DMF Related Impediments to First Cycle Approvals of ANDAs

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Disclaimer

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Generic Drugs & GDUFA

- GPhA 2015 Report: Nearly 8 in 10 prescriptions filled in the United States are for generic drugs.

- Generic Drug program has increased access of affordable medicine to the American people and world wide.

- Significant backlog of pending generic applications.

- 80% of the API used in FDA-approved drugs sold in this country are manufactured outside US, and 40% of finished drugs consumed here are manufactured elsewhere.

- Key goal of the GDUFA I program is to bring safe, high-quality, affordable generic drugs to market in a timely manner.
GDUFA I – Enhancements for DMF

• Completeness assessment (CA)

• List of CA-complete DMF on the FDA website.

• Facility Inspections: GDUFA will also ensure that foreign and domestic industry participants in the U.S. generic drug system are held to consistent, high-quality standards and inspected biennially, with comparable rigor and frequency, using a risk-based approach.
Analysis of DMF CR First Cycle Response Times for Type II API DMFs

• 98% of DMFs being reviewed for the first time are found inadequate and issued a DMF CR letter.

• Most of these DMFs will receive two or three cycles of review before becoming adequate.

• Reducing both the total number of review cycles and the time for response from the DMF holder is critical to increasing the chances for a first cycle ANDA approval.
Current state of DMF first-cycle response times.

• To illustrate the current state of DMF first-cycle response times we analyzed the following:
  • Time for response to the first DMF CR letter for reviews conducted between January 2015 and June 2016.
    • 521 total DMFs in the dataset.
    • 75 were excluded because no response had yet been received.

• The data shows the following:
  Mean response time: 161 days (~5.5 month)
  Median response time: 133 days (>4 month)
  - Minimum: 11 days
  - Maximum: 667 days

• Conclusion: First cycle response times are currently too long to be compatible with first-cycle ANDA approvals in an 10-month or 8-month review clock.
DMF 1st Cycle Response times by Cohort

- DMF response times in 60 days or less allow for a good chance that the DMF will become adequate within a 10-month review clock.
- DMF response times in 60 to 90 days result in a significantly reduced chance that the DMF will become adequate within a 10-month review clock.
- DMF response times in excess of 90 days virtually guarantee the DMF will not be adequate within a 10-month review clock.
DMF Review Timeline for the Best-Case Scenario

• ANDA Filing completed by day 60 but in practice OGD/DFR is generally complete by day 45.
• Kickoff meeting (start OPQ review process, including DMF) held at or around day 60 - day 75.
• First ANDA IR and DMF CR letter issued at day 120*.
• DMF CR letter response received at day 180 (60 day response is less than half of the current median response time).
• Review of DMF response completed and DMF Easily Correctable Deficiency (ECD)** letter issued at day 220***.
• ECD response received at day 234.
• Review of ECD response competed on day 248 with review conclusion adequate.
• Overall OPQ recommendation to OGD on or before day 270.

• *Note that GDUFA II requires that the ANDA first IR letter and the DMF letter be issued (at least) in parallel.
• **Note: An ECD for a DMF is the functional equivalent of an IR for an ANDA and a response is usually requested within 10-business days.
• ***It is not typical at present for a DMF to be adequate after just one-cycle plus an ECD.
DMF response in 60 days or less allows time for 2 full cycles, including an ECD in a ten month clock.

There is a good chance the DMF will be adequate.

*Note: ECD responses expected within 10 business days unless the holder asks for an extension.
Best Case DMF Scenario

ANDA Filed (Day 30)

DMF CR issued (Day 120)

Issue ECD (Day 220)

Review complete adequate (Day 248)

ANDA CR

133 day response

Not sufficient time for a second DMF review cycle.

OPQ recommendation to OGD (Day 270)
DMF response in 90 days allows time for 2 full cycles, but may not allow time for an ECD.

The loss of the ECD will reduce the odds that the DMF is adequate.

Note that the data shows 68% of 1st cycle responses exceed 90 days.
Bottom Line

• Based on our analysis, unless DMF response times are significantly reduced, it is possible that up to one-third of original ANDAs could be ineligible for a first cycle approval due to an inadequate API DMF.

• Both Industry and FDA should strive to lower the “attrition rate” due to the DMF.
What can Industry do to improve?

• **Improve the quality of DMF submissions** so that there are fewer deficiencies and fewer review cycles needed to get the DMF to adequate status.

• **Avoid deficiencies in key areas** that require a long time to respond and/or consume significant Agency resources to review.

• Applicants should clearly **communicate the ANDA action timeline** to their DMF holder (remember that the DMF is part of your application).

• Make effective **use of the T-con and email** (GDUFA II) options for getting clarification on deficiencies so responses are complete.

• Respond quickly (within 10 –days) when the Agency issues an ECD.

• Make it your goal to respond to DMF 1st cycle letters in NMT 60-days and NMT 30-days for subsequent cycles.
DMF Deficiencies That Impede 1st Cycle Approval

Issues that may cause significant deficiencies in S.2

• Non-reported (hidden) facilities (DS manufacturing site or routine release or stability testing facility): If the facility needs inspection this can take a considerable amount of time.

• Outsourcing the majority of the manufacturing process: Lack of information about the outsourced process may generate multiple deficiencies. It also raises the risk that this facility may need inspection which can take a considerable amount of time.

• Multiple intermediate vendors: Reporting multiple intermediate vendors may cause deficiencies if adequate data isn’t provided to show equivalent quality of material or if there are significant differences in the manufacturing processes between vendors.

• Declaring unacceptable starting materials: This may result in a request to move SM’s back which is a significant amount of work.
Significant deficiencies in S.2, cont

• Setting **high limits for impurities** in IPC’s and Intermediate specifications without supporting data: This may result in the request for spike/purge studies for impurities which are not tested in the DS specification.

• Not considering by-products when discussing fate of residual intermediates: Discussion of the fate of materials should include data on by-products that may form due to continued reaction downstream or this may result in further questions. These requests may necessitate impurity synthesis and development of new analytical methods.

• Not addressing impurities such as regioisomers, stereoisomers, longer/shorter chain analogues in SM’s: This may result in a request for that data. You may also discover the presence of DS analogues which are difficult to purge and which may require process modification.

Issues that may cause significant deficiencies in S.3

• Setting limits over ICH Q3A IT for regular impurities without adequate justification: Safety studies which are submitted will require a **Pharm Tox consult** which can take a significant amount of time.

• Submitting data from comparison to RLD using only retention times: This may result in a request for further data as HPLC RT is not a specific test for ID.
Issues that may cause significant deficiencies in S.4

• Not submitting full **method validation** information for USP impurities when using an in-house method: This will result in further method validation activities.

• Not submitting full method validation information for in-house impurities when using a USP method: This will result in further method validation activities.

• Submitting analytical methods which lack the needed sensitivity for their intended purpose: This will result in further method validation activities.

Issues that may cause significant deficiencies in S.6

• **Changes in CCS without stability data** to support the change: This will result in a request for stability data which could take significant time to acquire.

Issues that may cause significant deficiencies in S.7

• Lack of **mass balance** during forced degradation studies: Raises question about whether analytical methods are stability indicating. May result in requests to re-do the study.

• Out of Specification results in stability data without accompanying root cause report: This will generate requests to explain OOS results.
Potentially Genotoxic Impurity (PGI) Control

• DLAPI is following ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

<table>
<thead>
<tr>
<th>Impurity Control</th>
<th>Data Review Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC Options 1, 2, 3, or 4 as outlined in ICH M7, see 8.1-8.4, Tables 2, 3, 4, and Appendix 2*</td>
<td>With proper scale, number of batches, and spike purge, review is immediate</td>
</tr>
<tr>
<td>Submission of negative (Q)SAR data</td>
<td>Internal Consult: 2 weeks turnaround</td>
</tr>
<tr>
<td>Submission of negative AMES data</td>
<td>Internal Consult: 3 months turnaround</td>
</tr>
</tbody>
</table>

• *Both duration of use and maximum daily dose are critical to determination of TTC. Include discussion of these parameters in the submission
Potentially Genotoxic Impurity (PGI) Control: (Q)SAR

ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk states that **negative** (Quantitative) Structure Activity Relationship, or (Q)SAR, predictions for impurities with alerting structures, **if generated with M7 compliant methodologies**, can be used to justify control of the impurity at ICH Q3A levels in lieu of submission of AMES data.

DMF holders are strongly encouraged to:

1) Analyze the synthetic route (including reagents, solvents, etc.) beginning with the starting material specification to the final drug substance for alerting structures
2) Perform (Q)SAR analysis using models demonstrated to be fit for purpose
3) Submit the data and methods for review; **general statements without supporting data are not acceptable**

References:


Potential Genotoxic Impurity (PGI) Control: AMES Assay

Critical Aspects
Per OECD Test Guideline 471 and/or ICH S2(R1) and ICH M7:

- Combination of 5 bacterial strains
  - TA98, TA100, TA1535, either TA1537 or TA97 or TA97a, and either TA102 E. Coli WP2 wwa or E. Coli WP2 wwa (pKM101); phenotype should be confirmed

- Dose range
  - spaced at half log intervals in triplicate
  - when establishing top dose, consider
    1. toxicity (e.g., thinning of background lawn or reduction in background revertants)
    2. solubility
    3. limit dose for non-toxic, soluble test articles is 5000 µg/plate

- Metabolic activation: with and without liver S9
- Controls: positive and negative

- Data interpretation:
  - $\geq 5$ non-toxic doses should be analyzed
  - control values should be consistent with historical ranges
  - positive response typically requires dose-related increase in at least 1 strain with or without metabolic activation
What can FDA do to help?

- Expand the review clock and increase the time available for industry to respond by picking the DMF up “ahead” of the Drug Product review (this will be resource and workload dependent).*

- Allowing for just one additional touch (full cycle or ECD) can significantly improve the odds of a DMF reaching adequate status in a 10-month clock.

- Use ECDs effectively (assumes industry can respond within the 10-days allotted).

- Efficiently use the GDUFA II email option to quickly answer queries from industry to clarify issues related to deficiencies.

*Note that this is not a requirement in the GDUFA II commitment letter.
What an expanded DMF review timeline might look like

ANDA Filed (Day 30)

DMF CR issued (Day 90) - before the 1st IR for the ANDA

DMF Review Starts (Somewhere between Day 15 and Day 30)

1st cycle DMF Review

90 day response

DMF response received (Day 180)

Issue ECD (Day 210)

Review complete adequate (Day 238)

ECD response received (Day 224)

OPQ recommendation to OGD (Day 270)

Approval
Please Keep in Mind……..

• Between 40% and 50% of ANDAs in any given year reference DMFs that have previously been reviewed and found adequate.

• Typically these DMFs only require review of unsolicited amendments since the last review.

• In most cases the DMFs remain adequate or require only an ECD (functional equivalent of an IR for an ANDA) and present little risk to a possible first cycle ANDA approval.

• One issue that can cause problems is the submission of unsolicited DMF amendments in close proximity to the action date.

• Note that ANDAs for first generics nearly always reference a previously unviewed DMF.
Unsolicited Amendments

- Even when a DMF has been found adequate poor submission timing of an unsolicited amendment to a DMF can disrupt the action timeline.
- Unsolicited amendments re-open the DMF review and when this happens in close proximity to the action date it will create problems and may even result in an ANDA CR thus delaying an approval.
- DMF holders should avoid submitting unsolicited quality amendments within 90-days of the an action date if possible.
- Applicants must communicate action timelines to the DMF holders so they are aware. *It appears to us that DMF holders are generally unaware of the action timelines.*
- Note that most unsolicited amendments for DMFs that we review do not directly impact the API material that was actually used in the exhibit batches of drug product for the ANDA. Thus, many of these changes would be appropriately reported to the DMF and the ANDA post-approval.
To avoid issues with unsolicited amendments......

- Applicants and DMF holders must communicate with each other and remember that the DMF is an integral part of the application.
- Applicants should inform DMF holders about the expected action timelines for their ANDAs.
- Both the applicant and the DMF holder should be aware of the current status of the DMF.
- For information on DMF status:
  - No Further Comment Letters
  - First Adequate Letters (coming in GDUFA II)
  - Email us at DMFOGD@FDA.HHS.GOV with your status inquiry.
GDUFA II – Enhancements

• CA for 90% of Type II APIs within 60 days of the later of the:
  – DMF Submission
  – DMF Fee Payment

• FDA will ensure that DMF review comments submitted to the DMF holder in parallel with the issuance of review comments for the ANDA.

• FDA will identify and communicates deficiencies in “real time”.
  – Applicants can correct deficiencies in current review cycle
  – Increase odds of approval in current review cycle.
  – Reduce number of cycles to approval.
  – Increase overall rate of approval.

• Pre-submission meeting for complex substances and products.
• First Adequate Letter

• Concept drawn from PDUFA.
Chart 16. First Cycle Approval Rate Under PDUFA

CDER NME NDAs/BLAs†
First Action Approval Rate

Fiscal Year of Receipt

First Cycle Approvals

- 1993: 36%
- 1994: 23%
- 1995: 30%
- 1996: 50%
- 1997: 35%
- 1998: 25%
- 1999: 54%
- 2000: 31%
- 2001: 25%
- 2002: 50%
- 2003: 48%
- 2004: 42%
- 2005: 45%
- 2006: 52%
- 2007: 52%
- 2008: 46%
- 2009: 43%
- 2010: 46%
- 2011: 70%
- 2012: 72%
- 2013: 78%
- 2014: 89%
- 2015*: 95%
Summary

• >40% of ANDAs in any given year reference DMFs that have previously been reviewed and found adequate.

• ~98% of DMFs being reviewed for the first time are found inadequate. Most DMFs will receive two or three cycles of review before becoming adequate.

• Improve the quality of DMF submissions so that there are fewer deficiencies and fewer review cycles needed to get the DMF to adequate status.

• Applicants should inform DMF holders about the expected action timelines for their ANDAs.

• Respond to DMF 1st cycle letters in NMT 60-days and NMT 30-days for subsequent cycles.

• Avoid submitting unsolicited quality amendments within 90-days of the action date if possible.
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