Real-Time Communication During the CMC Review with the Office Of Pharmaceutical Quality (OPQ)

Real-Time Communication Webinar
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Real-Time Communication During the CMC Review with OPQ

- Overview

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Office of Lifecycle Drug Products (OLDP)
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What is Real-Time Communication?

- Real-Time Communication means communication with an ANDA applicant and an exchange of information prior to the issuance of a formal FDA action.
  - Action: Tentative Approval (TA), Approval (AP) and/or Complete Response (CR)
- Real-Time Communication does not replace OGD’s formal communication methods, but rather enhances the review process in an effort to increase transparency and decrease the number of review cycles.
Why Real-Time Communication?

- GDUFA establishes goals dates for original submissions and subsequent amendments.
- GDUFA requires open and transparent communication with the industry.
- Our current process of formal communications tends to promote multiple review cycles.
- We are striving for more informal communication to resolve issues in real-time and reduce the number of review cycles.
Number of Cycles to ANDA Approval

Cycles for OGD ALL Approvals/Quality Cycles
2009 through July 2014

Prepared by Yuexia Li
ANDA Review

Do deficiencies require substantial expenditure of FDA resources?

- YES
  - Issue Major CR
    - Encourages firms to get it right the first time;
    - Long term impact of raising submission quality

- NO
  - YES
    - Issue Minor CR
  - NO
    - Issue requests to the applicant

Real-Time Communication
Advantages of Real-Time Communication

- Transparent process and communication.
- Less time lost in multiple cycles.
- Applicant and FDA work to achieve better understanding and increased trust.
- Applicant can better forecast product plans.
- Encourages higher quality submissions.
Real-Time Communication During the CMC Review with OPQ

- Review Perspective

**Glen Smith**, Acting Deputy Director
Office of Lifecycle Drug Products (OLDP)
Office of Pharmaceutical Quality (OPQ)
CDER, FDA
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Definitions

- **Fatal Flaw**: Significant flaws in the design of a drug product such that the proposed product will not be able to meet all conditions of use of the reference listed drug. If a fatal flaw is identified, all review activities including compliance will be stopped.

- **Major Deficiency**: A situation where necessary information does not exist in the application, or is so flawed as to require new information to be submitted. These deficiencies will require a substantial expenditure of FDA resources and must be included in a Complete Response letter from OGD. See Appendix I for examples.

- **Minor Deficiencies**: Issues that cannot be resolved using the real time communication process, and must be included in a Complete Response letter from OGD.

- **Chemistry Information Request(s) and Clarification Question(s)**: Issues which could be resolved during the real time communication process.
Definitions

- **Regulatory Business Project Manager (RBPM):** A centralized project manager for the quality assessment of applications. RBPMs are the former PQRPMs with expanded leadership role.

- **OGD Target Action Date (TAD):** An internal deadline for formal FDA action on a submission. TADs are assigned by OGD after consultation with the review disciplines, including OPQ. A TAD is not a GDUFA goal date and will generally be earlier in time than the applicable GDUFA goal date.

- **Discipline Review Date (DRD):** A deadline established at which time the results of a discipline (e.g. chemistry) review process must be communicated by the Office of Pharmaceutical Quality (OPQ) to the Office of Generic Drugs (OGD). This date is established to ensure all commitments required under GDUFA are met.

- **Target Review Date (TRD):** A deadline set according to OPQ management policy by which a chemistry review must be completed. This date is established to ensure that the RBPM has sufficient time to complete all tasks prior to communicating the results of the review to OGD.
Real-Time Communication Process

• The Real-Time Communication process requires:
  – Understanding and following the Flow Chart in the next slide, and
  – Always meeting all Target Review Dates and Target Action Dates.
Start Review

Fatal Flaw

Yes → Stop review, inform the RBPM

No → Continue and finish review

Is chemistry adequate?

Yes → Finalize review

No → Do the set of deficiencies require a substantial expenditure of FDA resources per guidance?

Yes → Finalize review for Complete Response letter and classify as “MAJOR”

No → Will the real time communication result in missing the target review date (TRD)?

Yes → Finalize review for Complete Response letter and classify as “MINOR”

No → Issue Information Request to the applicant

Is the response received within the specified time frame?

Yes → Yes

No → No

Real Time Communication Yes

End
This represents a “maximum” case, with two information request and subsequent reviews for the applicant. Note that start and finish times for each step in the review timeline can be adjusted as circumstances require, but the target review date is set at 255 days and the total time cannot exceed 269 days.
Major Amendment Review Timeline

Amendment Review Cycle
255 Days

Receipt Date
Target Review Date
Discipline Review Date
GDUFA Goal Date

Prepare Review for OGD - 14 Days

Day 0
Day 255
Day 270
Day 300

To OGD
Minor Amendment Review Timeline

Amendment Review Cycle
45 Days

Receipt Date

Target Review Date

Discipline Review Date

GDUFA Goal Date

Prepare Review for OGD - 14 Days

To OGD

Day 0

Day 45

Day 60

Day 90
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- Project Management

Robert (Bob) Gaines, Division Director
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Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality (OPQ)
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Procedure Details

• If the chemistry technical review reveals no fatal flaw(s) or major deficiency(ies), the real time communication process is started. Reviewers and RBPM collaboratively determine if real time communication with the applicant would be a viable approach based on the target review date (TRD).

• Reviewers and the RBPM collaboratively determine a specified time frame within which the applicant should respond. The specified time frame shall only exceed 30 calendar days on rare cases.

• Typically no more than two rounds of real time communication are recommended.
Procedure Details

• RBPM will call applicant to notify of upcoming information request and to confirm contact information.
• RBPM can not and will not provide application status details beyond what will be sent via the information request.
• Information request will be relayed to the applicant via telephone, fax or secured email, with the above specified time frame included.
• All communication with the applicant must be appropriately documented in the official document archival system.
Points to Consider

1. A response to all items in an Information Request is preferable, and the applicant is encouraged to provide a complete response to all the requests. However, if the applicant cannot provide a full response to all items, they should provide a response to as much as they can, with the realization that the remaining items will have to be addressed in the future, either as an additional information request or as part of a Action Letter issued by OGD.
2. The normal maximum response time for the applicant is 30 calendar days and extensions of the response times are discouraged. However, the response time can be extended a short period of time (e.g. 1 or 2 days) if all the requested information can be addressed with this extension. We encourage industry to communicate with the OPQ RBPM to request the 1 to 2 day extension and also to notify the RBPM if the requested IR request response date will not be met.

*Note: Discipline Review Dates and GDUFA goals must be met in all circumstances.*
Points to Consider

3. The reviewer may make a telephone call to the applicant after reviewing a response if that call will quickly resolve any remaining issues. However, a RBPM should always be present and care must be taken to meet Discipline Review Dates and GDUFA goals. The reviewer should work with the RBPMs to make sure any telephone requests are adequately documented.
Points to Consider

4. If the applicant does not respond or contact the RBPM, Real Time Communication is ended at the end of the allotted time and the Information Requests become Minor Deficiencies to be included in a Complete Response Letter from OGD.
5. It should be made clear at the start of the Real Time Communication process that unsolicited information in a response is not acceptable, and may be considered a Major Amendment for original applications submitted before October 1, 2014, and a Tier 2 Unsolicited Amendment for original applications submitted after October 1, 2014.
Appendix I

- For examples of what could be considered Major Deficiencies, please read “Guidance for Industry ANDA Submissions - Amendments and Easily Correctable Deficiencies Under GDUFA.” Additional examples may include lack of risk mitigation for high-risk Critical Quality Attributes (CQAs) or manufacturing processes, missing pivotal batch data, insufficient data to demonstrate drug substance sameness (especially for complex drug products), insufficient information to support Q3 attribute sameness for the purpose of biowaiver, fundamental formulation flaws that necessitate reformulation, and absence of analytical methods or method validation.

Real-Time Communication

Questions?