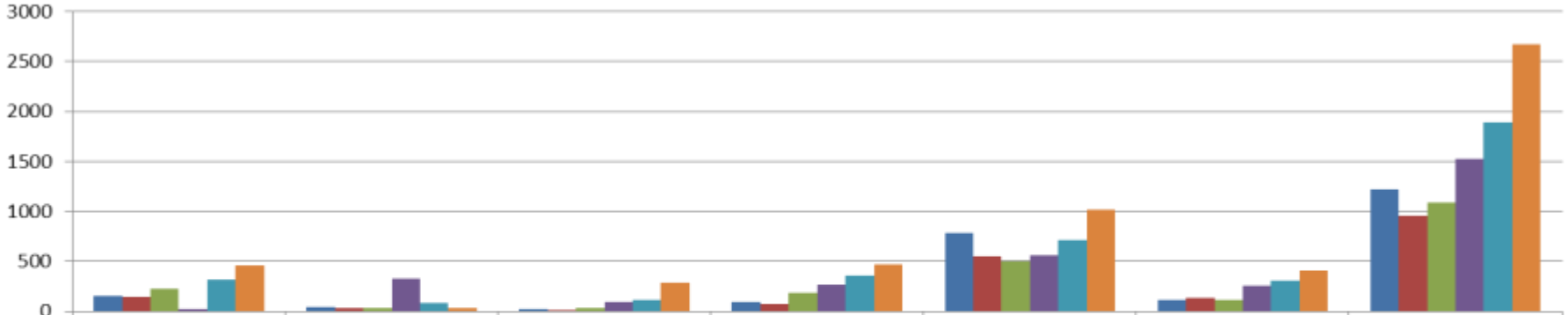
Q1/Q2 Evaluation Request

- Relevant RLD sponsor
- Application number
- Proprietary name
- Active ingredient
- Dosage form
- Route of administration
- RLD approval date
- Whether the product is prescription, over-the-counter, or in the "Discontinued" section of the Orange Book, which lists drug products that have been withdrawn from the market

Helpful Tips for Controlled Correspondences

- Submit controls via email to GenericDrugs@fda.hhs.gov
- Submit the control on corporate letterhead, as an attachment to the email
- Send email from a corporate email address
  - To apply for a secure email pathway, contact: secureemail@fda.hhs.gov
  - Do not submit controls to individual FDA employees
  - Do not submit additional copies of a control in paper form, by courier, or fax
  - Controlled Correspondence on behalf of a foreign applicant must be submitted by the U.S. Agent

Controlled Correspondences Received Per Discipline
FY 12 - FY17



	Office of Bioequivalence (Division of Bioequivalence)	Office of Bioequivalence (Division of Clinical Review)	Office of Generic Drug Policy (Orange Book & Policy)	Office of Pharmaceutical Quality (Chemistry)	Office of Regulatory Operations (Division of Filing Review & Division of Labeling Review & Immediate Office)	Office of Research & Standards	Grand Total
FY 12	156	48	20	95	780	118	1217
FY 13	141	35	9	78	552	138	953
FY 14	225	29	29	184	502	118	1087
FY 15	25	322	94	269	556	253	1519
FY 16	316	80	110	358	713	307	1884
FY 17	460	29	289	465	1014	411	2668

Controlled Correspondence Review Disciplines

- OGD's Office of Bioequivalence
- OGD's Office of Research and Standards
- OGD's Office of Regulatory Operations, Division of Filing Review
- OGD's Office of Regulatory Operations, Division of Labeling Review
- OGD's Office of Generic Drug Policy
- OPQ's Office of Policy for Pharmaceutical Quality

Resources for Controlled Correspondence

- Draft Guidance for Industry, *Controlled Correspondence Related to Generic Drug Development (November 2017)*

- GDUFA II Commitment Letter https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

Contact

Controlled Correspondence:

genericdrugs@fda.hhs.gov

ANDA Filing Status:

ANDAFiling@fda.hhs.gov

DFR Rescission Requests or RTR questions:

DFRSupervisor@fda.hhs.gov

Resources for Filing

- Draft Guidance for Industry ANDA Submissions — Content and Format of Abbreviated New Drug Applications (June 2014)
- 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)
- Guidance for Industry Providing Regulatory Submission in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Revision 3, May 2015)
- Draft Guidance for Industry Controlled Correspondence Related to Generic Drug Development (November 2017)
- Draft Guidance for Industry Requests for Reconsideration at the Division Level Under GDUFA (October 2017)
- Draft Guidance for Industry ANDA Submissions- Refuse-to-Receive Standards: Questions and Answers (October 2017)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