Spring Educational Meeting Minutes

Location: The Key Bridge Marriott · Arlington, Virginia (Georgetown Ballroom)

Date: Thursday, April 19th, 2018

Time: 8:00am – 4:30pm EST

Attendees: (See Attachment 5)

Agenda Topic	Presenter
Welcome, Introductions, Reading of Meeting Guidelines & Meeting Logistics	Sharon Starowicz

Sharon called the meeting to order and welcomed attendees. Sharon read the meeting guidelines verbatim and reviewed the meeting and dinner logistics, and attendees (both OSMA members and guests) introduced themselves. Sharon introduced Lisa Boyle to present the guest speakers.

DOD Overview	Mark Melkerson

QUESTIONS

At the last OSMA Fall meeting, Jonathan Peck discussed the ORCA project. Has FDA considered how ORCA might play into the Alternative 510k Pathway?
The intent is to follow the EU approach, with meeting the Essential Principles and trying to work the Essential Principles into the existing regulatory framework. The goal is to harmonize. The first step is to review data for well-established devices. FDA recognizes how difficult it is to obtain a predicate device for substantial equivalency comparison and testing. The goal is to perform comparison testing with your device to that of established principles and if your test data has an outlier, then justification would be required to support the S&E of the device. FDA's goal is to publish the data. The 510(k) alternative pathway program would be the approach to develop and establish performance criteria data.

What is the status?
The cervical interbody fusion cage paper will be published. Now, concentrating on pedicle screws, lumbar systems, anterior plating systems and cervical pedicle screw systems. FDA has started aggregating the data, beginning with established devices. FDA may publish but only subsets of the data. It is important to have a sufficient sample size to make an appropriate analysis.

Is there a plan to expand?
Alternative 510(k) pathway program is office wide; it is not limited to just orthopedics. The Orthopedics Branch was considered the test case. The publication was the first step to see if it could be done. It has been helpful for internal reviewers to have benchmark data. However, this is by no means a quick process.

Is there a potential to leverage the data?
The thought process originally came out of discussions from IMDRF. How much external organizations utilize this data is up to them.

TPLC Future Direction & FDA Strategic Priorities	CAPT Raquel Peat, PhD, MPH

1,800 dedicated CDRH staff members
190,000 products
18,000 device manufacturers
21,000 worldwide device manufactures

Office of Product Evaluation and Quality (OPEQ) is considered the "Super Office".
The goal of TPLC is to provide a collaborative path forward by striving for internal collaboration across premarket, surveillance and compliance activities.

TPLC efforts have been in discussions for more than 15 years and it started with drugs and IVD.

- 2002 IVD
- 2012 reorg and included radiological devices
- 2016 more focus on TPLC

It has been challenging to change the philosophy and it has taken years. The intent is to merge offices together to provide a shared responsibility. The approval process will be team based (8 to 12 review staff) and will provide an integrated approach. There will be a lot of new positions with TPLC activities. The intent is to prevent the review staff from being isolated (in a silo approach) but rather provide a cross functional approach to the review and approval of devices.

Office of Health Technology 6 (OHT6)
Office Director – Raquel Peat
Deputy office director – Mark Melkerson
Chief Medical Officer – Vincent Devlin

The OSMA membership is encouraged to reach out to the leadership team with any thoughts or inputs related to the re-organization. CDRH welcomes input.

QUESTIONS

Regarding the TPLC and OPEQ initiatives, when I submit a 510K what changes will I see as industry?
When you submit a submission, all of the staff will be in one particular office. You will know your point of contact within the office and feedback should be provided in a timely manner.

Will the Clinical post approval studies, go to the same team? Yes.

What does the premarket interaction or discussion look like for a review of a clinical report and/or an annual report?
The team will work closely together with that particular study. The goal is regardless of the application, it'll be reviewed within the Office and further consultation outside the team will not be required.

Regarding the 2018-2020 Strategic Priorities for patient input and patient preference initiatives, will there be a collaborative effort amongst NEST and MDIC communities?
Right now, it'll be under MDIC. There are further discussions regarding if it'll be MDIC or its own entity.

The Safety Action Plan will provide more information regarding the collaborative communities.

Where does FDA get the approval for the reorg and what is the timeline for announcing staff names for the lower levels of the organizational chart?
Within the organization, it has to go through department clearances. It has to go through a committee in Congress. Approval should be provided by this year. Not sure if it requires approval by the House or the Senate. Likely the House.

Since the post market side will be performing premarket reviews due to the re-org, is there an expectation that different questions will be forthcoming?
Yes, you should anticipate different questions due to the integration effort. As we mature into the OPEQ, a lot more questions will be likely asked in regard to quality and S&E of devices. In the post market arena, questions will differ should there be a systemic issue with quality. It'll help utilize the expertise within the industry. FDA is still heavily invested in the least burdensome approach but at the same time, working to improve transparency.

How will the Office of Clinical Evidence operate?
There will be a touch point in the OHT and OCEA staff and it will be a team-based approach. If there is RWE, a lot of the info doesn't need to be in a clinical study. We are collaborating now and it'll extend within the new office. This will not have a big effect on industry. Something more internally, consistent in the approach amongst groups. Each team will be able to address each asks.

Is there a new pilot program described as a least burdensome flag for 510k review – are you familiar with that?
There is a program that they are trying to do. The program gives you 10 days to contact the next level up to determine if a request is truly least burdensome. If you have talked to the reviewer, the Branch Chief (who signs off on the additional information request by email/letter) then you could reach out to Dr. Devlin, Mark Melkerson or Kate Kavlock. Stay tuned for more information around this program.

ODE Update/FDARA — Constance Soves, PhD

In line with FDARA, FDA's proposed Class I accessories list should be published in August 2018. FDA's intention is not to up class. There are other mechanisms to re-classify. There are some recommendations within the GD regarding submission expectations. The sponsor should state in the cover letter the accessory classification request and identify the risk profile. Looking forward to working in collaboration with OSMA on this effort.

QUESTIONS

Out of curiosity, could a trade association submit a retrospective reclassification effort or does this need to come directly from the device manufacturer?
The statue says manufacturer. However, there has been a lot of discussions internally on this option. At this time, it has to be manufacturer. Not sure if that will change at this time.

What about new product codes?
FDA understands the complications. We do not have any expectation or intention to create new product codes. If it makes sense, we could create one, if needed. At this time, no intention to create a new product code for class 2 non-implant accessories.

ELP Program used to have quarterly calls for proposals, has that changed? When is the next call?
There have been some funding issues that have caused the program to be reevaluated and reassessed. Money is tight. Those that are already established with sponsors, will be funded. May not be another call this year. The program just received their budget and are in the process of assessment. The staff really appreciates the opportunity to participate in ELP.

Biocompatibility Guidance — Jennifer Goode

QUESTIONS

If a proposed 510(k) device contains color additives which are not CFR listed, what information is needed to support use of the color additives?
See FDA's February 12, 2016 webinar (slides, audio presentation and transcript – includes 1 hour Q&A)
https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm484421.htm

Biocompatibility of Orthopedic Devices — Aprajita Garg

QUESTIONS

For new a 510(k) which includes a device with a new material (new for FDA), there is no predicate cleared with FDA. However, there are biocompatibility tests for the material itself and this testing shows that the material itself is biocompatible according to ISO 10993 and CDRH's 2016 Biocompatibility Guidance. Is biocompatibility testing needed for the final product? Or is it sufficient to evaluate the manufacturing steps, e.g., do chemical analysis with a toxicological risk assessment?

- For truly novel materials, endpoints beyond those identified in ISO 10993-1 may be needed. (See "novel" in CDRH's 2016 Biocomp Guidance.)
- Processing of new materials may result in different extractables and or surface properties that could impact the biological response.
- Often for new materials, biological testing alone or in conjunction with chemical characterization is recommended unless otherwise justified (e.g., data from the literature to demonstrate that processing is unlikely to impact chemistry or surface properties).

For a new 510(k) with components made from medical grade stainless steel (according to recognized standards like ISO7153-1), do the stainless steel components need to be tested for biocompatibility? Or is it sufficient to:
(1) State that the material itself is biocompatible, and
(2) Conduct a chemical analysis with a toxicological risk assessment to evaluate concerns with the manufacturing aids?

Are there any biocompatibility tests which cannot be covered with a risk assessment (e.g. material mediated pyrogenicity)?

- For stainless steel devices/components, a description of the manufacturing materials with a literature review to address toxicity potential may be sufficient. Analytical extractables testing with a traditional toxicological risk assessment often is not needed.
- The presence of a passivation process during manufacturing can address biocompatibility risk for surface residues from chemicals used prior to the passivation process.

If you have device that has polar and non-polar extractions on a final finished form (FFF) device, do you do it again if the material is not found (do you need to do additional measures if they don't come out as extracted)?
If a biocompatibility test is done on an extract, the solvents used are just nonpolar/polar. Those solvents are not amendable. When hexane is used, it is more aggressive. The point is that hexane may be more aggressive, but the solvents used can't be used for analytical chemistry. You won't have a direct comparison. You need to use solvents that can work with analytical chemistry.
We don't have a more physiological solvent to be used. If you do analysis and get something with hexane, decide if the level is an issue. If it is, you will need to do something to address it and assess the risk. Hopefully FDA will be reasonable to accept it.

Often the worst case final finished form device for testing is not equivalent to a final finished form device on the market.
If you are doing EO sterilized device that is worst case FFF, it is good, but it depends on the device type. Polymer may be not so great. Depends on the device. Worst case conditions need to be considered for non-orthopedic devices where they are commonly sterilized before use and can be re-sterilized up to 2 times for a procedure, if not used. For one time sterilized product (and it isn't going to be resterilized), there could be variability in the manufacturing, batch to batch biocompatibility would not be expected but if the chemistry is sensitive, separate testing across batches to demonstrate that chemistry variability would not be expected. Chemistry needs to demonstrate equivalence.

Patient indirect contact vs user indirect contact?
Some devices are intended to treat the patient, and some are intended to protect the clinician. Some of the masks that are reviewed are actually not for a patient, but still need to demonstrate biocompatibility. The next version of 10993 tried to address the difference between "body contact" and "patient contact". It should be done before the end of this year.

Master file for PEEK for worst case, defining worst case process and have that on file with FDA, so any submission could point to that information and rationale for why those materials would fall into worst case, would FDA consider this vs. having every submission contain the info?
Depends on who is providing the Master File and at what stage. The concern is, is it a PEEK part and do we understand it. We don't have any requirements on who submits a Master File, whether it be a Company or an Organization. As long as the master file includes a letter of reference, it is an acceptable process for us. CDRH has no requirements for a Master File. Our Q-submission process could be used to have discussions on what is appropriate for rationales. The sponsor could have a pre-submittal meeting to review the Master File prior to submission. That would be helpful.

FFF – if something is polymerizing, FFF isn't going to be the final product. It's going to be when its combined and put together in the body. It goes back to pyrogenicity; only seen it twice in orthopedics. It is how you define FFF, if the constitutes are not put together until time of use.

Endotoxin Update — Elizabeth Gonzalez

OSMA comment: Two years ago, the membership was very burdened by the new testing requirements and the cumbersome requests for additional information. In response, OSMA created a working group to collaborate with FDA and ST72. The outcome has been very rewarding and without reservation, the membership is very appreciable of the collaboration efforts to date. Thank you.

QUESTIONS

As an alternative for batch testing, a method has been proposed to use process control procedures. This includes the assessment of out of specification measurements. One of the previous questions from FDA was how to contain and address product manufactured in a process with an out of specification point. A total recall of released product could negatively impact patients due to lack of device availability. We would contend that an out of specification measurement can and will happen in any process. If this happens and the firm has procedures to address this situation, will this be sufficient for continued processing if documented and justified?
FDA agrees that the sponsor should have a plan for dealing with out of specification results and that the response should be risk-based and not limited to recall.

Can it be confirmed that, as is now stated in the new ST72 standard, that the testing required is on product contained in a single package and not the full systems for large implant products?
The endotoxin limit is being applied to a sterile barrier system

Are accessories to the surgical procedure included in those recommended for endotoxin testing according to ST72? For example, jigs, blades, pointers, trials, etc. Materials usually found in a loaner tool set.

- Surgical accessory devices do not remain in the body following the procedure
- Endotoxin testing is therefore not needed for these devices

Since any surgical implantation results in local inflammation, the risk of inflammation is known for this effect and is well studied. Is it acceptable that for orthopedic implants, localized inflammation should be listed as a known risk but not one associated with endotoxin if below a tested limit?
FDA agrees that if the device meets FDA-recognized endotoxin limits(typically 20 EU/device*) this is sufficient to address the concern regarding endotoxin-mediated inflammation
* Could be lower if the device is in contact with cerebrospinal fluid or is an ophthalmic device

Are temporary implants (e.g., mandible extractors, external fixation pins) able to be removed from endotoxin testing if resulting risk assessments conclude endotoxin is not a risk?

- FDA does not believe that the time an implant is in contact with the patient should be the deciding factor for whether or not the device should be non-pyrogenic.
- A pyrogenic response could be caused either by a contaminated device in contact with the patient for 24 hours or by one that is in contact for 30 days.

- A risk based assessment could be used to determine that an alternative to batch testing may be appropriate.

For products such as bone cement where there is a powder and liquid component but each cannot be tested individually, these are currently mixed with sterile non-pyrogenic water made into testable coupons and tested as per the standard for releasing lots. Is this an acceptable practice?

- FDA recommends that the LAL testing be performed on the final finished device, which should include the same components, mixing, and handling that would be used in the final product.
- In the case of the bone cement, creating testable coupons allows the final form of the device to be tested for endotoxin.

For biocompatibility testing, FDA will ask questions if mixed but not yet polarized and the polymerization occurs after it is placed in the body. Polymerization step is when the toxic components may occur. If polymerized and degrades, could come out in degradation.
FDA will ask the sponsor to address what they expect to happen chemically during degradation.

OSMA Accessories TF Lunch with FDA	Sharon Starowicz

Sharon reviewed the presentation slides.

Mark: This is not specific to just Orthopedics. The broach is sized to fit the implant. How do you address risk other than having some level of design controls? The risk of instrument failure must be taken into account. Manual surgical devices tend to be devices that are not device specific.

One concern, if they are in Class I but designed to be used specifically with an implant system, the concern would be over design controls. Class I, subject to design controls? FDA is doing a look back across all of the device areas, not just orthopedics. This initiative originated with accessories that are unique to a PMA device but are not class III (i.e. guide wires). If you had a company that came in with a guide wire for use with company ABC… how do we ensure it'll work. For a given instrument, how do we interpret the classification jointly?

For a new Class I instrument, but it was referenced as class II in a prior submission, how do we handle that?
Not sure how to answer that right now.

Real World Evidence from a Global Perspective & NEST Update

The Future of Global Evidence Generation: Advancing the Role of Innovative Data and Methods	Michelle McMurry-Heath, MD, PhD

Real world data vs real world evidence
Real world data is any pre-clinical, bench test or raw data that you are gathering.
Once you put the patient outcomes into the methodology (statistically significant results and able to interpret the results), that is RWE.

There are key steps to getting there and it is a market phased approach.

QUESTIONS

How are you going to get data and not be at market?
It is a little bit of a chicken and an egg thing. The intent is to use RWE in a clinical setting. There is the thought of using other international standards as an entry level point. The CE mark could be used as an entry ticket to the US market for higher risk patients and then preserve the device over time or remove it from the market.. It might not work with the new EU MDR, as this is evolving very quickly. The idea is to look at other international areas of entry.

CDRH RWE Overview and FDA's Perspective on Future RWE — Josh Chetta

HCP's have been combing devices from different device manufacturers. It has been found that HCP's are taking components from device manufacturer A and device manufacturer B to create device C. It is no longer just an off-label issue but they have essentially become a new manufacturer by compiling their own devices. This action should be done under an IDE with the use of a registry to collect data.

Observational vs investigational – if you are observing and not interfering, it might be a method for device manufacturers to obtain data.

NEST Overview and Future Vision — Rachael Fleurence, PhD

QUESTIONS

Do you see there is any overlap between AJRR and NEST?
We are in touch with AJRR and our role is to work to support their efforts. The director of AJRR is looking to expand the registry (currently it is mostly level 1 registry data). There are over 1 million people enrolled with that data set.

Traditionally, the main players are registries. That's how RWE has been used in the device world. Not every device has a registry. NEST is looking for ways to provide data for devices that don't have registries.

For devices that do have registries, we are not in competition with them. No reason for NEST to be messing with it. NEST can provide contacts and links and services to registries.

We are working with AJRR. For confidentiality reasons I cannot expand but they don't have access to everything that they need, and we help link them with contacts.

How does NEST function financially?
Hard to answer. There are two parallel tracks regarding what we offer and the legal finances. That work is ongoing. NEST is using their own resources to fund studies. At this time, NEST uses its own resources to fund studies along with health care systems and agreements with manufacturers. In the future, companies would pay NEST. No one has access to data due to privacy. The health systems will continue to create data and it will require agreements amongst all of the parties to access private data.

Healthcare systems are using Epic systems for UDI purposes. Is it possible to pull data from this resource?
Epic software system has a line item specific to UDI. Health systems can use it when they want but it is not usable for research data. It's considered raw data. There are no standards around data collection for this purpose at this time. Epic Systems is used to just collect data. Maybe in the future this could be utilized but in these early stages, it is more efficient to work with the healthcare systems and their clinical data research warehouses.

With the test cases referenced, is NEST going to share that information?
Yes. We will need to navigate the confidentiality issues but at the very least, NEST will share the high-level methods and lessons. First have to work through the kinks, legal agreements, etc. The second round of test cases will be proposed this summer. Real world data for the pediatric space is a good resource for companies.

Typical length of a test? 2 years?
Not sure yet. Starting to have conversations around how to define the study and the study design. Hopefully retrospective/observational should be shorter… prospective may be longer.

Real World Evidence Panel Discussion	Michelle McMurry-Heath Josh Chetta Rachael Fleurence Jing Xie Dr. Stephen Weber Dr. Vincent Devlin

What are the benefits of NEST for a larger company?
Rachael: Even for large companies, with resource and technical expertise, it is still good to identify which healthcare systems to work with, build the agreements and governance and access reliable data sources. We are digesting that work for larger companies by developing a set of data structures. NEST is independent from FDA and still needs to go thru the normal hurdles (there is no special relationship with FDA). It is also a benefit to smaller companies who may not have the time, resources or expertise in house.

Jing: From a large company perspective, it provides a more confident method for generating data. It will cover a variety of usage. It's not easy. It is not readily available to get robust and quality data.

Are we starting to develop these case studies?
Dr. Weber: RWE is good, but it has to be good RWE. All trying to get our heads around what that would look like. Some examples: sponsor wanted PMA with registry level 1 data. Good registry with 1,000's of subjects. Only data available was survivorship. Not sure if they are happy with it. Control groups – a particular application. The ability to pool data is largest benefit. Pure registry data but when you look at it is not provable too small, they couldn't' use it for their application.

Is it part of the plan to have OCEA build and focus on what does and doesn't work?
Josh: OCEA is to consolidate the expertise that has been distributed amongst the offices. Trying to identify needs for the front level review staff. One of our major goals is to hopefully make these data transparent and public. Once we establish a conventional process, the intent is communicate it out as much as possible.

Michael: As a reviewer, we struggle with the premarket. When you are collecting RWE and compare it to an investigational study – the end points aren't going to match up. With Standard of care, how are you going to bridge that gap? Can you move the standard of care to obtain better data points? Is that the limitation of RWE? Or are you going to make attempts to get data points to use it in a premarket (expand indications and you need something beyond survivorship).

Rachael: RWE in the premarket space, so we need to be careful. If we are talking about the meeting current standards that require randomized standards, it is possible to use RWE in a specific sense.
Possible to launch an investigational randomized study with RWE using electronic health records and doing follow-up during the course of care. You would be able to specify the end points. There are pilots underway to see how these trials could be run. You can't just use any type of data to support a need.

There are a number of opportunities but at the same time, we need to be careful to meet premarket needs.

Josh: Exploring possibilities for how we can use this in the future but it will require collaboration.

Jing: Using RWE is not just the data itself, it is to explore the existing data into the routine. Reduce the burden.

For the post approval process, we have leveraged real world data to come to an agreement with FDA on next steps. It was a success story. You can negotiate. Historically, the agency is not fond of OUS data. When entertaining the idea of RWE, will the agency welcome OUS data?

Dr. Devlin: There is a recent GD on accepting clinical data that lays out the requirements for OUS data. As Josh mentioned, there would be different patient protection measures. The agency, is open to considering foreign data.

Mark Melkerson: One of the first uses of retrospective data and OUS data was in orthopedics. In terms of open to foreign data, whether it's real world data or controlled studies, the issue is the quality of the data. Biggest problem with examples of RWE, is they expect the data to be of a certain quality. And when it's 56% follow-up… can't draw a conclusion when data is missing. For RWE data – are you collecting the right data to answer the question? Most registries don't answer the question with the data collected. The RWE GD talks about relevance and reliability of data. It needs to be quality data. It's the totality of the evidence.

CAPT Raquel Peat: Within the Center, ex-US data has been used. Not a novel space. Whether it be RW or not, it just needs to have good quality and reliability. Open to US and OUS data.

How could RWE help meet the EU MDR clinical requirements?
Jing: The regulation will increase clinical data requirements, not depth of the data and on all devices. No grandfathering allowed for prior devices. New regulation will significantly increase the burden. Need to have an innovative way to come up with clinical studies for devices. RWE could bring a new perspective – how can we come up with a new way to generate data. Challenge is connectivity. Need to identify the source and bring it together. It would benefit the US but it would also benefit the global harmonization approach.

Michael Owens: Not OUS data but hesitation using a marketing study that a company might use to support a regulatory decision. Clinical data from EU for a marketing setting (OUS data inefficiencies due to marketing study since only interested in certain end points) It's not rejecting OUS data, it was just generally not robust data.

Rachael: A Smart App study (conducted at Yale and Mayo Health Systems) is recruiting patients at this time. The intent is to follow patients after bariatric surgery. The goal is to see if patients are willing to be engaged. It is a small study (50 patients). It is a trial run that includes clinical research with patient consent. This is an example of how we need to be careful in how we define software. Is the software doing something from a clinical perspective and is it aggregating data?

Michael Owens: Public workshop for smart orthopedic implants (active or passive). RWE is a huge potential for this space. Cover the engineering, technical, clinical and patient cyber security and regulatory for this new technology space. Goal is to discuss objective measurements in the clinical space.

Mary Claire McCorry: The pediatric data that we have been analyzing is very messy. Many devices are silent on the pediatric space. RWE could be really helpful to identify how these devices are being used. It would help assess, is there even a problem? We don't have the data that even says people are jerry rigging (modifying) devices and conducting off label use. There are likely decades of use that FDA is not aware of. It would be great to get those uses on label.

Dr. Devlin: Design of the RW studies will take more planning and forethought. Very important to collect the data you need and not collect with a bunch of incomplete data.

Dr. Weber: RWE can surprisingly not have biased results. Objective performance data for a control group, but only a US group. Totally different results comparing EU and US.

Josh: Come talk to FDA about RWE. Trying to be open and invest in it. Want accurate data and need your help to identify issues

Rachael: Encourage attendees to look at the website. Love to do another call this summer. If you have ideas for tests, contact me.

Jing: This is only going to increase. Creativity and innovation are critical for all stakeholders. Industry, we don't know what is going to work but the best approach is to work together in a collaborative partnership with regulators, engage in proactive discussions and understand data up front for different markets and come up with a robust data collection plan.

Attachments	
No.	Name
1	OSMA Spring Educational Meeting Presentation (morning, part 1)
2	OSMA Spring Educational Meeting Presentation (morning, part 2)
3	OSMA Spring Educational Meeting Presentation (afternoon, part 1)
4	OSMA Spring Educational Meeting Presentation (afternoon, part 2)
5	Attendee List