Road to First Cycle Approval for Post – Approval Changes – CBER/FDA Perspective

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Outline

- Good Review Management Principles and Practices
- Changes to an Approved Application
- Proportional analysis of CR letters
- Elements of a Good Submission
- Elements of a Poor Submission
- Summary

Good Review Management Principles and Practices

- Goal is to increase first cycle approvals
- Expectations for Applicants – management of the issues prior to submission
- Communication is key to minimize problems
- Emphasis on submission of a complete supplemental application

Good Review Management Principles and Practices

- Well-planned and well-managed review
- Open and frequent communication and collaboration during the review
- Early communication of deficiencies to permit corrective action
- Greater consistency in FDA staff's interaction with applicants

Changes to an Approved Application (PAS-CBEs)(1 of 2)

21 CFR 601.12(b)(3) and 601.12(c)(3):

(i) A detailed description of the proposed change

(ii) The products involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

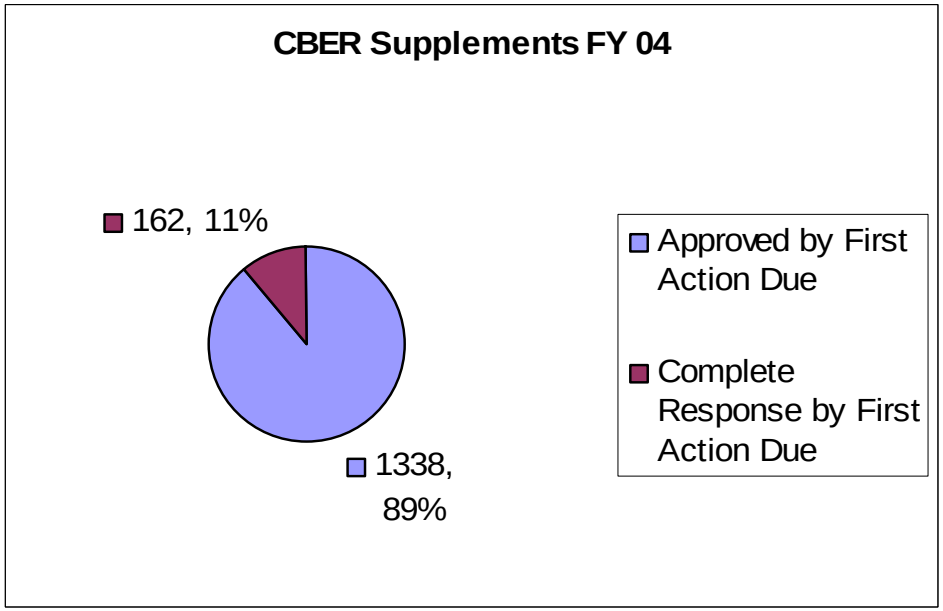
Changes to an Approved Application (PAS-CBEs) (2 of 2)

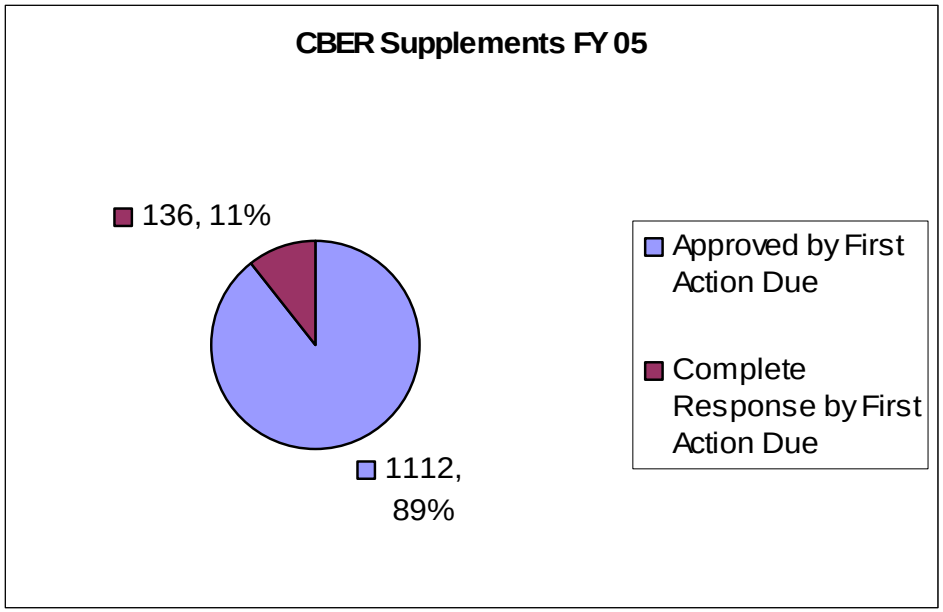
21 CFR 601.12(b)(3) and 601.12(c)(3):

(v) The data derived from such studies;

(vi) Relevant validation protocols and data; and

(vii) A reference list of relevant standard operating procedures (SOP's).


CBER Supplements FY 04
162, 11%
1338, 89%
Approved by First Action Due
Complete Response by First Action Due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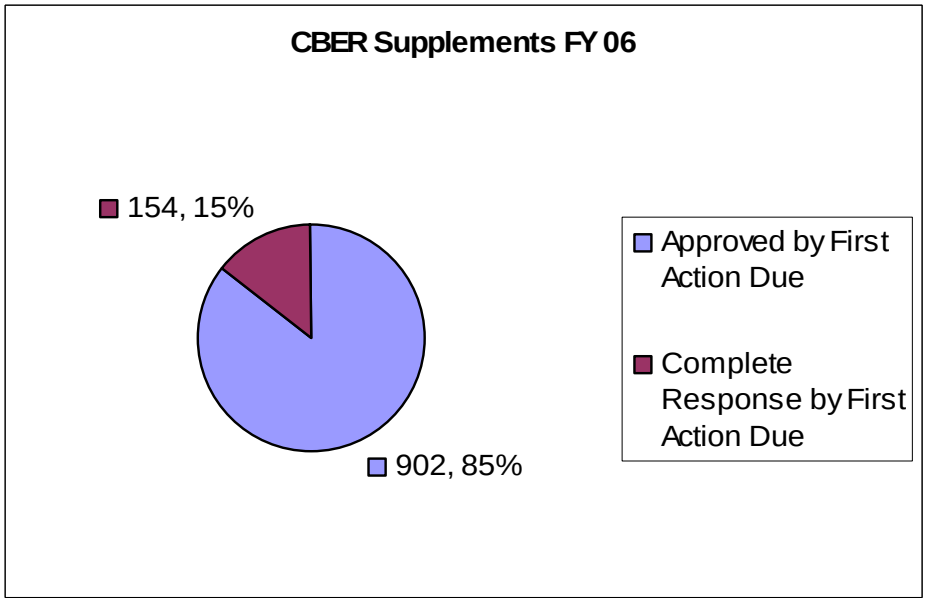
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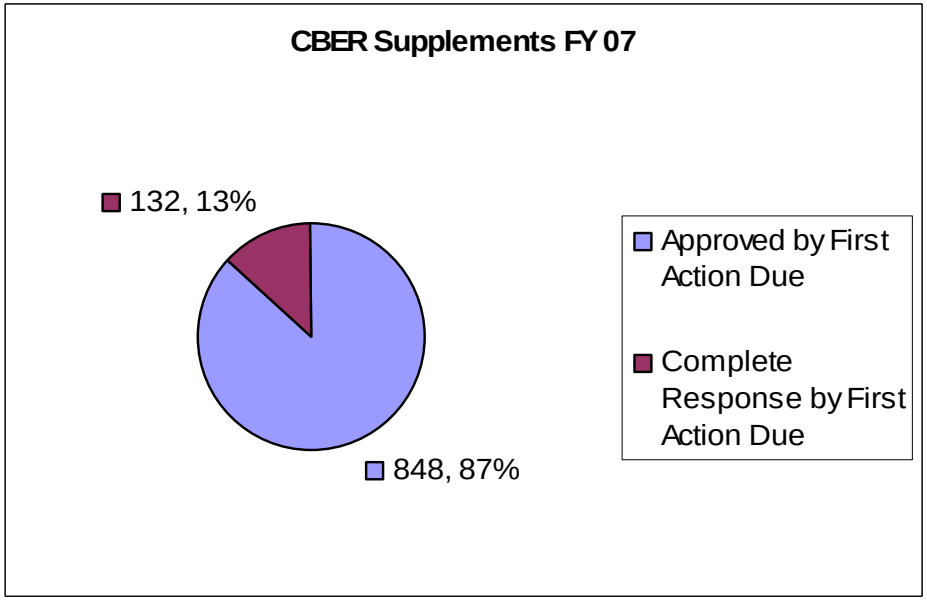
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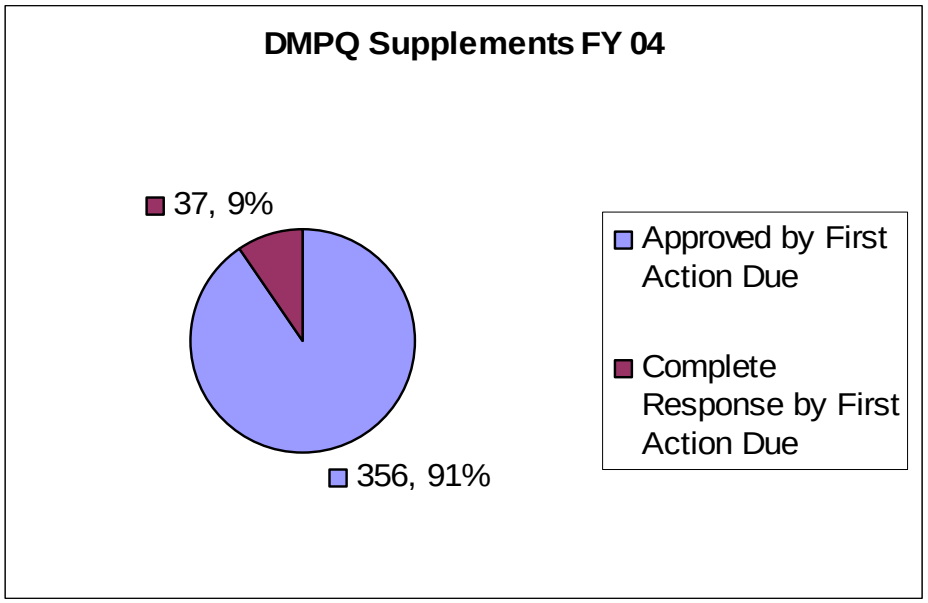
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356, 91%
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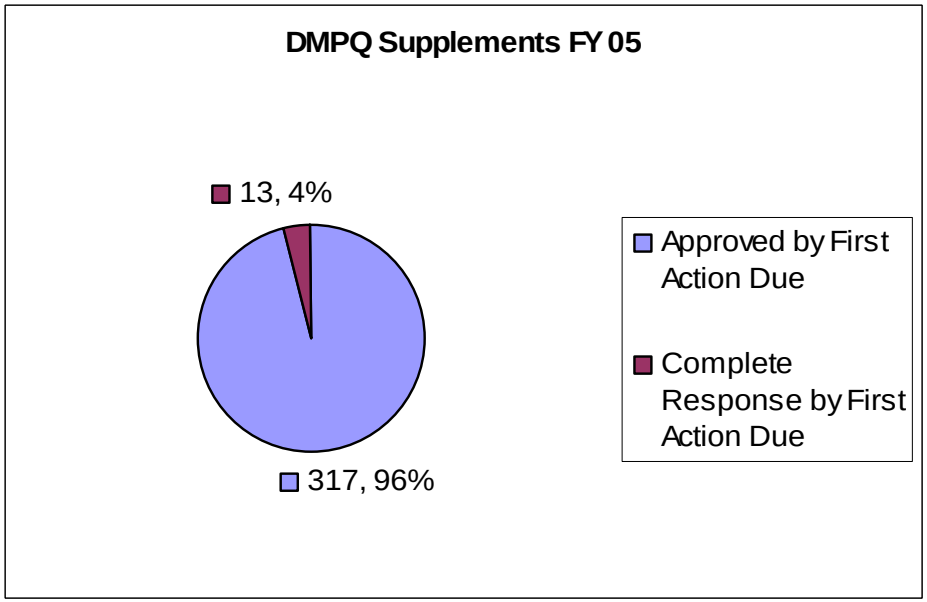
Complete Response by First Action Due


DMPQ Supplements FY 05
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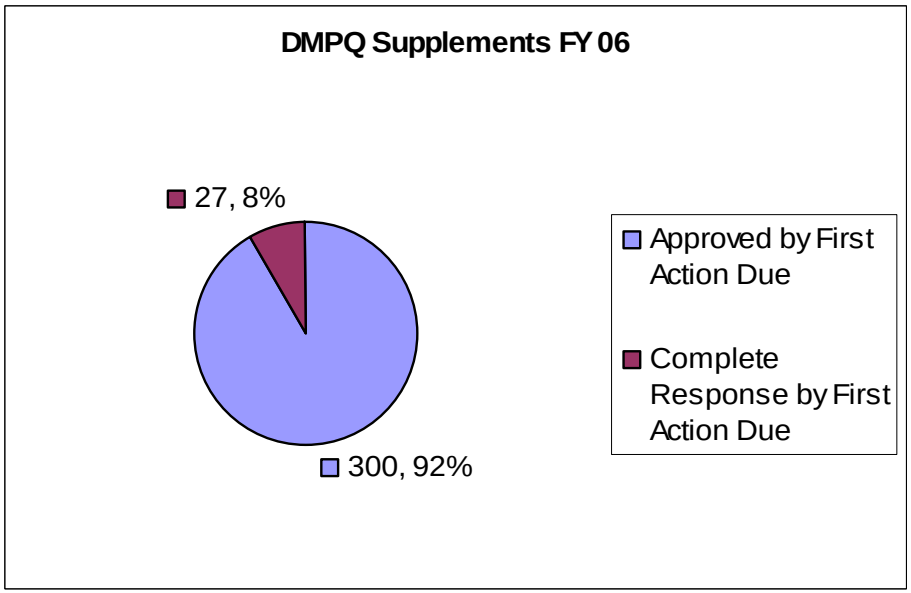
Complete Response by First Action Due


DMPQ Supplements FY 06
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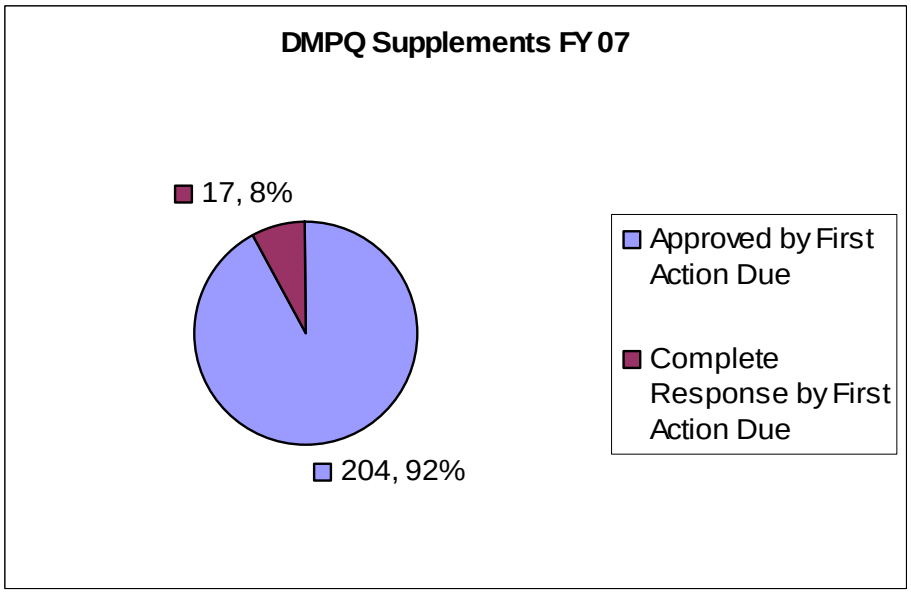
Approved by First Action Due
Complete Response by First Action Due


DMPQ Supplements FY 07
17, 8%
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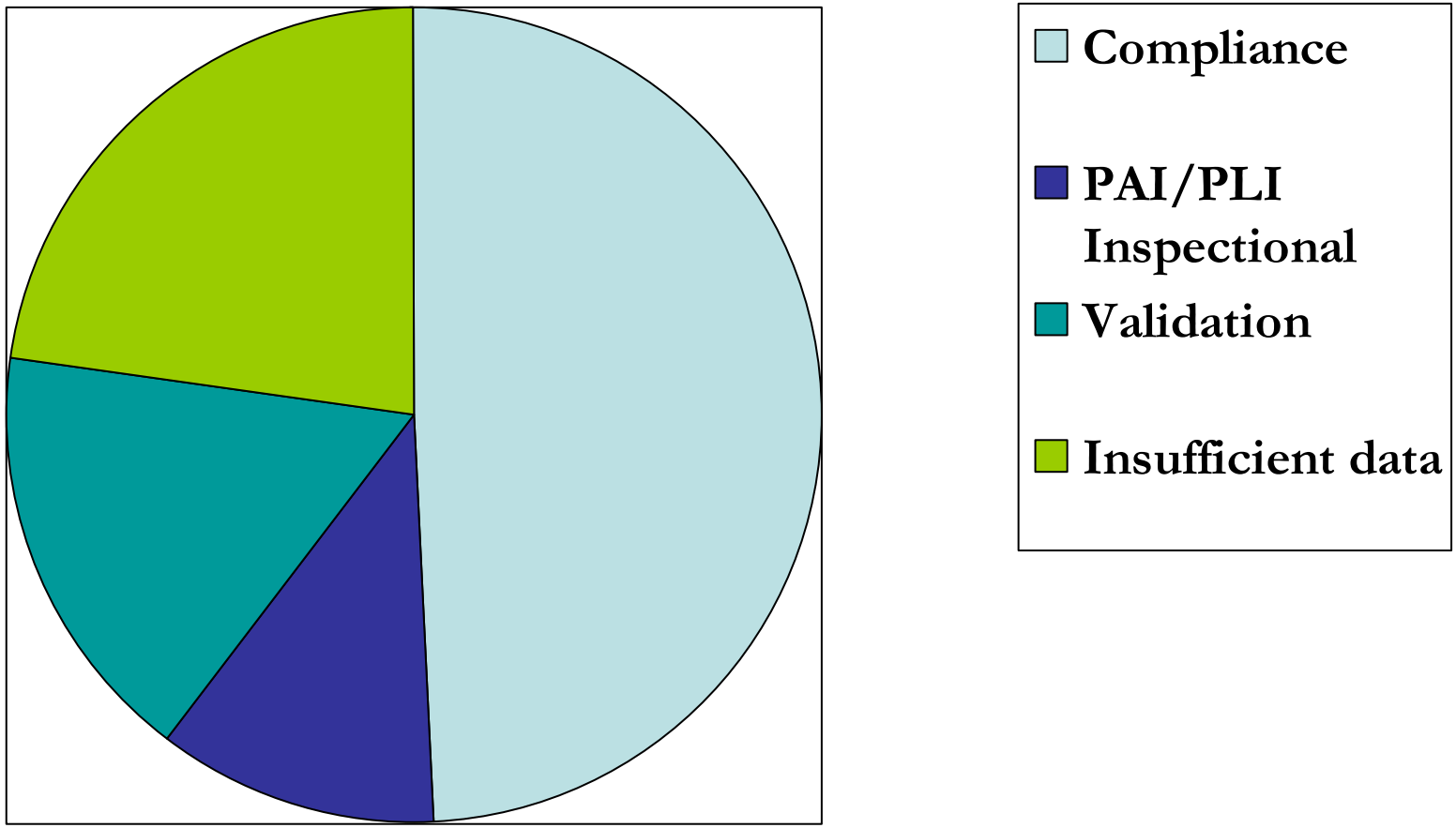
Approved by First Action Due
Complete Response by First Action Due

Complete Response Letter Issues (CBER DMPQ 2004-2007)



Elements of a Good Submission

- Many submissions are organized for an efficient review and contain the correct information
- When questions are raised during the review, reviewers generally get a response in a reasonable timeframe
- Complex submissions are often discussed before they are submitted to minimize problems during the review

Example of a Good Supplement

- Early communication on problems with meeting specifications within stability testing period
- Information sent to CBER for discussion; multiple discussions on the subject (Type C Mtg)
- Root cause appeared to be changes made to the assay
- Applicant determined appropriate resolution to assay issue
- While the complete resolution to the problem took time, the review of the supplement went smoothly

Elements of a Poor Submission (1 of 2)

- Summaries don’t include full scope of the changes covered by the submission
- Lack of product data in the submission, thus submission is a “proposal” and not a supplement – more specific to DMPQ supplements for changes to equipment.

Elements of a Poor Submission (2 of 2)

- Inclusion of too much information –
  - For equipment, may see the entire IQ/OQ/PQ submitted
  - Submits the entire updated CTD section and only one subject includes the change
- Issues communicated early in the review - sometimes responses received late in the review process

Examples of a Poor Submission (1 of 4)

- Submission for a new area for fill and finish also included a change to the container closure that wasn't mentioned in the cover letter
- Change in multi-product contact equipment didn't have data from representative products; data was generated and one of the products failed stability – change was not implemented for that product

Examples a Poor Submission (2 of 4)

- Supplement for a new area and scale-up contained data from equipment no longer in use, and contained a comparability protocol for a scaled-up process that was being implemented; data from the scaled-up process was not available at the time of the submission
- Supplement for a transfer of the same manufacturing process to a new location without considering the impact of the equipment and scale differences. Eventually the production cycles changed and led to multiple review cycles.

Elements of a Poor Submission (3 of 4)

- During an inspection, it was discovered that one of the facilities used in the manufacture of the product was not submitted – file had to be updated to include the location

Elements of a Poor Submission (4 of 4)

- During an inspection: It was discovered that the transfer of the production step to a new contract facility did not include the following:
  - Process validation at the production scale on the line submitted in the supplement
  - No data for comparability for the addition of a secondary manufacturing line, of which they intended to use once the contract facility was approved

Summary

- Most submissions are approved within the first cycle, however, improvements in the quality of the submissions and Center review management will increase the chances of the first cycle approval.
- Good communication before and during the reviews are essential to ensure goals are met
- Cover letter should include description of all changes
- Advance notice of significant submissions is encouraged, as well as changes to agreed upon plans (timeframes or filing strategy)