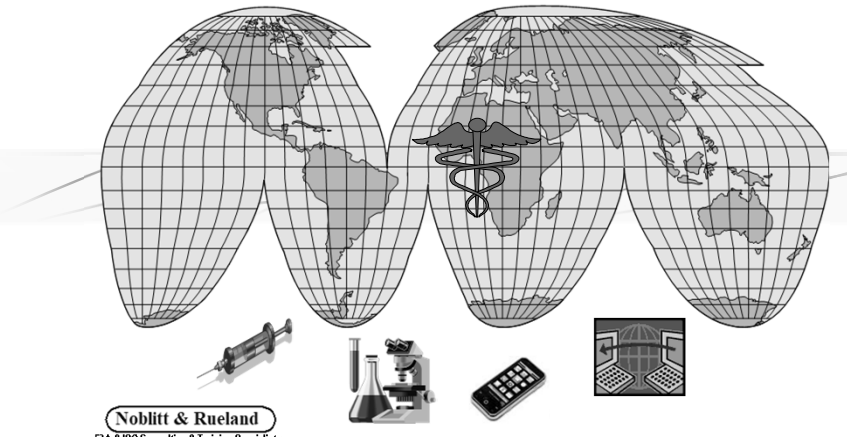
UCI Medical Device Regulatory Awareness - Implications for Start-ups -



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Noblitt & Rueland

- Consulting & Training Company
- >30 Years
- Specializing in FDA & ISO related issues
- Primarily focused on medical device regulatory & quality
- Trained over >5000 medical device manufacturing employees on numerous FDA & ISO topics
- Consulting on Medical Device submissions, 510(k), CE Mark, PMA submissions, compliant quality systems, QSR/GMP, ISO 13485, auditing, software, Risk Analysis, Design Control, IEC 60601-1, Electronic Recordkeeping, clinical studies, and FDA enforcement problems, etc.

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Brent Noblitt Biography

Brent Noblitt is co-founder and Senior Partner of the consulting firm Noblitt & Rueland. Mr. Noblitt specializes in international and U.S. medical device strategic planning, development, and marketing. His consultation has been used to market medical devices throughout the world. Mr. Noblitt's associations range from start-up ventures to Fortune 100 corporations. His marketing background and technical training allows him to comprehend and advise on the marketing planning process and opportunities of various technologies. Prior to founding Noblitt & Rueland, Mr. Noblitt held management & executive positions in the medical device industry. Mr. Noblitt's product experience includes various critical care devices, cardiac output computers & pulmonary catheters, extravascular lung water computers, ultrasound devices, phono-angiography, computerized patient databases, patient monitoring systems, disposable & reusable pressure monitoring devices & accessories, ejection fraction computers, continuous mixed venous oxygen saturation systems & catheters, surgical laser systems, implantable defibrillators, pacemakers, continuous blood pressure control systems, as well as, home healthcare delivery systems. His academic training includes a B.S. and M.S. in Electrical Engineering-Biomedical from Purdue University complemented by an M.B.A. degree earned from Pepperdine University and he is a member of ASQC-Biomedical & Healthcare Divisions, Association for the Advancement of Medical Instrumentation (AAMI), and the Orange County Regulatory Affairs Association (OCRA).

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Medical Device Regulatory Awareness Training

- SESSION OBJECTIVES
  - Gain insight into regulations for medical devices especially as related to Start-up companies.

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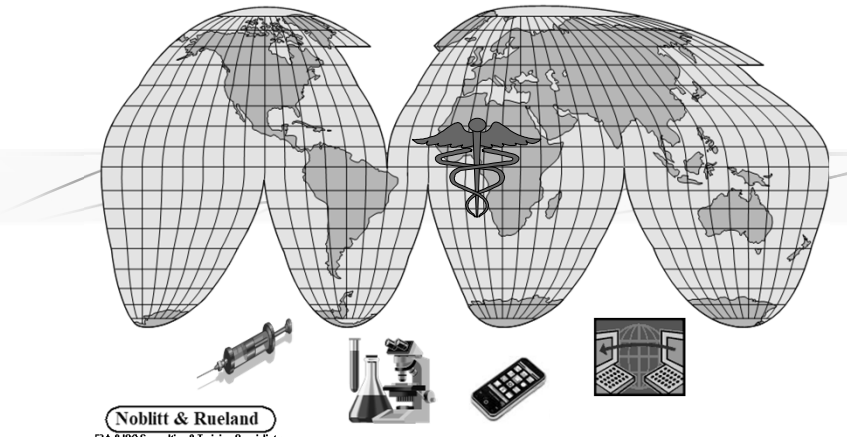
Regulatory Overview
(US Focus)



7

FDA Purpose

U.S. FDA = United States Food and Drug Administration

- Government watch dog over Foods, Drugs, Devices, Cosmetics, etc.
- Protect Public Health
  - Establish controls
  - Review & inspect safety & efficacy of medical devices
  - Regulate design & manufacturing
    - Inside US &
    - Outside US for use in US
  - Expects documentation: “Not written down it didn’t happen.”
- FDA takes their responsibility very seriously…they carry a big stick! Not just a traffic cop.
- Los Angeles District Office ~2 miles away (new people)

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How does FDA protect the public health?

THROUGH ENFORCEMENT

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FDA Enforcement Tools

- NAI (No), VAI (Voluntary), OAI (Official Action Indicated)
- 483 Observations (inspections)
- Warning Letters
- Recalls
- Seizure
- Consent Decree
- Injunction
- Prosecution
- Civil Penalties
- Debarment from industry
- Import Detention
- Criminal Proceedings, etc.
- Withdrawal of Product Approval
- Disqualification (clinical investigators)

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Other ways FDA protects that will have major impact on a start-up

- Not Approving or Clearing Medical Device Submissions
- Product Recalls (example: recalling a product sold without a required approval or clearance)
- FDA facility inspection findings that lead to a Warning Letter or worse (public information)

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Basic Manufacturer Requirements

- Registration & Listing with FDA
- Submissions…leading to regulatory approval or clearance to legally market a medical device in U.S.
  - Exempt, non-exempt, 510(k), PMA, De Novo
- Quality system…a controlled & documented process for manufacturing a medical device in compliance with a regulatory body's requirements/regulations. (Use of contract manufacturer can off-load some of these requirements.)
  - 21 CFR Part 820 Compliant (very similar to ISO 13485:2016)
  - FDA will inspect (goal is every 2 years)
- California companies must also be licensed by the state.
  - $2,454/1st year, $3,988/2 yrs, will inspect very quickly

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Start-up Regulatory Considerations

- Regulatory Strategy
  - Classification of Product/Device
  - Required regulatory avenue
    - Clinical Studies required? ($$$, Time)
- Regulatory Costs
- Organization Infrastructure
- Exit Strategy thoughts
- Recommendations

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Classification & Regulatory Strategy

- Need to determine the Device classification early (critical)
- Is it a Device by FDA Definition? Wellness product?, etc.
- Class I or Class II exempt (no submission required)
- Class I or Class II non-exempt
  - 510(k) submission required ($ to $$), FDA fee: $11,594 / $2,899*
  - Must show substantial equivalence to a predicate device
  - Clear predicate(s) identifiable? If not, De Novo route feasible?
    - De Novo FDA Fee $102K / $25K* plus clinical data/trials usually needed
- Class III
  - Most Class III devices require PMA ($$$ to $$$$$)
    FDA fee: $341K / $85K* / $0 (1st PMA fee waived if <$30 mill)
  - Probability of approval mainly based on achieving clinical endpoints during clinical studies ($$$)
- Examples from FDA database…

* Small Business Designation= sales < $100 million

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Device Example A

Device	Over-the-counter Powered Light Based Laser For Acne
Regulation Description	Laser surgical instrument for use in general and plastic surgery and in dermatology.
Definition	The device is intended for over-the-counter (otc) use to treat patients with mild to moderate acne vulgaris. The device is intended to emit energy in the red and blue region of the spectrum, specifically indicated to treat mild to moderate acne vulgaris.
Physical State	Light Source
Technical Method	The outputs are pre-tuned to a particular wavelength with a narrow spectral bandwidth.
Target Area	Mainly on the face, but can be on the back or on the other parts of the body. Treatment area is 5x6 cm (at a time.)
Regulation Medical Specialty	General & Plastic Surgery
Review Panel	General & Plastic Surgery
Product Code	OLP
Premarket Review	General Surgery Devices (DHT4A) General Surgery Devices (DHT4A)
Submission Type	510(k)
Regulation Number	878.4810
Device Class	2
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Summary Malfunction Reporting	Eligible
Recognized Consensus Standards	• 12-102 ANSI IES RP-27.2-00/R17 Recommended Practice for Photobiological Safety for Lamps and Lamp Systems - Measurement Techniques • 12-249 IEC 62471 First edition 2006-07 Photobiological safety of lamps and lamp systems • 12-297 ANSI IES RP-27.1-2015 Recommended Practice for Photobiological Safety for Lamps and Lamp Systems - General Requirements • 12-321 ANSI IES RP-27.3-17 Recommended Practice for Photobiological Safety for Lamps - Risk Group Classification and Labeling
Implanted Device?	No
Life-Sustain/Support Device?	No
Third Party Review	Not Third Party Eligible

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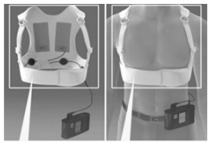
Device Example B



Device	Wearable Automated External Defibrillator
Definition	The device is an automatic external defibrillator which monitors and treats a patient for ventricular defibrillation. Device is intended to be worn in home or in hospital settings as prescribed and overseen by a physician.
Review Panel	Cardiovascular
Product Code	MVK
Premarket Review	Cardiac Electrophysiology, Diagnostics, and Monitoring Devices (DHT2A) Cardiac Electrophysiology, Diagnostics, and Monitoring Devices (DHT2A)
Submission Type	PMA
Device Class	3
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Summary Malfunction Reporting	Ineligible
Recognized Consensus Standard	• 3-132 ISO 27185 First edition 2012-02-15 Cardiac Rhythm Management Devices - Symbols to be Used With Cardiac Rhythm Management Device Labels, and Information to be Supplied - General Requirements
Implanted Device?	No
Life-Sustain/Support Device?	Yes
Third Party Review	Not Third Party Eligible

Difference & Impact: Example B vs Example A
Probably >$1+ Million, several years to market and increased regulatory & liability risk

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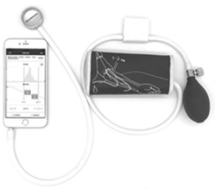
App Example



© Accutension Smartphone Auscultatory BP

Device	Blood Pressure Cuff
Regulation Description	Blood pressure cuff.
Definition	A blood pressure cuff is a device that has an inflatable bladder in an elastic sleeve (cuff) with a mechanism for inflating the bladder. The cuff is used to determine a subject's blood pressure.
Regulation Medical Specialty	Cardiovascular
Review Panel	Cardiovascular
Product Code	DXQ
Premarket Review	Cardiac Electrophysiology, Diagnostics, and Monitoring Devices (DHT2A) Cardiac Electrophysiology, Diagnostics, and Monitoring Devices (DHT2A)
Submission Type	510(k)
Regulation Number	870.1120
Device Class	2
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Summary Malfunction Reporting	Eligible

Recognized Consensus Standard

- 3-96 ISO 81060-1 First edition 2007-12-01
  Non-invasive sphygmomanometers - Part 1: Requirements and test methods for non-automated measurement type

So all health apps are medical devices?
No…some are considered "general wellness products" which are may not be considered medical devices.
Be very, very careful! Guidance is available.

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Regulatory Costs

- If 510(k) Submission required
  - Generally speaking, $3K - $50K++ to achieve FDA 510(k) clearance, when testing costs are included & depending on the device
  - Most don't require clinical data/trials, but some do (~5%)
  - ~90-180+ days from submission to FDA clearance (if well written)
- If PMA Submission required, in general >$100K - $1M++ to achieve FDA approval
  - Substantial clinical data/trials needed
  - ~250 days to 3+years from submission to approval
- FDA Establishment Registration Fee $5,236/yr (FY 20)
- Quality System (GMP) implementation required? Not trivial to implement or maintain. FDA will inspect. Personnel needed?

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Organization Infrastructure

- Brick & Mortar vs Virtual Company
- Virtual Company Infrastructure is acceptable by FDA
  - Utilization of consultant(s) for regulatory expertise
    - Submissions & installation of Quality System if necessary
  - Design & manufacturing can be done by vendors (i.e. contract manufacturers)
- Internal hire vs External consultant
  - At a minimum, periodic ongoing regulatory/quality support will be needed

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Company / Investor Exit Strategy Thoughts

- If exit strategy is to obtain 510(k) clearance and divest the company or sell the submission, a quality system may not be needed (i.e. no manufacturing planned)
- A Quality System and manufacturing are <u>not</u> required to obtain 510(k) clearance…however elements of a QS may be needed for a submission (i.e. Design Control, Risk Management, Software Quality Assurance, etc.). If manufacturing is planned, a FDA compliant Quality System will be required.
- Quality System is needed for PMA approval or to manufacture a Medical Device in most cases.
  - FDA will inspect prior to granting PMA approval

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Recommended Start-up 1st Step: Regulatory Assessment

- Perform or have a regulatory assessment done by someone knowledgeable and experienced in medical device regulations (decipher gray areas)
- Benefits
  - Understand
    - regulatory pathway (classification, etc.)
    - clinical studies & what testing is required ($)
    - potential regulatory costs ($ to $$$$$)
    - likely regulatory timeline/delays (mos to years)
    - regulatory risks
  - Marketing/Financial Strategy mesh with Regulatory Requirements? ex. Prescription vs OTC (over-the-counter), 510(k) vs PMA
  - Provides information for an intelligent discussion with potential investors & financial planning

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Start-up: Product Development Recommendation

- Development vs Feasibility?
- Recommendation: Create & Document a Design Control process for development; especially,
  - Design Control
    - FDA will expect/require compliance with Design Control requirements 21 CFR Part 820.30
    - Submission & eventual Quality System
  - Risk Management (part of Design Control)
    - Risk and Hazard Analysis (submission & quality system)
  - Software
    - FDA expects/requires software to be developed under a defined and documented process as part of Design Control
- Creating retrospective documentation is no fun!
- Benefits: creation of high quality, safer devices quicker and achieve FDA clearance faster.

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Good Luck!

- Welcome to the medical device world!
- More info & questions?
  - MDM, booth 1329
  - Call / email with questions
  - Training Medical Device courses offered
    - Anaheim, Disney Resort, July 20-24, 10 courses
    - See www.fdaconsulting.com for more info

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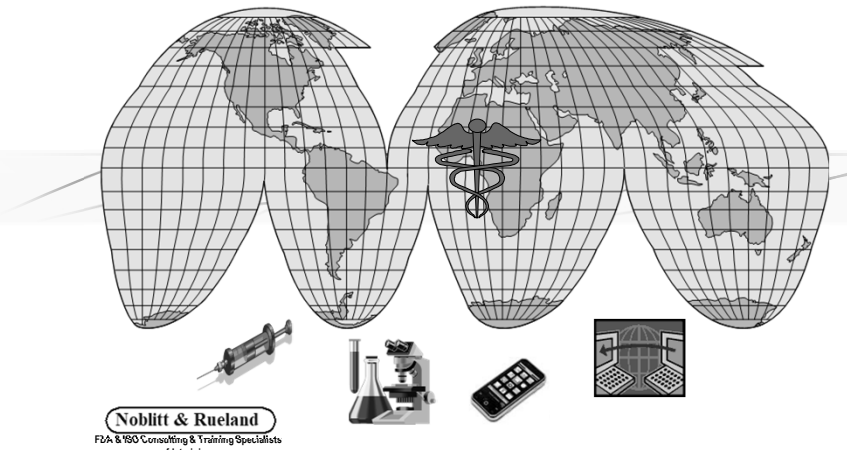
Thank You!



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Hot/New Regulatory Topics

- Presidential Election…New Direction? More/less Regulation?
- CE Marking (Europe) major changes coming
  - EU Medical Device Regulation (MDR, IVDR, # Notified Bodies)
- Single Audit Pilot Program, MDSAP, (U.S., Australia, Brazil, Canada, and Japan) Gaining Acceptance, $$
- Device Tax (2.3%) repealed
- Cybersecurity
- Breakthrough Device Designations
- Risk Management / ISO 14971 update
- Recalls (increase in recent years)
- Usability / Human Factors
- Post Market Surveillance
- AI / Machine Learning gaining FDA acceptance
- FDA Guidance Documents/Programs growing fast (staying current is important)

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