Regulatory Update – May 2013

SQA just completed another very successful meeting. Below is a high level summary of the various regulatory updates. Kudos to both CDRH and CVM for being very well represented, but CDER reps from the GLP BIMO program were absent for the second year in a row. Jean Toth-Allen presented a great clinical update. Luckily, Francisca Liem from EPA was able to make it this year. The closing session was a panel discussion of questions submitted prior to the meeting. Sitting on the panel were Francisca Liem – EPA; Chrissy Cochran – FDA; Jean Toth-Allen – FDA; Vernon Toelle – FDA. Vernon and Jean are the co-chairs of the FDA GLP Modernization working group.

EPA

EPA will undergo furloughs through September due to the budget constraints, just like the rest of the government. In 2012, EPA conducted 99 facility inspections and 245 data audits. The increase in inspections is due to the new desk-top approach. About 66% of the inspections resulted in no findings. Field sites had the highest compliance rate at 100%, while Product Chemistry, Biotech, Antimicrobial and Insect Efficacy and Toxicology labs had less than a 50% "no findings" rate. As in the past, Subparts B, G, and J resulted in the majority of findings. Findings were about the same as in years past. However, a couple "new" findings were noted:

- Inadequate separation of Study Director and Management
- Data was generated at a facility not referenced in the final report
- Copies were not true and exact copies
- Historical SOPs missing from the archives
- Archives accessible to unauthorized personnel

EPA rejected 22 studies in 2012, with 15 being Product Chemistry and 7 Insect Efficacy. Three studies at one lab were voluntarily withdrawn and replaced, while 3 registrations were voluntarily cancelled and 1 suspended. Just last month another 8 studies were rejected. The reasons for rejection include:

- No raw data
- No characterization data
- Non-independence of QA
- FSR did not reflect raw data
- No accountability records for the test substance

In addition to the rejections, one Sponsor was fined $28,000 for 4 studies.

Frances also presented two GLP Alerts:

- Only individuals with primary intellectual responsibility (SDs) should be listed as authors
- Reports need to include the name and address of all performing laboratories along with the performing labs internal project number
- Any published document referenced in the final report must contain a complete reference

FDA – General

As mentioned earlier, CDRH and CVM had a great presence at the meeting. Chrissy Cochran from CDRH provided an update of inspection observations, with Vernon Toelle adding some statistics. FDA conducted 60 total GLP inspections last year with 4 being CBER directed, 36 from CDER, 11 from CDRH, and 9 from CVM. CFSAN is apparently undergoing organizational changes and conducted no inspections. Of those, that have been classified, 56% were NAI, 41% VAI, and 3% OAI. Some of the observations include:

- No records of equipment calibration
- Personnel clothing not appropriate – lab coat was too short resulting in street clothes dragging across samples
- Protocol amendments not signed by the SD

- Study Director did not review the final report and did not even know what was stated in the final report
- No QA statements
- QA audited studies they had actually worked on
- QA did not assure deviations were reported to the Study Director

There is not a "single voice" for FDA GLP issues. All inquiries are handled through the working group. Current GLP trends/issues include:

- Testing Facility, Study Directors, and QA in small facilities
- Test Article Characterization
- Sponsor Responsibilities
- Multi-site study issues
- Portions of studies that are not conducted in compliance with GLP

The GLP inspectional database is hopefully going to be updated by the end of the year. ORA has an inspectional database, listing all closed ORA inspections. However, this database does not include GLP studies, so it is critical that the GLP database be updated.

GLP Modernization

The document is complete and under internal review. However, it is the government and an agency document is not easily moved through the system. The comments from the ANPRM have been considered by the working group and many have been addressed. Hopefully the PR notice will be issued by the end of the year. They have to conduct the financial assessment and asked how many businesses that would be impacted are considered "small businesses" of under 500 employees. There is also a philosophy change in writing the NPRMs.

The GLP working group consists of representatives from each center; NCTR, ORA, and Office of the Chief Council. USDA, EPA and NIH have also been consulted in the modernization.

The document harmonizes with OECD and EPA to the extent possible, but there will be changes. From everything I have heard, the new GLPs will keep all the flexibility we have now plus add some.

It appears that even with modern technology, the signed pathology report is still going to be the "raw data", and the pathologists exemption will stay intact.

CVM

Enforcement strategies – FDA will be focusing on compounding pharmacies, FSMA implementation and FDASIA implementation. No current FDA employees will be furloughed, as the agency put off hiring new inspectors for the Food Safety program.

There is no regulation for Animal Health devices. This is a concern of CVM, as there may be some companies making devices for veterinary use and "slipping" them into the human market.

CDRH

Chrissy Cochran gave an outstanding presentation on CDRH. CDRH conducted 305 total inspections last year, with 11 being GLP. Of the 11 GLP inspections, 10 were in the US and 1 was International. Items of interest include:

- FDA has no problem with the Study Director being located at the Sponsor as long as the Sponsor has the appropriate infrastructure. There must be clear lines of communication and the SD must be trained on any SOPs at the testing facility that they may function under. It is critical that the Sponsor have the "GLP triangle" adequately identified (Management, SD, QA). If the Sponsor

does not have the appropriate GLP infrastructure, keep the SD at the CRO and have the Sponsor become involved where necessary (surgery, etc.), and just make sure everything is well documented and transparent.

- Final Reports must include the name of all scientists involved in the study, and these individual scientists (i.e. surgeons) must write reports.
- CDRH reviewers are looking closer at methods and protocols to make sure they have been updated to reflect current technology.
- 510k's are expected to be conducted in compliance with GLPs.
- CDRH highly recommends that device companies follow the Cardiovascular guidance document for all studies where it may be applicable.
- Studies recently submitted and found to be deficient include one where the IDE study was stopped and restarted. The agency questioned the data and found out over 100 animals were included in the IACUC protocol but only 8 were reported in the FSR
- Another study found that the greyhounds used on study were not from a USDA vendor. These animals were traced through the Greyhound national registry by the tattoos.
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CDRH Cadiovascular Guidance document

- Companies need to follow the Cardiovascular Guidance document.
- This document was issued because companies were cherry picking data, there was inadequate assessment of data, data were not being reported, pathology was not completed on all animals, breeds were not being identified, there was incomplete information on entrance criteria, no records for animals with AEs or found dead, and there was no way to determine how many animals were used in a study

OTHER PRESENTATIONS – there were a lot of quality presentations – I will highlight a few

GMOs

We were treated to an excellent presentation by Kanthasamy Karunanandaa, PhD, from Monsanto on Bioinformatics Data generated to Support registration of Plant Biotechnology Products. This session was extremely education as he stepped through the process of identifying potential allergens in transgenic crops. Although companies are voluntarily submitting this information to FDA CFSAN, it is not required and has not been GLP. However, it appears that the EU is requiring these types of studies to be GLP. When claiming compliance to GLPs, it appears (from my perspective and since this information is already being sent to FDA), that the compliance claim would have to be with FDA GLPs as the issue is entirely food safety.

GMPs

There were two great presentations given by Dr. Jim McCormack and Linda Palagi-Lynn on GMP applicability to GLP studies. Bottom line is that GMPs do not apply and technically cannot be adhered to as they are only for manufactured finished product. Companies are required to perform characterization on test articles under GLP. If not GLP, a complete description of what quality standards were used is needed. If a company cites GMP, then FDA can hold you to GMP which is really not applicable. The clinical trials material for Phase 1-3 are not full GMP, but are based on guidance documents. Hopefully this discussion will continue at future meeting and possibly the PRCSQA chapter meeting in November.

History of GLPs and recent citations

Another outstanding set of presentations. Dr. McCormack rehashed the issues and studies that lead up to the GLPs, while Barbara Munch detailed recent warning letters and 483's tied back to the regulations and how some of the early problems are still being seen in inspections

GLP World Cup

I may be a bit biased as part of the team, but the World Cup was a lot of fun. Twelve teams competed in the GLP quiz show. Most comments afterward indicated that the sessions were very informative. Hopefully we can continue this next year!