OSMA BUSINESS & EDUCATION MEETING
Thursday, October 24, 2024
Renaissance Baltimore Harborplace Hotel
Baltimore, MD

DAY TWO- OSMA FDA-FOCUSED EDUCATION MEETING

READING OF MEETING GUIDELINES AND VIRTUAL HOUSEKEEPING
Ehab Esmail, *OSMA President*

Ehab opened the meeting and read the meeting guidelines, followed by words of welcome to our FDA guests and introductions. He noted that OSMA was celebrating its 70th year anniversary and shared some noteworthy facts about OSMA's history.

OSMA PERFORMANCE SURVEY (Ryan Belaney)

Ryan shared that the OSMA performance survey had been conducted and results would be shared with FDA in the near future. He did highlight the favorable FDA satisfaction response.

OSMA WORKING GROUP UPDATES

Biocompatibility (Danese Joiner-Fox)

Danese referenced the recent publication of a *Weight of Evidence Framework*, led by Whitney Christian of Medtronic. She highlighted the OSMA-sponsored biocompatibility panel session that was held in June at OMTEC and noted that the working group was compiling comments on the FDA guidance documents.

MR Labeling/ Testing (Grant Baker)

Grant acknowledged that there was a gap between existing standards/ guidance and regulatory expectations for MR safety. The group will focus its efforts on developing and publishing a position paper.

ORTHOPAEDIC ALLIANCE ROUNDTABLE (OAR) UPDATE
(Sharon Starowicz)

Sharon presented an OAR update to our FDA guests (reference summary from Day One notes).

OFFICE OF HEALTH TECHNOLOGY (OHT) 6: ORTHOPEDIC DEVICES
DIRECTOR'S OPENING REMARKS (RDML Raquel Peat, Ph.D., MPH, *FDA*)

Rear Admiral Peat was unable to attend the OSMA meeting due to an unexpected conflict. She offered to reach out after the meeting to provide an update.

ACCREDITATION SCHEME FOR CONFORMITY ASSESSMENT (ASCA) PROGRAM UPDATES (Eric Franca, Ph.D., *FDA*)

Dr. Franca introduced the ASCA program and its goal to streamline conformity assessment in premarket review by using ASCA-accredited testing labs (107 to date), reducing the time needed for FDA's conformity assessment element of device review. It capitalizes on FDA-recognized standards (i.e., biocompatibility and electrical safety) and is folded into eSTAR. ASCA submission elements include a cover letter, ASCA declaration of conformity (automatically generated through eSTAR) and an ASCA summary test report (using a standardized template). The summary report eliminates the need for FDA to see full test reports, moving testing issues to the ASCA test lab and improving the quality of testing and reporting. This abbreviated review eliminates the need for lengthy internal consults and complete test report review, resulting in fewer AI requests. A workshop was held on April 17, 2024 to discuss expanding the ASCA program to include additional standards (draft guidance is out for comment). Another ASCA workshop will be held on November 6, 2024 to discuss the potential inclusion of the chemical characterization method for biocompatibility testing. ASCA is a global program and there are five accreditation bodies in the US. FDA does not do in-person inspections of the labs (depends on accreditation bodies) but can if a problem is noted. Labs can be removed from the ASCA program if quality issues are noted.

UPDATE ON MAGNETIC RESONANCE TESTING FOR ORTHOPEDIC DEVICES (Vikansha Dwivedi, BSME, *FDA*)

Ms. Dwivedi provided an overview of the interactions of medical devices within the MR environment. The scope of current FDA guidance applies to all devices that might enter the MR field and provides definitions of MR compatibility. Most orthopedic devices are classified as MR conditional. The hazard depends on the materials used in the device, the device function and where in the body it is intended to be used. The assessment should take into consideration all variables to ensure that a clinically relevant worst-case heating scenario is assessed. RF heating is the most challenging. Worst case and in vivo translation of RF heating are characterized using total electric field (E field) or specific absorption rate (SAR) scaling. Common MR testing and labeling concerns include the spatial field gradient less than 20 T/m, device testing conducted on a different device, worst case rationale not provided and missing test reports. Industry is aware of scenarios where radiology departments are turning down products due to overly restrictive MR labeling. Industry also noted inconsistency among FDA reviewers in requests for implant cards. Ms. Dwivedi reiterated that an implant card should always be requested if there is MR labeling. FDA recognizes that manufacturers want to use a single label format for their devices sold globally and is working toward harmonization; however, this could take a long time. FDA is collaborating with multiple groups and exploring options, including MDDT. The OSMA MR working group expressed interest in partnering with FDA on developing new standards.

MRI SAFETY EVALUATIONS: COMMON DEFICIENCY QUESTIONS
(David Gross, Ph.D., *MED Institute*)

Dr. Gross referenced multiple MRI safety standards and expressed a desire to have MR testing included in the ASCA program. He noted concerns with forcing devices to be labeled as MR unsafe due to excessive, non-clinically relevant testing conditions. Reliance on legacy device testing may be acceptable. FDA is working toward qualifying a MDDT for RF-induced heating. Other opportunities, such as the use of computer modeling and simulation, should be explored. For devices in mixed media or completely in bone, gel testing may not be appropriate. There is no bone phantom and physical testing is not an option. Future standards are needed. Referring to recent expectations for device labeling, manufacturers can delineate MR parameters based on anatomical location. The key take home message is predictability will drive MRI safety and collaboration between regulators, academia and industry works.

BIOCOMPATIBILITY UPDATE
(Teresa Palacios Hernandez, Ph.D., *FDA*)

Dr. Hernandez discussed analytical chemistry testing, toxicological risk assessment, chemical characterization and toxicological risk assessment (TRA) tools. ISO 10993-1 prescribes biocompatibility assessments. There is a steady increase in utilization of analytical chemistry testing and TRA in premarket submissions, especially complex submissions, and there has been a high demand for Q-sub interactions since ISO 10993:2020 was published. Dr. Hernandez reviewed common analytical chemistry testing concerns, the typical content of a TRA report and when a TRA is used for medical device evaluation. There has been an upward trend over the past five years of TRA data being included in OHT6 submissions, particularly for novel materials and manufacturing technologies. Common issues related to TRA reports in OHT6 were reviewed. ISO 10993-17:2023 (partial FDA recognition) clarifies how TRA fits in with the overall biological evaluation within a risk assessment process. In summary, analytical chemistry testing and toxicological risk assessment offer an alternative to animal testing that, with increased standardization, could be least burdensome.

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO) AND AMERICAN SOCIETY FOR TESTING AND MATERIALS (ASTM) ARTHROPLASTY UPDATE (John Goode, MS, *FDA*)

Mr. Goode began his presentation by noting that devices fail, but we try to avoid failures through least burdensome preclinical screening and evaluation, which can include testing. He reviewed the arthroplasty standards published in the 18 months (14 new or revised standards published, 4 withdrawn), as well as the standards that are in balloting/ development. FDA recognized standards may be searched in a database by typing in the product classification code and pulling up the relevant standards. Mr. Goode reviewed the structure of the ANSI/ASTM Technical Advisory Group (TAG) to ISO/ TC150. He encouraged broader participation in standards development with opportunities for harmonization, and noted the calendar of upcoming meetings.

DIVISION OF HEALTH TECHNOLOGY (DHT) 6A, DHT6B AND DHT6C HIGH LEVEL UPDATES
(Jiping Chen, MD, Ph.D., Ronald Jean, Ph.D., Laurence Coyne, Ph.D., *FDA*)

DHT6A, 6B and 6C divisional updates were presented, including organizational structure and noteworthy product approvals. A new team has been created within DHT6B (spinal devices) for Non-Fusion Spinal Devices that encompasses total disc replacements, spinous process spacers, spinous process plates (fusion), anterolateral plates (fusion), SI joint fixation devices and laminoplasty plates. A premarket submission quality pilot program was introduced in DHT6B in April of 2024 where 510(k) submissions meeting certain criteria were brought to a decision in an expedited manner. Preliminary results from the pilot suggest that for 67% of the cohort, a decision could be made in less than 25 days vs. the other 33% of submissions ineligible for the pilot resulted in a total time to decision closer to 60 days. Although these are preliminary results, they suggest that an organized, complete submission helps both industry and FDA. DHT6C continues to receive large numbers of Q-submissions and encourages all sponsors to take full advantage of this program. DHT6C also continues to review and grant increasingly greater numbers of breakthrough device designation and Safer Technologies Program (STeP) requests.

EXPERIENTIAL LEARNING PROGRAM (ELP) UPDATE AND INSIGHT
(Alan Myers, MA, *FDA*)

ELP site visits afford CDRH staff with innovative opportunities for training. They are not intended for FDA to inspect, assess, judge or perform a regulatory function. ELP Requests for Proposals (RFPs) are published two times each year with FDA topics of interest- the next will occur in the Spring. Site visits can be either on-site (limited to10 participants) or virtual depending on budget. FDA participant selection is open to anyone that is interested and each OHT has at least two ELPs each year. FDA and industry also remain interested in participating in FDA Vendor Days.

FDA UPDATES: INSPECTIONS AND COMPLIANCE
(Keisha Thomas, MS, *FDA*)

As of October 1, 2024, FDA has implemented some organizational changes. The former Office of Regulatory Affairs (ORA) has transitioned to the Office of Inspections and Investigations (OII), whose core mission is to focus on inspections, investigations and import operations. Most compliance functions and staff are being re-aligned to the Centers to simplify operations and speed decision-making. There will be no changes to the recall process. Device review will continue to follow the TPLC review model and work across the CDRH review offices. FY 2024 inspection data was reviewed. There were 1715 FDA inspections in FY 2024. CAPA remains the most cited inspectional observation, followed by complaint handling, process validation and medical device reporting. Forty-one (41) warning letters were issued (70% related to unapproved device charges) and there were 1017 device recall events (80 for OHT6). Ms. Thomas described the Voluntary Malfunction Summary Reporting (VMSR) program that permits bundling of “like events” into a single report. Final guidance was published in August of 2024.

The new QMSR was discussed, along with compliance enforcement dates. FDA published the final amendment to 21 CFR Part 820: *Quality Management System Regulation (QMSR)* on February 2, 2024; harmonizing the current Quality System regulation for medical devices by converging its requirements with international quality management system requirements. Revisions to Part 820 replace most of the existing regulation with an incorporation by reference to the 2016 edition of International Organization for Standardization (ISO) 13485 - *Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes.* There is a 2-year transition period from the Quality System Regulation to the Quality Management System Regulation. QMSR effective date is: February 2, 2026. Manufacturers are encouraged to identify and understand the regulatory changes, conduct a gap analysis, identify differences, and revise processes and procedures to incorporate the changes.

DE NOVO DECISION ANALYSIS
(Peter Yang, *FDA*)

The De Novo decision analysis refers to an assessment of MDUFA IV De Novos by OPEQ/ORP staff. 70% of De Novos had a pre-submission; 19% with an IDE; 38% had indications for use meaningfully change over the pre-submission history. Most De Novo questions revolve around benefit, as most do not have a "slam dunk" benefit/risk proposition upon initial review. OHT6 has one of the fewest numbers of De Novos. Mr. Yang addressed OSMA's questions as follows:

<u>Clinical Data as a Special Control</u>

The principles for establishing clinical data requirements as a special control are the same as for any special control:

- Must be the least burdensome means of mitigating risk, i.e., no other means (e.g., bench testing or animal testing) of mitigating a particular risk
- Required for all devices within the new regulation
- Must consider how clinical data will be used in substantial equivalence determination

Depends in part on benefit-risk proposition of the regulation and whether it has been adequately defined by the De Novo device.

<u>Increased Use of Postmarket Special Controls</u>

Postmarket special controls are an evolving area and FDA has used them recently in several De Novos to reach granting decisions. Postmarket special controls implementation includes:

- Pre/postmarket balance as FDA deems necessary, including terminating postmarket requirements
- Explicit postmarket study outlines directly in the granting order (similar to other postmarket requirements language)
- Removal of a special control requires the rulemaking/panel process

<u>The Benefit/Risk Proposition</u>

The benefit-risk worksheet is not a calculator in which reviewers tally wins and losses. It is there to ensure that FDA has assessed all benefit-risk factors in its decision-making and acknowledged

what has been demonstrated in an objective manner. Recognize that there may be inherent differences between how FDA views your benefit-risk proposition and how you view it.

Inspections for De Novos

FDA reserves the authority to inspect De Novo facilities (1) for data integrity purposes and (2) to understand critical or novel manufacturing processes (21 CFR 860.240(c)).

Legal Interpretations and De Novos

Given the complexities of the De Novo classification process, how do you foresee legal interpretations impacting the future of medical device regulatory approvals and the balance between innovation and safety?

- The De Novo process is established by the FD&C Act and by regulation. It serves as an important pathway to establish appropriate controls for low to moderate risk devices, which streamlines the market introduction of innovative devices.
- Each De Novo by definition is a unique type of device, but FDA works very hard to achieve consistency in how De Novos are reviewed and granted.

Key Challenges in Collecting Clinical Data for De Novos

With the increasing use of the De Novo pathway for novel medical devices, what are the key challenges the FDA faces in ensuring robust clinical evidence for these devices?

- Structural issues faced by companies, like regulatory expertise, business timelines, medical device company milestones, and capital
- Companies collecting data with significant margin to support robust FDA authorization vs being carried to the finish line
- Getting companies and FDA on the same page and having critical conversations about opportunities and limitations

How is the Agency addressing these challenges to maintain high standards of safety and effectiveness?

- Total Product Lifecycle Advisory Program (TAP)
- FDA strives to communicate/ collaborate to set up companies for success.
- But keep in mind: "Should this have marketing authorization?" and "Is it actually a good product?" are two different things.

DIGITAL HEALTH INSIGHTS
(Kathryn Drzewiecki, Ph.D., *FDA*)

Dr. Drzewiecki presented the FDA definition of Digital Health Technology (DHT). FDA is taking a risk-based approach to the regulatory oversight of DHT. The Digital Health Policy Navigator helps manufacturers consider whether a software function is potentially subject to or the focus of FDA's regulatory oversight as a device. Relevant guidance for DHTs that are devices address multiple function device products, software submission content and cybersecurity submission content. Predetermined change control plans (PCCPs) are applicable

to all device types, not just AI/ML devices- refer to recent draft guidance. Modifications that are appropriate for inclusion in a PCCP include those that are intended to maintain or improve the safety or effectiveness of the device, are specific, and can be verified and validated.
The proposed components of a PCCP include a description of modifications, modifications protocol and impact assessment addressing risks and benefits. FDA encourages manufacturers to engage early and often by submitting a pre-submission to discuss a proposed PCCP. The Digital Health Advisory Committee will be meeting on November 20-21, 2024 to discuss total product lifecycle considerations for generative AI-enabled devices.

DIGITAL HEALTH- INDUSTRY PERSPECTIVE
(Teal Bjoraker- *Medtronic*)

The categories and regulatory boundaries for defining FDA's regulatory oversight of digital health technologies was discussed. Those falling in the gray area are subject to enforcement discretion. The 21st Century Cures Act excluded certain software functions from the definition of a device. A non-device Medical Device Data System (MDDS) is a software function solely intended for certain purposes (i.e., electronic transfer, exchange, electronic storage or retrieval, electronic conversion of medical device data from one format to another according to a preset specification or electronic display of medical device data) without controlling or altering the functions or parameters of any connected medical device. It is cautioned, however, that combining data to provide new insights, such as those related to correlation or causation, may push it out of MDDS. Clinical Decision Support (CDS) software was also discussed. The distinction between Device CDS vs Non-Device CDS (not regulated) and is based on whether the software substitutes, replaces or directs the judgement of the healthcare provider, supports time critical decision making or provides specific preventative, diagnostic or treatment output or directive, which are all features of Device CDS and subject to FDA regulation. Multiple Function Devices are devices having at least one regulated function. FDA will evaluate the impact of the non-device function only with respect to how it may impact the safety and effectiveness of the regulated function(s). AL and ML technologies were also discussed. The definition of AI varies by jurisdiction. AL/ML models are dependent on the integrity of data during model development. Algorithms can be locked or adaptive- there are many challenges with adaptive algorithms, and the risks must be identified and safeguarded. In the postmarket environment, it is important to ensure that the model performs as expected over time. Ongoing monitoring and clinical data collection are key. Bias of the data may be naturally occurring or unintended. It is important to assess the presence and validity of biases. It is also important to ensure that the training and data sets are equally representative of the disease process. PCCPs are no longer limited to AI/ML technologies, and can ensure more rapid improvements. Although harmonization efforts are underway, software and AI regulations still vary widely by country. Optimizing for one may be at the expense of another.