

CDER Small Business & Industry Assistance (SBIA) 2020 Generic Drugs Forum

Application Case Studies on FDA's Action Letter Timing

Regulatory Project Managers
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Generic Drugs Forum 2020 - April 15, 2020

Learning Objectives

- Review real case studies
- Provide tips for success
- Provide resources

Agenda



- Prioritization
- Late Discipline Review Letter (DRL)/Information Request (IR) Response Amendments
- Unsolicited Amendments
- Requests for Reconsideration (RfR)
- Post-Complete Response Letters
 - Meeting Requests
 - FDA Expectations
- Challenge Questions
- Observations and Concluding Remarks

Prioritization

Manual of Policies and Procedures (MAPP) 5240.3

Best practices for requesting priority review

MAPP 5240.3- the “Prioritization MAPP”

- Issue: How and when should an applicant request priority review on amendments?
- Background: ANDA was granted priority review in the first cycle. A Complete Response Letter (CRL)-Major containing deficiencies and comments from the Agency was issued to the applicant. Applicant did not request priority review with their CRL response and the ANDA was not prioritized.
- Decision: ANDA received standard review instead of priority review.

MAPP 5240.3- the “Prioritization MAPP”

- Factors Considered: FDA will only **evaluate** whether a priority review may be granted if:
 - 1) There is an explicit request from the applicant at the time of submission, to include the prioritization factor(s) for which the applicant believes the submission qualifies, or
 - 2) In the absence of an explicit request, FDA determines that the submission relates to a drug shortage, public health emergency or that the submission meets the requirements of section 505(j)(11)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

MAPP 5240.3- the “Prioritization MAPP”

FDA will only **consider** a request for priority review when:

- 1) The cover letter to the submission clearly states “Priority Review Requested” and references the ANDA number;
- 2) The basis for the request is consistent with MAPP 5240.3;
- 3) The applicant clearly and briefly states the basis for the request, including prioritization factor(s); and
- 4) The applicant includes sufficient supporting documentation for the request.

MAPP 5240.3- the “Prioritization MAPP”

- Impact:
 - The submission on slide 5 was not evaluated or considered for a priority review
 - Note: Priority review does not always equal shortened goal date. Submissions that are eligible for a priority review may receive either a shorter goal date or an expedited review, as defined in MAPP 5240.3

MAPP 5240.3- the “Prioritization MAPP”

- Lessons Learned:
 - Applicant must request priority review with each submission
 - Cover letter should clearly state “Priority Review Requested” and reference the ANDA number. It must contain the basis for the request, consistent with the MAPP, including the prioritization factor(s). Applicant must also include sufficient supporting documentation.

MAPP 5240.3- the “Prioritization MAPP”

Helpful Hint:

If FDA has received a submission and assigned the submission a goal date, the agency will not adjust the goal date for that submission even if we subsequently grant the submission priority review

MAPP 5240.3- the “Prioritization MAPP”

- Filers that submit paragraph IV (PIV) certification no longer receive automatic priority review upon original ANDA submission
 - Submission must be ready for final approval at or before the goal date for that submission.
 - Applicant must clearly state “Request for final approval” in the cover letter and provide adequate documentation showing the application will be eligible for final approval at or before the goal date.

MAPP 5240.3- the “Prioritization MAPP”

- FDA will prioritize submissions that will be ready for final approval at or before the goal date under the following circumstances:
 - Submissions from applicants who satisfy the statutory definition of “first applicant” at the time of submission. Applicants must summarize in the cover letter the basis for the priority review request and provide documentation confirming the application will be ready for final approval at or before the goal date.

MAPP 5240.3- the “Prioritization MAPP”



- FDA will prioritize submissions that will be ready for final approval at or before the goal date under the following circumstances (continued):
 - Submissions from subsequent applicants who were blocked from final approval by 180-day exclusivity qualify for prioritization once the relevant 180-day exclusivity has been triggered and until it has expired.
 - Other submissions containing a PIV certification that do not qualify under either sub-bullet above, if there are fewer than four approved drug products, including the Reference Listed Drug (RLD), listed in Orange Book at the time the submission is received by FDA.

Late Information Request (IR)/ Discipline Review Letter (DRL) Response

IR/DRL Case Study Overview

1. Late response when a response date is provided
2. Response to IR/DRL when a response date is not provided
3. Incomplete response/third party issue

IR/DRL - Example 1

- Issue : Late response to IR/DRL (when a response date is provided)
- Background:



IR/DRL (Example 1 cont.)

- Decision: Defer the amendment
- Factors considered:
Applicant responded later than the response due date
- Impact:
CRL issued nearly identical to the IR/DRL

IR/DRL (Example 1 cont.)

- Lessons Learned:
 - Adhere to the response due dates
 - Communicate with the Discipline Project Manager
 - May request a short extension of time
 - Could have potentially issued an early CRL

IR/DRL – Example 2

From: XXXX@email.com
To: XXX<XX.XXX@fda.hhs.gov>
Subject: RE: ANDA-XXXXXX/ CR Letter

Hi XXXX,

We received a Discipline Review Letter (DRL) dated 07/24/2019.

In the DRL, the Agency has not mentioned any cutoff date to respond.

Based on the DRL, we responded on 10/17/2019.

However, as per CR letter, the Agency has not reviewed our DRL response and we got CR-Major.

We request agency to review our point and find a way to review our DRL response which was already filed.

As you are aware that if we will consider CR- Major then our application will be delayed more than X to X months. In this case it was not our mistake because the Agency has not defined any timeline in DRL letter.

IR/DRL (Example 2 cont.)

- Issue : A DRL is issued (with no response date provided) and the applicant responds within cycle
- Background:



IR/DRL (Example 2 cont.)

- Decision: Defer the amendment and issue a CRL with nearly identical deficiencies to the DRL
- Factors considered:
 - The CRL was issued with major deficiencies
 - Applicant's response to DRL was close to the GDUFA date

IR/DRL (Example 2 cont.)

- Impact:
 - Applicant may have expedited their work to submit the response within cycle, but it still did not allow enough time for review
 - Subsequent cycle continued to include major deficiencies

IR/DRL (Example 2 cont.)

- Lessons Learned:
 - DRLs are not generally classified as a major or minor. However, if the DRL response contains information that requires a more thorough review or gratuitous information not requested by FDA, FDA may defer review of the response

IR/DRL (Example 3)

- Issue: DRL/IR response was incomplete
- Background:
The applicant was contacted regarding the incomplete response and indicated that their contract labeler (third party) was closed for the summer



IR/DRL (Example 3)

- Decision: Issued a Labeling-only CRL just prior to the first possible approval date
- Factors considered:
 Labeling was the only discipline that was not adequate and the applicant could not commit to a response within a reasonable time period

IR/DRL (Example 3)

- Impact:
Additional cycle
- Lessons Learned:
 - Respond completely to the IR/DRL
 - Remain aware of third parties' availability

Helpful Hints

- Adhere to the requested response date
- Communicate with the Discipline Project Manager
- Depending on the timing and content, FDA may determine that a response cannot be reviewed this cycle
- Submit high quality, complete submissions

Unsolicited Amendments

GDUFA I vs GDUFA II Amendments

GDUFA I

- Tiered system
- Goals based on:
 - Solicited (submitted in response to a CRL Amendment)
 - Unsolicited (submitted on the applicant's own initiative)
 - Delaying- Contains information not requested by FDA that is the result of changes to the RLD or USP monograph, changes to RLD labeling, a REMS modification, or generic approval requirements reflected in CP responses.
 - Nondelaying: Contains information not requested by the FDA that is not the result of changes to the above.
 - Major
 - Minor

GDUFA II

- No Tiered System
- Goals based on:
 - Standard
 - Priority
 - Major
 - Minor
- A response to an IR/DRL neither stop nor add to the review clock.
- If a response to an IR or DRL contains information not requested by the FDA **or if FDA determines that the information provided requires a more thorough assessment, FDA will classify the submission as a major or minor amendment with a corresponding goal date.**¹

¹ ANDA Submissions- Amendments to Abbreviated New Drug Applications Under GDUFA Guidance, July 2018

Unsolicited Labeling Amendment

- Issue: Extension of goal date due to updated labeling.
- Background:
 - ANDA goal date March 2
 - The RLD updated their labeling to add a newly approved pediatric exclusivity.
 - FDA provided all applicants model labeling with a carve-out template on December 5.
 - Applicant submitted their update on December 19.

Unsolicited Labeling Amendment (cont.)

- Decision: The amendment was considered an unsolicited amendment, extending the goal date out by 3 months from the date of receipt.
- Factors considered:
 - Applications approved or those applications seeking approval prior to the expiration of the exclusivity may need to update their ANDA label in accordance with the model label to support approval.
 - FDA determined that the information provided requires a more thorough assessment and classified the submission as a minor amendment with a corresponding goal date.
- Impact: FDA must review all applicants who are also affected by this RLD update and requires time to review the material.

Unsolicited Labeling Amendment (cont.)

- Lessons Learned:
 - Labeling amendments submitted in order to be consistent with the latest RLD update are considered Minor and will be assigned a 3 month goal date.
 - The FDA sometimes provides all applicants with a Labeling template to assist in getting their labeling consistent with our recommendations. In such instances, a response is considered a minor unsolicited amendment under GDUFA II.
 - If DLR had not requested the ANDA's labeling to match the RLD, the alternative would have been to issue a Labeling only CRL.

Late Unsolicited DMF Amendment

Late Unsolicited DMF Amendment

- Issue: Approval delayed due to a late unsolicited amendment from the Drug Master File (DMF) holder
- Background:
 - ANDA goal date March 1
 - First approvable date March 2
 - Last primary review adequate on February 1
 - DMF submits an unsolicited amendment on February 12
 - Applicant states the DMF amendment submitted doesn't need review for this particular ANDA.

Late Unsolicited DMF Amendment (cont.)

- Decision: Extend goal date 3 months (from DMF submission)
- Factors considered:
 - DMF submission was minor
 - Review team nearly finished
- Impact:
 - Missed first possible approval date
 - Applicant appeared unaware of DMF change

Late Unsolicited DMF Amendment (cont.)

- Lessons Learned:
 - First approval date was clear for this product
 - Make sure DMF holder(s) know key timeframes
 - Unsolicited amendment was not necessary for ANDA approval (or other ANDA approvals)

Delayed Unsolicited Amendments

Delayed Unsolicited Amendment

- Issue: Holding on to an unsolicited amendment to avoid goal date extension.
- Background:
 - ANDA goal date March 1
 - CR issued on February 20
 - Applicant states they did not submit information during previous CR response cycle because it would be considered an unsolicited amendment and extend the goal date.
 - Applicant requested the Agency to convert the CR to an IR.

Delayed Unsolicited Amendment (cont.)

- Decision: Agency denied the request to convert submission to an IR and processed the CR amendment as a minor amendment with a 3 month goal date.
- Factors considered:
 - Review team finished their work.
 - CRL already issued.
- Impact:
 - The delayed unsolicited amendment extended the goal date from the time the CRL response was received.
 - Incomplete information generated another minor amendment cycle.

Delayed Unsolicited Amendment (cont.)

- Lessons Learned:
 - Take the time to do it right.
 - Communicate with the RPM if you have concerns and submit the information as soon as possible to minimize the GDUFA date extension.
 - Even if the goal date is extended, if the review team is able to incorporate the amendment in the current cycle, the Division of Project Management will issue an action ahead of the goal date.

Requests for Reconsideration (RfR)

Requests for Reconsideration Overview

- RfR Not Accepted
- RfR Denied
- RfR Granted

RfR Not Accepted (Example 1)

Scenario

- CRL-Minor issued on 3/25/19 for labeling deficiencies
- CRL response submitted 4/01/19 included RfR to reclassify CRL-Minor as an IR

RfR Not Accepted (Example 1 cont.)

Decision

- RfR was not accepted

Rationale

- It is not possible to change the classification of the minor CRL to an IR

RfR Denied (Example 2)

Scenario

- CRL-Major issued on 10/29/18 due to bioequivalence deficiencies that were identified during the review process
- Applicant responded on 4/1/19 proposing to use a new active pharmaceutical ingredient (API) supplier, Facility B, to address the deficiencies & requested to reclassify CRL from Major to Minor
- Deficiencies were identified at Facility B, after the facility was cited as the API supplier
- Applicant stated they had withdrawn the API supplier, Facility B, from this application and would like to reinstate Facility A as original API source

RfR Denied (Example 2 cont.)



Decision

- RfR was denied

Rationale

- The addition of a new facility constitutes a major amendment
- A deficient facility constitutes a major amendment
- This is consistent with the Draft Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (October 2017)

Outcome

- CRL Response retained Major classification

RfR Granted (Example 3)

Scenario

- CRL-Major issued on 7/12/19 due to bioequivalence deficiencies that were identified during the review process
- Applicant requested RfR on 8/16/19
- Applicant submitted CR Response on 8/23/19

RfR Granted (Example 3)

Scenario (cont.)

- OGD asked applicant to “Please provide justification with supporting data including, but not limited to a new Certificate of Analysis (CoA) for said batch including the re-testing date along with the underlying data to support the information in the CoA to The Office of Pharmaceutical Quality (OPQ)....” ***If OPQ deems the said batch was not stable at the time of conducting BE studies, the said bio-batch will be deemed unacceptable and so will be the fasting (# XXXX- XX) and fed (# XXXX-XX) BE studies.***

RfR Granted (Example 3)



Scenario (cont.)

- Applicant proposed to provide the justification on the biobatch stability and statistical data. FDA therefore will not need a substantial expenditure of FDA resources, since the justification of biobatch stability and statistical data are confined to limited data and are specific to the deficiencies.

RfR Granted (Example 3 cont.)

Rationale

- The bioequivalence deficiency in the CRL was classified as “Major” because the deficiency(ies) pertain to inadequate in vivo bioequivalence studies due to bio-batch stability and statistical issue.
- As noted in Appendix A, Section B.1 (a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018), the assessment of the response will require, in FDA’s judgment, a substantial expenditure of FDA resources.

RfR Granted (Example 3 cont.)



- Review team noted that the applicant submitted the requested stability data, which is considered to be minor in nature, in their CRL resubmission, dated 11/11/2019
- Bioequivalence assessment team contacted the OPQ assessment team and received their concurrence on granting the RfR to reclassify the CR response as a minor amendment. Based on the above information, the applicant's request for reconsideration of the classification of the amendment (from "Major" to "Minor") was granted.

Outcome

- Application approved a couple months later in 2020

Case studies regarding
Post-Complete Response Letter Meeting
Request appropriateness

Overview

- Applicant's query after receiving a CR Letter, "When is a Post-CR Letter Meeting Request appropriate?"

Applicant's query after receiving CRL



- Issue: Applicant calls the RPM and provides a detailed clarification/justification for a specific deficiency on a recently issued CR (minor) Letter
- Request involves requesting FDA to waive the need for a specific test suggested in the deficiency
- Applicant also highlighted that:
 - Procuring a fresh batch for the test will be time consuming
 - They will provide assurance of the quality by not performing test
 - Only one approved product on market, so the more expedient approval of this product will increase generic access

RPM's response to Applicant's query

- Applicant was informed by the RPM that this is not something that can be handled by the RPM over the phone/email
- Applicant was also informed that they may
 - either submit Post-CR Letter Meeting Request, if seeking clarification of a deficiency, or
 - submit their justification with the CR resubmission
- Applicant insisted on emailing the justification to the RPM to solicit a response from Quality discipline

RPM's response to the Applicant (cont.)

- Decision: Applicant was told that their email inquiry (regarding omitting a test) requires a thorough review during open cycle and cannot be responded to via email
- Factors considered:
 - Inquiry received during closed cycle
 - Inquiry not received via Electronic Submissions Gateway
 - Requires a thorough assessment
 - Not a clarifying question

Efficient ways of communicating with FDA

- Impact:
 - Inefficient use of the Applicant and Agency's resources
- Lessons Learned:
 - Modifying or providing explanation of a deficiency is beyond the purview of the Project Managers
 - Phone/email inquiries are neither official nor appropriate
 - In this case, the explanation to the deficiency is best suited for CR resubmission amendment

Efficient ways of communicating with FDA (cont.)

- After a CRL is issued, typically an applicant may
 - Respond completely to all the deficiencies or request extension
 - Request for reconsideration/reclassification
 - Request Post-Complete Response Letter Meeting

Post-Complete Response Letter Meeting Request

What is a Post-CRL Meeting Request

- Post-CRL meeting
 - Is used by applicants to seek clarification concerning deficiencies identified in a CRL
 - Is available for both major and minor CRLs and for first and subsequent review cycles
 - Is only granted, if the request poses questions to clarify identified deficiencies
 - Request **should** be submitted via ESG within 10 calendar days of issuance of the CRL
 - Request cover page should identify the submission as a “**Post-Complete Response Letter Meeting Request**”

Complete Post-CRL Meeting Request

- A post-CRL meeting request may be granted if:
 - A post-CRL meeting request has not already been granted for the same CRL
 - The proposed questions seek clarification concerning deficiencies in the CRL
 - A complete meeting package is submitted
 - For requests containing both clarifying and non-clarifying questions, the Agency may grant the meeting, in part, to only answer clarifying questions

Complete Post-CRL Meeting Request Package



- A **complete** post-CRL meeting request package should include:
 - A list of proposed questions seeking **clarification** of the deficiencies identified in the CRL, grouped by discipline
 - The requested format of the meeting (**t-con or written response**). If requesting t-con, the meeting request package should also include:
 - A proposed agenda outlining how the 30 minutes allotted for the post-CRL meeting should be apportioned to each proposed question
 - A list of specific review disciplines asked to participate in the requested teleconference
 - A list of all individuals, with their titles and affiliations, who will participate in the requested meeting from the applicant's organization and consultants

Post-CRL Meeting Commitments and Timelines

- Goal date assignment
 - Goal date only available for original, complete packages submitted within 10 calendar days of issuance of the CRL
 - If an original, complete package is submitted outside the 10-calendar-day window, the request may be granted but will be ineligible for a goal date

Post-CRL Meeting

Commitments and Timelines (cont.)

- For requests submitted within 10 calendar days of CRL issuance
 - Written Response
 - Granted or denied within 10 calendar days of receipt of an ESG request
 - If granted, FDA will provide a written response within 30 days of request
 - Teleconference
 - Schedule date provided w/in 10 cal. days of receipt of ESG request
 - Conduct meetings (held on an FDA-proposed date) within 30 days of receipt of a written request

Post-CRL Meeting Request

- Other issues, including questions requiring further Agency review, disputes about classification of complete response amendments, or new information submitted by the applicant, will not be addressed in a post-CRL meeting
- FDA will generally grant only one post-CRL meeting request (either teleconference or written response as requested by the applicant) per CRL, covering only questions submitted in a single complete post-CRL meeting request package. Questions submitted on a rolling basis, or subsequent to original package, will not be considered.

FDA's Expectations of Industry Upon Re-Submission of Complete Response

Case studies regarding required documents accompanying a Complete Response (CR) submission and lessons learned.

Overview

- Updated Guidances and Other Updates
 - Bioequivalence (BE)
 - Reference Listed Drug (RLD) Labeling
 - USP Monograph changes
- Patents/ Exclusivities
- Unsolicited Information

Updated Guidances and Other Updates

- Issue: Applicants are responsible for monitoring any changes (including RLD changes such as labeling updates, USP changes, guidance recommendations), assessing the impact of the change on their ANDA, and submitting any necessary amendments

Updated Guidances and Updates

- Background:
 - CR-Minor Action Letter sent to applicant on January 11, 2019
 - CR-Response addressing the deficiencies is submitted on March 15, 2020
 - Applicant addresses the deficiencies listed in the CR letter but:
 - Fails to check the Product-Specific Guidances for Generic Drug Development for any updates
 - Fails to check Drugs@FDA for recent Reference Listed Drug (RLD) Labeling updates
 - GDUFA goal date of June 14, 2020 assigned

Updated Guidances and Updates

- Factors considered:
 - Review teams notified to initiate their reviews
 - A recent Product-Specific Guidance was posted on January 2, 2020 pertaining to the RLD of the ANDA
 - The RLD updated their labeling a few weeks prior to January 2, 2020
- Impact:
 - GDUFA goal date extended in accordance with the submission date of updated BE guidance/ RLD labeling update amendments
 - Unapprovable if not addressed

Updated Guidances and Updates

- Lessons Learned
 - Understand the impact of continually monitoring FDA sources
 - Product-Specific Guidances for Generic Drug Development;
<https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>
 - Drugs@FDA; <https://www.accessdata.fda.gov/scripts/cder/daf/>
 - Before re-submitting a CR-Response, review guidances as well as recent RLD labeling updates
 - GDUFA goal dates may be affected by the specific amendment being submitted

Patents and Exclusivities

- Issue: Incomplete Submission of Patent/ Exclusivity Information
- Background:
 - CR response submitted on January 16, 2019
 - ANDA given goal date of April 15, 2019 (Minor Amendment)
 - RLD listed Patent 1234456 ('123) with an expiration date of December 15, 2019 in the Orange Book

Patents and Exclusivities

- Factors considered:
 - Review teams notified to initiate reviews
 - ANDA applicant has certified PIV to Patent '123 but does not provide documentation of delivery of notice to patent owner and RLD holder
 - All disciplines are complete and adequate
 - No response/ communication from US Agent

Patents and Exclusivities

- Impact:
 - Approval cannot be granted
 - CR has to be issued
 - Extension of time before approval

Patents and Exclusivities

- Lessons Learned:
 - Always monitor Orange Book for new patents/exclusivities
 - Submit all required documents such as notices of certification and litigation information in a timely fashion
 - Open communication with Regulatory Project Manager (RPM) is strongly encouraged
 - Patent amendments do not affect GDUFA goal date

Tips

- Always submit a **COMPLETE** CRL-Response
- Communication with the RPM is vital
- Always monitor FDA resources pertaining to your ANDA especially before submitting a CRL-Response
- Make sure the cover letter clearly states what is included in the ENTIRE submission
- Creating a table that chronologically describes patent/exclusivity information would be helpful

Resources

- Guidance for Industry, Post-Complete Response Letter Meetings Between FDA and ANDA Applicants Under GDUFA (Dec. 2018):
<https://www.fda.gov/media/108337/download>
- Draft Guidance for Industry, Requests for Reconsideration at the Division Level Under GDUFA-(Oct. 2017):
<https://www.fda.gov/media/108398/download>
- 21 CFR 314.110 (Complete response letter to the applicant)

Resources (cont.)

- Guidance for Industry, *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018):
<https://www.fda.gov/media/89258/download>
- Product-Specific Guidances for Generic Drug Development:
<https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>
- Drugs@FDA: FDA-Approved Drugs:
<https://www.accessdata.fda.gov/scripts/cder/daf/>
- Orange Book:
<https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>

Resources (cont.)

- CDER Guidance Webpage:
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm>
- GDUFA Webpage:
<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>
- CDER Small Business & Industry Assistance (SBIA):
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm>

Challenge Question #1

Do unsolicited amendments have the potential to impact your application's approval time?

Yes

No

Challenge Question #2

Do DMF amendments have the potential to impact your application's approval time?

Yes

No

Observations

- Program interested in maximizing approvals and ensuring access to quality generic drug products
- Review teams really care about Goal Dates
 - Lots of internal tracking
 - Management is involved
 - No one wants a late CRL
- RPMs take role as champion of application very seriously
 - Lot of effort to coordinate approval packages
 - Personally invested in application success

Concluding Remarks

- Don't rush and submit incomplete submissions
- Share key dates with contractors, DMF holders, etc.
- Share information with discipline PMs and RPMs so they can help navigate best path forward
- Let's work together to approve more applications
- Process is working well for quality, new submissions!

