Medical Device Regulatory Science: A View from 20 Years at FDA's Device Center

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Outline

- Medical Devices
- FDA Regulation of Medical Devices
- Medical Device Regulatory Science
- Regulatory Science Examples
  - MAQC-II
  - Expedited Access Program
  - Adaptive Designs
  - Using Real World Evidence
    - Balancing PreMarket and PostMarket Data Collection
    - Bayesian Statistics in Clinical Trials
- Concluding Remarks

What are Medical Devices?

Definition by exclusion: any medical item for use in humans that is not a drug nor a biological product

intraocular lenses
MRI machines
breast implants
surgical instruments
thermometers
(drug-coated) stents
home kit for AIDS
diagnostic test kits
bone densitometers
artificial hips

PRK lasers
pacemakers
defibrillators
spinal fixation devices
glucometers
artificial hearts
hearing aids
latex gloves
artificial skin
software

The World of Medical Devices

- Devices evolve; they are constantly being improved.
- Rapidly changing technology; average market life of a device is 1-2 years.
- The medical device industry is very innovative and is a vital economic engine of the US.

Kinds of Devices

- Therapeutic Devices – Intended to treat a specific condition or disease
- Aesthetic Devices – Provide a desired change in a subject's appearance through physical modification of the structure of the body
- Diagnostic Devices – Provides information when used alone or in the context of other information to help assess a subject' s condition.

Diagnostic Devices

- Can be used for
  - Diagnosis
  - Screening
  - Monitoring disease or medical condition
- Types of devices
  - *In vitro* diagnostic devices
  - Imaging systems
  - Other *in vivo* devices

Wireless Devices

- Internal
  - control heart rhythm
  - monitor hypertension
  - provide electrical stimulation of nerves
  - operate as a glaucoma sensor
  - monitor bladder or cranial pressure
- External
  - monitor vital signs
  - assist the movement of artificial limbs
  - function as a miniature “base station” for collection and transmission of various physiologic parameters

U.S. Food and Drug Administration (FDA)

- FDA mission – to promote and protect the public health
- FDA regulates about 25% of the GDP of U.S.
- FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

Food and Drug Administration

- Science-based agency that values transparency and innovation
- Regulates about 20-25% of the GDP of U.S.
- Makes enormous amount of pre-market and post market (adverse event reports) information available; preliminary information for FDA Advisory Committees and transcripts
- Companies generate data on which FDA bases almost all decisions
- FDA does not take cost into account in approval decisions

Center for Devices and Radiological Health (CDRH)

- Regulates medical devices and radiological products (not just medical radiological products)
- Examples of radiological issues:
  - Laser pointers and laser light shows
  - Cell phones
  - Microwave ovens
  - In 1998, the rollout of HDTV in Dallas created an interference with medical devices in local hospitals. FDA and FCC worked together to resolve the problem.

U.S. Medical Device Classification

- Class I – General Controls (low risk)
- Class II – Special Controls (through FDA guidance) (medium risk)
- Class III – requires PreMarket Approval unless it was on the market or substantially equivalent to one on the market in 1976. (high risk)
- For Class I or II, unless exempt, a 510(k) is required.
- Classification of a particular device can be appealed.

Types of U.S. Regulatory Submissions

- IDE – Investigational Device Exemption – if approved, allows for the study with a new significant risk device to be conducted in the U.S.
- PMA – PreMarket Approval Application
- 510(k) – PreMarket Notification that the new product is "substantially equivalent" to a predicate device
- *De Novo* Classifications– Evaluation of the Automatic Class III device type for devices of low to moderate risk but there is no predicate device
- HDE – Humanitarian Device Exemption

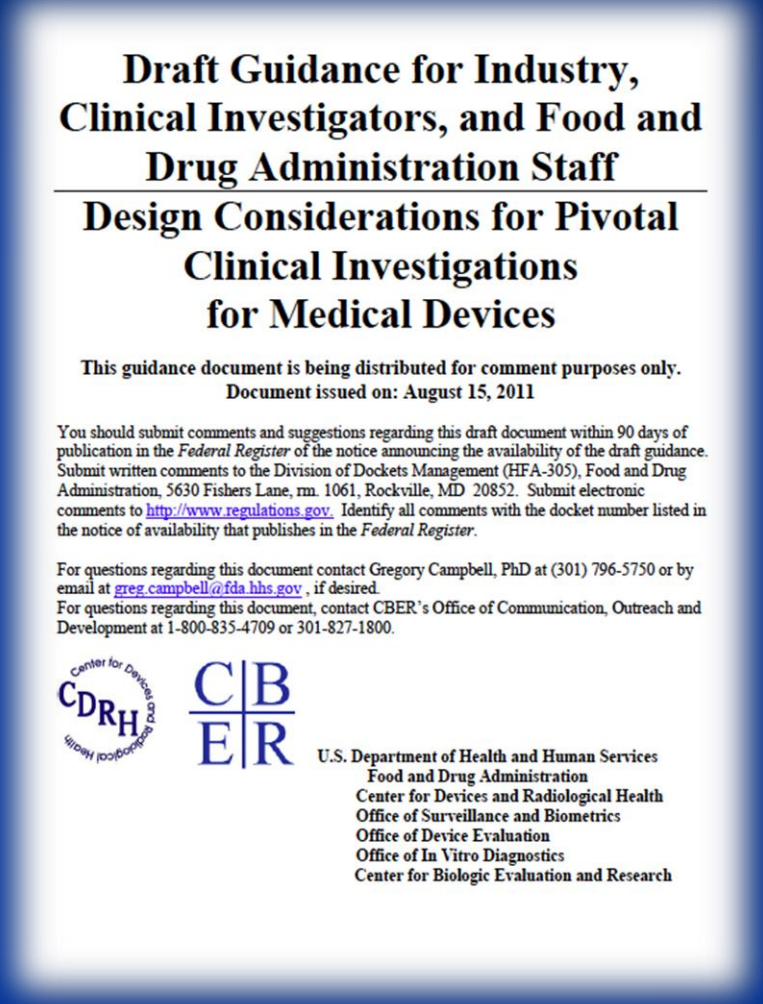
Wireless Device Examples

- Ingestible telemetric gastrointestinal capsule imaging system used to detect abnormalities in the small bowel or esophagus consists of a capsule containing a light source, camera, transmitter and battery required a 510(k) authorization
- System using an ingestible event monitor and a body patch for medication adherence, measuring steps, rest and heart rate, pH, temperature, pressure required a 510(k) authorization.
- Implantable pacemaker that utilizes telemetry to relay information and instruction is a Class III device requiring a PMA.

Wearable Technology and Mobile Medical Devices

- Wearable technology: sensors on skin, watches, clothes, etc., that report the current condition of the person
- Wearable technology and mobile apps could be for general health and fitness and sometimes can function as medical devices (making a medical claim)
- The Internet of Medical Things
- Smart phone apps for medical purposes

Pivotal Clinical Study Design Guidance



Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff

Design Considerations for Pivotal Clinical Investigations for Medical Devices

This guidance document is being distributed for comment purposes only.
Document issued on: August 15, 2011

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Gregory Campbell, PhD at (301) 796-5750 or by email at greg.campbell@fda.hhs.gov , if desired.
For questions regarding this document, contact CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Surveillance and Biometrics
Office of Device Evaluation
Office of In Vitro Diagnostics
Center for Biologic Evaluation and Research

- Discusses several concepts that are fundamental to Good Device Development Practices with respect to clinical trials.
- Finalized Nov. 7, 2013
- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf

Stages of Medical Device Clinical Studies

1) Exploratory Stage – first-in-human and feasibility/pilot studies, iterative learning and product development.
2) Pivotal Stage – definitive study to support the safety and effectiveness evaluation of the medical device for its intended use.
3) PostMarket Stage – includes studies intended to better understand the long-term effectiveness and safety of the device, including rare adverse events.

Not all products will go through an extensive exploratory clinical stage but may have extensive non-clinical studies, including bench testing and animal studies.

Regulatory Science at CDRH

- Office of Science and Engineering Laboratories (OSEL)
  - Division of Applied Mechanics
  - Division of Biology, Chemistry and Materials Science
  - **Division of Biomedical Physics**
  - **Division of Imaging, Diagnostics and Software Reliability**
- Office of Surveillance and Biometrics (OSB)
  - **Division of Biostatistics**
  - Division of Epidemiology

FDA and Engineering

- FDA has more than 200 engineers, almost all in CDRH, in either regulatory science or in review

Two FDA Guidance Documents

- Radio Frequency Wireless Technology in Medical Devices
  - Issued in final form August 13, 2013
  - Contact is Donald Witters of OSEL's Division of Biomedical Physics
- Mobile Medical Applications
  - Issued in draft form September 25, 2013
  - Contact is Bakul Patel

FDA Guidance on Mobile Medical Applications

- http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf
- Issued in Feb. 9, 2015
- Consistent with "Medical Devices Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices" issued on February 9, 2015.
- No effort to regulate health and wellness devices
- Regulatory discretion for some medical device mobile apps based on risk.

Innovative Regulatory Science Examples

- MAQC-II
- Expedited Access Program
- Adaptive Designs
- Using Real World Data
  - PreMarket-PostMarket Balance
  - Clinical Trials Using Bayesian Statistics

MAQC II

- Microarray Quality Control Project—FDA Critical Path effort
- The MAQC-II Project: A comprehensive study of common practices for the development and validation of microarray-based predictive models
- Leming Shi of FDA's NCTR was the overall coordinator for the Project; MAQC II has a number of working groups, including Regulatory Biostatistics Working Group.
- Investigators donated samples and microarray manufacturers donate microarrays (4000 microarrays in all)
- Six pairs of datasets (training set and an independent test set) with a total of 13 endpoints
- Analysis groups from 36 organizations in 9 countries built classification models using statistical methods, Statistical models, machine learning techniques, Bayesian networks and neural networks.

MAQC-II Consortium Effort

- 36 Data Analysis Teams built models; only 17 built models for all endpoints.
- 19,696 models in all were built. For each endpoint, each team was required to nominate a single well-performing model (nominated model) and freeze it for the validation phase; there were 323 nominated models in all. Each team reported how they built all models in terms of Good Classifier Development.
- The validation datasets were kept not released until models were frozen. The validation was conducted centrally to produce individual predictions and then performance measures.
- Work published in *Nature Biotechnology* in 2011.

Expedited Access (EAP) Program

- Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions: Guidance for Industry and Food and Drug Administration Staff
- http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393978.pdf
- Issued in final form April 13, 2015.

Types of Clinical Evidence for EAP

- Two-Phase Studies
  - Approval can be based on intermediate or surrogate endpoints with a pre-specified criterion such a predictive probability of overall success for the primary endpoint.
- EAP is similar to Accelerated Approval Pathway for pharmaceutical drugs.
- FDA encourages the sponsor to have early interaction with the Agency.

Expedited Access PMA (EAP) Program

- Criteria for EAP Designation
  - Device is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition
  - Device meets one of the following criteria:
    - Represents breakthrough technology that provides a clinically meaningful advantage over existing technology
    - No approved alternative treatment or means of diagnosis exists
    - Device offers significant, clinically meaningful advantages over existing approved alternative
    - Availability of the device is the in the best interest of patients (i.e., addresses an unmet medical need)
  - Sponsor submits an acceptable draft Data Development Plan

Some Types of Adaptive Designs

Adaptive designs can make preplanned changes:

- Sample size re-assessment (blinded or unblinded)
- Drop treatment arm
- Change randomization ratio
- Adaptive enrichment

FDA Draft Guidance on Adaptive Clinical Study Designs

- FDA issued draft guidance "Adaptive Designs for Medical Device Clinical Studies" in May, 2015.
- http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446729.pdf

Several Key Adaptive Points

- Devices have some unique challenges for adaptive studies: unblinded studies, one-arm studies, diagnostic studies
- Simulations are absolutely essential to understanding the operating characteristics of the design.
- The fixed sample size design is almost always a fantasy! So almost always consider sample size recalculation.

Balancing Premarket and Postmarket Data Collection

- Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval: Guidance for Industry and Food and Drug Administration Staff
- http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393994.pdf
- Finalized guidance issued April 13, 2015.
- Legal basis: Section 513(a)(3)(C) of FD&C Act:
  - In making a determination of a reasonable assurance of the effectiveness of a device for which [a premarket approval application] has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.

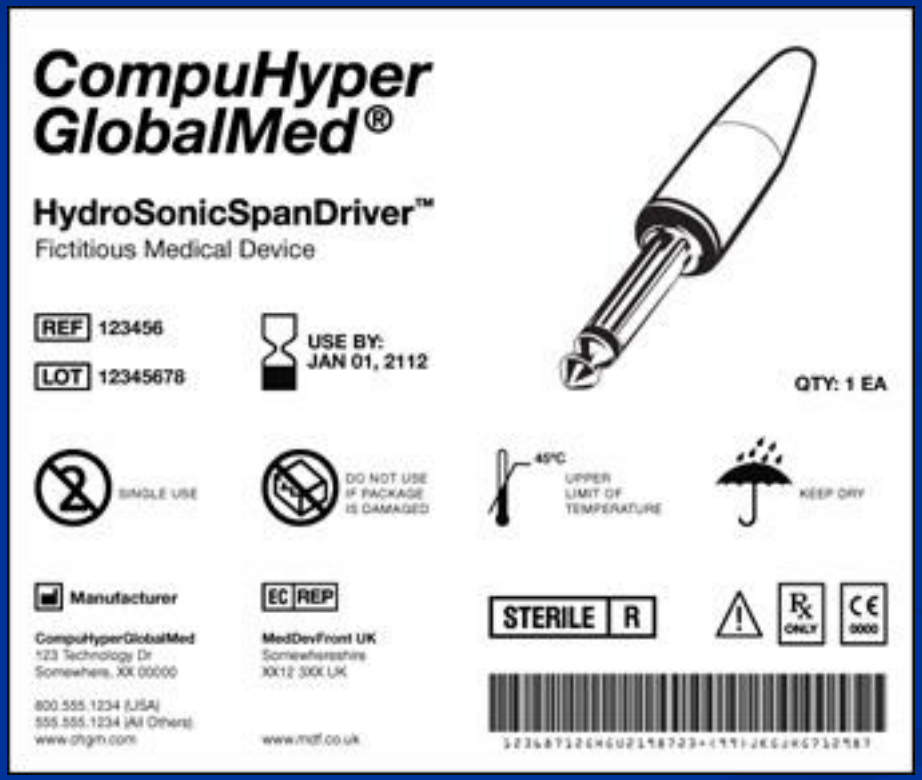
Balancing Premarket and Postmarket Data Collection

- "FDA may consider it acceptable to collect certain data in the postmarket setting, rather than premarket under certain circumstances when FDA has uncertainty regarding certain benefits or risks of the device, but the degree of uncertainty is acceptable in the context of the overall benefit-risk profile of the device at the time of premarket approval."

Innovative PostMarket Activities

- National Medical Device PostMarket Surveillance Strategy: "Strengthening Our National System for Medical Device PostMarket Surveillance: Update and Next Steps (April, 2013)
- http://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf
- Electronic Health Records (EHR)
- Unique Device Identifiers (UDI)
- High-Quality Registries

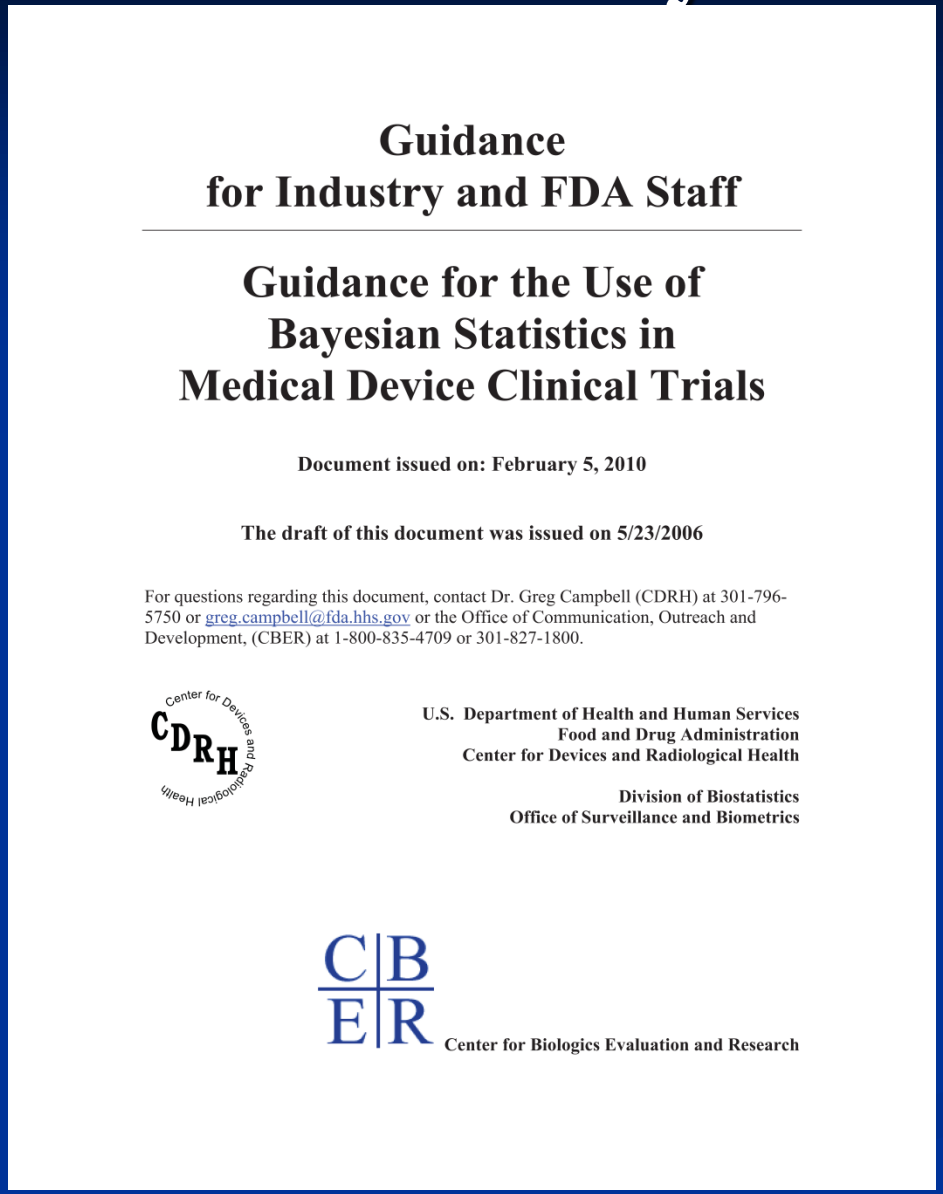
Unique Device Identifiers



Real World Data Using Bayesian Statistics

- Bayes rule or theorem (named after Thomas Bayes) is a way to combine current data with prior information. It can calculate the updated probability of an event given new data using both the prior probability of the event based on previous information and the likelihood of the new data.

FDA Bayesian Guidance



Guidance
for Industry and FDA Staff

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

For questions regarding this document, contact Dr. Greg Campbell (CDRH) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-835-4709 or 301-827-1800.

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- Finalized February 5, 2010.
- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm

Two Bayesian Approaches

- Bayesian hierarchical modeling using data from one or more prior studies to "borrow strength" from them.
- Bayesian adaptive designs, usually with non-informative priors
  - Usually these designs are Bayesian group sequential
  - The BIG advantage here is to model the primary outcome in terms of intermediate endpoints.

Bayesian Adaptive Designs Using Predictive Probability

- Predictive posterior probability was used to decide:
  - Stop enrollment, wait 6 months and do final analysis
  - Stop trial for futility
  - Continue enrollment
- Predictive posterior probability is calculated according to pre-specified rules agreed upon between FDA and the sponsor.
- Predictive posterior probability is only for sample size adaptation, not for making of study success decision.

Discuss with FDA

- Come in a meet with review divisions in CDRH before launching any registration trials for medical devices and take advantage of what are called pre-submission meetings for CDRH.

Where to Go to Get Help

- Device Advice: Comprehensive Regulatory Assistance
- http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

Conclusion

- FDA is committed to encouraging medical device innovation and in streamlining clinical trials.
- There are a number of possible clinical study designs.
- Meet with FDA in a pre-submission meeting
- It is an exciting time for the medical device community.
- We can all make a difference.

Thank you!