U.S. Food and Drug Administration

GDUFA Generic Drug User Fee Amendments of 2012

Completeness Assessment for Type II DMF Under GDUFA

Wei Song, Ph.D
DMF Review Staff
OGD/OPS/CDER

Outline

- DMF Fee User Collection
  - Basics of DMF user fee: What/Why/Who
- Completeness Assessment (CA) Metrics
  - First six-month CA submission study
- Common Incomplete Comments in CA review

What is the DMF User Fee?

- It is one-time payment during the whole DMF lifecycle
- The DMF user fee payment triggers the completeness assessment
- "Complete" DMFs are deemed "available for reference" and will be listed on a publicly available FDA website

http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.pdf.

Why do We Need Pay DMF User Fee?

- On and after Oct 1, 2012, type II DMF holders must pay a user fee and pass the Completeness Assessment (CA) before the type II DMFs can be referenced by an Abbreviated New Drug Application (ANDA), ANDA amendment, or ANDA prior approval supplement (PAS).

What Happens for Failure to Pay DMF Fee?

- For referencing a DMF that fails to pay DMF user fee:
  - ANDA sponsor will receive a notification from Office of Management (OM) that the DMF fee is due in 20 calendar days.
  - After 20 days the ANDA submission will be **Refuse to Receive** (RTR) and the application fee will be forfeited.

- For referencing a DMF that fails the CA:
  - ANDA will get "**Refuse to Receive"** by OGD and a 75% refund of the submission fee could be granted.

Who can pay DMF fee?

- Anybody!

- DMF holders

- ANDA holders

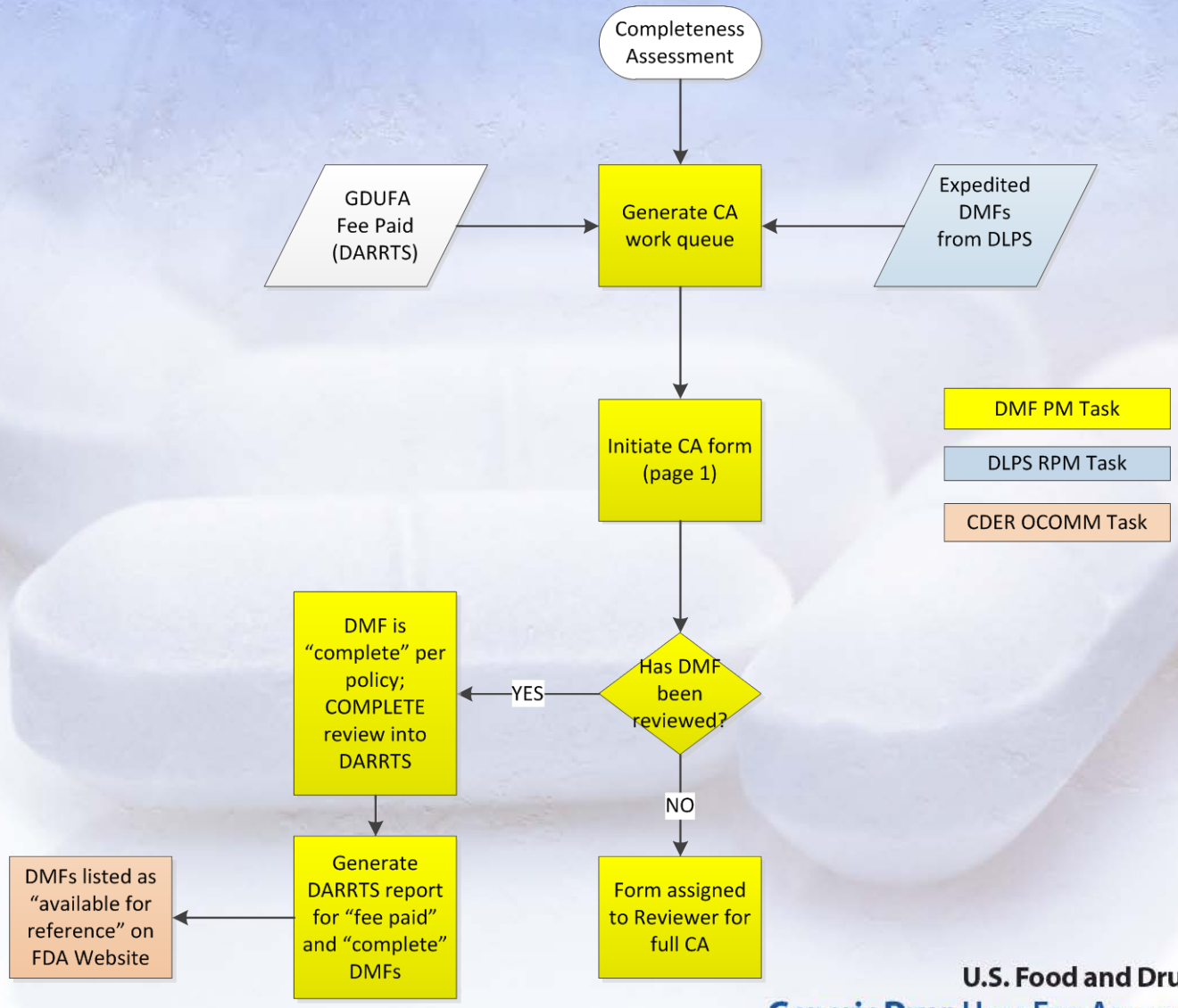
The Facts of Completeness Assessment

- Completeness assessment (CA) is similar to the current ANDA filing review. The criteria of CA is higher than the administrative check used at central document room.

- A “complete” DMF should contain sufficient information for a full scientific review.

- The purpose of CA is to improve DMF submission quality and reduce the scientific review cycles

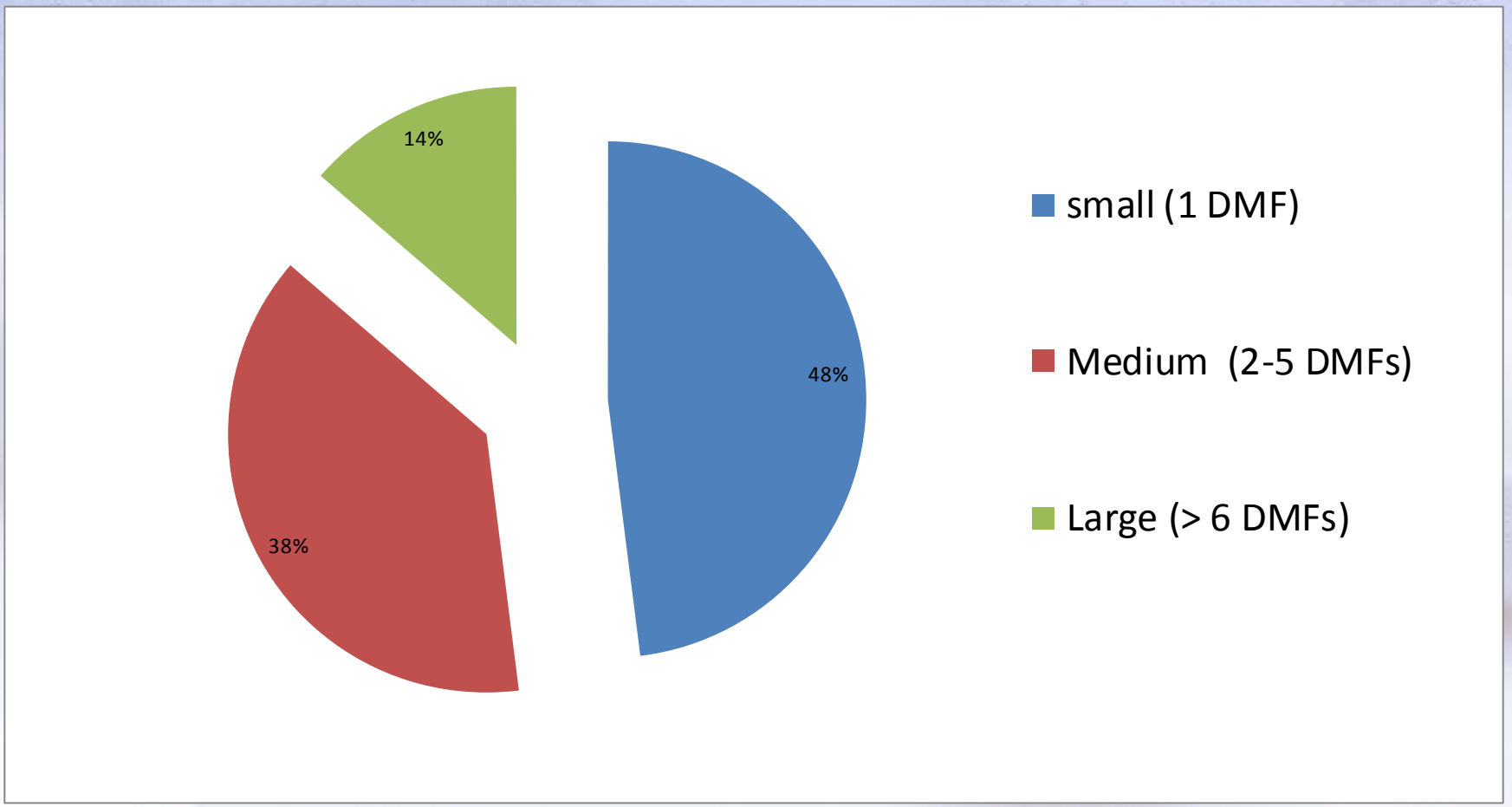
DMF CA Queue Generation



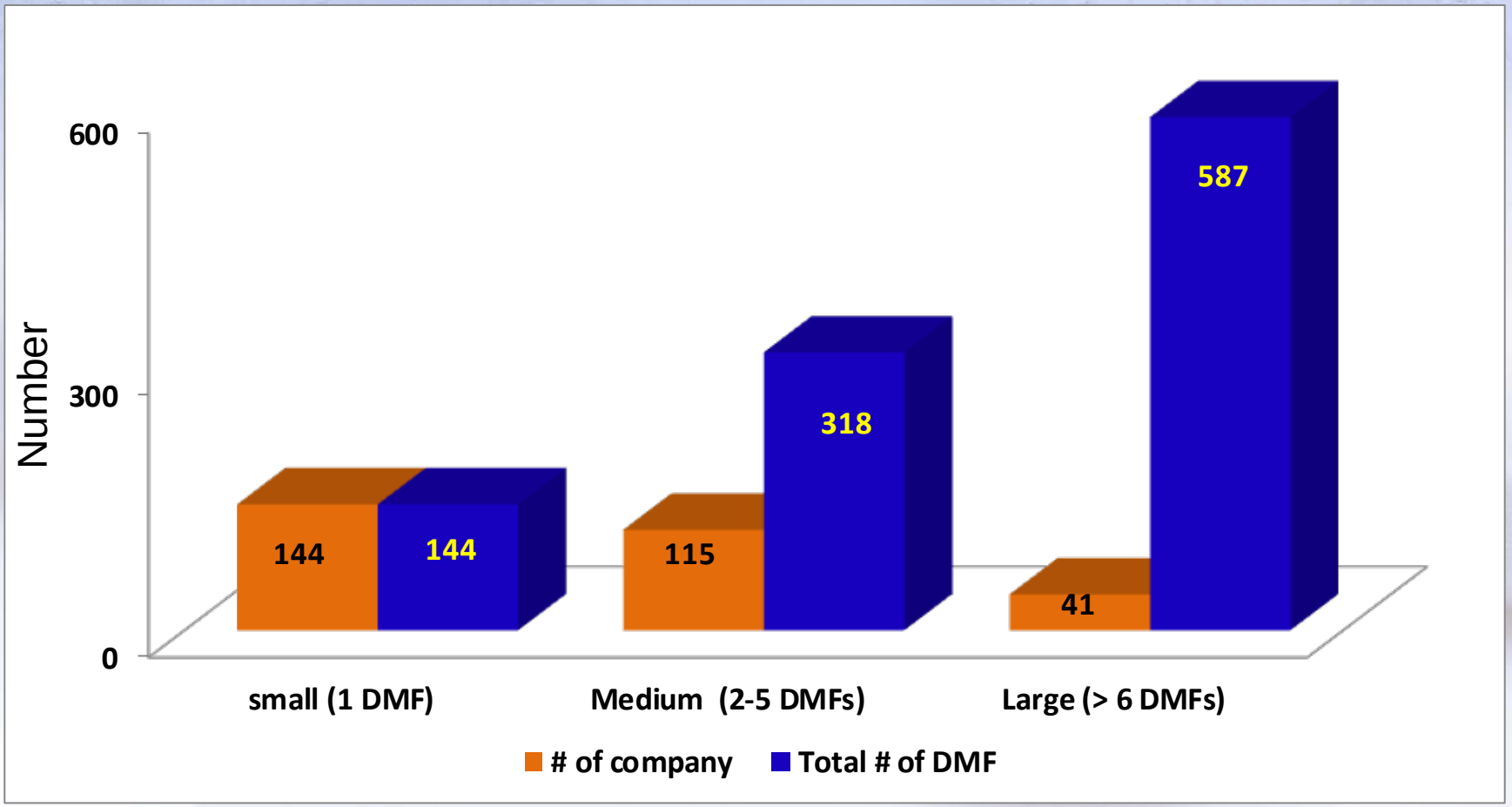
Details of DMF Submissions in the First Six Months

- The first payment was received on October 25, 2012
- Until April 16, 2013, FDA received 1049 DMF user fee payments
- These DMFs were submitted by 300 DMF holders

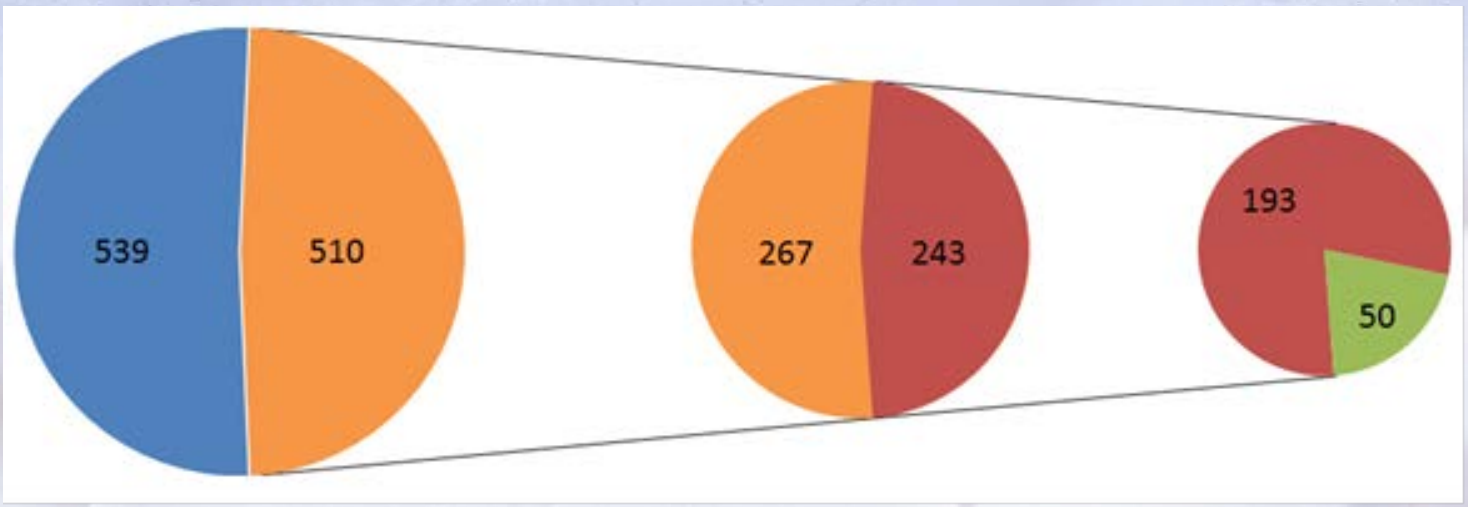
Distribution of DMF Holders (N=300)



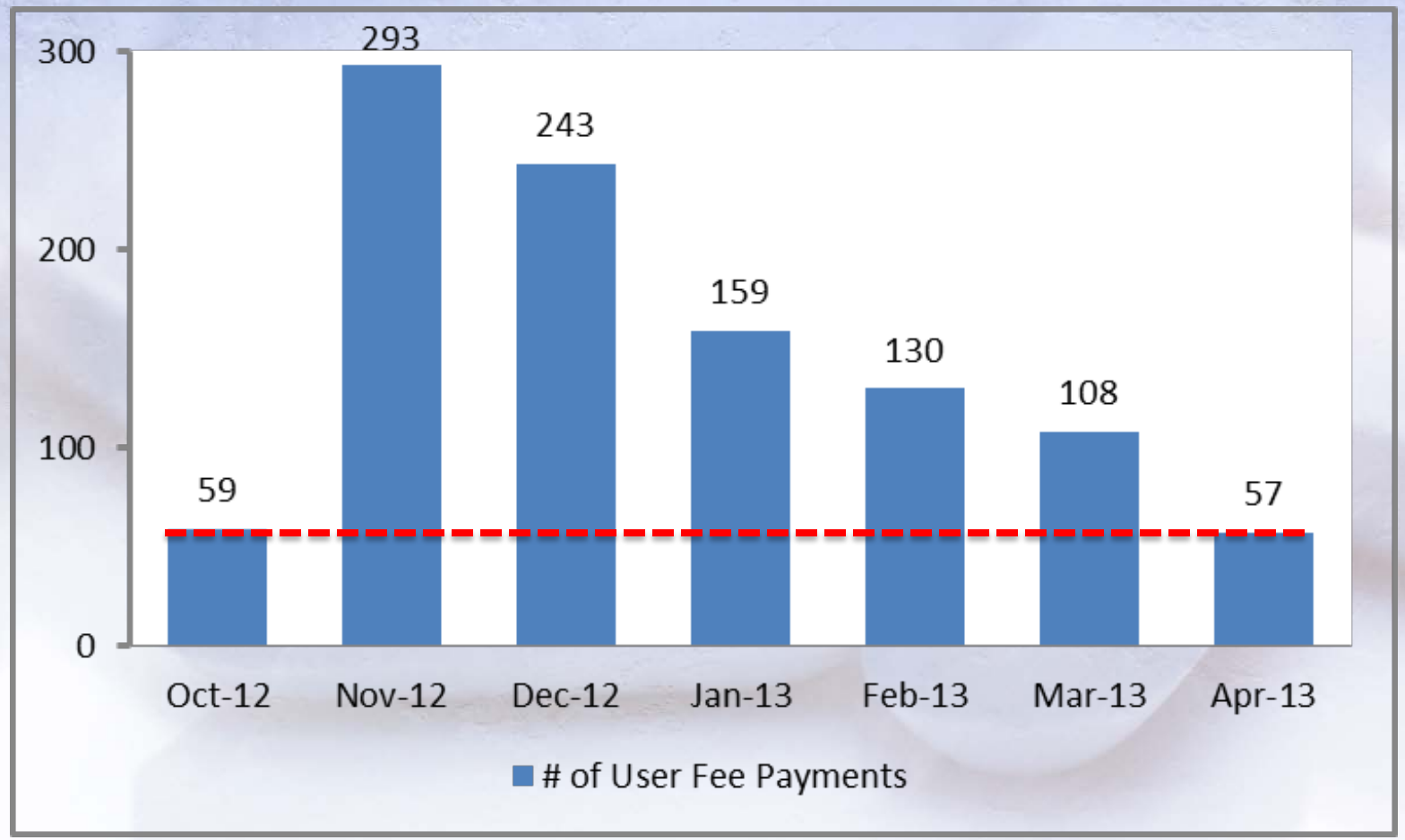
Distribution of DMF Submissions (N= 1049)



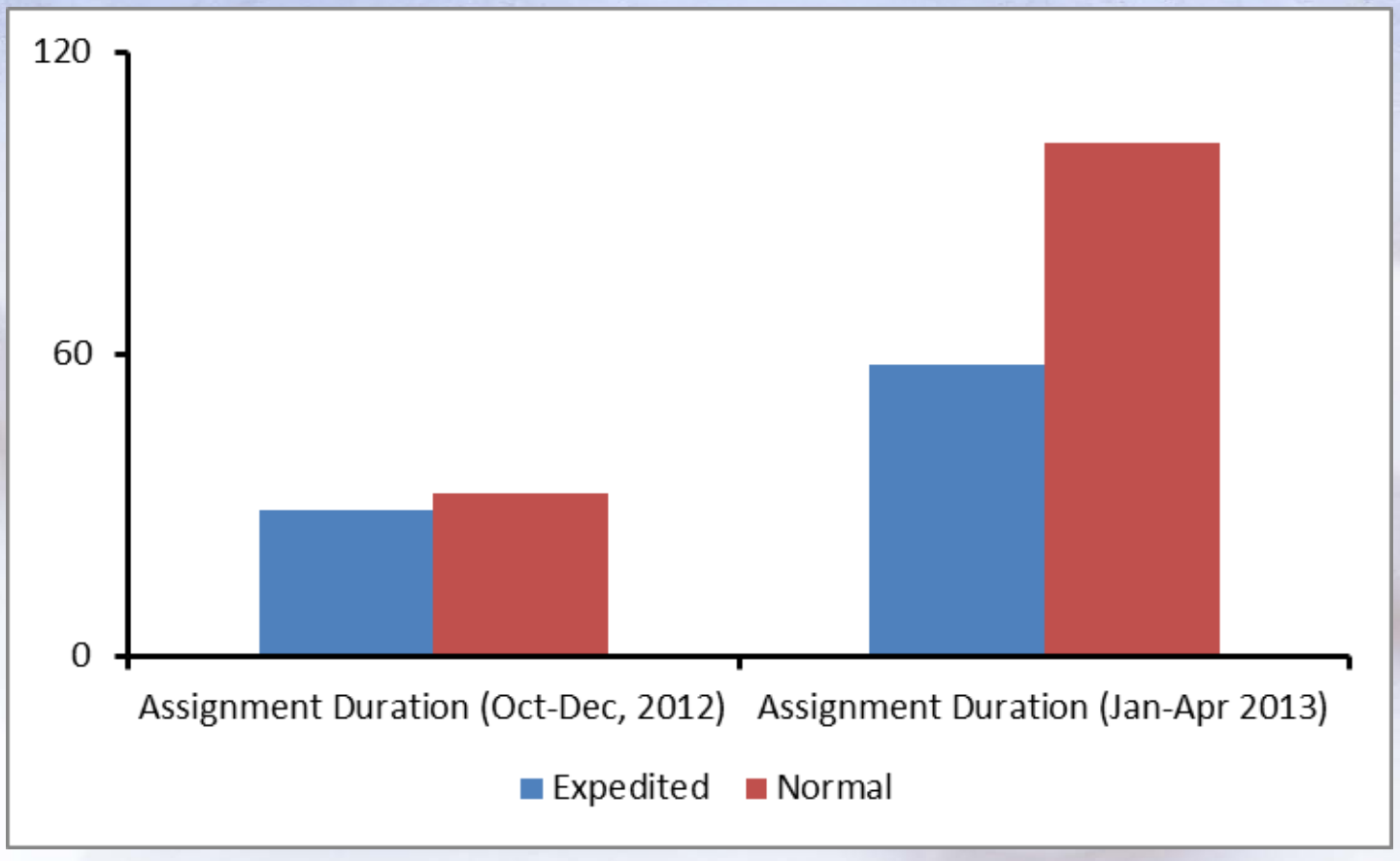
A Snapshot of DMF CA Review Progress (10/25/2012-04/16/2013)



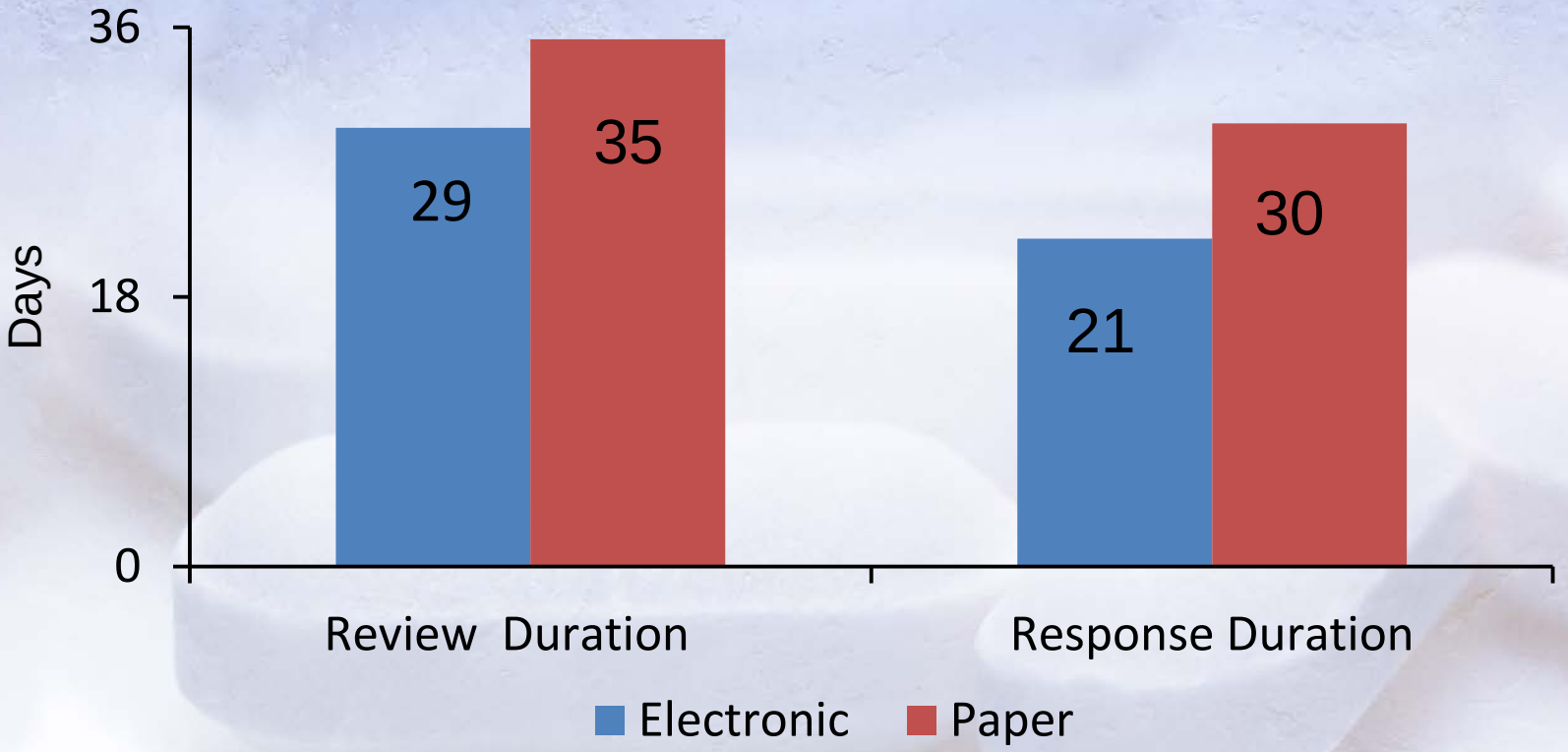
Received User Fee Payments by Month in First Six-Month



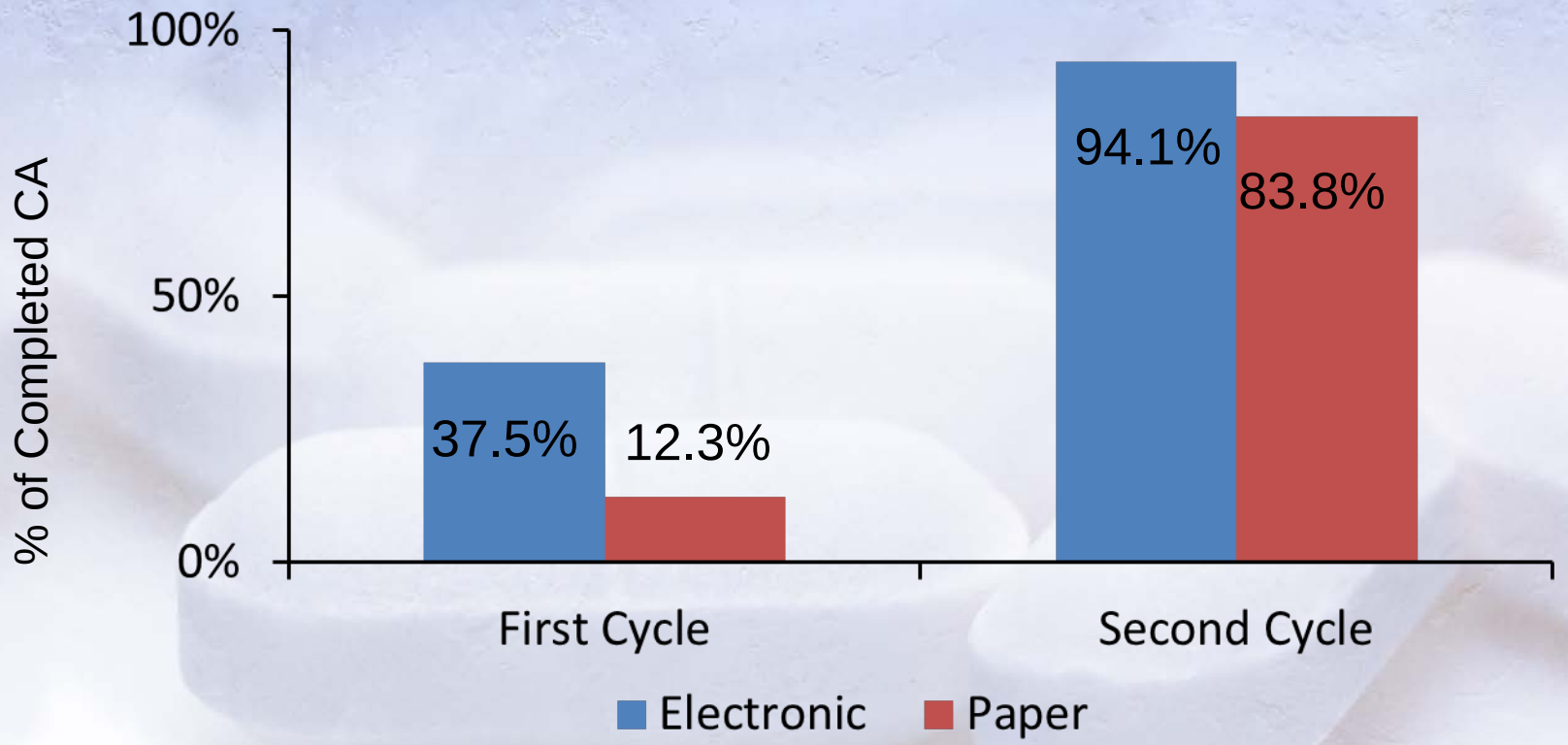
Prioritization of CA Review Reduce the Risk of RTR Received by ANDA Holder



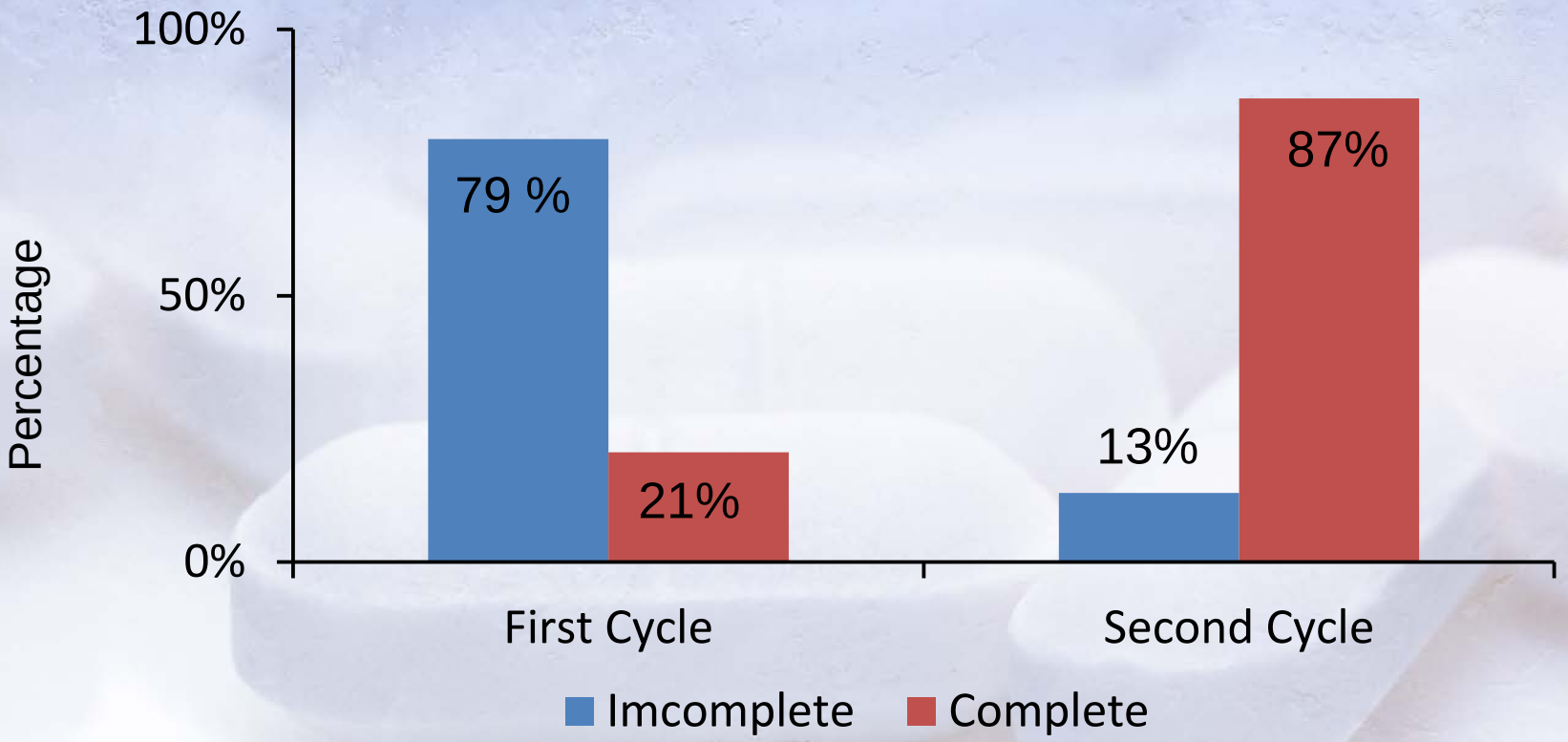
Electronic Submission: More Efficient



Electronic Submission: Higher Quality



CA Review Improve Submission Quality



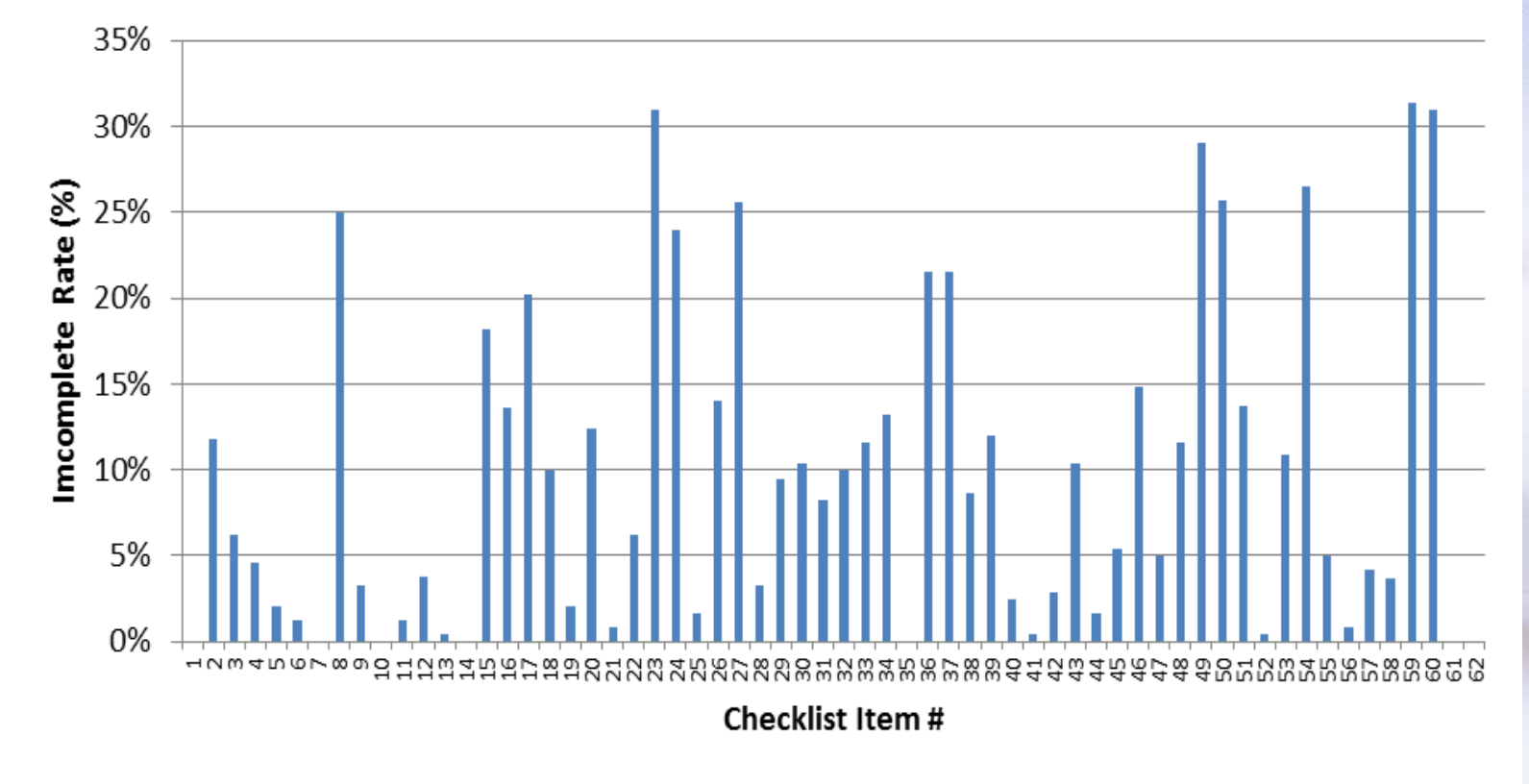
Format of Checklist

Questions are arranged according to CTD format:

- Administrative/General Information (Item # 1~11)
- 2.3.S QOS (Item # 12)
- 3.2.S.1 General Information (Item # 13~15)
- 3.2.S.2 Manufacture (Item # 16~36)
- 3.2.S.3 Characterization (Item # 37~40)
- 3.2.S.4 Control of Drug Substance (Item # 41~45)
- 3.2.S.5 Reference Standards or Materials (Item # 46~51)
- 3.2.S.6 Container Closure System (Item # 52~54)
- 3.2.S.7 Stability (Item # 55~58)
- 3.2 R Regional info (Item # 59~62)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf

Checklist: Missing Information



Incomplete Items Observed During First Cycle CA Review -1

- Administrative/General Information Section

- Question # 2 (Cited by more than 10% of submissions) :
  If it has been five years since the DMF has received a complete update, or there have been more than 5 amendments, a complete update will be required. The requirement for complete update does not apply to the DMF if the entire DMF is in electronic format.

- Question # 8 (Cited by more than 25% of submissions) :
  The container label should include, but not limited to, the following information: weight of the material, **date of manufacture**, **retest date**, complete name and address of the manufacturer, **appropriate storage conditions, numerical temperature range**, and caution statement.

Incomplete Items Observed During First Cycle CA Review -2

❑ 3.2. S.1 General Information

- Question # 15 (Cited by more than 15% of submissions) :
  The general properties section (S.1) should include basic information such as chirality, polymorphism, hygroscopicity, aqueous solubility, solubility in various organic solvents, and melting range for the drug substance, etc.

❑ 3.2. S.2 Manufacture

- Question # 16 (Cited by more than 10% of submissions) :
  The complete name, address, function, and contact information, including the name of on-site responsible individual is needed for the manufacturer. If the intermediate is outsourced, the manufacturing site of the intermediate should be provided. Separate facilities, used for additional processing and release testing, should also be included in this section.

Incomplete Items Observed During First Cycle CA Review -3

- 3.2. S.2 Manufacture

- Question # 17 (Cited by more than 20% of submissions) :
  A true starting material should be a substance of defined chemical properties and structure. It should be a commercially available chemical in a **pre-existing, non-pharmaceutical market** in addition to its proposed use as starting material per ICH Q 11. If a late stage intermediates is designated as regulatory starting material, a determination should be made if sufficient information on its manufacture and control are provided to evaluate the quality control strategy.

  Further discussion regarding regulatory starting materials :
  FDA Perspectives: Designation of Regulatory Starting Materials in the Manufacturing of Drug Substances: Impact on ANDA Review Time
  Scott, B., Pharm Tech 36(1) pp. 63-66 (2011)

Incomplete Items Observed During First Cycle CA Review -4

- 3.2.S.2.3. Control of Materials:

- Question # 23 and 24 (cited by more than 20% of submissions) :
  For each starting material, a representative in-house CoA **and** the corresponding vendor's CoA from the each approved supplier are needed.

- Question # 27 (cited by more than 20% of submissions) :
  For each reagent and solvent used in the manufacture of the drug substance, a representative in-house CoA **or** the corresponding vendor's CoA from the each approved supplier is required.

Incomplete Items Observed During First Cycle CA Review - 5

- 3.2.S.2.5 -2.6 Process Validation:

- Question # 34 (Cited by more than 10% of submissions) :
  The summary should include the description for the validation batches, starting material analysis, in process controls, intermediates and final API analysis which can be presented in a tabular format.

- Question # 36 (Cited by more than 20% of submissions) :
  The summary should include the rationale of starting material designation, critical material attribute identification, process optimization, justification of control strategy.

Incomplete Items Observed During First Cycle CA Review - 6

- 3.2.S.3. Characterization

- Question # 37 (Cited by more than 20% of submissions) :
  The characterization information should sufficiently to elucidate the structure of the drug substance.

  2D NMR, Chiral HPLC comparison, specific optical rotation, single crystal XRD, etc. may be needed to address stereo-chemical features.

  The representative spectra should be legible to read.

  Peak assignment tables are very helpful for interpreting IR, NMR, MS spectra.

Incomplete Items Observed During First Cycle CA Review - 7

- 3.2.S.5 Reference Standards and Materials

- Question # 49 (Cited by more than 25% of submissions) :
  For each identified impurity, the source, the lot number, and the CoA for both reference standard and working standard should be provided.

- Question # 50 (Cited by more than 25% of submissions) :
  Non-compendial reference standard should be characterized and quantified.

- Question # 51 (Cited by more than 25% of submissions) :
  For impurities with compendial RS available, comparative data, like over-laid IR spectra, between the USP RS and the in-house WS should be provided.
  The representative spectra should be legible to read.

Incomplete Items Observed During First Cycle CA Review - 8

- 3.2.S.6 Container/Closure System:

- Question # 54 (Cited by more than 25% of submissions) :
  For each packing component, the corresponding source information, specification, and representative COA is needed

- 3.2.S.R Regional information:

- Question # 59 (Cited by more than 30% of submissions) :
  The representative Executed Batch Records translated into English is needed.

- Question # 60 (Cited by more than 30% of submissions) :
  For exhibit batch(es), required information includes yields, results of in-process controls, and analytical results for intermediates.

Suggestions for a Successful CA Review

- Proactively initiate the DMF completeness assessment by paying the DMF fee as early as possible (6 months before ANDA submission)
- Follow the draft CA guidance and checklist
- Provide high quality submissions with sufficient supporting data
- Submit the DMF in CTD format and preferably in electronic format.