Regulation of Medical Textiles and Premarket Applications

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PALADIN MEDICAL
Your champion for product success.

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Background

- Paladin Medical, Inc. serves start-up medical device manufacturer with premarket applications
- We help implement basic quality systems focused on QSR 820/ISO compliance-design control & review
- We help with the quality handshake between textile contractors and client medical device producer.
- Experience extends to nearly every kind of device and biomaterial since 1974.

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Overview

- Sufficient testing and qualification before market approval? *When is it ever enough?*
- Changes to traditional regulatory pathways raise cost and anxiety for all parties
- More time, money and increasingly rigid standards do not necessarily make devices safer or shield producers from liability challenges
- Risk-based strategies and supplier/producer cooperation may improve speed to market

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Do medical textiles continue to meet the risk-benefit challenge?

FDA has been blamed for lax oversight of certain implanted medical textiles even though products met user needs and regulatory and quality obligations

Fabricated from a wide variety of well-characterized biocompatible mesh materials into various shapes for numerous successful surgical procedures and integral parts of non-invasive devices!

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In the 1960's and 1970's medical textile iconic images were doctors in masks and gowns, wrapped instruments and bandages.

TODAY:

FDA has 46 classifications for MESH devices and all but 2 are for MESH IMPLANTS.

All but 1 of the 44 classifications for *implantable MESH devices are CLASS 2*

***CLASS 2 devices do not have "pre-emption" protection in a court of law**

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FDA guidance documents have not kept up with other FDA policies for safety and effectiveness evaluations, contributing to unpredictable premarket reviews

- *Vascular grafts (2000)*
- *Stents, filters (2010)*
- *Annuplasty rings (2001)*
- ***Surgical Mesh (1999)***
- *Gowns and Drapes (1993)*

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1999-Surgical Mesh Guidance

XII. Final consideration :"Recent technological advances" ~~ *what about even the old technologies*~~~ "Review of such products may require additional information than that described in this Guidance document, because the products can raise new types of questions about device *safety and effectiveness*~~

1. Will the device assemble in a safe and effective manner?
2. Will excess, unreacted material migrate to new locations ~ ~~and form unwanted polymer at new anatomic sites?
3. Will chemical reactions with adjacent human tissues occur?

Was this a MESSAGE in a BOTTLE from 1999?

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If we are this far behind with guidances for conventional mesh regulatory requirements how will be deal with a SMART TEXTILE?

This Smart Digital T-shirt by hWEAR monitors your heart. It has conductive fibers woven in, performing the job of an ECG machine and transmitting vitals to your doctor's smartphone.

Cybersecurity?
Data security?
Wash & Wearability?
Biocompatibility?
FALSE DIAGNOSIS?

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FDA Classification and Submission Rules are dynamic but are they ready for your innovation?

- Class I
  - (Most) do not require a premarket notification (510(k)) but still require LISTING and Registration
- Class II
  - (Most) require a 510(k) and L & R
- deNOVO- *new
  - deNOVO when new intended use/new indicated use OR new technology without a PREDICATE- but judged reasonably safe
- Class III PMA
  - Premarket Approval, evidence of safety and EFFICACY

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FDA has been re-working the clearance process

- Strict adherence to **Refuse to Accept**
- Constraints on "acceptable" PREDICATE
- Challenges to "equivalence" even when guidance gives latitude
- Strict adherence to "special control" guidance
- *deNOVO* whenever new technological risk
- Combination products - more "drug" reviews

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Complexity of Combination Products

- Even if the principle mode of action is as a "device", a textile medical device can be particularly complicated if the drug is applied to or inside the textile!
  - Affect of textile processing on the drug
  - Affect of polymer and drug together
  - Drug-GMPs apply to the product as soon as the drug is combined with the device- all the way to the customer.

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deNOVO

- If your product is **Not Substantially Equivalent** (NSE) review defaults to ~~~Premarket Approval application (PMA) or petition for classification
- **deNOVO is the better alternative when**
  - after an NSE determination
  - there is no valid predicate, , and
  - device is low to moderate risk and risk-benefit is apparent.

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FDA's handling of "combination products"

- MODE of ACTION is at the core:
  - Device and drug
  - Device and biologic
  - Thin line between diagnostic and therapy when a sensor triggers drug delivery?
  - Mode of action blurs when device delivers energy and a drug
  - Claims for therapeutic fibers?

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Smart fabrics mean high tech hurdles

Not your usual textile testing

- FDA Software Guidance(s)
- IEC 60601 and collateral standards- test service provider makes a difference
  - EMC/EMI requirements
  - Electrical safety for recharging
- Wireless Guidance
- Cybersecurity Guidance
- Mobile Medical Apps

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USE of STANDARDS

- ISO 10993 and PARTS now dominate the FDA's thinking for biocompatibility- *BUT:*
  - Must have a **BIOLOGICAL RISK ASSESSMENT**, not just a stack of test reports *!!!*
  - Must understand how FDA "modifies" the standards by way of their guidance: **Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"**
- ***Complete Form 3654 for EACH standard cited***

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TOXICOLOGY ≠ Biocompatibility

- Extraction Chemistry is now dominating the qualification of "biocompatibility"
- EXHAUSTIVE EXTRACTION of FINAL DEVICE
  - And yes, sterilization can change the chemistry
- TOXICOLOGY EXPERT to write the report
  - NOT ENOUGH TO DO ISO 10993 testing anymore!

BUT such expensive testing and analysis does not resolve the biomaterials maxim: *Is the material suitable for its intended use???*

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"Better things through chemistry!"

Detail your chemistry!

-know your base polymer at its source
-know all processing aids
-validate each cleaning process
-surface characterize the textile
-FTIR and SEM
-test the extraction solution(s) for pH-
-this can cause false failures in toxicology tests
-Consider ISO 10993-18 provides step by step methods and expectations

Textile processing aids and cleaning processes alter the surface chemistry of polymer

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Common "Chemistry" mistakes

- Raw Materials age in storage and can change physical and chemical properties, altering textile properties once fabricated, so require confirmation testing periodically
- Changing a raw material "source" will usually change the chemistry in some way and you need to know exactly how!
- Different textile processes can affect the same raw material differently—e.g. strain, heat, contamination so don't assume
- Textiles must be post-processed to remove "fines" and processing aids, and this affects final chemistry
- Sterilization processes can affect final chemistry

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Anticipate Animal Testing

- For any implantable textile anticipate GLP animal testing in a qualified protocol- *even if it is a Class II*
- Carefully plan histology & histomorphometry (there is a lot of junk-science claims about "porosity"
- Consider PRE-SUBMISSION meeting with FDA to discuss animal study protocol and specimen analysis Expect at least 6 months implant data-serial sacrifice
- *Pre-qualify your lab, not all are equal*

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Colorants!

- "color additives are considered unsafe, and thereby adulterated, unless a regulation is in effect listing the color additive for such use"
  - Must conform to 21 CFR Parts 73 & 74
- *Testing according to ISO 10993 alone is not sufficient information for use of a colorant*

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Human Factors

- If you build it, will they be able to use it?
- Is your wearable technology smarter than a six-grader?
- Do you really understand the environment—not just the weather, but also distractions, comfort, constrictions, restrictions involved with an intimate garment for the age-specific user, cleaning, disinfection, washing?

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Shelf-life Aging

- Any sterilized polymer-based medical textile will likely require real-time shelf-life aging data in final sterilized package.
- FDA does not accept "accelerated aging" data (alone) to prove product fitness for the shelf-life claim of the product--acceleration can cause false failures. Plan early.

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Clinical Study Quandary

- Many 510(k) devices are pushed to clinical trials without clear objectives for the studies
  - Even if for 510(k), study must still meet scientific rigor ~ *may need IDE; and trial disclosure*
- Clinical study design may fail to properly evaluate real-life device performance, fail to demonstrate effectiveness (no controls, no outcome measure, wrong data, underpowered, time too short)
- *DeNOVO* frequently requires TWO clinical trials!

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*BUT WHAT ABOUT **Rest of World?***

- *Standards are NOT harmonized*
- ISO 13485:2016 is overly "prescriptive"
- ISO 10993-1 has just *Rev'd AGAIN!-2018*
- ISO 14971 interpretation overkill~*ANNEXES*
- ISO Registrars & Medical Device Single Audit Program (MDSAP)
- ***NOT SAFER-NOT MORE EFFECTIVE-MORE PAPER!***

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EU?

- The EU is implementing major changes to device market entrance with new "MDR"
  - Effective date May 26th 2020 for already approved devices
- EU has different "risk-based" strategy so "classification" is not consistent with US and the classification rules change for some products, pushing the classification higher
- EU may be more difficult than US for some products, thus flipping preferred first market

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Notified Bodies/ISO certification

- There are now fewer qualified Notified Bodies for medical device CE-marking
- Some Notified Bodies also serve as ISO registrar, *but not all do*. ISO registrars are busy now due to ISO 13485:2016 upgrades
- Myth that FDA is "soon switching to ISO" has caused confusion in US, push to certify

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What about Canada & BREXIT?

- Canada is the first country to exclusively adopt MDSAP- single audit program for quality inspection.
- BREXIT has created a black hole for the future of medical device approvals in Great Britain. The draft "no deal guidance" hopes to establish a regulatory system that mirrors the key elements of EU MDR. Created new "UK Responsible Person". Must be eventually approved by Parliament.

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STRATEGIES FOR WORLD-WIDE MEDICAL TEXTILE SAFETY AND PERFORMANCE

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Where do you fit in the chain?

- Component supplier only- “off the shelf”
- Limited selection available for custom specification and supply agreement
- Looking for contract manufacturer to do it all
- Want textile contractor and we’ll modify the surfaces or construction
- We’ll control product from material to finished goods - packaging and sterilization

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US-Regulatory requirements based upon place in the supply chain?

- We only supply a non-critical COMPONENT
- We supply a subassembly or critical component
- We are contract manufacturer providing critical processed medical textile
- We are “specifier” of device and submit premarket application
- We are manufacturer of finished medical device (producer) and submit premarket application

- Typically supply only by purchase order to catalogue specification
- Require **supply agreement**/ may or may not require R & L;
- Supplier agreement + quality agreement and R & L as contract manufacturer
- Supplier agreement + quality agreement and R & L as “specifier” and/or manufacturer w/ textile contract manufacturer also registered

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MAF: Device Master File

- Determine if your materials supplier has established a Device Master File (MAF)
- If you are a supplier or converter, consider establishing a MAF for your customers
- MAF is filed with CDRH-FDA as a resource "library" and accessed by FDA reviewer at the time of filing via letter of access-
- MAF can't answer all the questions for everyone
- *But it says there is a commitment to quality*

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If you put it into interstate commerce

MEDICAL DEVICE MANUFACTURER'S RESPONSIBILITY

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Quality Responsibilities are universal

- Know your quality requirements early--***PLAN***
- Create a "quality culture" in your teams and vendors
- Establish a quality traceability chain ***(quality plan)***
- Select qualified material vendors who certify their results, set agreement terms early- *don't HOARD*
- Select FDA registered medical material converters
- Select FDA registered contract manufacturers
- Seek out textile contractors with a MAF
- *Moi ISO, Vous ISO?*

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MEDICAL DEVICE PRODUCER RESPONSIBILITIES

- Take a lesson in textiles: understand how they are made
- Understand basic process vulnerabilities and variabilities and sterilization impact
- Understand that the process is more than just "knitting or "weaving"
- Understand that textiles have a finite life!

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Qualify, Test, Verify, Validate : *repeat as necessary*

- Pre-qualify vendor and process controls
- Audit records and supply chain controls
- Plan verifications and "first article inspection"
- Validate that your product meets user requirements~~~*all INPUTS*

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Total Lifecycle Management

- KNOW your customer-- *Voice of Customer*
- Understand & implement ***EFFECTIVE*** Design Control and Review and Risk Assessment.
- ***USE*** Design-FMEA, user-FMEA and pFMEA
- ***MITIGATE*** thru Verification & Validation
- SUPER-manage first two years of complaints
- *Listen to the user community*

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Thank you

Questions?

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