Regulatory Education for Industry (REdI):
GENERIC DRUGS FORUM

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Current Regulatory Practice in Type II API DMF Review

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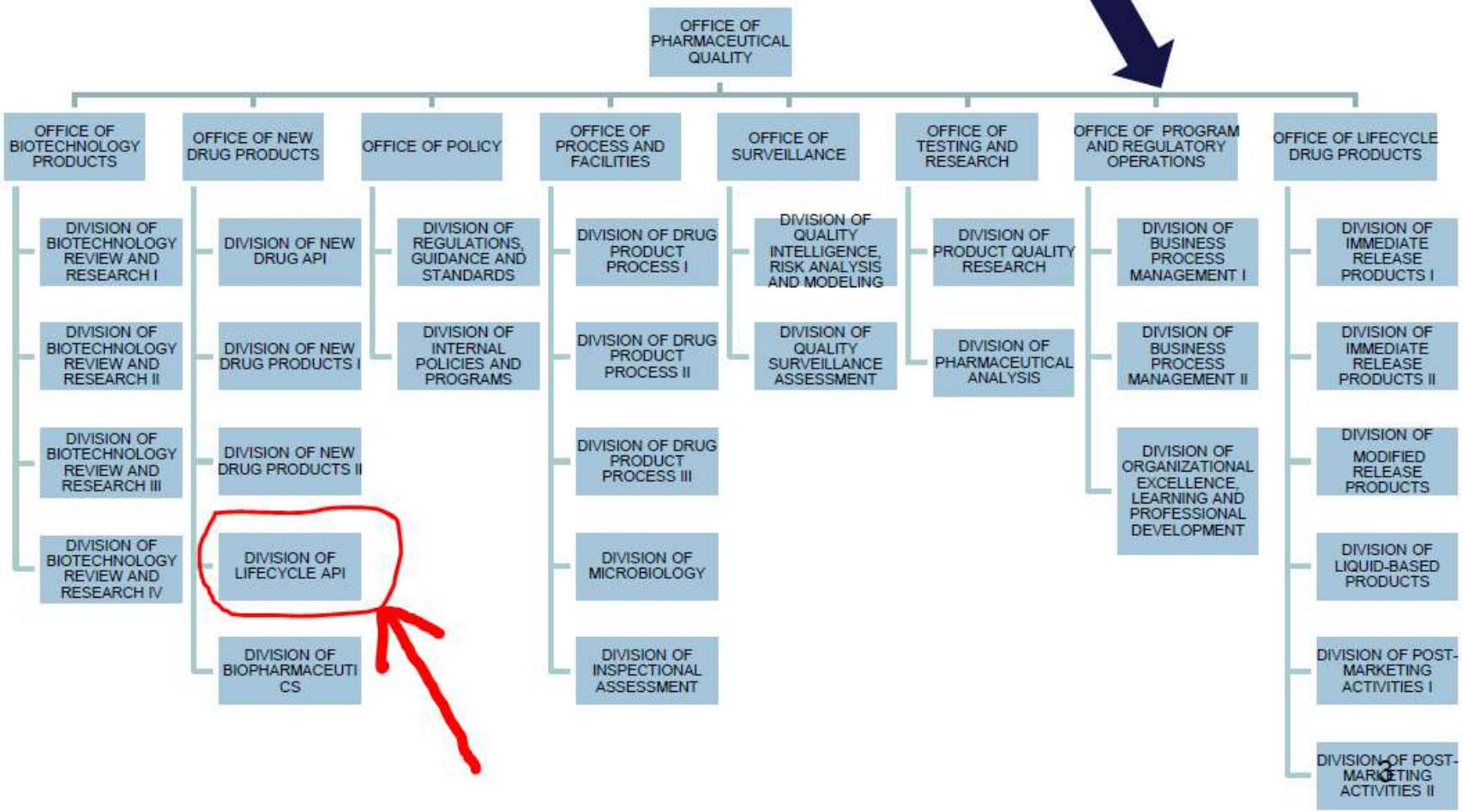
Really?

Outline

- Overview of DLCAPI
- Completeness Assessment
  - CA timelines and metrics
  - To avoid an RTR to ANDA due to incomplete DMF
  - Some clarifications
- API QbR-QoS
- ‘Real Time Communications’

Transition of DMF Review Staff to DLCAPI

Organizational Structure - Office of Pharmaceutical Quality



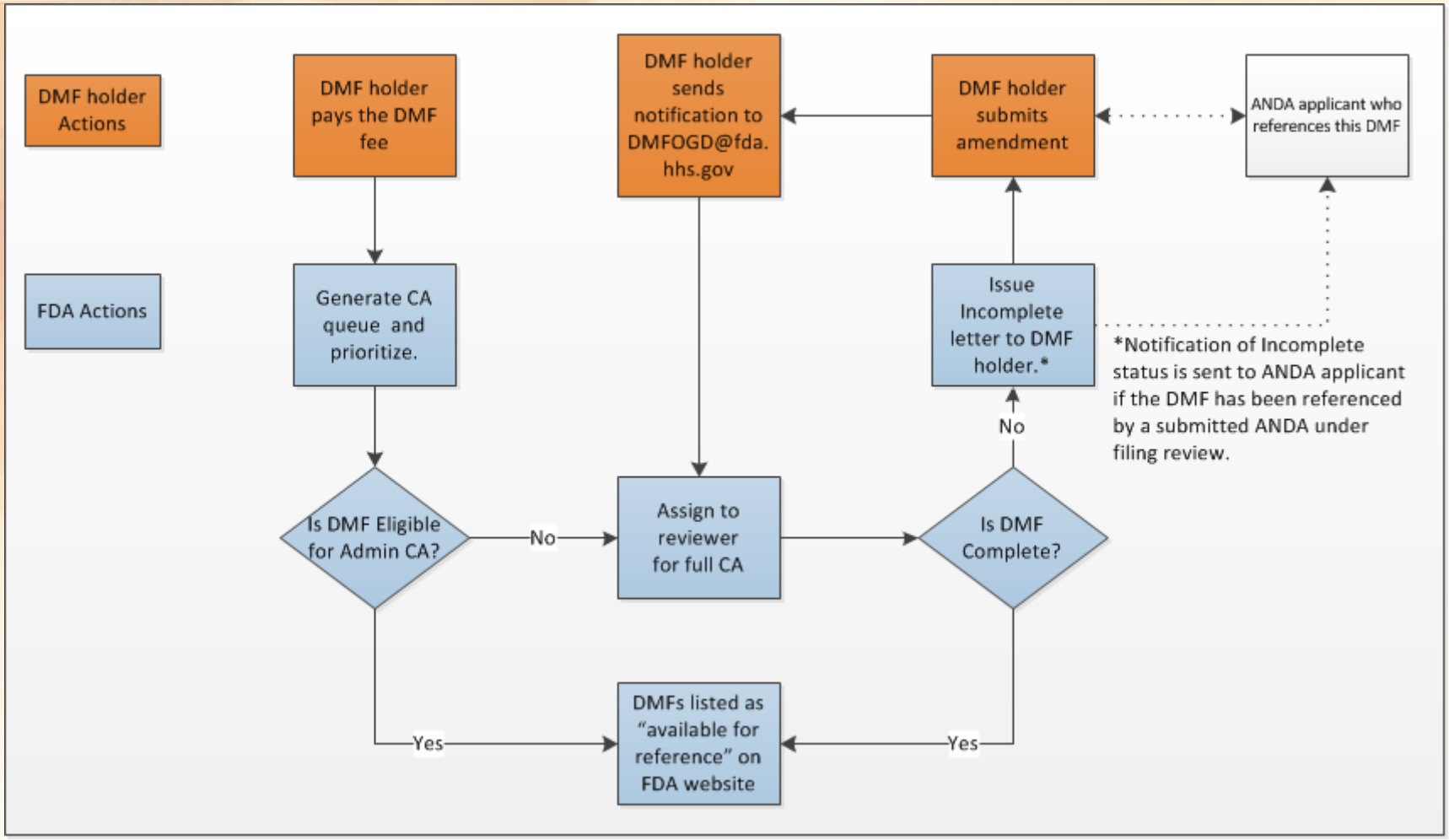
Transition of DMF Review Staff to DLCAPI

- **Perform review of API CMC information in support of ANDA submissions**
- **Concentrate subject matter expertise on API review**
- **Increase consistency of DMF/API reviews**
- **Focal point for API quality issues related generic submissions**
- **Facilitate implementation of related GDUFA initiatives to improve API review**

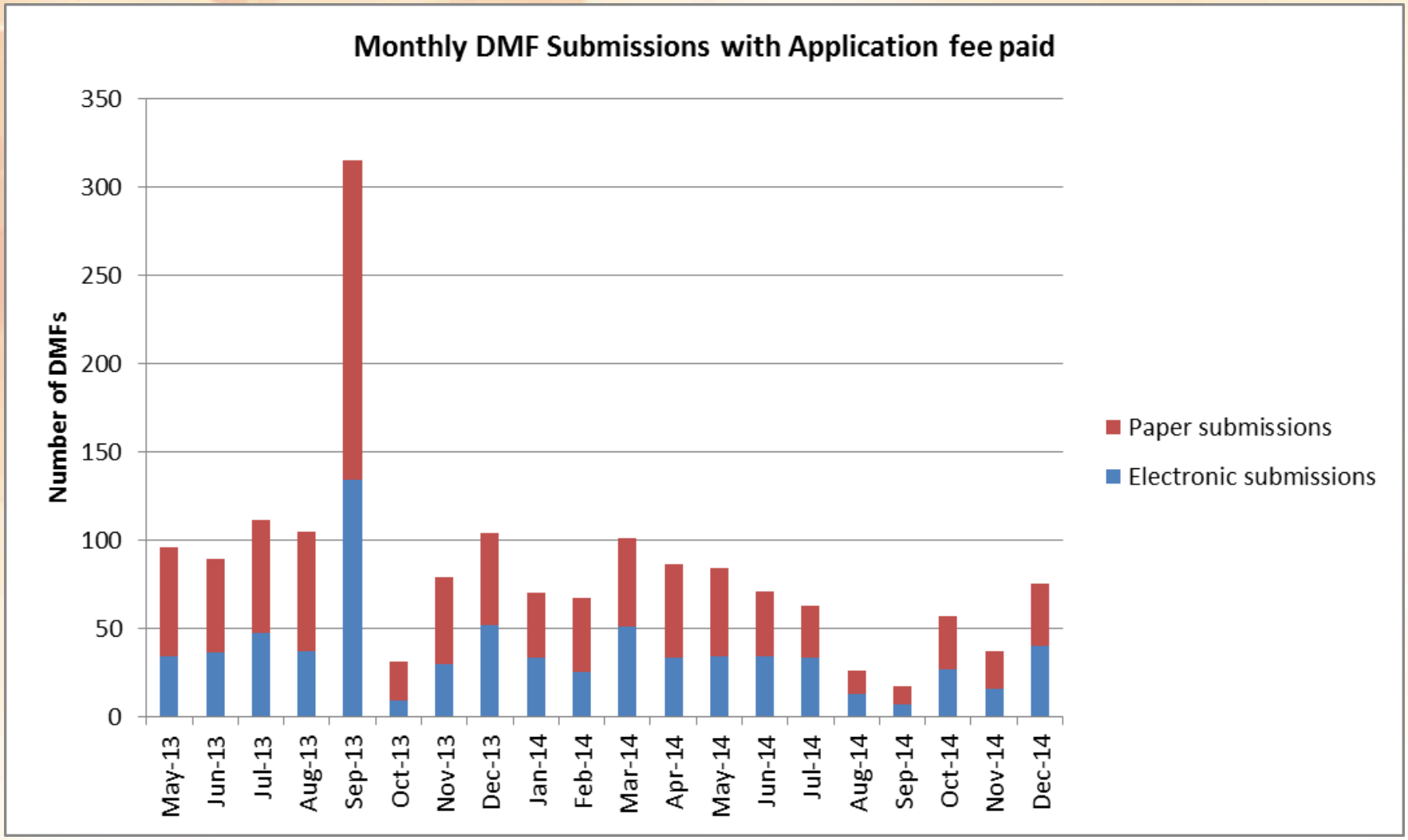
DMF CA under GDUFA

- **In order to file an ANDA all referencing Type II DMFs for the API must be "Available for Reference"**
- **Completeness Assessments (CA)**
  - **Perform an initial Completeness Assessment on a Type II API DMF when the GDUFA DMF fee is paid**
  - **Publish the criteria used for the CA (Draft Guidance)**
  - **Publish a list of all DMFs that are "Available for Reference" (fee paid and passed the CA)**

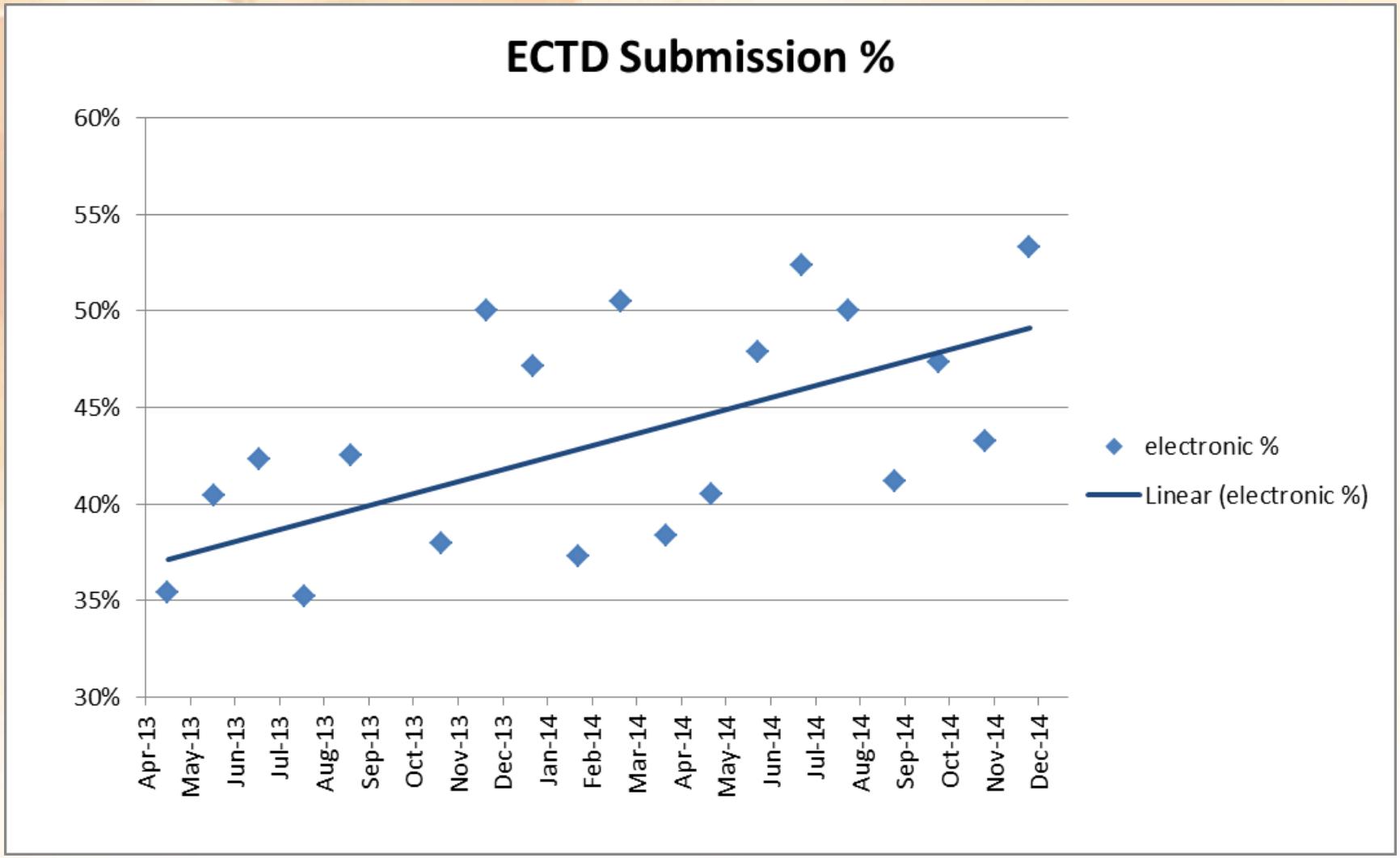
CA Process Flow



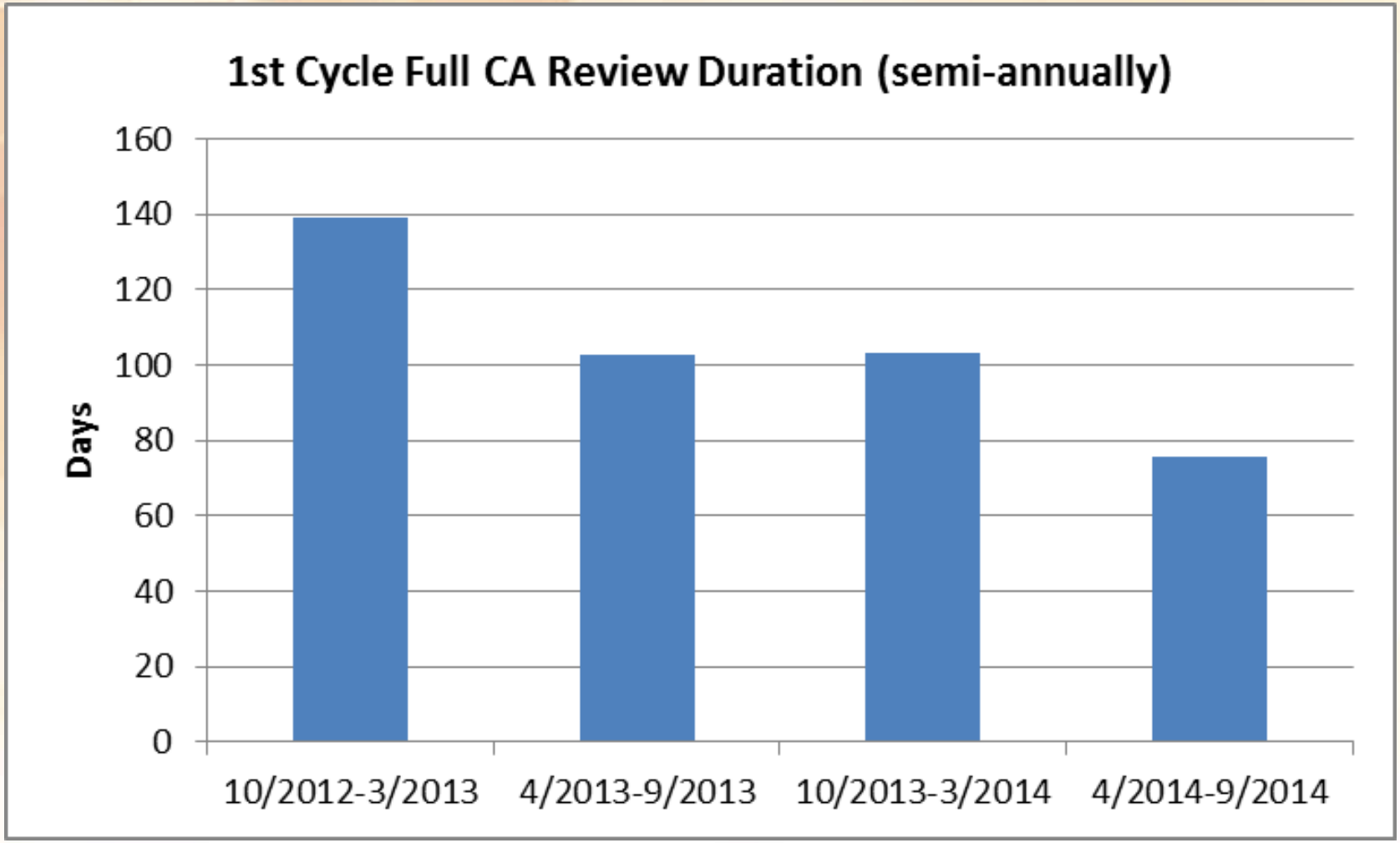
DMF Fee Payments



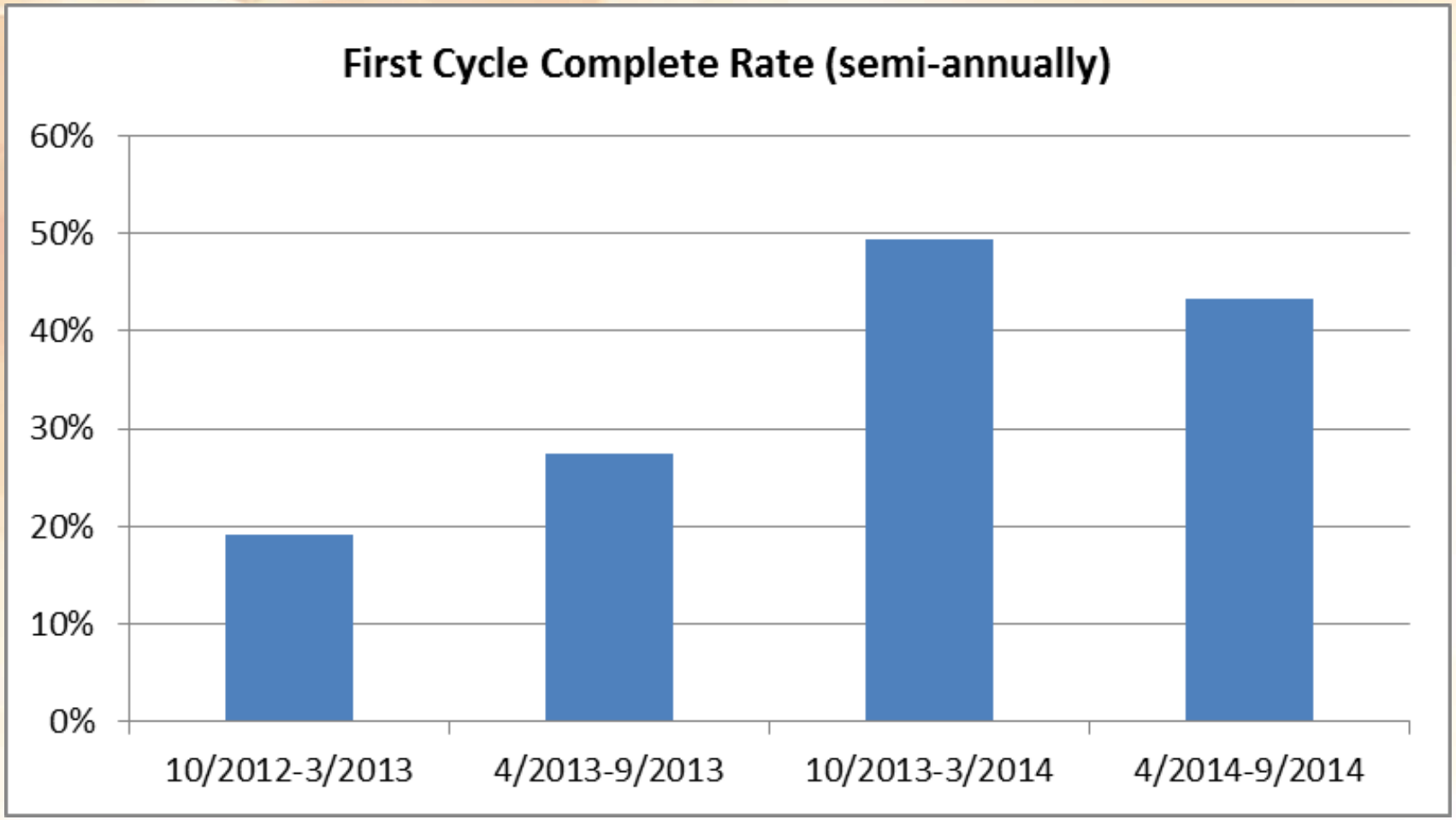
ECTD DMF Submissions



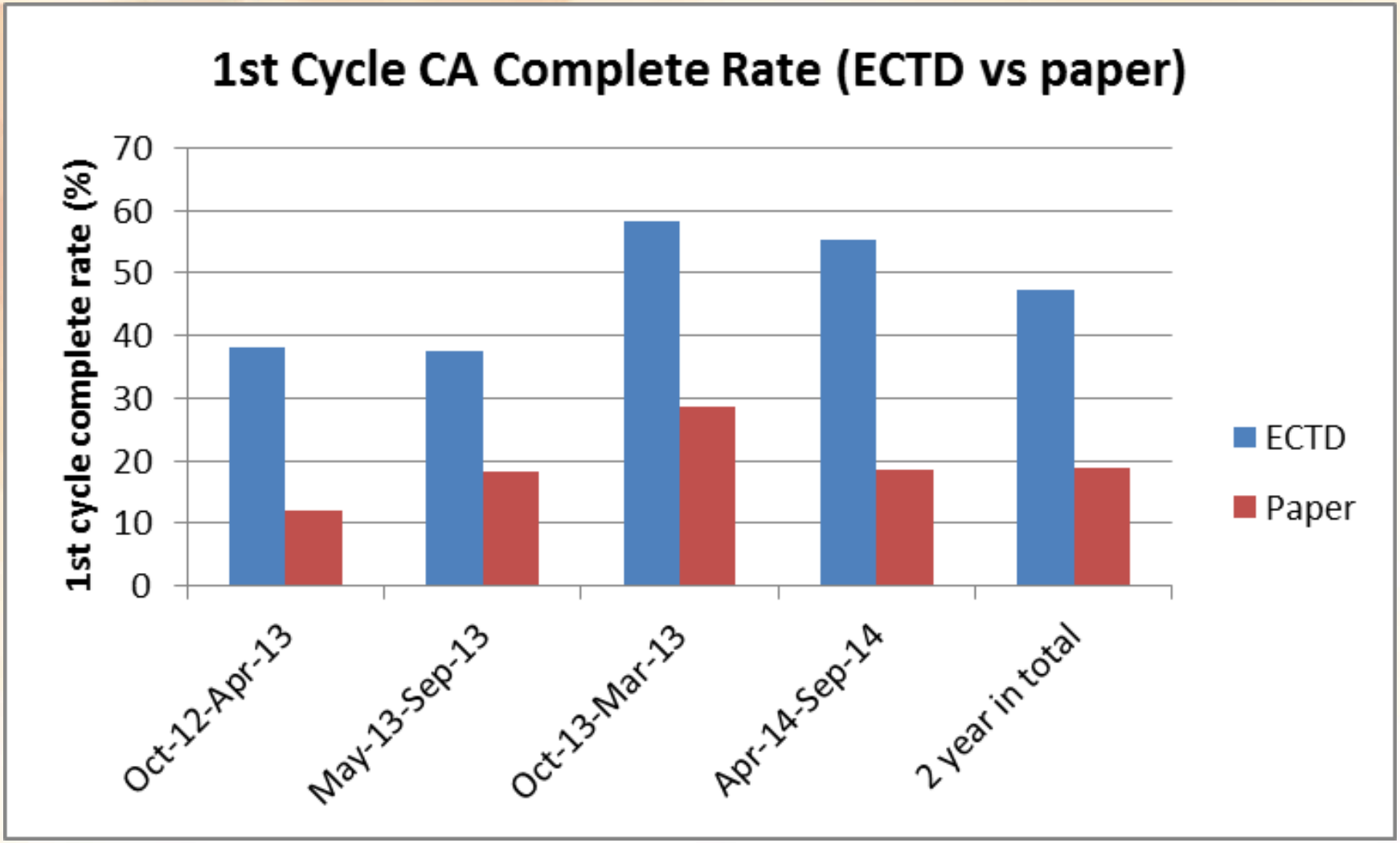
1st Cycle Full CA Review Duration



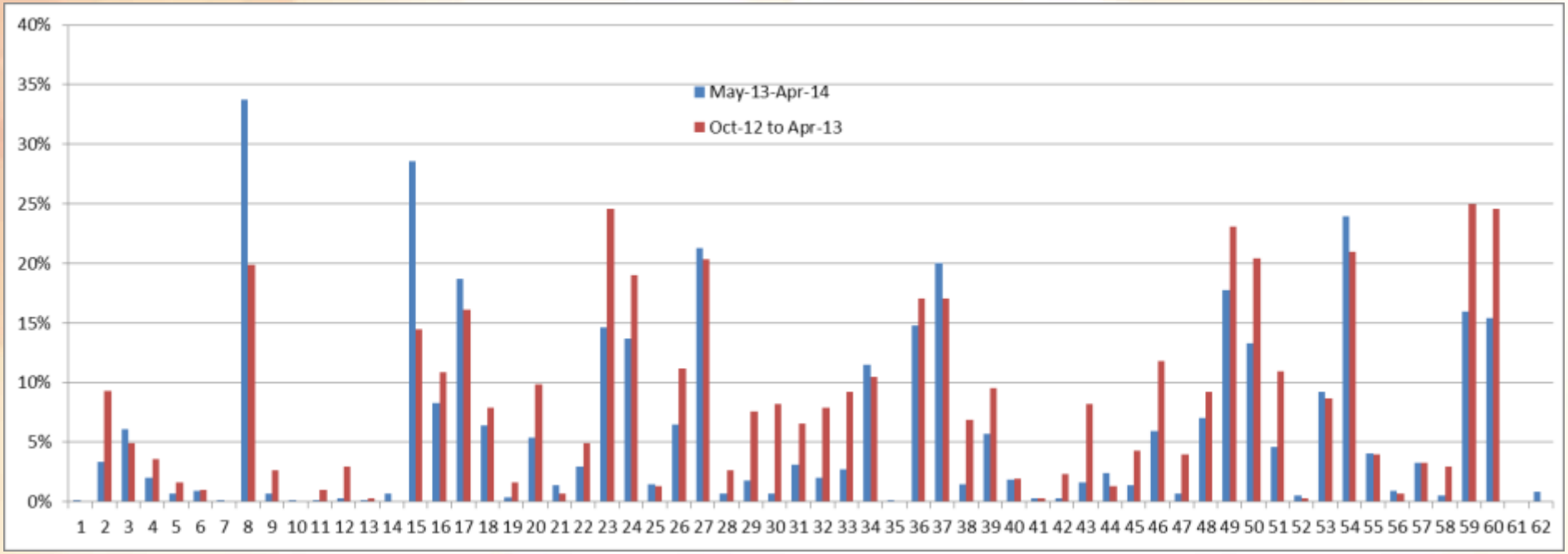
First Cycle Complete Rate (full CA)



First Cycle Complete Rate (ECTD vs paper)



First Cycle Incomplete Profile*



***Completeness Assessment of Type II Active Pharmaceutical Ingredient Drug Master Files under Generic Drug User Fee Amendment: Review Metrics and Common Incomplete Items.**
The AAPS Journal, Vol. 16, No. 5, September 2014

Avoid an RTR due to the DMF

- **Make sure the DMF is on the "Available for Reference" list prior to ANDA submission**
- **Communicate with the DMF holder so they know the ANDA submission timeframe**
- **Pay the DMF fee six-months in advance of the planned ANDA submission date**
  - **This will allow sufficient time for two cycles of CA review (if needed)**
- **Submit a high-quality DMF (preferably in eCTD format)**

Be Proactive!

- **Know if the DMF is eligible for an administrative CA**
- **Make sure the choice of starting materials is appropriately justified**
- **For older DMFs, know whether a complete update needs to be submitted….and submit ahead of payment!**
- **Make sure FDA has the current contact information (fax number, phone number and email)**
- **Respond to Incomplete letters as quickly as possible**
- **Provide notification of amendment as instructed on the fax cover sheet!**
- **Contact us with CA status requests if the DMF is not on the list or you have not received a "DMF Incomplete" communication (DMFOGD@FDA.HHS.GOV)**

Clarifications on DMF fee payment/CA

Do DMFs for manufacturing API intermediates pay GDUFA fees and undergo CAs?

No, only the DMF for the finished API is required to pay the fee and be "Available for Reference".

Note that if a DMF is referenced for an intermediate by the API DMF, as part of the CA we do check that it is filed and in active status.

Clarifications (cont'd)

Can/When does a mixture of components qualify as an API?

When the active component is unstable and cannot be shipped on its own a DMF for a mixture (e.g. API plus an excipient) can qualify as the API under GDUFA. We ask that a justification be submitted to the DMF when this claim is made. Note that these situations also have important facility fee implications.

Clarifications (cont'd)

What is the stability data requirement to pass the CA? Do the provisions of the new stability guidance apply?

The guidance requirements apply to the full scientific review. To pass the CA the firm needs to demonstrate that stability studies have started (i.e. one batch with a time point beyond initial).

Clarifications (cont'd)

The CA requires that a DMF be for a single API produced by a single manufacturing process. What constitutes a single process?

Clarifications (cont'd)

DMF should be limited to one process although multiple manufacturing sites for a single drug process is permitted when the same process is utilized in each of those sites.

Certain process alternatives/changes may be permissible with sufficient supportive information provided. e.g.:

- **Validated reprocess/rework procedures**
- **Micronization leading to different particle sizes**
- **Addition of a stabilizing antioxidant for stability purpose**
- **Alternate crystallization procedure to produce a different polymorph**
- **Minor process variation that is the same chemical transformation with little risk to the impurity profile**

Factors which are indicative of a second process

- **Significant process alternation resulting in different impurity profile and requiring different control strategy**
- **Different starting materials**
- **Different Intermediates**

API Question Based Review (QbR)

- **API QbR-QoS started from DMF Review Staff and was revised in a joint effort with ONDQA/OC in anticipating the proposed reorganization to form Office of Pharmaceutical Quality**
- **It becomes part of MaPP 5015.10 published on Nov 19, 2014.**
- **These questions should be addressed by the DMF holder and ANDA applicant when preparing the QoS for submissions.**

API Question Based Review (QbR)

- **QbR-QOS is designed with the expectation that the drug substance submissions (DMF, and ANDA) is organized in the CTD format.**
- **QOS (Module 2) follows the scope and outline of Module 3 of the submission.**
- **Information provided in response to the QbR-QOS should be consistent with the information provided in Module 3.**

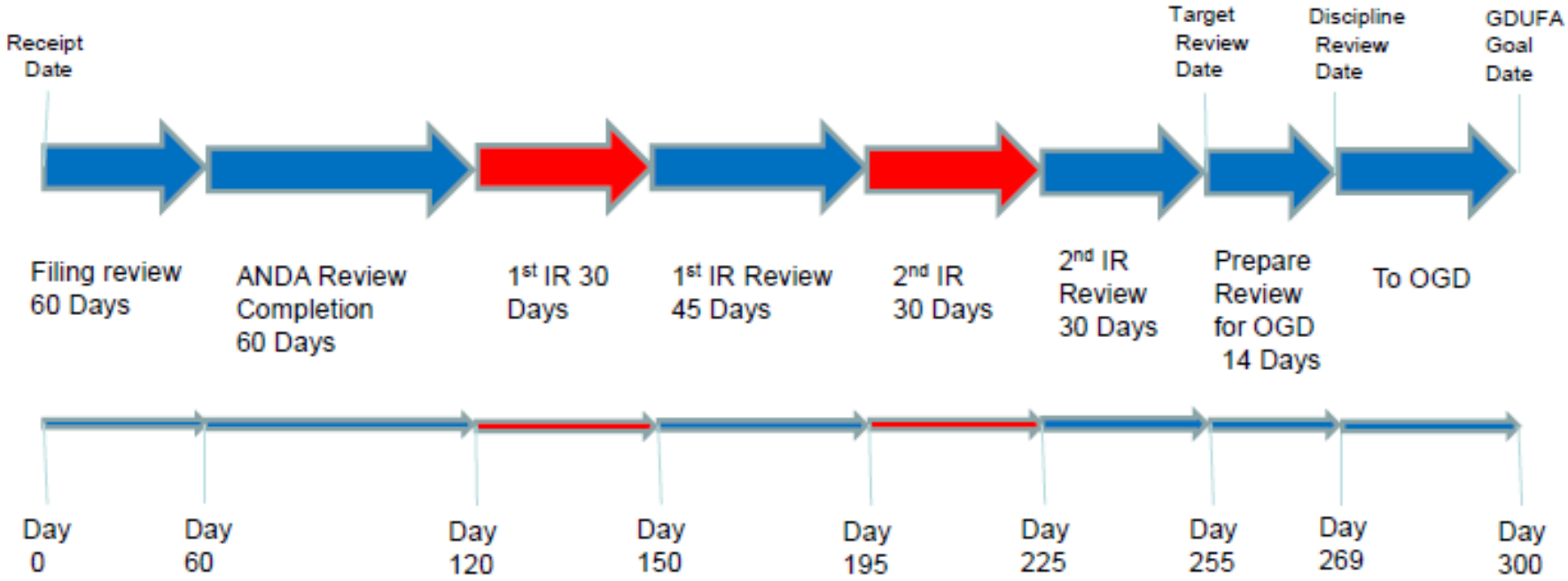
Real-Time Communication for ANDAs

- **ANDA Real-Time Communication Webinar December 5, 2014, by Susan/Glen/Robert**
  - **Real-Time Communication means communication with an ANDA applicant and an exchange of information prior to the issuance of a formal FDA action.**
  - **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.**

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.**

Original ANDA Review Timeline



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.

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‘Real Time Communication’ for API DMFs

- **‘Real-Time Communication’ for API DMFs means communication with the DMF holder in sync to ANDA Real-Time communication timeline.**

- **‘Real-Time Communication’ for API DMFs can be issued as either IR or CR letter.**

- **“*Please note that in an effort to improve the efficiency of the ANDA review process, your customer has been issued comments under “Real Time Communication” and given a 30 day timeline to respond. This process works best if the DMF holder can also respond within the 30-day timeline. Therefore please make every effort to respond to the issues raised in this letter by [date here]. If you believe you cannot respond by this date please contact the Project Manager listed below and provide an estimated timeline for your response*.”**

Acknowledgement

Dr. David Skanchy

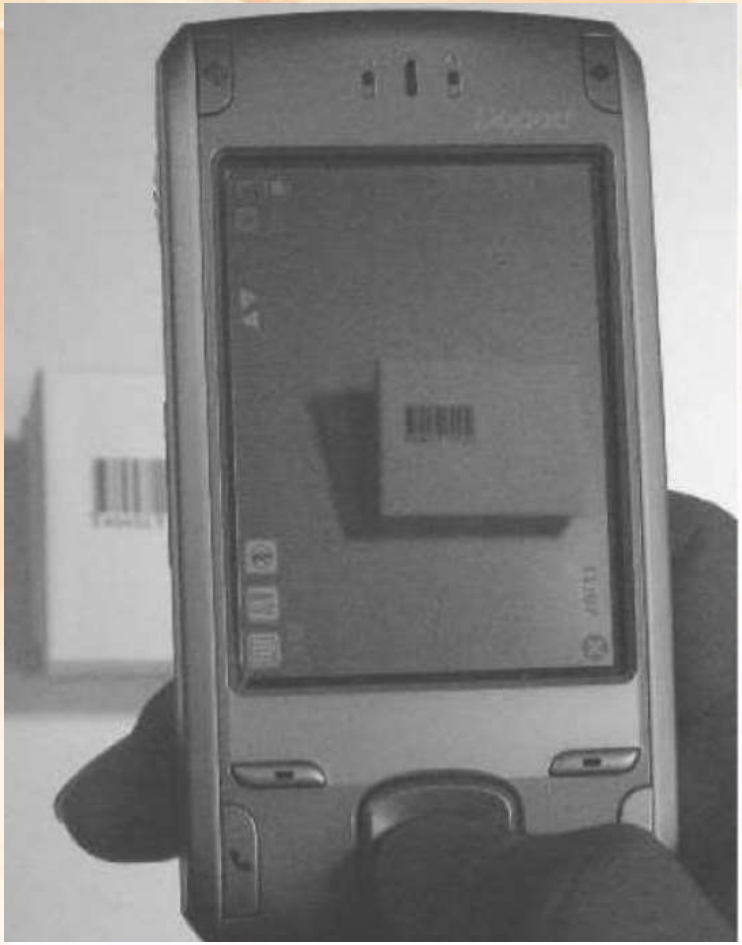
Dr. Jayani Perera

Dr. Diandian Shen

Dr. Humcha Hariprakasha

Ms. Manhong Liu

Thank you!



Questions?

Session Evaluation: surveymonkey.com/s/GDF-D1S7