Generic Drugs Forum

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Drug Master Files from an Abbreviated New Drug Application Perspective – with Q&A

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Outline

- Updates on DMF review enhancements per GDUFA II
  - Completeness Assessment (CA), Teleconference/Email exchange, First Adequate (FA) letter, No Further Comments (NFC) letter
- Types of DMF letters
- Timely Consult and Information Request (TCIR) process
- Common administrative issues
- Common stumbling blocks that may affect ANDA approval

Completeness Assessment (CA)

- *Commitment Letter*: "Complete the initial completeness assessment review for 90 percent of Type II API DMFs within 60 days of the later of the date of DMF submission or DMF fee payment."
  - From 10/01/2017 to 08/20/2018
    - Total number received and completed = 401
    - Total completed within 60 days = 383
    - % completed within 60 days = 95.5%

How to Avoid an RTR Due to The DMF

- Submit a high-quality DMF in eCTD format
  - See checklist in Draft Guidance for Industry: Initial Completeness Assessments for Type II API DMFs Under GDUFA
- DMF must be on the "Available for Reference" list prior to ANDA submission
- Communication between DMF holder and ANDA sponsor on timeline for ANDA submission
- DMF fee paid well in advance (6 months recommended) of the planned ANDA submission date
  - This will allow sufficient time for two cycles of CA review (if needed)

Common CA Deficiencies

- Label
  - Numerical storage conditions
  - Caution statements “Rx only” and “Caution: for manufacturing, processing and re-packing only”
- General properties
- Container Closure System
  - source, specs and representative COA for each packaging component
- Representative in-house and/or vendor COAs for each raw material used in process
- Additional physical and/or chemical characterization for drug substance
- Manufacturing process/Starting material designation
- Source, lot number and COA for impurity reference standards
- Executed batch records, translated into English
- Yields, results off in-process controls and analytical results for exhibit batches
- Representative vendor’s COA for starting materials

Teleconferences

- *Commitment Letter*: “FDA will grant and conduct teleconferences when requested to clarify deficiencies in first cycle DMF deficiency letters.”
  - Request in writing within 20 business days of issuance of the first cycle DMF deficiency letter, identifying specific issues to be addressed.
  - FDA may provide a written response when the T-con is granted. The FDA will schedule the teleconference at the DMF holder’s discretion.
  - FDA strives to grant such teleconferences within 30 (calendar) days

Email Exchange

- *Commitment Letter*: “In lieu of a teleconference, the DMF holder may submit a request for an email exchange between FDA and the DMF holder. The request must identify specific issues to be addressed. After FDA responds to the request, the DMF holder may submit, and FDA will respond to, one follow up email to obtain additional clarification.”
  - DMF holder should follow detailed instructions for requesting an email exchange in the DMF CR letter
  - The FDA will strive to respond within 30 days of receiving the initial email exchange request (current average response time is 15 days)

Teleconference vs. Email Exchange

- Teleconference:
  - 10 requests from 10/01/2017 to 08/20/2018
    - All 10 granted
    - 30% granted within 30 days
- Email Exchange:
  - 56 initial requests (and 10 follow-up requests) from 10/01/2017 to 08/20/2018
    - Responded to 95% within 30 days
    - Average response time was 15 days

First Adequate (FA) Letter

- *Commitment Letter*: "Once a DMF has undergone a full scientific review and has no open issues related to the review of the referencing ANDA, FDA will issue a First Adequate Letter."
  - Similar format to the NFC letter under GDUFA I
  - Target to issue within 30 days of finalized, adequate DMF review
  - 259 FA letters were issued in the first year of GDUFA II

DMF No Further Comments (NFC) Letter

- *Commitment Letter*: "Once a DMF has undergone a complete review and the ANDA referencing the DMF has been approved or tentatively approved, FDA will issue a no further comment letter."
  - Identical to the NFC letter under GDUFA I
  - Target to issue within 30 days of approval action on referencing ANDA
  - 974 NFC letters were issued in the first year of GDUFA II

DMF Letters Explained

DMF Complete Response Letter

- Same as the GDUFA I letter
- Issued for the TYPE II API DMF only
- Includes deficiencies from all disciplines, including consults.
- Includes DMF facility status information

- Regulatory implication: DMF is inadequate and cannot support an approval action.
- Review status: DMF review cycle closes when the letter issues (i.e. can support a CR action on a referencing ANDA).

DMF Deficiency Letter

- Issued to communicate deficiencies in cases where the DMF CR letter does not apply
- Issued for non-API type II (i.e. secondary DMFs for intermediates), non-type-II DMFs, DMFs referenced only by an NDA/IND

- Regulatory implication: DMF is inadequate and cannot support an approval action.
- Review status: DMF review cycle closes when the letter issues (i.e. can support a CR action on a referencing application).

DMF Information Request (IR) Letter

- Easily Correctable Deficiency Letter under GDUFA I.
- Issued to communicate deficiencies in cases where the holder should be able to respond quickly and get the DMF to an adequate status
- May be issued relatively late in an ANDA review cycle
- RBPMs set the response timeline (usually 10 to 30 days) but they have discretion
- Can be used to meet the Mid-cycle commitment

- Regulatory implication: DMF is inadequate and cannot support an approval action until issues are resolved
- Review status: DMF review cycle remains open and response is reviewed upon receipt
- If response to IR letter is not received in requested timeframe, comments can be converted to a CR or deficiency letter and the DMF review cycle closed.

DMF Additional Comment (AC) Letter

- Called an Information Request Letter under GDUFA I.
- Issued to communicate very minor comments that *do not* make the DMF inadequate
- Usually issued relatively late in an ANDA review cycle when an approval action is imminent
- Typically used when comments are minor and not enough time to resolve them by an IR.

- Regulatory implication: DMF is adequate and can support an approval action
- Review status: DMF review cycle closes with an adequate recommendation
- Expect a response within 6 months but holders should coordinate with applicants before responding to an AC letter
- FDA times the issuance of the AC letters to minimize the chance that a response will interfere with a planned action date

Timely Consults and Information Requests (TCIR) Process

Why?

- In an effort to improve the opportunities for first cycle approvals, OPQ asked each review discipline to identify areas where early communication with the applicant could facilitate resolving issues early in the review cycle.
- Two areas that were identified for DMFs were consults and facility discrepancies (“hidden facilities”).
- Why consults? Because they can often take a long time to resolve.
- Why facilities? Because new facilities discovered late in the ANDA review cycle do not allow sufficient time for evaluation or inspection and would prevent an approval.

TCIR - Hidden Facilities

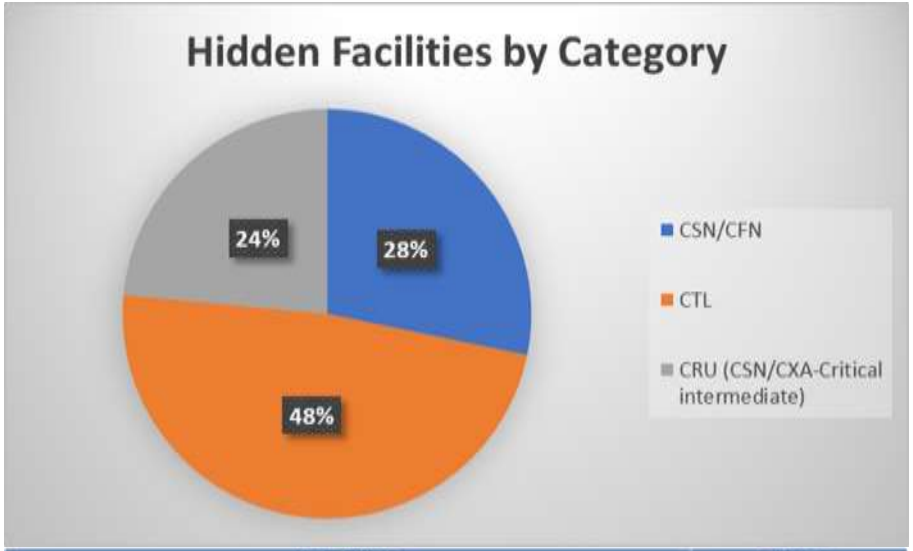
- The Division of Lifecycle API (DLAPI) TCIR triager checks for the following types of “hidden” facilities by comparing those listed in the ANDA 356h form to those listed in section 3.2.S.2.1 of the DMF.
  - API manufacturing facilities, including facilities manufacturing critical intermediates* and those performing post-synthesis operations, such as micronization.
  - API testing facilities that perform routine release and stability testing of the API.

**A risk based paradigm is used to determine if an intermediate manufacturing facility is critical and Office of Process and Facilities (OPF) makes the final determination if an intermediate facility warrants evaluation.*

TCIR - Hidden Facilities (cont.)

- Number of applications with at least one hidden facility = 186
- Total number of hidden facilities identified = 255
- Overall percentage of ANDAs with a hidden facility issue: 17.8%*

*This high number is indicative of poor communication between applicants and DMF holders regarding the DMF related facilities that support their ANDAs.



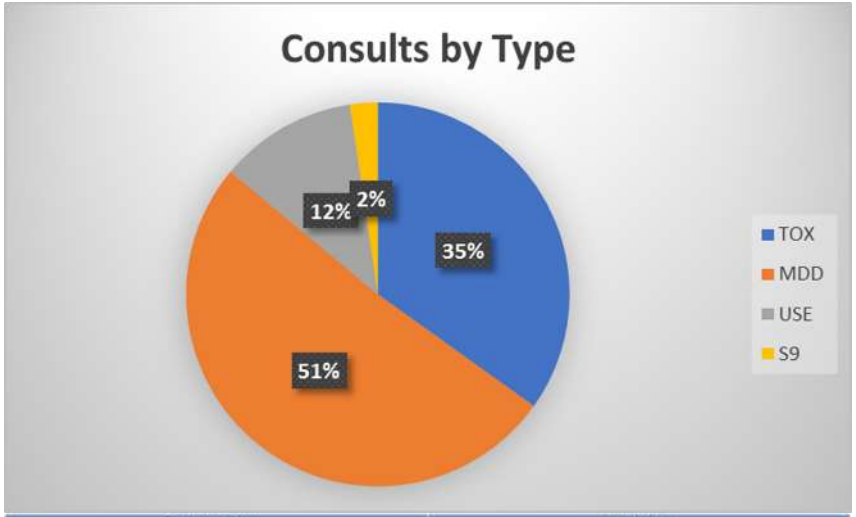
Facility Type	Number
CSN /CFN (Non-Sterile API by Chemical Synthesis/Non-Sterile API by Fermentation)	72
CTL (Control Testing Laboratories)	123
CRU (CSN/CXA (Plant/Animal Extraction Purified API)-Critical Intermediate)	60

TCIR - Consults

- DLAPI TCIR triager examines the RLD Product Label for foundational consults and section 3.2.S.3.2 of the DMF for Pharm/Tox related information and prepares and submits these consults to OGD/DCR.
  - Foundational consults are those related to the labelled use of the drug product such as maximum daily dose (MDD), duration of use, patient population and advanced cancer indication. Having these consults resolved early is critical to the DMF reviewer since they serve as the basis for applying ICH Q3A (organic impurities), ICH Q3C (residual solvents), ICH Q3D (metals), and ICH M7 (PGIs) guidance to the assessment of the impurity control strategy for the API.
  - Pharm/Tox related information includes studies submitted by the DMF holder such as AMES test data or literature studies used to support their impurity control strategy.

TCIR – Consults (cont.)

- Number of applications with at least one consult= 39
- Total number of consults submitted= 43
- Overall percentage of ANDAs with consults: 4.2%



Consult Type	Number
TOX (Pharm/Tox)	15
MDD (Maximum Daily Dose)	22
USE (Product Use)	5
S9 (Advanced Cancer)	1

Takeaway Message

- Communication between DMF holder and ANDA applicants regarding all critical DMF facilities is key so that facilities are identified and inspected early in the process.
- DMF holders should identify any potentially consultable information and highlight it in the DMF submission
  - If the consultable information is buried in the DMF and the DLAPI assessor doesn't see it until the last minute, there is a high likelihood that the application will be delayed due to Agency consults

Common Administrative Issues

Admin Issues

- Converting from paper to eCTD format – no new DMF number needed, just add the appropriate number of zeros to the beginning of the number to make six digits
- Internal name change – provide official government certificate of change in amendment
- Transfer – need transfer letter from previous holder and acceptance letter from new holder in amendment
- All transfers (internal and external) – need US Agent appointment letter with new holder name, signed DMF statement of commitment from new holder name, updated LOAs with new holder name
- Change to holder or facility address, must submit an amendment
- A logo change cannot be submitted in an annual report, must submit an amendment

Admin Issues (Cont.)

- Every submission should include an administrative information page and a cover letter.
- LOAs should be in 1.4.1 (do not have to resubmit the original letters each time) – list of authorized firms should be in 1.4.3
- Separate LOAs for each DMF and each referenced party
  - Cannot submit one LOA for multiple parties
  - Cannot submit one LOA for multiple DMFs
- DMF subject = DMF title; use consistently
- If monograph is added, just adding “USP” to the cover letter doesn’t change the title – submit an amendment

Admin Issues (Cont.)

- An annual report (AR) is due every year to keep DMF active
  - Submit list of active and withdrawn LOAs in each AR
  - Overdue notice after 3 consecutive years of no AR - no reply after 90 days, DMF may be closed
- Reopening a closed DMF – holder signed reactivation letter, DMF statement of commitment, US Agent appointment letter, LOAs
  - If closed, complete resubmission of DMF per current guidelines is required
  - Acknowledgement letter sent upon reactivation
- NO QUALITY INFORMATION should be submitted in an AR (even stability data!)

Other Common Barriers to Approval

Unsolicited Amendments

- Unsolicited amendments to the DMF that are submitted in the last third of an ANDA review cycle may have adverse consequences for the applicant.
  - May cause an extension of the goal date to allow sufficient time for review.
  - The DMF amendment may be deferred to the next review cycle and cause or contribute to a CR for the ANDA.
- It is clear from the timing of these submissions that the DMF holder is not aware of the ANDA status and action timeline.
- Many of the unsolicited amendments do not contain information that is critical to review prior to an approval for the referencing application.

Unsolicited Amendments (cont.)

- Holders should communicate with sponsors regarding action timelines for referencing applications and plan their submissions accordingly.
  - Let customers with pending applications know when you are going to submit a DMF amendment.
- DMF holders should be aware of the status of the DMF
  - FA, NFC letters
  - Ask us! (DMFOGD@fda.hhs.gov)
- Limit the number of unsolicited amendments by combining minor changes to decrease the chances of interfering with an ANDA action.

Major DMF Deficiencies

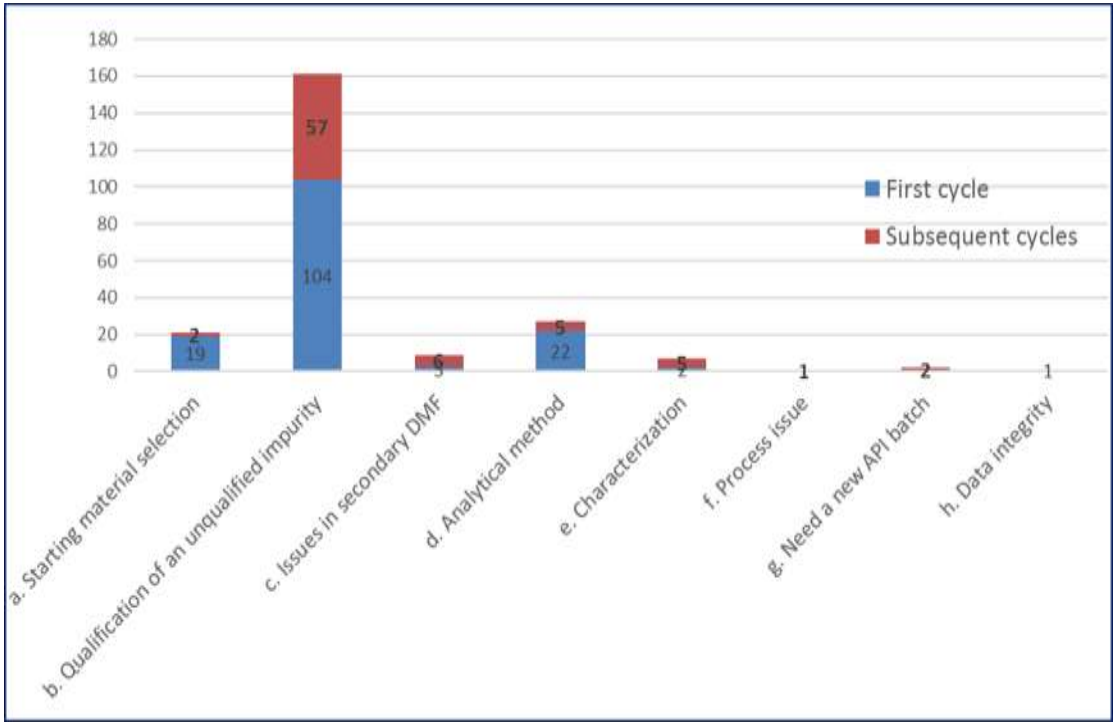
- With the publication of Guidance for Industry, ANDA Submissions-Amendments to Abbreviated New Drug Applications under GDUFA, the deficiencies in the drug master files (DMF) may affect the major or minor category of ANDA amendments, which impacts an application's review goal dates.
  - Standard Major – 8 or 10 months (depending on if preapproval inspection is required)
  - Standard Minor – 3 months

Major DMF Deficiencies

- Inadequate selection or justification of starting materials.
- Toxicological studies are needed to qualify an unqualified impurity.
- Reference to a secondary DMF which has not been reviewed, is currently inadequate, or requires submission of a technical dossier from a third party supplier with significant additional manufacturing information.
- Failure to provide adequate analytical methods or method validation which would require significant new method development.
- Insufficient physical or chemical characterization data to demonstrate structure, form, or drug substance sameness (especially for complex active pharmaceutical ingredients (APIs)) in the DMF.
- Major change in drug substance manufacturing process with inadequate supporting data.
- Requirement to manufacture a new API batch.
- Data reliability issue in the DMF or manufacturing/testing facilities.

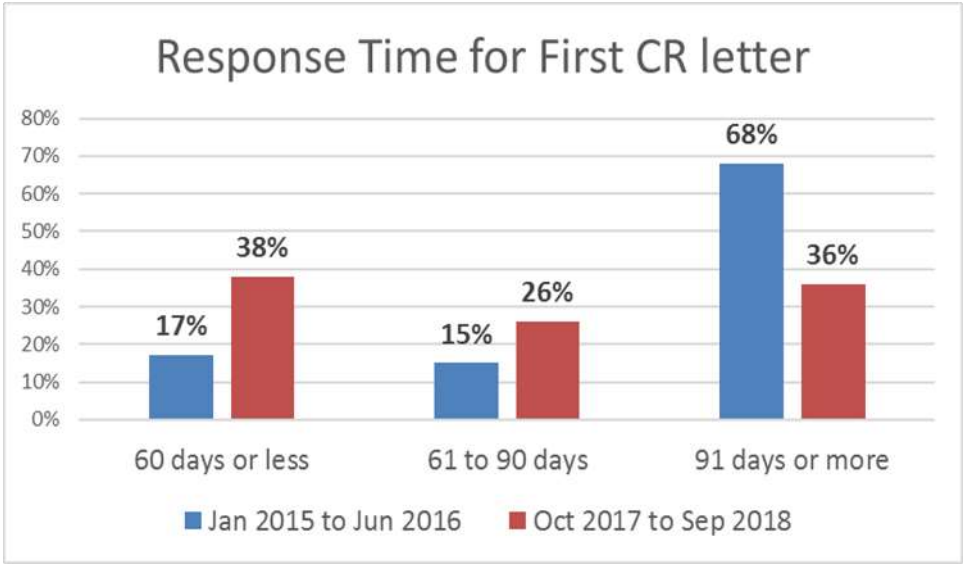
Major DMF Deficiencies

- 191 DMFs reviewed by DLAPI have major deficiencies, including 121 first cycles that accounted for over 30% first cycle DMF reviews.
- 84% of major deficiencies - “qualification of an unqualified impurity.”
- See talk tomorrow for more discussion on unqualified impurities



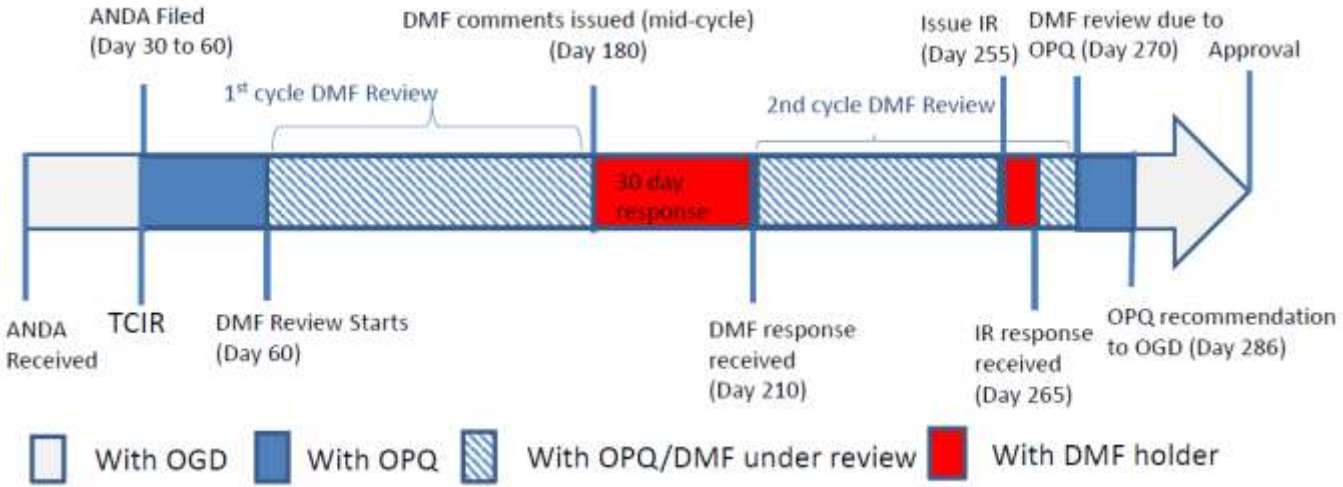
1st Cycle Response Times

- 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 touches 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.



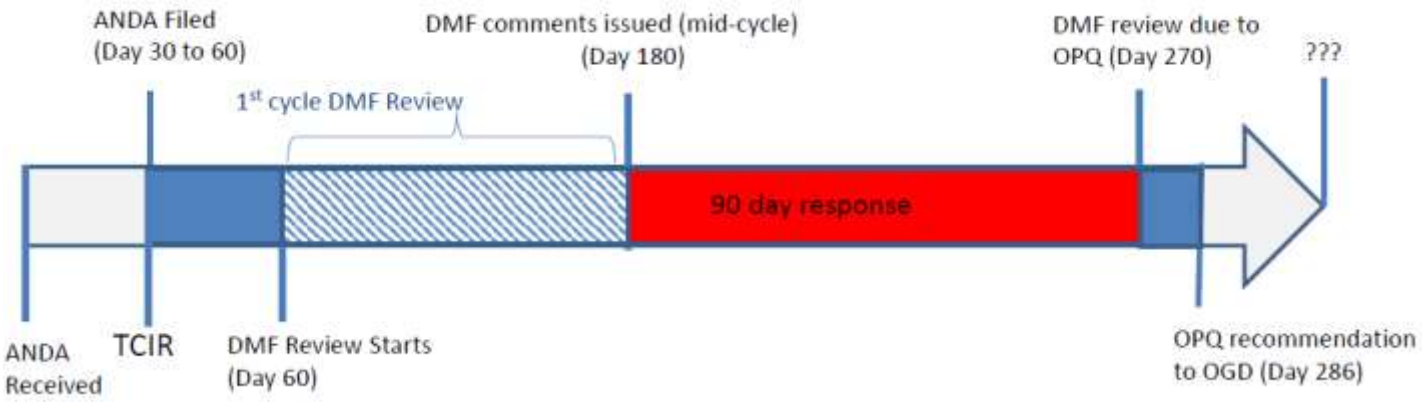
1st Cycle Response Times

- Best case DMF scenario
  - DMF response in 30 days allows time for 2 full cycles, and possibly an IR to resolve very minor issues.



1st Cycle Response Times

- 90-day response scenario
  - DMF response in 90 days does not allow for a second cycle at all.



What can you do?

- Respond to CR/deficiency letters in thirty days.
- Respond to Information Request (IR) letters within the requested timeframe.
- Provide complete responses that address all the issues raised to reduce the need for subsequent cycles
- Use email exchanges to get clarifications quickly.
- Avoid deficiencies in key areas that require a long time to respond and/or consume significant Agency resources to review.

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