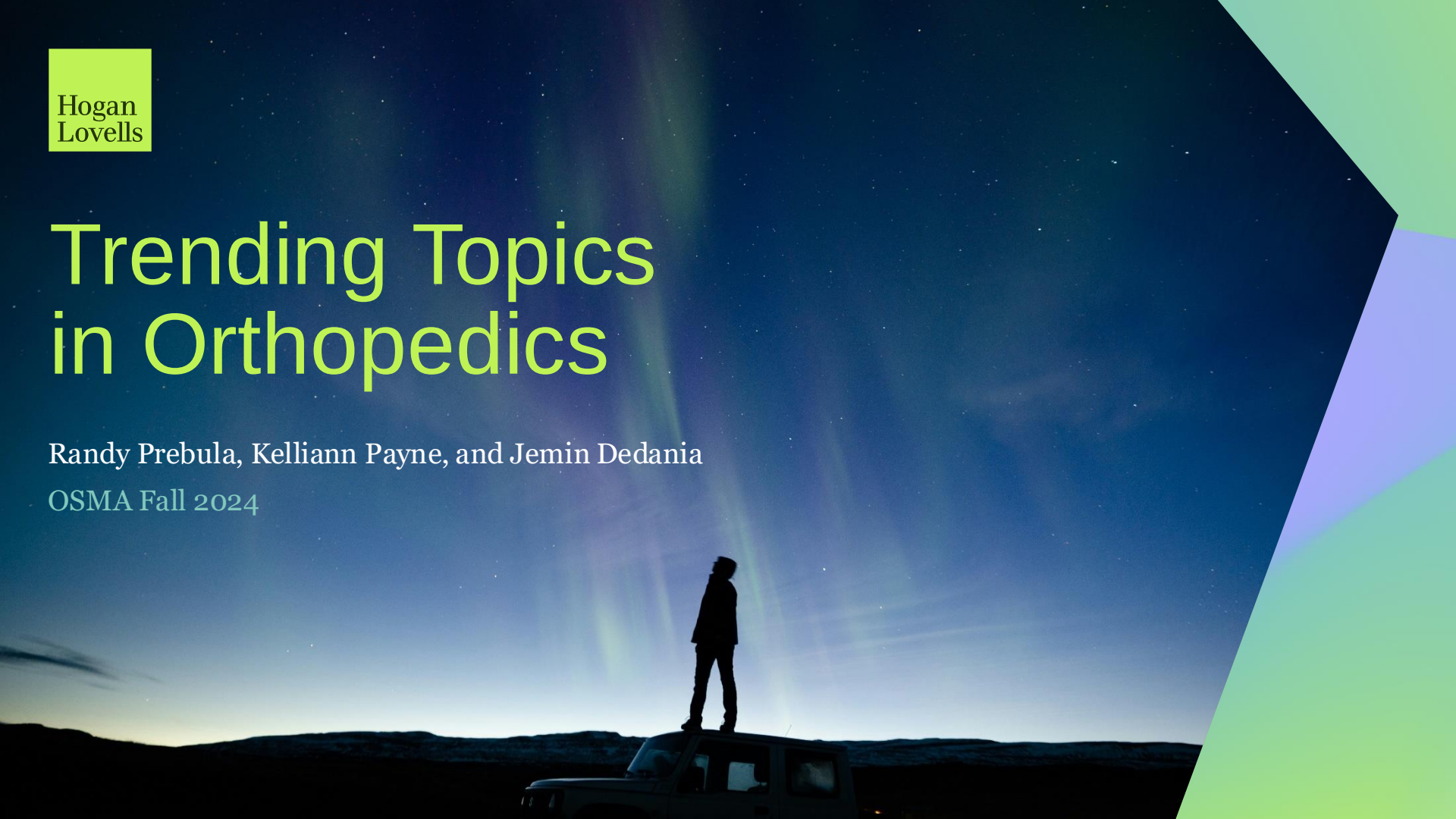

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Trending Topics in Orthopedics

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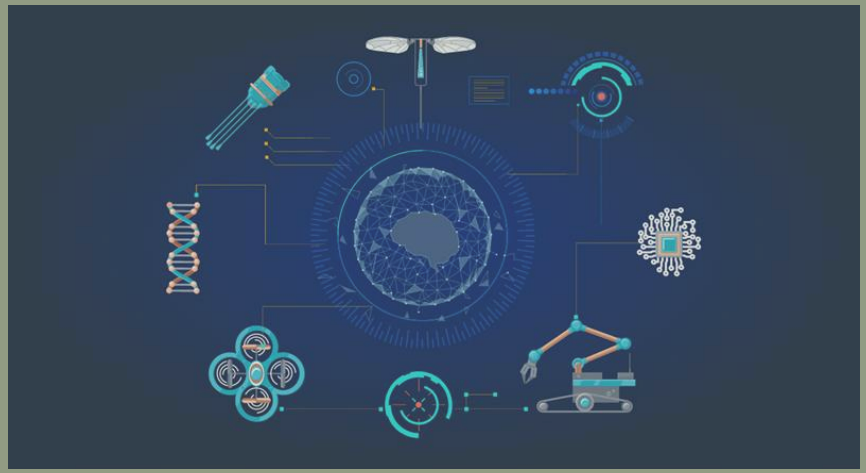
OSMA Fall 2024

Agenda

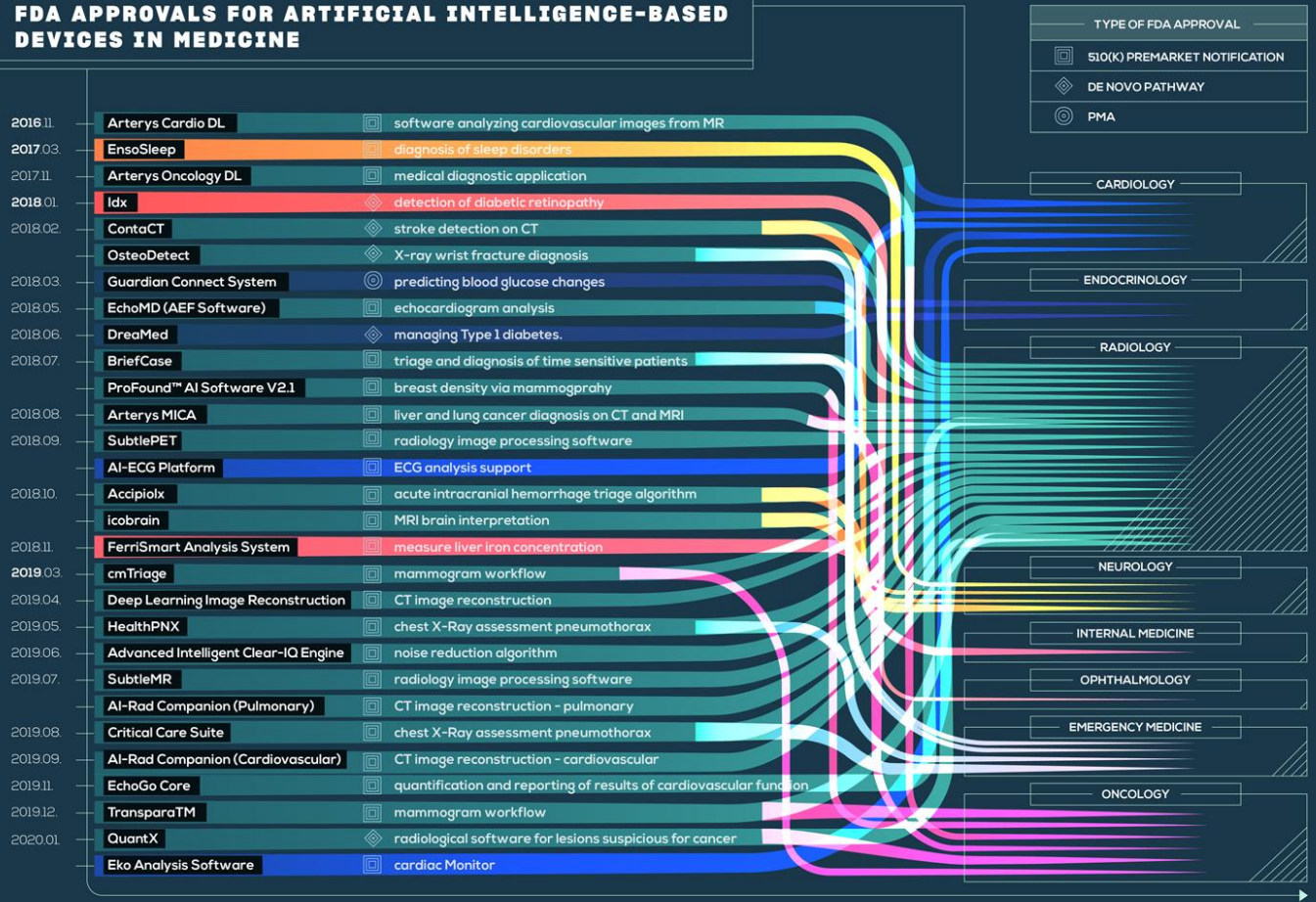
- Introduction
- Overview
- Digital Trends
- Advancements in Technology
- Post Market
- Discussion

Digital Trends

- Artificial Intelligence/Machine Learning (AI/ML)-Enabled Medical Devices
- Predetermined Change Control Plan (PCCP) Guidance and Examples
- Virtual and Augmented Reality Devices



FDA APPROVALS FOR ARTIFICIAL INTELLIGENCE-BASED DEVICES IN MEDICINE



Evolving Regulatory Framework for AI/ML-Based SaMD

- April 2019 - Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback
- January 2021 - Artificial Intelligence and Machine Learning Software as a Medical Device Action Plan
- October 2021 - Good Machine Learning Practice for Medical Device Development: Guiding Principles
- April 2023 - Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions - Draft Guidance
- October 2023 - Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles
- March 2024 - Artificial Intelligence and Medical Products: How CBER, CDER, CDRH, and OCP are Working Together
- June 2024 - Transparency for Machine Learning-Enabled Medical Devices: Guiding Principles
- August 2024 - Predetermined Change Control Plans for Medical Devices – Draft Guidance

AI as Medical Device: FDA Expectations

- Algorithm is frozen at time of the marketing submission
  - AI can be used to evolve the algorithm during development
  - Consistent with long-standing FDA policy that final, finished devices are cleared or approved, and not "concepts"
  - Reflects the need for FDA to evaluate existing performance
- All relevant testing must be completed with the frozen algorithm at the time that a marketing submission is filed
  - FDA will not conditionally clear or approve a medical device
  - Addresses concern that products reach the market only to have subsequent data demonstrate a lack of safety or effectiveness

AI/ML SaMD: Marketing Authorization Trends

- Vast majority of AI/ML devices granted marketing authorization have been in Radiology, but expanding to other fields
- Many AI/ML devices have been granted Breakthrough Designation in the past
- AI/ML devices often granted marketing authorization via the de novo request pathway due to changes in technological characteristics
  - Each new de novo provides Special Controls for new device regulation
- Clinical data are used to support most marketing submissions
- CDRH published an Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Device List, which the agency updates periodically
- Relevant AI/ML-Based SaMD Examples:
  - OTS Hip (K232140): used for orthopedic hip surgical procedures where a reference to a rigid anatomical structure, such as the pelvis, can be identified relative to a CT-based model of the anatomy. The system helps surgeons accurately navigate a compatible prosthesis to the preoperatively planned position.
  - VEA Align and spineEOS (K240582): assists with pre-operatiove planning of spine surgeries. Uses biplanar 2D X-ray images to generate an initial placement of patient anatomic landmarks using a machine learning-based algorithm.
  - ARVIS® Shoulder (K240062): computer-controlled surgical navigation system used to provide intra-operative measurements to surgeons to help select and position orthopedic implant components.

Agency Guidance on Predetermined Change Control Plans (PCCPs)

- FDA issued the AI/ML PCCP draft guidance document in April 2023
  - Early engagement with FDA is encouraged
  - Only limited changes may be made via PCCP
  - CDRH division reviewing the marketing application will determine whether the scope of proposed modifications is appropriate for inclusion in a PCCP
  - Superiority standard (versus substantial equivalence) to be determined – "improvement" is key
- Recognition by FDA that:
  - Software products are intended to be updated on a regular and frequent basis
  - AI/ML potentially allows for more frequent (or continual) optimization of algorithms
  - Innovative approaches are needed to support the iterative nature of SaMD, including AI/ML
- Goal:
  - "[A] PCCP, as part of a marketing submission, is intended to provide a means to implement modifications to a Machine Learning-Enabled Device Software Function (ML-DSF) that generally would otherwise require additional marketing submissions prior to implementation."
- FDA intends to publish the final guidance document during FY2024

Agency Guidance on PCCPs (cont.)

- FDA issued a broader draft guidance document on PCCPs for all medical devices, not just software in August 2024
- Draft guidance focused on five guiding principles:
  1. Reasonable assurance of safety and effectiveness and substantial equivalence of devices with PCCPs
     - The device, including all modifications proposed in the PCCP, must meet the regulatory standard required of that type of application
  2. PCCPs may be a least burdensome option to support device modifications
  3. PCCPs are part of a device's marketing authorization
  4. PCCPs are specific
     - FDA stresses that a PCCP should include only a few, specific modifications that can be verified and validated, and that do not cover an excessively broad scope
  5. PCCPs harmonize with existing FDA Device Modifications guidances
     - Device Modifications guidances exist to help manufacturers ascertain whether a new marketing submission is required prior to implementing a modification.

International Consensus on PCCP Guiding Principles

- FDA, Health Canada, and MHRA released a PCCP for ML-Enabled Devices Guiding Principles document in October 2023
- Provided five foundational considerations for PCCP development:

1. Focused and Bounded
   - A PCCP should be limited to specific changes a manufacturer intends to implement
   - Changes are limited to modifications within the intended use or purpose of the original devices
2. Risk-based
   - Value and reliability of a risk-based approach that adheres to the principles of risk management
3. Evidence-based
4. Transparent
   - Clear and appropriate information and detailed plans for ongoing transparency to users and other stakeholders
5. Total Product Lifecycle Perspective

PCCP Required Contents

Description of Modifications:

1. Modifications related to quantitative measures of ML-DSF performance specifications
2. Modifications related to device inputs to the ML-DSF
3. Limited modifications related to the device's use and performance (e.g., for use within a specific subpopulation)

Modification Protocol:

1. Data management practices, which outline how new data will be collected, annotated, curated, stored, retained, controlled, and used by the manufacturer for each modification
2. Re-training practices, which are the processing steps that are subject to change for each modification and the methods that will be used by the manufacturer to implement modifications to the ML-DSF
3. Performance evaluation protocols, which describe the processes that will be followed to validate that the modified ML-DSF will meet the specifications identified as part of a specific modification, in addition to maintaining the specifications that are not part of the modification but may be impacted by it
4. Update procedures, which describe how manufacturers will update their devices to implement the modifications, provide appropriate transparency to users, and, if appropriate, updated user training about the modifications and perform real-world monitoring, including notification requirements if the device does not function as intended pursuant to the authorized PCCP

Impact Assessment:

1. Compare the version of the device with each modification implemented to the version of the device without any modifications implemented
2. Discuss benefits and risks, including risks of social harm, of each individual modification
3. Discuss how activities proposed within the Modification Protocol continue to reasonably ensure the safety and effectiveness of the device
4. Discuss how implementation of one modification impacts the implementation of another
5. Describe cumulative impact of implementing all modifications

Sample Language for PCCPs

- Examples of Limitations of a Pre-Determined Change Control Plan
  - No change to the intended use of the device
  - No change to the input type
  - No change to the output type
  - Performance of modification(s) can be completely evaluated by the original test methods
- Examples of Potential Changes
  - Training on additional data
  - Optimizing hyperparameters
  - Changing number of layers in the neural network
  - Changing type and parameters of layers in the neural network
  - Changing connections between layers in the neural network
  - Changing predictors in machine learning algorithms
  - Changing loss function
  - Changing pre-processing
  - Using weight and/or activation quantization

Software Modifications, Triggering a Marketing Application

- Modifications need to be assessed to determine if a new regulatory submission is required
  - Modifications that could raise new questions of safety or effectiveness typically require a new submission
- Changes that may require a new 510(k) may include:
  - A change that introduces a new risk or modifies an existing risk that could result in significant harm
  - Changes to risk controls to prevent significant harm
  - A change that significantly affect clinical functionality or performance specifications of the device
- Bug fixes are minor modifications and do not affect an algorithm's output or performance (e.g., cybersecurity fixes, code errors, communication faults)

AI/ML SaMD with a PCCP in Orthopedic Context

- Example of a cleared PCCP in an Orthopedic application:
  - BoneMRI (K233030)
    - "The BoneMRI application uses an algorithm derived from machine learning (ML) to detect bone images from MRIs obtained using a specific gradient echo acquisition sequence. The algorithm training sets included images from multiple clinical sites, multiple anatomies, and multiple scanners to ensure that the trained algorithm was robust with respect to the approved indications for use. MRIguidance will make future algorithm improvements under a Predetermined Change Control Plan (PCCP). In that plan, a protocol is provided to mitigate the risks of the algorithm changes leading to changes in the device's technical specifications or negatively affecting performance specifications directly associated with the indications for use of the device…In accordance with the PCCP, all algorithm modifications will be trained, tuned, and locked prior to release of the application."
    - Modifications that may be made under the PCCP:
      - Re-training to **improve** ML model performance with additional training data
      - Validation of additional scanner support

Virtual and Augmented/Extended Reality Devices

- Augmented Reality (AR)
  - Sometimes referred to as extended reality
  - Overlaying or mixing simulated digital images with the real world as seen through a camera or display, such as a smartphone or head-mounted display
  - Common uses: surgical planning, intraoperative procedures, and post operative rehabilitation therapies
- Virtual Reality (VR)
  - Fully immersive experience that may require a headset
  - Completely replaces user's surroundings with a simulated, interactive virtual environment
  - Common uses: patient care in domains like pain management and mental health
- No formal FDA guidance has been published on the topic
  - CDRH formed Medical Extended Reality Program in 2021
  - Held Patient Engagement Advisory Committee Meeting in 2022 discussing risks and benefits of the technology
  - As of September 2024, CDRH has published a List of Medical Devices that Incorporate AR and VR

Examples of Relevant Applications

- xvision Spine System (K220905): an image-guided navigation system that is designed to assist surgeons in placing pedicle screws accurately, during open or percutaneous computer-assisted spinal surgery. It uses wireless optical tracking technology and displays to the surgeon the location of the tracked surgical instruments relative to the acquired intraoperative patient's scan, onto the surgical field. The 2D scanned data and 3D reconstructed model, along with tracking information, are projected to the surgeons' retina using a transparent near-eye-display Headset, allowing the surgeon to both look at the patient and the navigation data at the same time.

- STELLAR Knee (K232176): uses established surgical navigation techniques to provide information to help track patient bony landmarks in real time to assist the surgeon in determining resection angles and measurements as required in knee replacement surgery. The software locates in a 3D reference frame the instruments which include marker arrays. All collected coordinates are treated by software algorithms to provide the surgeon with the relevant orientation of the tracked cutting guide. STELLAR Knee software is installed on a wearable Head Mounted Device (HMD) which includes an embedded camera and displays intraoperative information to the user.

How to Approach FDA for Clarity

Digital Health Policy Navigator

- Online tool to help determine whether a product's software function may be a focus of FDA regulatory oversight

- Link to launch the Tool

Feedback for a Future Premarket Submission

- Request a pre-submission outlining the product, proposed regulatory pathway, and data plans
- FDA will schedule a teleconference in 2.5-3 months
- Requests for Feedback on Medical Device Submissions Guidance

Interpreting Digital Health Guidance

- Send questions or a product description (for initial regulatory assessment) to FDA's Digital Health Center of Excellence at DigitalHealth@fda.hhs.gov
- FDA usually replies informally in ~2 weeks

Advancements in Technology

- Additive Manufacturing
- Biocompatibility
- Combination Products
- Resorbable Metal Technologies
- Surface Modification

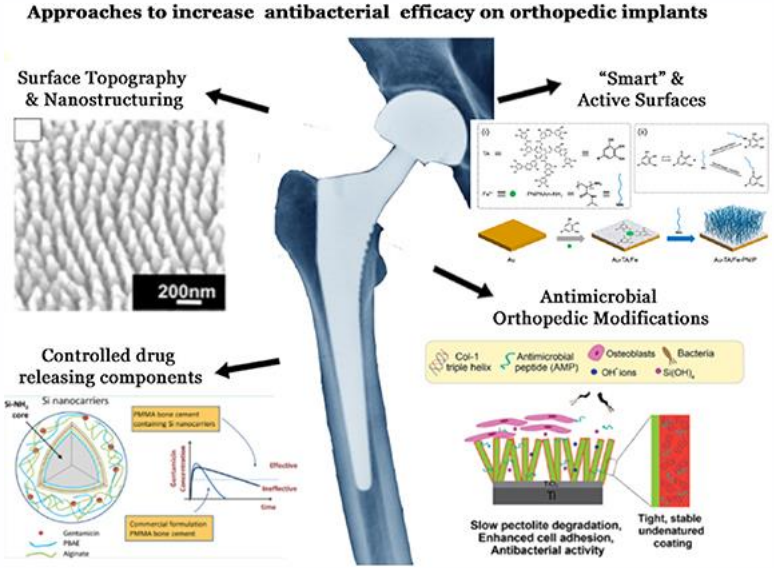
Biocompatibility

- Instruments now require 5 tests
  - Cytotoxicity, sensitization, irritation, material mediated pyrogenicity, and acute systemic toxicity
- All O's can be treated as X in the biocompatibility testing table found in Attachment G of the FDA's Biocompatibility Guidance on Use of ISO 10993-1.
- Avoid chemical characterization, when possible, do the testing if at all possible
  - Working with a lab, company, and/or toxicologist that has extensive knowledge and an internal library of chemical compounds, especially for new materials
- Always consider a risk-based approach
- FDA putting out more biocompatibility guidance for labs
  - Biocompatibility Testing of Medical Devices - Standards Specific Information for the Accreditation Scheme for Conformity Assessment (ASCA) Program : Draft Guidance for Industry, Accreditation Bodies, Testing Laboratories, and Food and Drug Administration Staff
  - Chemical Analysis for Biocompatibility Assessment of Medical Devices: Draft Guidance for Industry and Food and Drug Administration Staff

Combination Products

- Growth factors
  - rhBMP-2
  - rhPDGF
  - iFactor P-15
- Change in indications, change in carrier requires extensive clinical study

- FDA/CDRH/OHT6 antimicrobial paradigm remains the same:
  - Prevent Bacterial Colonization (Device PMOA)
  - Prophylaxis and/or treat active infection (Drug PMOA)



Resorbable Metal Technologies

- Magnesium (Mg) and its alloys are considered the next-generation biodegradable biomaterial for orthopedic applications.[1]
- Hydrogen gas formation and rapid absorption are the main risk.
- The RemeOs Screw LAG Solid was recently granted in **DEN220030** as the only Mg-based orthopedic screw designed for fracture and osteotomy repair as well as deformity or malalignment correction.
  - FDA has also granted German manufacturer Medical Magnesium GmbH Breakthrough Device status for its orthopedic and trauma care plate system but this device has not yet been cleared/approved.
  - FDA additionally granted Bioretec's RemeOs Spinal Interbody Cage implant Breakthrough Device status.
- Based on the special controls of DEN220030:
  - Regulatory impact if using a different Mg alloy
  - Product must be taken out to full absorption
  - Other indications will need clinical data

1. https://www.odtmag.com/issues/2024-05-01/view_columns/fda-regulatory-challenges-for-magnesium-based-orthopedic-devices/

Additive Manufacturing

- Additive manufacturing remains front and center in submissions and orthopaedic applications
- Follow FDA guidance on submitting all documents requested and manufacturing information Technical Considerations for Additive Manufactured Medical Devices
  - Materials
  - Design, printing, and post-printing validation
  - Printing characteristics and parameters
  - Physical and mechanical assessment of final device
  - Biological considerations of final devices (e.g., cleaning, sterility, biocompatibility)

- Keep the ADM section organized given eSTAR issues
- When submitting, include in your device description purpose of the file, if the additive section is new, similar, or identical to a previous submission.
  - Modifications to ADM, walk FDA through in detail
  - Include images of device

Surface Modification

- Focus on technologies shifting to surface modification to create a better environment for osseointegration, reduce inflammation, and/or prevent implant failure.

- For the review of these devices, FDA is focusing on
  - Biocompatibility
    - ❑ Extensive wear particle testing
  - Durability of coating and full characterization of the properties
  - Adhesion of the coating
    - ❑ Expect to use standard test methods established for normal coatings

- See latest OrthoBond DeNovo Petitions
  - DEN220015 and DEN210058
  - (ii) Evaluation of coated implant initial fixation;
  - (iii) Evaluation of coating integrity
  - (ix) Coating characterization, including a detailed description of the substrate morphology and coating process and an evaluation of coating physicochemical properties such as density, thickness, chemistry, and uniformity.

Post-Market

- ISO 13485 Harmonization
- Enforcement Trends
- Registry Data Analysis and MDR Review
- Increase in Warning Letters

CFR 820 incorporation with ISO 13485 elements

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- On February 2, FDA published its long-awaited proposed rule entitled, “Medical Devices; Quality System Regulation Amendments,” which would amend the GMP requirements of the QSR in 21 CFR Part 820, to incorporate by reference the vast majority of the ISO 13485 items.
  - Overall Harmonization is accepted globally.
  - A companion document that includes the new QMSR requirements could be necessary.
  - The final rule aims to align the U.S. regulations more closely with the International Organization for Standardization (ISO) standard 13485:2016, the international consensus standard for medical devices, by converging most of the quality management system (QMS) requirements used by FDA and regulatory authorities from other countries.
  - FDA inspectors could emphasize different points compared to other regulatory bodies and auditing entities.
  - Medical device makers and importers have until February 2, 2026, to modify their quality systems to meet the now renamed QMS Regulations (QMSR).

FDA proposes to conform the Quality System Regulation to the ISO 1348 - Hogan Lovells Engage

FDA Enforcement Trends (Most Currently Available)

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- The overall number of inspections dipped severely from FY 2015 to FY 2023 due to COVID restrictions.
  - 2,534 FDA medical device inspections (domestic/foreign) in FY 2015 to 1024 in FY 2024 to date.[1]
  - Increased industry participation in MDSAP also partly responsible
- FDA has ramped back up inspections and issuing many notices of foreign inspections to pre-COVID levels.
  - Agency's initial approach was re-inspections of companies which received 483s, Warning Letters, and Delayed Inspections of new market entrants (2018-2020Q1).
  - Recent focus on supply chain-oriented inspections (e.g., initial importers of Chinese products being inspected).
- FDA focus on certain product types
  - Proper scope of use AI/ML Software
    - e.g., A SW to detect certain lesions being used for diagnostic purposes
  - Device modification and labeling claims
- Continued focus on recalls and communications to the patient level (OHT-6).

FDA U.S. FOOD & DRUG ADMINISTRATION DATA DASHBOARD

1. https://datadashboard.fda.gov/ora/cd/inspections.htm

Registry Data Analysis and MDR Review

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- FDA has been combing registry data (UK and AUS) and looking at explant rates between competitors. Even if within an anticipated range, if a company's explant rate is higher than the others, this could trigger FDA to start asking questions.
- Concern with reliance on registry data is that it is not specific – it is all comers explant data only without context or identification of failure mode.
  - As we have seen in OHT6, FDA has not always consistently accepted registry data in submissions.
  - There are some cases and instances where FDA has allowed the use of this data.
- Given the TPLC model, FDA is also looking to MDRs and asking for additional information.
  - Usually starts out with pro-forma questions and is then followed up with detailed, very specific questions.
  - Some communications go multiple rounds with FDA until the company acquiesces to take some type of action (e.g., customer notice, design change, recall, etc.).
  - We have seen this across all OHTs and is likely the result of CDRH Re-org.

Increase in Safety Communications

- FDA had a major focus on Safety Communications and Warning Letters regarding syringes. There was still a number of safety communications aimed at orthopedic manufacturers in 2024. [1]

- The devices were all implant systems, and the notices were for the following reasons:
  - Undocumented significant modifications
  - Defective packaging
  - Risk of device failure
  - Increased risks

1. https://www.fda.gov/medical-devices/safety-communications/2024-safety-communications

Orthopedic PMA and general inspections

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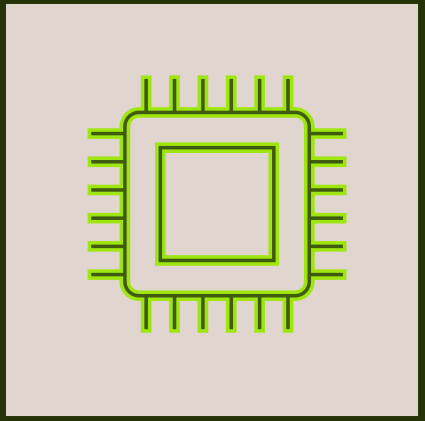
- Ortho PMA purchasing controls, supplier controls inspected during QSIT
  - Anyone that handles the finished device is a device manufacturer
  - Anything to be coated to be finished, increased scrutiny
  - If your device has multiple vendors, FDA requires that you provide information for all entities, they could all be inspected

In Summary:



Digital Trends

FDA continues to put final and draft guidance in this space. The space continues to evolve and FDA along with industry have to play catch-up. FDA remains focused in on cybersecurity questions.

Biocompatibility

Biocompatibility continues to be a difficult hurdle for companies. FDA has released further direction on testing and is working with ISO. Consider doing the testing and having a good toxicologist on-hand and available if you do chemical characterization.

Surface Technologies

Even bigger focus for companies in this space to create a better environment for osseointegration, reduce inflammation, and/or prevent implant failure. FDA review focusing on biocompatibility, extensive coating characterization and testing.

Post-Market

FDA continues CFR 820 incorporation with ISO 13485 elements. Inspections focusing on software and device modifications. There have been a number of orthopedic safety notifications.

Questions?

Thank You!

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Digital Heath

Advancements in technology are revolutionizing the way in which the health care industry functions.

With the development of new products and services also comes a fluctuating regulatory environment While innovation in the health care and life sciences industry leads to better lives and a wide range of opportunities, this also brings a new set of risks.

We advise at the cutting edge of technology with expertise in digital health areas – including artificial intelligence, big data, blockchain, cybersecurity, use of consumer grade wearables, digital therapies, virtual clinical trials, and telehealth – by bringing together our experience from many angles of our life sciences practice.

Our cross-jurisdictional team of more than 50 life sciences and health care lawyers with a focus on digital health take a technology-based approach to counseling on digital health products and services. We provide you with strategic guidance on how to leverage opportunities for growth, minimize legal barriers, comply with rules, protect your data, and realize its value.

Our team advises on the design, approval process, and regulation of digital health products. We regularly work with companies and health care providers on pricing and reimbursement frameworks. We advise on all aspects of health privacy and cybersecurity, including breach response, risk assessment, privacy policies, and transactions.

Representative experience

- To assist a client in expediting a product to market, we obtained the FDA's designation of expedited review status for a novel orthopedic and women's health device and negotiated favorable review timetables.
- Advising a client on the development of a new digital health product consisting of a mobile app for the patient and web based apps for HCPs.
- Counseling a major pharmaceutical company on the development and regulatory requirements for mobile applications and smart drug delivery tools to be used by patients.
- Advised companies developing digital therapeutic tools on the regulatory pathway and associated clinical data needs.

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Slide 4 – Benjamins et al. npj Digit. Med. 3, 118 (2020).https://doi.org/10.1038/s41746-020-00324-0

Slide 16 – https://www.te.com/en/industries/medical-technologies/medical-resources/medical-trends-whitepapers/smarter-medical-instruments-minimally-invasive-surgery.html

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