



2015 PDA/FDA Joint Regulatory Conference

Managing Submission Quality

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Agenda

- Background
- General Tips
- Controlled Correspondence
- Filing Tips
- Review Tips
- Contractor Tips
- Labeling Tips
- Recent Concerns
- Additional Information

Generic Drug Program

Available

Safe

Effective

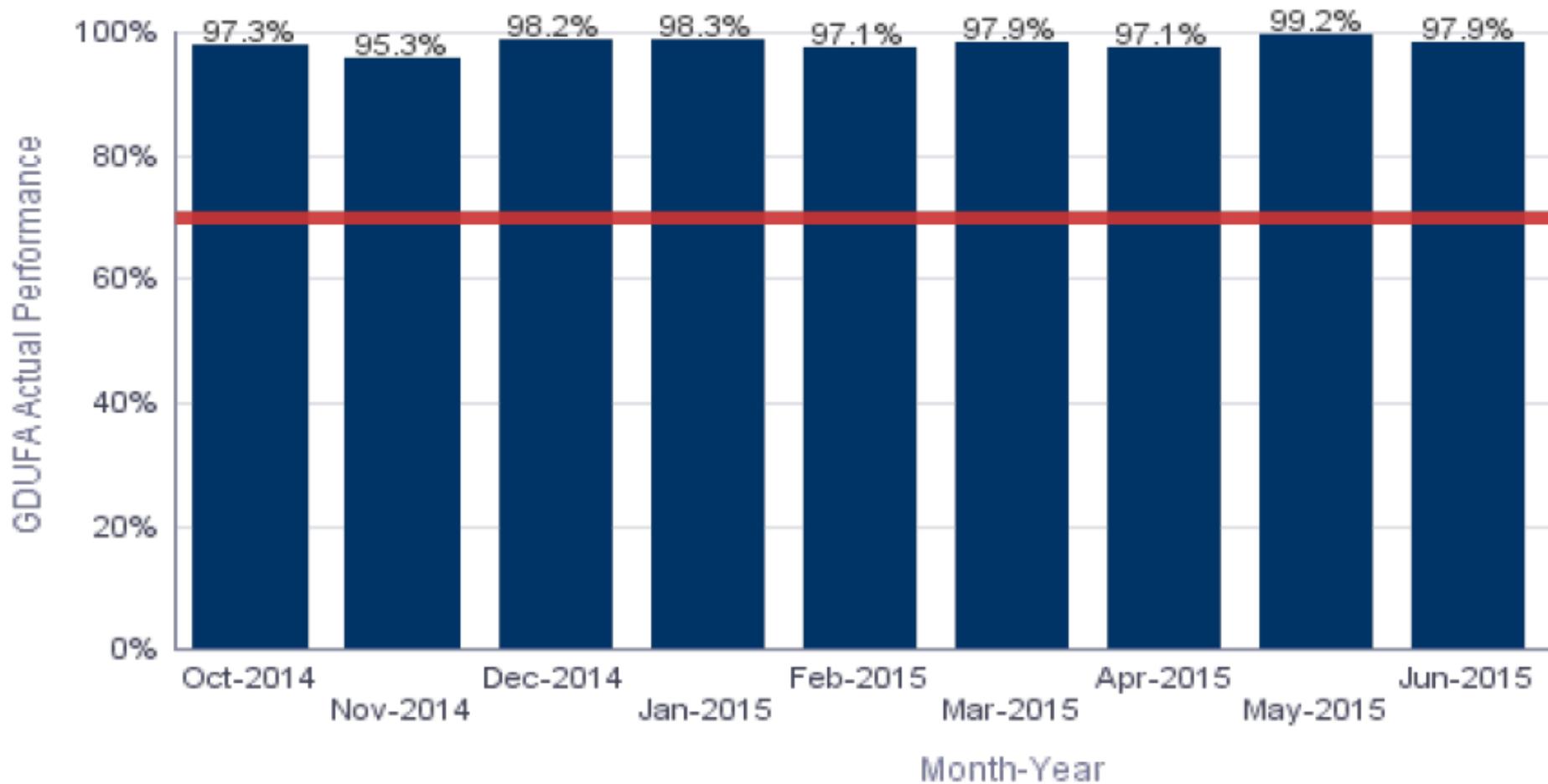


Quality

Substitutable



Control Correspondence



ANDA Filing Time Frames

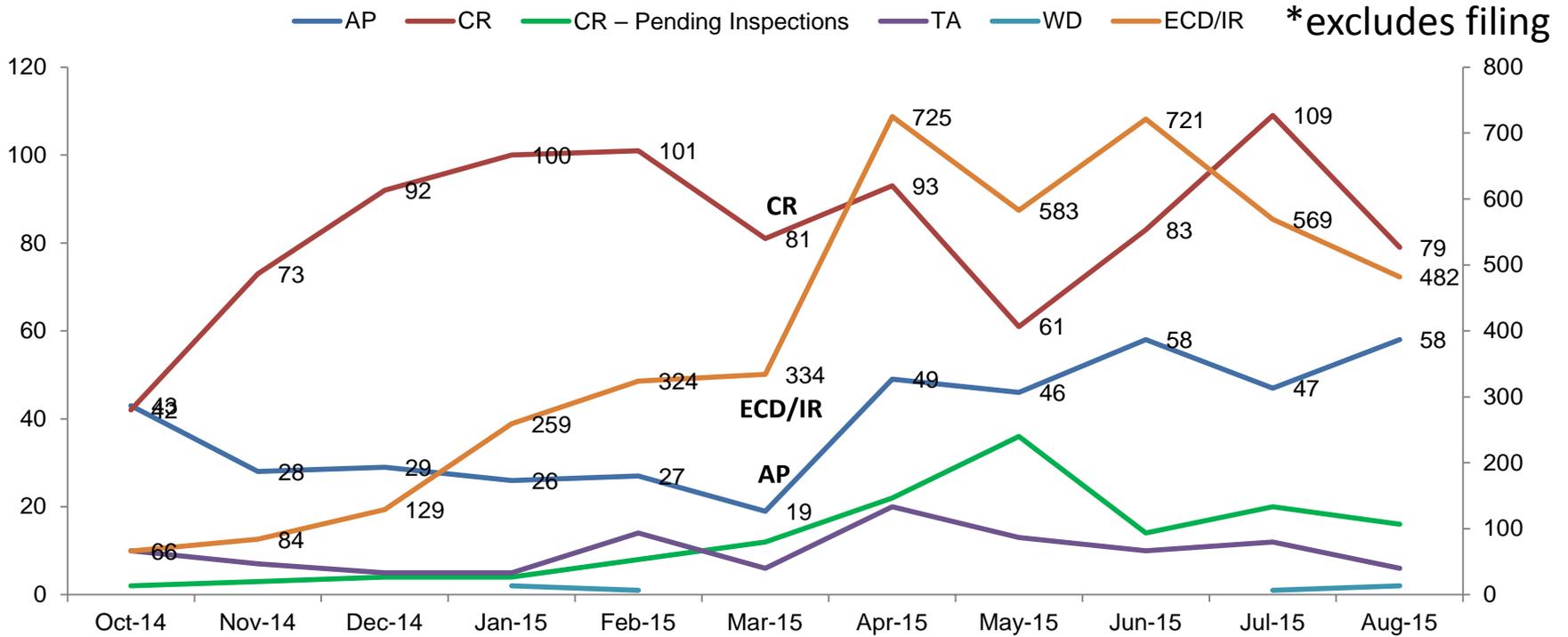
- Typical assessment time
 - Current/GDUFA Year 3 submissions: 31 days
 - Prior submissions/backlog: about 100 left
 - Check-list:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM320405.pdf>

ANDA Filing Time Frames (cont.)

- Guidance on Refuse-to-Receive Standards:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf>
- Electronic format:
 - “highly recommend”
 - GDUFA review goals only apply to electronic ANDA submissions

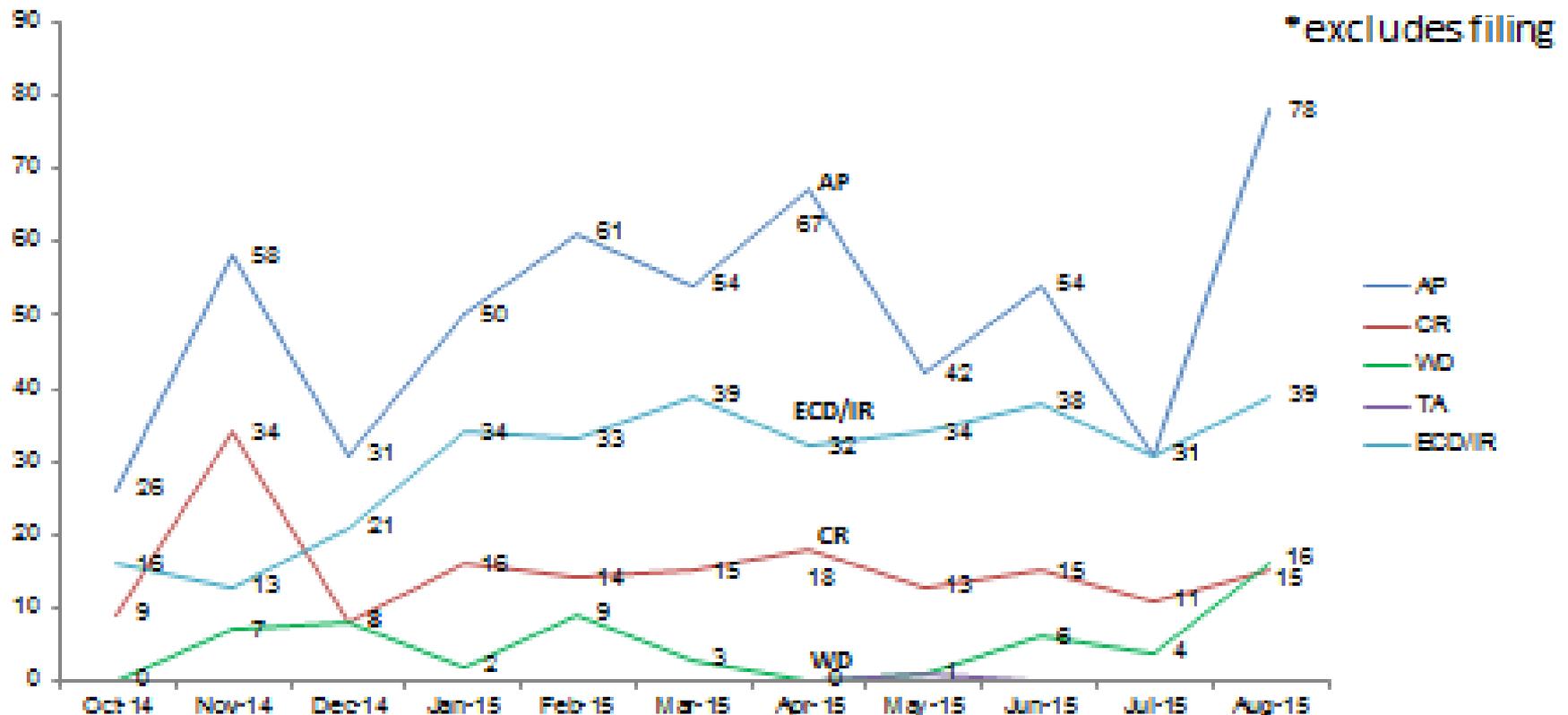
ANDA Originals – Actions Taken

s)



	Oct 2014	Nov 2014	Dec 2014	Jan 2015	Feb 2015	Mar 2015	Apr 2015	May 2015	Jun 2015	Jul 2015	Aug 2015	Grand Total
AP	43	28	29	26	27	19	49	46	58	47	58	401
CR	42	73	92	100	101	81	93	61	83	109	79	871
CR Pending Inspections	2	3	4	4	8	12	22	36	14	20	16	135
TA	10	7	5	5	14	6	20	13	10	12	6	103
WD				2	1			1		1	2	5
ECD/IR	66	84	129	259	324	334	725	583	721	569	482	4276

ANDA PAS – Actions Taken



	Oct-2014	Nov-2014	Dec-2014	Jan-2015	Feb-2015	Mar-2015	Apr-2015	May-2015	Jun-2015	Jul-2015	Aug-2015	Grand Total
AP	26	58	31	50	61	54	67	42	54	31	78	592
CR	9	34	8	16	14	15	18	13	15	11	15	189
WD	0	7	8	2	9	3	0	1	6	4	16	58
TA	0	0	0	0	0	0	0	0	1	0	0	1
ECD/IR	16	13	21	34	33	39	32	34	38	31	39	350

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General Tips

- “Say what you do. Do what you say. Prove it. Improve it.”
- Know your product.
- Capture that knowledge in the application.
- Meet the application criteria.
- Comply with any requests and completely address any deficiencies.
- Repeat the above for contractors.

General Tips (cont.)

- Consider your audience – Agency.
 - Don't make them hunt for your information.
 - Consider what they will be looking for.
 - Provide it.
 - Building a reputation for quality submissions.
 - “A grumpy Agency staff member is not your best friend.”

General Tips (cont.)

- Provide sufficient information.
- Present information that is well organized and clear.
- Use links to other sections.
- Provide NDA and/or ANDA number when communicating with Agency.
- Carefully consider the 356(h) contact – CEO may not always be the best contact.

General Tips (cont.)

- Be honest – remember it is often less about what happens and more about how you address the situation.
- If you are citing a Controlled Correspondence, include the question and the response in your application.
- Similar for meetings with Agency.

Show the value for today

General Tips (cont.)

- Present the data.
 - Reviewers are scientists and they like to analyze data.
 - Don't get caught with missing data.
 - Use clear labels and figures.
 - Make the data easy to read and compare.
 - Make sure the data supports the story.

General Tips (cont.)

- Explain deviations from guidances.
 - Provide rationale.
 - Provide supporting data.
- Make sure your company is speaking with one voice.
 - Funnel contacts with the Agency to a couple staff members.
 - Make sure backup contacts are in place.

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Controlled Correspondence Tips

- When submitting Controlled Correspondence (a request for information related to generic drug development), include relevant reference listed drugs (RLD), as applicable, including application number, proprietary (brand) name, 278 manufacturer, active ingredient, dosage form, and strength(s).
- Link: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm411478.pdf>

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Filing Tips

- Submit a complete application – avoid “Refuse-to-Receive.” (similar to Refuse-to-File)
- Use the checklist.
- Fully complete the 356(h) form.
- Assure Drug Master Files (DMFs) have undergone Completeness Assessments.
- Respond completely and timely to IRs related to filing deficiencies.
- Cite the issue in the response.

Filing Tips (cont.)

- When correcting communicated eCTD deficiencies, check all documents for the identified deficiencies & correct where needed.
- Place information in the proper sections of the ANDA hierarchy.
 - Comparative dissolution data should be placed in modules 2.7 and 5.3.1.3

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Review Tips

- Avoid inefficient use of reviewer time – yours is not the only application.
- Organize information to tell the story.
- Use the application to show that you know the product.
- Minimize duplication of information within a submission.
- Proofread – applications have been rejected because of simple omissions.

Review Tips (cont.)

- Learn from your deficiencies and minimize duplication in subsequent amendments and new applications.
- Address all the deficiencies.

Review Tips (cont.)

- Use clear cover letters.
 - Type of submission.
 - Clearly highlight/outline key attributes of the submission such as type or tier.
 - Identify potential consults.
 - Help direct your submission to the appropriate review groups.

Review Tips (cont.)

- Electronic Common Technical Document (eCTD).
 - Standard electronic format for submissions.
 - Reviewers need well formatted eCTD submissions.
 - Goals do not apply to non-eCTD ANDAs.
 - Send electronic submission questions to: ESGHelpDesk@fda.hhs.gov
 - Link: <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>

Review Tips (cont.)

- Use appropriate bookmarks.
 - Make sure it is not too long.
 - Make sure the name is tied to the destination/content.
 - Match the Table of Contents description.
 - Make sure someone unfamiliar with the application will know what content they will see before they click the bookmark.

Review Tips (cont.)

- Reviewers appreciate links instead of searching for a reference (table, figure, document, section, etc.).
- Make sure hyperlinks work.
- Make the application easy to navigate.

Review Tips (cont.)

- Watch for guidance updates.
- Watch for compendia changes and update your application accordingly.
- Make sure OGD has all legal documents and update as needed.
- Include patent updates.
- Submit a new 356h when regulatory contact changes.

Review Tips (cont.)

- Provide complete and timely responses.
- Goal dates are important to FDA too.
- No response to IR or easily correctable deficiency (ECD) (used primarily for generic drugs) triggers a CR (consumes Agency resources).

Review Tips (cont.)

- Work with your Regulatory Project Manager (RPM). (If you cannot reach the RPM, contact the Team Leader then Supervisor.)
- Contact the RPM, not the discipline unless specifically requested.
- Contact the Discipline PM for your delays in responding to IRs.
- OGD cannot rescue ANDAs.

Review Tips (cont.)

- If Tentatively Approved*, make sure any changes are reported in a timely manner.
- For supplements that provide for alternate manufacturing facility, revised labeling and labeling to reflect the new manufacturer may be submitted in the annual report.
- Properly and clearly identify the types of changes in a supplement.

* meets FDA's requirements, but patent and/or exclusivity protection exists 31

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Contractor Tips

- Know the quality of your contractor.
- Integrate contractor data into your submission. *(analogy)*
- Make sure your contractor is doing the right things.
- You are responsible for your contractor, not the FDA.
- Assure facilities are ready for inspection.

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Labeling Tips

- Submit labels and labeling in final print in your original submission (reduces cycles).
- Requirement for “same” labeling is the NDA reference listed drug (RLD) product, and not the current ANDA reference standard reflected in the Orange Book.

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Response to Filing Concerns

- New review practices will prevent inappropriate application of guidance standards.
- Rescissions have been primarily a result of old review practices that have since been corrected by the first bullet.
- **Enhanced** RTR standards have been developed and implemented, along with the necessary training to evaluate and enforce such standards.

Response to a Labeling Concern

- Many generic sponsors do not realize that the reference listed drug (RLD) designation in the Orange Book is only for bioequivalence purposes.
- If there was a NDA RLD and that NDA RLD is no longer marketed because it was discontinued or withdrawn, it still remains to be the RLD for labeling purposes.

Remember

- “Say what you do. Do what you say. Prove it. Improve it.”
- Know your product.
- Capture that knowledge in the application.
- Meet the application criteria.
- Comply with any requests and completely address any deficiencies.
- Repeat the above for contractors.

Questions?

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Guidances

- Guidance documents represent the Agency's current thinking on a particular subject.
- External focus
- Link

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

MAPP

- Manual of Policies and Procedures (MAPPs) are documentation of internal policies and procedures.
- Made available to the public.
- Link
- <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>

Office of Generic Drugs - Information

- Your RPM

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119463.htm>

- Web page:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119100.htm>

- Submission Requirements:

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



Filing

Top Reasons for RTR

- Incomplete/failed Bioequivalence studies
- Incomplete at time of submission (10+ deficiencies)
- Not Q1/Q2 to reference listed drug
- Stability (e.g., lack of 2 API and/or 3 test batches)
- Inadequate Drug Master File
- Inadequate justification of excipients

Top Reasons for RTR (con.)

- Inadequate dissolution
- Incomplete response
- No response within 10 business days
- Inadequate packaging

Form FDA 356h

- Follow the Instructional Supplement
- Field 13 Strength - Provide fill size
- Field 29 Establishment
 - Provide the manufacturing facility address or testing site address
 - Contact person should be the person at the manufacturing facility or testing site not a corporate office
 - Same with the information provided in 3.2.S.2 and 3.2.P.3.1
- Unexpired version

Form FDA 3674

- Fillable copy
- Updated/new form is required for resubmission and NSAs
- Unexpired version

Conviction Statement

- Should include that “all affiliates involved in the development and submission of the ANDA has not been convicted within the previous 5 years”
- Should not contain a qualifying statement (i.e., “to the best of our knowledge...”)

Patent Certification

- Use regulation wording
- Should match the Form FDA 356h

Environmental Impact Analysis Statement

- Cite the applicable regulation
- State “to the applicant’s knowledge, no extraordinary circumstances exist”
- Request for waiver
 - Cite applicable regulation

Annotated Labeling Comparison

- Should be visually highlighted and annotated
- Provide bookmarks

Electronic Common Technical Document (eCTD) Module 2

- 2.3 and 2.7 should be provided in MS Word
- Pilot tables and Pivotal tables should be submitted separately
- BE tables should not provide each table as a separate document

Module 2 (cont.)

- Table 4 - Separate table for each analyte
- Table 10 - LTSS data – cite all analytes, identify the exact location of the data including module, section, subsection, and page(s)
- Hyperlink to the data

Module 3

- Impurities (Characterization and Justification of Specification)
 - Provide summary tables following the document (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf>)
 - 3.2.S.3 Characterization, 3.2.S.4.5 Justification of Specifications, 3.2.P.5.5 Characterization of Impurities, and 3.2.P.5.6 Justification of Specifications

Module 3 (cont.)

- 3.2.P.1 Description & Composition of Drug Product
 - Flavoring and Coloring Agent – should provide component breakdown/composition or identify the specific location (and specify the date of submission of the particular flavoring/coloring agent) in the Type IV DMF LOA
 - Identify the hydration state or concentration for inactive ingredients
 - Buffering agent = quantify value rather than stating quantity sufficient
 - Iron calculation (full calculation, not just citing reg and stating that it's < 5 mg/day)

Module 3 (cont.)

- Reprocessing Statement – cite regulation
 - “No reprocessing will take place until a PAS is submitted and approved by the FDA/Agency”
- Container Closure System
 - Light transmission and water permeation testing

Module 3 (cont.)

- Stability Data
 - Ensure pull out date is correct/provided within the stability data (not as a separate table)
 - Pull out date for all stability data, not just accelerated
 - Provide 6 months of stability data for accelerated **AND** long-term
 - Stability data should indicate month, day, and year

eCTD Module 3 (cont.)

- **Stability Commitment**
 - From the applicant (even if they are not the drug product manufacturer)
 - “for each container closure system”
- **Information on Components**
 - Should be a consolidated tabular list

Module 5

- Tabular Listing of Clinical Studies
 - Identify pilot and pivotal tables
- Bioanalytical data should be located in 5.3.1.4
- Clinical Endpoint Study
 - SAS programs
- Placebo Formulation

eCTD

- Descriptive bookmarks for docs including SOPs,
 - E.g., appendix 1, appendix 2 OR addendum 1, addendum 2, etc. are non-descriptive
 - Appendices and addendums should also contain descriptive bookmarks
 - Package insert
 - In-vitro dissolution – more than 1 type, should provide bookmarks distinguishing between different strengths and different medias
 - Hierarchy of the bookmarks should reflect the hierarchy of the Table of Contents

eCTD (cont.)

- Page orientation
- Legibility issues – 3.2.R, 3.2.S
 - Graphs, chromatograms, XPT documents
- Font size from vendor

eCTD (cont.)

- Descriptive leaf titles
 - Differentiate MS Word and PDF
 - Identify sequence for documents that are provided in every sequence (e.g., Form FDA 356h, cover letter, etc.)
 - Identify the study by name rather than by the protocol number or validation number (unless it'll differentiate between similar studies)

eCTD (cont.)

- Applicant's should verify the PDF documents put together by third party companies
- Hyperlinks – open in a new window
- Should not duplicate files when responding to IRs

Misc.

- Typo issues → verify strengths, drug product, etc.
- ALL of the ANDA should be translated into English, no exceptions – this includes blank batch records and executed batch records (including addendums)



Labeling



Guidance for Industry and Food and Drug Administration Staff *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex*

- FDA recommends:
 - “**Not made with natural rubber latex**” or
 - “**The <vial stopper> is not made with natural rubber latex**”
- Manufacturers currently using statements such as "latex-free" or "does not contain latex" should submit revised labels and labeling as a CBE-0 supplement
- <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm342872.pdf>

USP: Ferrules and Cap Overseals

- “*Labeling on Ferrules and Cap Overseals*” section of USP General Chapter <1> Injections became official on December 1, 2013
- Restricts the labeling on ferrules and cap overseals to important safety messages critical for the prevention of imminent life-threatening situations
 - *Only cautionary statements may appear on the top (circle) surface of the ferrule and/or cap overseal of a vial containing an injectable product.*
 - *If no cautionary statement is necessary, the top surface of the vial, including the ferrule and cap overseal, must remain blank.*
- An ANDA that references a currently approved RLD which includes important safety language on the ferrule and/or cap should include the same language on its ferrule and cap overseal

Strength Presentation on Injections

USP General Chapters <1> Injections

STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS

For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL, not mg/1 mL.

An acceptable for contents of greater than 1 mL:

Total strength/total volume: 500 mg/10 mL

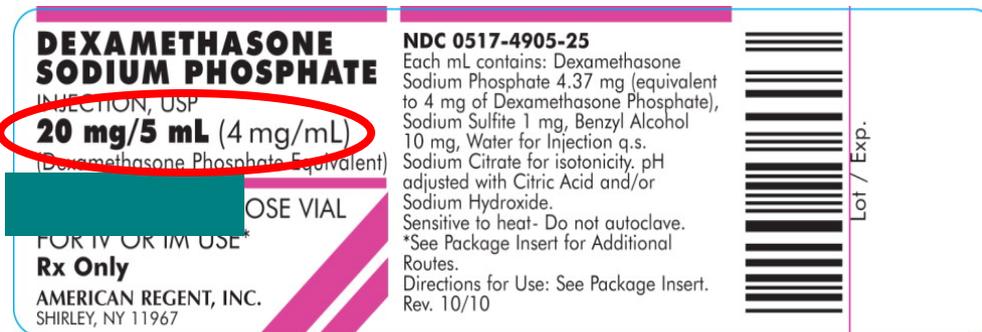
Strength/mL: 50 mg/mL

Product Strength on Injections

- Noncompliant



- Compliant





Chemistry

Major Deficiencies Defined

Major Deficiencies (9)

1. Unqualified impurity level(s) if tox studies are required
2. New source of API
3. New site of FDF manufacture
4. CQA failure or is not identified/controlled
5. Need full-term stability → expiration due to failed accelerated & intermediate
6. New packaging system needed
7. Unacceptable excipient due to exceeding IIG or clinical concerns
8. New analytical methods needed → not stability indicating or suitable
9. Biobatch is not representative of the commercial product



Minor Deficiencies Defined

Minor Deficiencies (14)

1. API: Need to identify/justify overage
2. API: Unidentified/unacceptable API-related impurities/chiral molecules
3. API: Polymorphism is inadequately justified/controlled
4. API: Unacceptable spec for residual solvents
5. API: Uncontrolled/unacceptable spec for particle size
6. API: Any other uncontrolled aspect related to potential DP CQA failure
7. Excipient: Lack of excipient control affecting DP CQA
8. DP: Unidentified/acceptable spec for impurities/residual solvents
9. DP: Unacceptable range for CQA or other relevant QA in DP release/stability spec
10. Inadequate method validation and request revalidation
11. Insufficient in-process control for CQA or related process parameters
12. Improper tablet score testing
13. Unacceptable stability testing // Unexpected trends
14. Unexpected trends observed during stability studies



Information Requests Defined

Information Requests (23)

1. Application QC issues (e.g., wrong DS, batch records, etc.)
2. Inconsistencies among different sections/modules
3. Missing easily retrievable docs (e.g., CoA, cGMP, etc.)
4. QOS is inconsistent with data in Module 3 or presents data not found in Module 3
5. API: Notice of DMF inadequacy or note to update DS spec based on DMF holder's spec
6. API: Physicochemical properties (e.g., pH, solubility, chemical structure) related to PD
7. Insufficient/missing retest date information
8. DP: Composition including function of excipients, grade, standard
9. DP: Additional info regarding PD related to potential CQA failure
10. Excipient: Additional info including impurities and residual solvent
11. Missing info for reference standards
12. Manufacturing process related to potential CQA failure

Information Requests Defined (cont'd)

Information Requests (23)

- | |
|---|
| 13. Insufficient or missing justification of low reconciliation |
| 14. Missing or IR regarding hold time |
| 15. Inadequate CCS testing per USP 661/671 or USP 1660/660, leachable/extractable |
| 16. Additional info regarding CCS (e.g., shipping study) |
| 17. Addition info or clarification regarding method validation |
| 18. Missing or inadequate method verification |
| 19. Request for further identity testing |
| 20. Note to update spec based on recommendations from other disciplines (e.g., BE & Micro) |
| 21. Updates to compendia needed |
| 22. Request for post-approval commitment |
| 23. Missing data that the applicant is like to have (e.g., batch records, stability data updates) |



Drug Master Files

Common deficiencies issued in 1st cycle Completeness Assessment (CA) Incomplete Letters

- Label.
- General Properties.
- Container Closure System; source, specifications, representative COA for each packaging component
- Representative in-house and/or vendor Certificates of Analysis (COA) for each reagent and solvent used in the manufacture of the drug substance.

... 1st Cycle CA... (cont.)

- Additional physical and/or chemical characterization information for the drug substance.
- Manufacturing process; Starting material designation.
- Source, lot#, COA for Impurity reference standards.
- Executed Batch Records.

... 1st Cycle CA... (cont.)

- Yields, results of in-process controls, and analytical results for intermediates for exhibit batches.
- Representative vendor's Certificate of Analysis (COA) of starting materials.

Misc.

- Carefully consider the 356(h) contact – CEO may not always be the best contact to facilitate rapid communications.
- Please update contact changes.
- Please make sure amendment cover letters clearly state the type of amendment being submitted to facilitate coding and triaging by FDA.
- Please enter correct FEIs on the 356(h).