Current Topics in FDA Reviews and Inspections of PET Drug Manufacturers

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It has been quite a journey with a lot of turns & twists as we have navigated our way through ANDA’s and NDA submissions, inspections, amendments, etc.
Performed an informal survey with industry members

- Found surprising uniformity in responses.
- Not surprisingly, this has been an educational experience for both the manufacturers and Agency inspectors.
- Overall desire to work with the Agency to improve the process on both sides... more on that to come.
1. Do you have any more PAI’s expected for 2015?

   a) Most indicated that all or almost of their sites had their Pre Approval Inspections completed!
2. What on average is the notification that you have received when you have been informed about an upcoming PAI.

a) Notifications have been as far out as 2 weeks and as short as 1 hour notice.

b) The short notice has been problematic.
   - operational hours typically worked
   - Staffing levels
   - Need to bring in resources to support the audit/operations
   - Multiple sites inspections in the same region for the same manufacturer
Results

3. In general have the inspectors had a good understanding of 21 CFR Part 212 during your PAI’s?

   a) Overall yes, they have a good understanding, and most have been involved in at least a couple of inspections.
   b) On the PAI’s there have been inspectors in training which has been good for them to see the sites.
   c) In the areas where 212 is not very specific, there has been variability in the inspectors interpretation.
      - Been problematic in writing responses when other sites within the organization have not had the same inspection result.
4. What has been your experience in responding to either 483’s or general observations from your PAI’s?
   a) Overall there has not been a lot of feedback from the Agency
      • Since this is relatively new to us it would be helpful to have feedback.
   b) Questions regarding 483’s
      • Agency has been responsive but the answers are not always clear.
   c) Have inspector's reviewed previous inspections
      a) Yes, majority of inspectors had reviewed previous PAI results for the sites within that company.
5. What has been your experience in response time from the FDA for amendments while your ANDA’s have been under review – timely or have taken longer than expected?

a) Overall, Amendment review/response has taken longer than expected
   • CBE 30’s submitted but no response in that time frame
   • Amendment submitted and responses have taken months before being received

b) Updates on review of ANDA’s also have taken longer to receive than anticipated.

c) This also applied to changes to facilities – closures/changes.
Results

6. Do you feel that more guidance documents would be beneficial for both the industry and inspectors?

1. PET Drug Applications - Content and Format for NDAs and ANDAs_2011 (PDF - 429KB)
2. PET Drug Applications - Content and Format for NDAs and ANDAs: Attachment I: Sample formats for chemistry, manufacturing, and controls (CMC) sections_2011 (PDF - 614KB)
3. Sample formats for Form FDA 356h_2011 (PDF - 601KB)
4. Positron Emission Tomography (PET) Drug SPL
5. Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PDF - 156KB)
6. FDA Oversight of PET Drug Products -- Questions and Answers (PDF - 499KB)
7. Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs (PDF - 369KB)
8. FDA Oversight of PET Drug Products -- Questions and Answers (PDF - 499KB)
Results

a) **Yes**, in the areas that Part 212 is not specific additional guidance documents would be helpful to reduce the variation we have seen with inspections.

a) Would help drive overall compliance and standardized practices.
Results

7. What areas of compliance do you feel would benefit most from having a more standardized industry approach?

a) How to complete an investigation (Non conformance, OOS)?

b) Method/Equipment validation procedures?

c) Operator qualification?
What are your concerns as we go from submitting our first ANDA’s, NDA’s to a more mature industry?

Cost of compliance?
How do we make PET easier for Pharma companies to work with us?
Part 11 compliance?
Educating new employees to a more standardized qualification process?
It has been a quite a ride so far!

To continue to be successful will require that as an industry we become more unified in our approach to compliance and quality. Continued work with the FDA as well as with Industry organizations will be key to ensuring we are all winners and PET continues to grow as a powerful diagnostic tool!
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Thank You

Special Thanks to the industry members who helped with this talk!