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Controlled Correspondence
An Industry Perspective
CC Issues and the Origin of Q1 Q2

Association for Accessible Medicines
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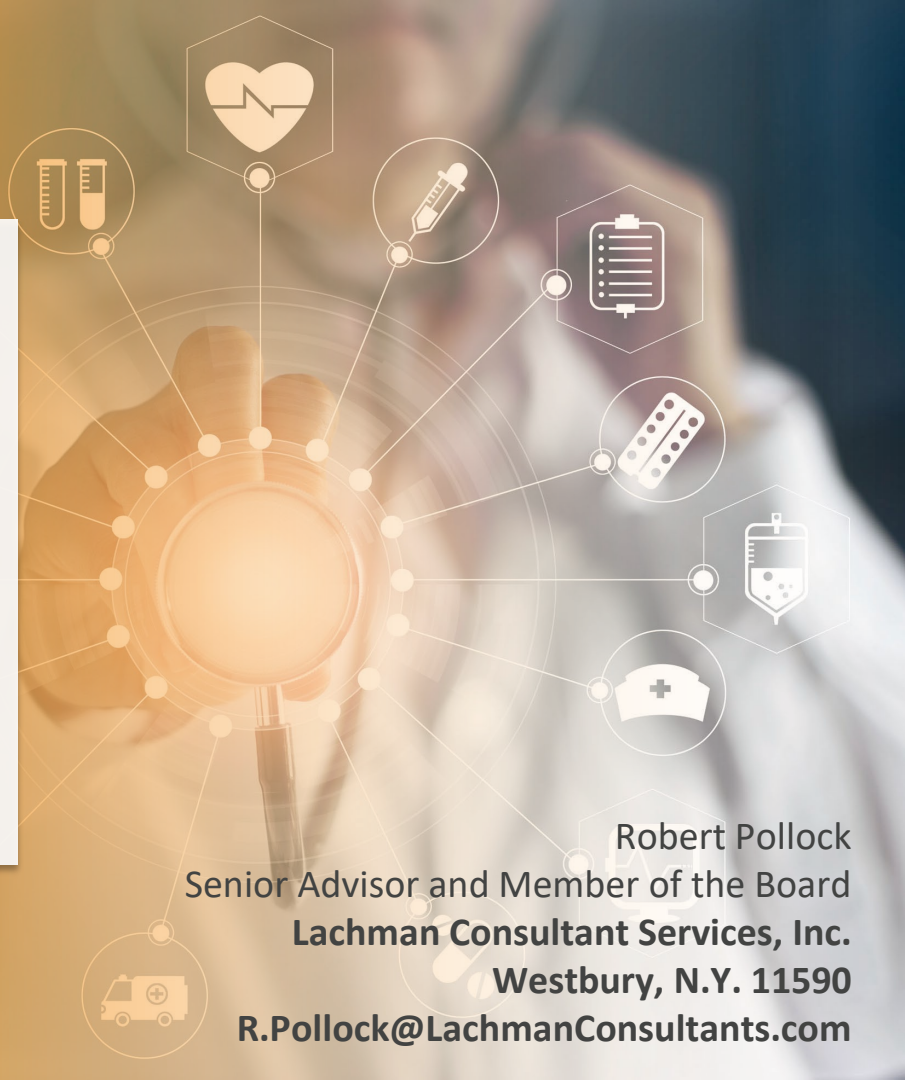

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Controlled Correspondence Submission Under GDUFA FYs 2013-2019*

Fiscal Year	Number of CC's
2013	953
2014	1087
2015	1472
2016	1883
2017	2667
2018	2933
2019	3206

* From FDA's Monthly Report of Activities of the Generic Drug Program

The Process is the Product
Why is Industry Concerned?

- FDA's ongoing challenge increased "volume"
- On its face CC process is straight forward
  - But it changes from time to time
  - Change leads to rejection of CCs – multiple submissions required causes delay.
- Lack in clarity of response or response misses mark
- Use of CC effective with single issue, less effective if the issue is complex, has multiple parts, or is cross disciplinary in nature
- Missing efficient process for follow-up

What is Working for Industry (Mostly)

- Next-Gen Portal is efficient
  - Easy to use and easy to attach documents
  - FDA responses are nicely archived in the portal
  - However, “link between Next-Gen and IID database doesn't populate the levels for common excipients. Industry mostly must manually enter the values”
  - The lack of being able to have a shared account for CCs (on FDA’s portal) a concern when employee on vacation, leaves company etc.). Request 2nd verification email address
- Response time usually within 60-days
- Can seek FDA feedback on a myriad of issues
- The CCs are timely acknowledged (versus going into a black hole)

Industry Issues with CC Responses

- Examples of frustrating responses or lack of response
  - CC question - Clarification of a specific guidance issue
    - FDA Response – “Read the guidance document”
  - Some responses do not make sense, or are like riddles
  - Withdraw of advice - Q1 Q2 advice withdrawn after 1.5 years
  - Various requests for road map to bring back discontinued sole source NDA product to market as an ANDA (BE, RLD and RS) pending well over 1 year and counting

Industry Problems with CC Responses (Cont'd)

- OGD provided Q1 Q2 advice on a product containing over 200 amino acid sequences.
- Agency rejected CC five times before accepting it for review/processing
  - The Agency identified one reason for rejecting CC. Upon resubmission of CC addressing the identified concern, it was learned that other concerns remained (resulting in multiple additional rejections after the resubmission of the initial corrected CC)

Industry Problems with CC Responses (Cont'd)

- Inconsistent messaging
  - Agency rejected CC because a previous/supporting CC was included (the supporting CC was closed out and was never accepted for review by the Agency). Based on the Agency's comments the CC was resubmitted without the supporting CC; Agency subsequently rejected the CC asking the supporting CC be included. Ultimately, the firm received final confirmation that the CC should NOT include this supporting CC; required three CC submissions as the Agency kept denying/closing out the submissions.
  - Agency confirmed that our application was not Q1/Q2 and noted that two separate CC's were required: The first to DFR for Q1/Q2 evaluation, the second to OPQ for assessment of proposed quantity of an excipient. Upon resubmission of the two CC's, the CC submitted to OPQ was **rejected**. The reason for rejection was the formulation would have to be accepted as Q1/Q2 by DFR before a second CC could be submitted to OPQ (this was not communicated clearly from the original communication)

Industry Problems with CC Responses (Cont'd)

- Unclear direction
  - Submitted a CC to confirm adequacy of threshold analysis of device and that no additional requirements for human factor studies would be required. Agency rejected CC and noted that RLD and test samples must first be submitted to the Agency, before the CC can be accepted. The Agency then provided individual contact information as to where these samples should be sent but information was originally not clear. Had additional direction/guidance been provided it would have resulted in a timelier response

Proposed Suggestions for Improvement

- Have FDA provide Q&A document on FAQs, FEPs(cut down on Volume of CCs)
- Have industry make certain their CC questions are clear and concise
  - Is the right question being asked?
- Develop an FDA/Industry telephone contact outreach process when lack of clarity on CC request or response
- More robust person-to-person feed back loop

Brief History of Q1 Q2

- DESI Program – mid 70's – ANDAs acceptable for DESI effective drugs.
  - Products for injection, topical use, ophthalmic and otic products typically could have different formulations.
- Passage of Hatch-Waxman 1984
  - DESI Products not much change
  - Post-62 products were originally treated same as DESI
- 1989 proposed rule placed limitations (21 CFR 314.94(a)(9)) on some dosage forms relative to changes that could be made to inactive ingredients from RLD.
- In the mid 90s discussions relative to ophthalmic and otic products became more contentious with new drugs staff leading to additional limits.

Brief History of Q1 Q2 (Cont'd)

- Lack of reliable and robust in vivo methods(BE study with clinical endpoints)for establishing BE for certain products questioned (including non-systemically absorbed oral products). FDA shifted to develop BE guidance using more sensitive in vitro methods, Q1 Q2 requirements and similar physicochemical parameters
  - Acyclovir cream and ointment – no competition for years – BE studies with clinical endpoints not feasible
    - First approval for ointment in 2013, cream in 2019
  - Cyclosporine ophthalmic emulsion BE guidance changed 3 times
    - Still no AP or TA!

Brief History of Q1 Q2 (Cont'd)

- Process became the "Price is Right" game
  - With guesses too high or too low, OGD would give directional guidance.
  - That ended sometime in in early 2015. (concern re proprietary information?)
- The current problem - how do you verify product as Q1 Q2?
- Today Q1 Q2 elicit the most frustrating CC issues from firms polled

THANK YOU!

Review of Next Steps…

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