The World of Medical Devices and Its Increasing Impact on Pharmaceutical Statistics

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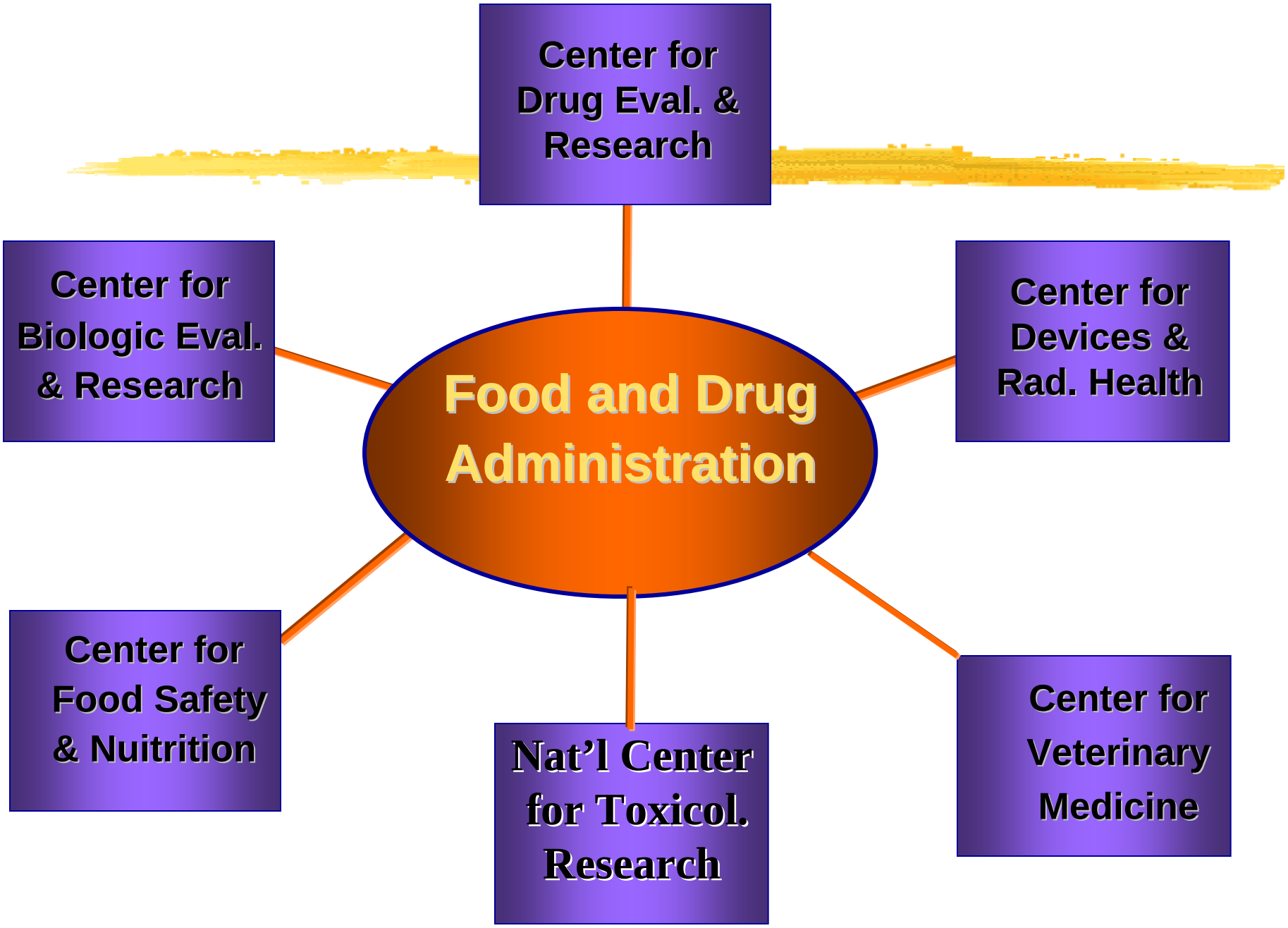
Outline

- What are devices?
- The nature of medical devices and their regulation
- Therapeutic device problems
- Diagnostic issues
- Bayesian statistics in medical device trials
- Surrogate endpoints
- FDA Critical Path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What are Medical Devices?

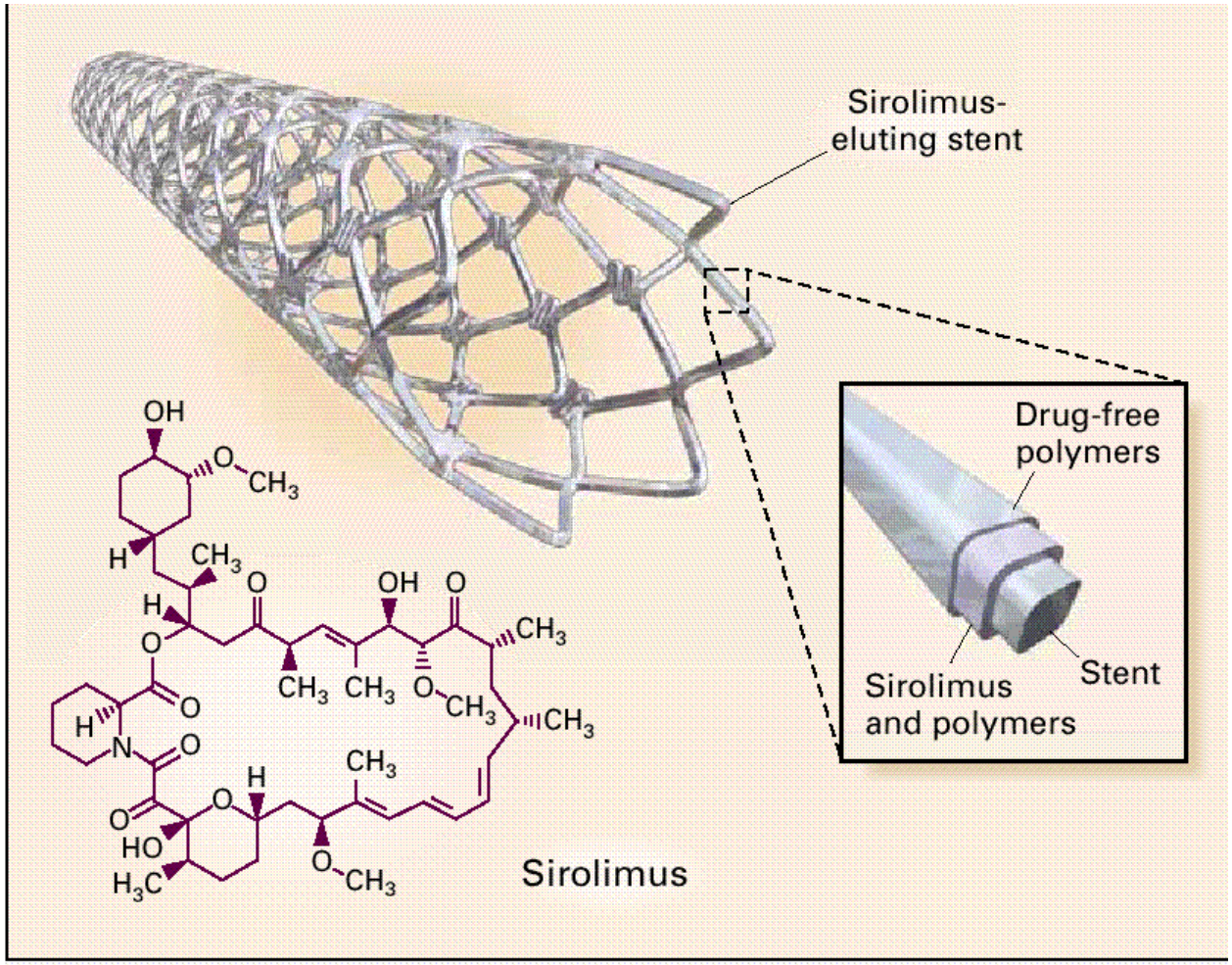
Definition by exclusion: any medical item for use in humans that is not a drug nor a biological product

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, etc

What is a Drug-Eluting Stent?

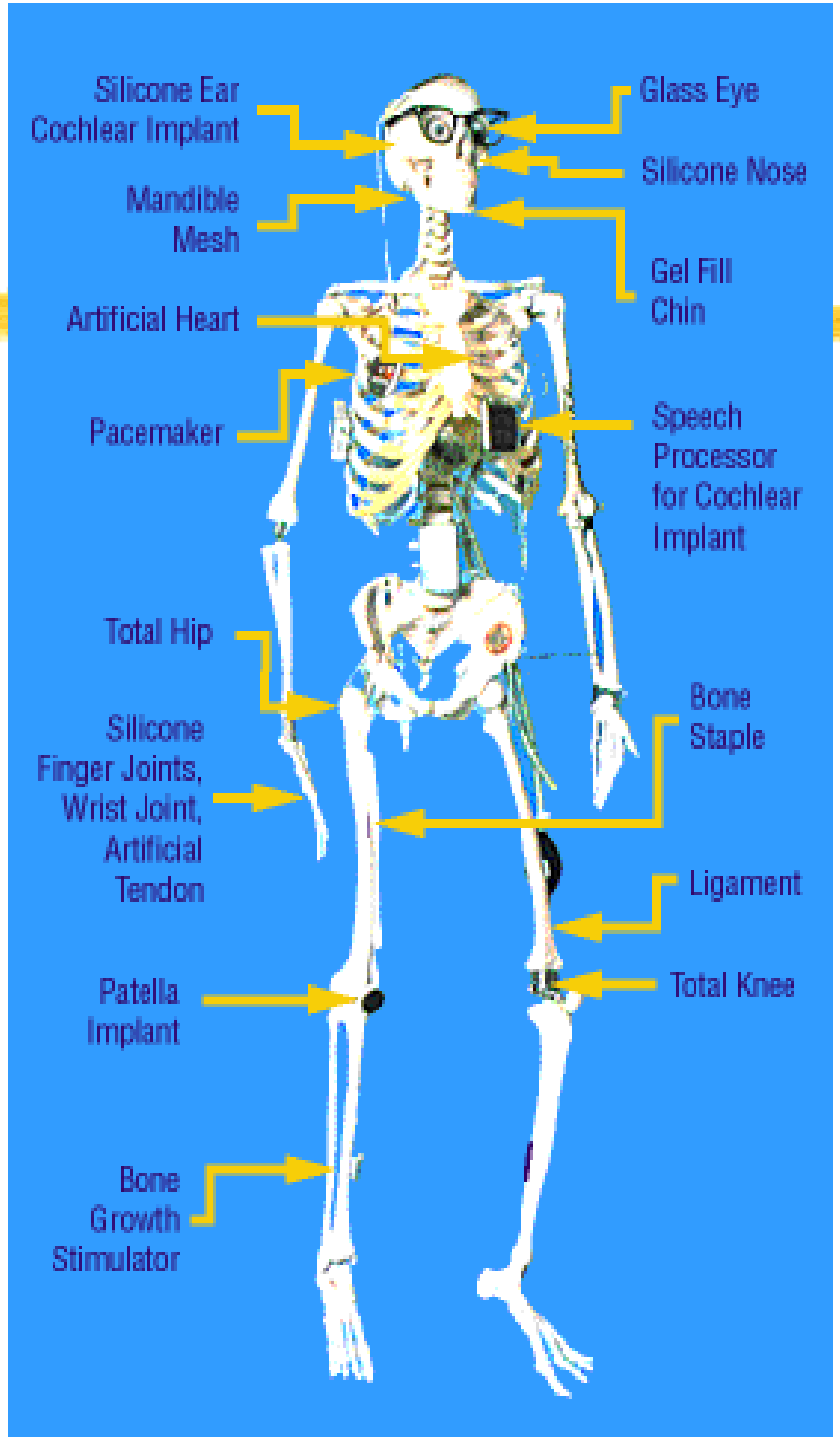
Example: **Cordis' Cypher™ Sirolimus-Eluting Coronary Stent**



Components

- Stent Platform & Delivery System
- Carrier(s)
- Drug

Meet Yorick


Silicone Ear
Cochlear Implant
Mandible
Mesh
Artificial Heart
Pacemaker
Total Hip
Silicone
Finger Joints,
Wrist Joint,
Artificial
Tendon
Patella
Implant
Bone
Growth
Stimulator
Glass Eye
Silicone Nose
Gel Fill
Chin
Speech
Processor
for Cochlear
Implant
Bone
Staple
Ligament
Total Knee

Devices Not Drugs -- The Differences

- Different Alphabet Soup
  IDE -- **I**nvestigational **D**evice **E**xemption
  PMA -- **P**re**M**arket **A**pproval
  510(k) -- Substantial Equivalence**---**not bioequivalence
- A Single Confirmatory Trial (not 2).
- A ‘Sham’ Control Trial may not be possible
- Masking (blinding) may be impossible for patients, health care professionals, investigators
- Usually don’t use Phase I, IIA, IIB, III, IV

Devices Not Drugs -- The Differences (Cont.)

- Bench/Mechanical Testing not PK/PD
- Mechanism of Action often well understood
  - Effect tends to be localized rather than systemic, physical not pharmacokinetic
- Pre-clinical Animal Studies (not for toxicity)
- Number & Size of Device Companies
  - 27,635 registered firms, of which 22,838 are US
  - Median device company size--under 50 employees (Many are new start-up companies.)
- Implants (skill dependent; learning curve)

The Nature of Medical Device Studies

- Whereas drugs are discovered, devices evolve; they are constantly being “improved”; life length of a device is 1-2 years.
- Rapidly changing technology

FDA Premarket Review for Market Entry

- Premarket notification (510(k))
  - "Substantially equivalent" to a predicate (pre-amendments or reclassified post-amendment devices)
  - Presumes safety and effectiveness of predicate imputed from marketing experience
- Premarket approval application (PMA)
  - Devices found not substantially equivalent to a predicate device
  - Class III pre-amendment devices, and transitional devices

“Substantial Equivalence”

- 510(k) pre-market notification process
- Comparison not to first approved device
- Danger of becoming worse than placebo (sham); this can be called predicate creep
- Change in technology could make old device obsolete
- No uniform process to set the non-inferiority margin

The Regulatory View in Devices

- Statutory directive for the FDA's CDRH:

  rely upon valid scientific evidence to determine whether there is reasonable assurance that the device is safety and effective.

- Valid scientific evidence for PMA is evidence from:
  - well controlled studies
  - partially controlled studies
  - objective trials without matched controls
  - well documented case histories
  - reports of significant human experience (21 CFR 860.7)

Statistical Issues

- Statistical Design (at the Planning Stage)
- Types of Clinical Trials, Endpoints, Analysis
- How to Avoid Sources of Bias (masking, randomization)
- Surrogate Endpoints (Late Loss in Drug Eluting Stents)
- Sample Size Determination
- Equivalence -- A Statistical Viewpoint

Other Statistical Issues

- Patient Drop-out, Intention-to-Treat Analysis, Patient Compliance
- Interim Analysis
  - Data Monitoring Committee (DMC)

    New final guidance
    http://www.fda.gov/cber/gdlns/clintrialdmc.htm
  - Continuous monitoring (blinded)
  - Group sequential monitoring (blinded)
- Resizing the trial (planned in advance)

Other Statistical Issues

- Analysis of Correlated (Clustered) Data
- Repeated Measures
- Time Series Data
- Survival Analysis; Censored Data; Truncated Data

Other Statistical Issues

- Validation of Statistical Assumptions
- Pooling Data from Multiple Centers
  - Treatment by center interaction
- Outliers
- Multiplicity
- Subset analysis (goin' fishin')
- Meta-analysis

Unique Challenges to Statistics by Therapeutic Medical Device Clinical Trials

- **New design challenges**

  adaptive or unconventional; historical controls; ethical issues.

- **Statistical equivalence**

  How can one use statistics to show that two devices are "substantially equivalent" (SE)

- **Post-market challenges**

  how to determine that a marketed device may pose a health risk without "denominator" data

- **Rapidly changing technology**

(One-arm) Historically Controlled Studies

- Most problematic, historical controls at an earlier point in time (temporal bias)
- Not a clinical trial (experiment), just an observational study, hence any comparative statistical inference compromised
- Most prone to bias
- Examples in CDRH:
  - IOLs, heart valves

Statistical Methodology for One-arm Studies

- Causal Inference
  - Propensity scores
  - Sensitivity analysis
  - Also useful in studies with missing data
- Counterfactuals

Diagnostic Devices

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

Examples of Diagnostic Devices

- genetic markers for cancer
- cervical cytology
- prostate screening antigen (PSA) test
- home drug test kit
- bone densitometry
- MRI
- ultrasound for breast cancer
- glucose meters for home testing
- chlamydia test
- creatine kinase test
- pregnancy tests
- microarrays

More Diagnostic Devices (Imaging)

- Ultrasound as an adjunct to mammography
- Automatic image analysis re-screener of Pap smears for cervical cancer
- Digital mammography
- Image checker (mammography)
- Caries Detector
- Radioimmunoassay drugs

Statistical Design Issues in Diagnostics

- Plan the type of study design; more than one design is possible. Potential problem is that FDA usually does not require an Investigational Device Exemption (IDE) for a diagnostic test.
- The Randomized Clinical Trial (the premier design for therapeutics) is of limited use in many diagnostic evaluations of tests.
- It is generally more efficient to use patient as his/her own control if new test is compared to a reference method.

More Design Issues

- Identify realistic target population.
- Define disease operationally (can't use the new test in that definition).
- "Gold standard" may not be possible.
- Different set of hypotheses for substantial equivalence claim ("prove the null hypothesis")
- Plan for multiple clinics (or centers) for FDA.

Bias in Design

- Case Mix-- (do not avoid the difficult cases; guarantee a realistic case mix)
- Observer bias--
  - Mask the test interpreters from diagnostic truth
  - Recall bias; fatigue bias; learning curve bias
- Misclassification bias
  - (verification, work-up)
- Inconclusive bias (do not drop out cases)

Diagnostic: Analyses Using ROC Plots

- Since the Receiver Operating Characteristic (ROC) plot is a plot over all sensitivities and specificities, it gives a global assessment, a visual presentation of the entire performance
- Very useful methodology in CDRH
- If the data are ordinal, one can use **latent variables** to build the theoretical ROC curve
- ROC methodology can be used in a variance components effort to model the variance due to readers, to cases and help plan the trial

Diagnostics: Lack of a "Gold Standard"

- Treat prevalence as an unknown complication and estimate it (impute the true disease status for each patient in the study)
- One problem: most schemes rely on the assumption of conditional independence: given the true disease state, the two tests are independent. This is often unlikely to be true.
- Latent variables (some using ROC)
- Bayesian approaches

Genetic Tests

- For most genetic tests, there is a manufacturer and a lab
- Complexity of Genetic Tests
  - Home-brew genetic tests
  - Tests in physicians' offices
  - High complexity lab kits
  - DNA microarrays (genomic test)

Types of Genetic/Genomic Tests

- Single Nucleotide Polymorphisms (SNPs)
  - Basically Qualitative Assay: Is the particular sequence present or not
  - Examples: Factor V Leiden, HLA typing, cytochrome P-450 superfamily SNPs (CYP2D6)
- Microarrays
  - Basically quantitative, measuring gene expression
  - Two types: cDNA array and Oligonucleotide array (Affymetrix)

The Role of Statistics in Microarrays

- A role in the design and the analysis
- Exploratory versus confirmatory
- Multiplicity: data mining versus data dredging
- Prospective versus retrospective

Diagnostics: Microarrays

- Exciting area that is fast developing
- Still in early stages
- Major statistical design issues
- Multiplicity problems
- As high complexity tests, regulated by CDRH
- Working group in Biostat. Div. for a number of years

Approved Tests

- A number of genetic tests have been approved for breast cancer (Her2-neu (c-erb-B2))
- One PMA was based on limited prognostic information
- At least two others (510(k)s) were based on patient selection for treatment using Herceptin (pharmacogenomic test)
- Roche Amplichip has been approved for CYP2D6 and CYP2C19 of the P-450 cytochromes

STARD and Reporting Genetic/Genomic Tests

- A statement was published in Jan, 2003 for all diagnostic tests: “Towards Complete and Accurate Reporting of Studies of Diagnostic Accuracy: The STARD Initiative” by P. Bossuyt et al. in *Clin Chem*, *Ann. Intern. Med.*, *BMJ* and *Radiology*
- 24 items to report in a study

Biomarkers and Clinical Trials

- Genetic analysis could be used to tailor the dose or the schedule during a trial
- Many trials now bank genetic samples for later analysis so microarray analysis becomes retrospective
- Post hoc analysis could be used (carefully) to identify poor metabolizers or persons with adverse events

Regulatory Perspective

- Two types of genomic investigations
  - One with good scientific basis a priori, well-understood prior to collection of the data
  - One that relies on the data to suggest the hypotheses; here more of a data burden might be expected.
- The FDA will keep in mind the risk/benefit trade-off.

Practical Considerations

- It may be that the use of microarrays is primarily for exploratory and hypothesis generation.
- Right now, microrarrays are very expensive and reproducibility is questionable.
- For discovery of SNPs, it is very useful but it is much cheaper to produce the SNP test which would tend to a more targeted and reproducible test.
- However, for patterns involving many genes, microarrays hold some promise

Bayesian Medical Device Trials Outline

- Why Bayesian medical device trials?
- What CDRH learned
- What has been accomplished
- Some myths dispelled
- Secrets of success
- More challenges in the future

Why Did CDRH Launch the Bayesian Effort?

- Devices often have a great deal of prior information.
  - The mechanism of action is physical (not pharmacokinetic or pharmacodynamic) and local (not systemic)
  - Devices usually evolve in small steps whereas drugs are discovered.
- Computationally feasible due to the gigantic progress in computing hardware and algorithms
- The possibility of bringing good technology to the market in a timely manner by arriving at the same decision sooner or with less current data was of great appeal to the device industry.

Early Decisions We Made

- Restrict to quantitative prior information. A subjective approach is fraught with danger.
- Companies need access to good prior information to make it worth their risk.
- FDA needs to work with the companies to reach an agreement on the validity of any prior information.
- Need to bring the industry and FDA review staff up to speed
- New decision-rules for clinical study success

Important Lessons Learned Early

- Bayesian trials need to be **prospectively designed**. (It is almost never a good idea to switch from frequentist to Bayesian or vice versa.)
- Companies need to meet early and often with CDRH. The prior information needs to be identified in advance as well as be agreed upon and legal.
- The control group cannot be used a source of prior information for the new device, especially if the objective is to show the new device is non-inferior.

Important Lessons Learned Early (cont.)

- Both the label and the Summary of Safety and Effectiveness (SS&E) of the device need to change.
- A successful company generally has a solid Bayesian statistician (or someone who really wants to learn) as an employee or consultant.
- The importance of simulation
- Entire FDA review team plays a big role

The Importance of Simulation

- We need to understand the operating characteristics of the Bayesian submissions.
- Why? The Type 1 error probability (or some analog of it) protects the US public from approving products that are ineffective or unsafe.
- So simulate to show that Type 1 error (or some analog of it) is well-controlled.
- Simulations can also be of help in estimating the approximate size of the trial and the strategy of interim looks. Usually Bayesian studies are not a fixed size.

Bayesian Workshop in 2004

- "Can Bayesian Approaches to Studying New Treatments Improve Regulatory Decision-Making?"
- Jointly sponsored and planned by FDA and Johns Hopkins University
- Presentations by Janet Woodcock, Bob Temple, Steve Goodman, Tom Louis, Don Berry, Greg Campbell, 3 case studies and panel discussions.
- Held May 20-21, 2004, at NIH
- August, 2005 issue of the journal *Clinical Trials* is devoted to this workshop

Legal Sources of Prior Quantitative Information

- Company's own previous studies: pilots, studies conducted overseas, very similar devices, registries
- Permission legally obtained to use another company's data
- Studies published in the literature.

  For the above, summaries of previous studies may not be sufficient to formulate prior; e.g., patient-level data are often necessary.

Bayesian Statistics: Submissions to CDRH

- At least 14 Original PMAs and PMA Supplements have been approved with a Bayesian analysis as primary.
  - The Supplements include stent systems, a heart valve, and spinal cage systems.
- Many IDEs have also been approved.
- Several applications for “substantial equivalence” (510(k)s)
- A number of reviews are in process.

Areas of Bayesian Application for Medical Device Studies

- Incorporation of **quantitative** prior information into a current trial, allowing the data from the current trial to "gain strength" as dictated through one of a number of methodologies.
- Prediction models for surrogate variables
- Analysis of multi-center trials (e.g., use hierarchical models to address variability among centers)
- Bayesian subgroup analysis
- Sensitivity analysis for missing data
- Flexibility of a Bayesian design and analysis in the event of an ethically sensitive device. This could be useful in a design with a changing randomization ratio in an adaptive design (as in ECMO). An added advantage is to increase enrollment and address investigator equipoise.

Dispelling Some Myths

- Does CDRH entertain only Bayesian submissions?

  NO, only about 5% of submissions are Bayesian.
- Are most of the Division of Biostatistics statisticians Bayesian?

  NO
- Do the Bayesians in CDRH do only Bayesian submissions?

  NO
- Does saying the words “Bayesian statistics” make for an incantation that leads automatically to approval?
  NO

Dispelling Some Myths (2)

- Does CDRH force companies to do Bayesian approaches?

  NO (although it may be "least burdensome"). It may be a trade for a possibly lower clinical burden but a higher statistical/computational burden

- Is there a lower success criterion for Bayesian submissions?

  NO. However, there is a different one. If a standard statistical analysis and a Bayesian analysis were to always yield the same basic conclusion, there would be no reason to consider a different approach. Often in the Bayesian approach there is prior information that is ignored in the frequentist approach.

New Draft Guidance

- Available today
- “Draft Guidance for the Use of Bayesian Statistics in Medical Device Trials”
- http://www.fda.gov/cdrh/osb/guidance/1601.html
- http://www.fda.gov/cdrh/osb/guidance/1601.pdf
- Comment period for 90 days from May 22
- Public meeting in Rockville MD in late July

Surrogates in Medical Devices

- DeMets, D. (2000). The role of surrogate outcome measures in evaluating medical devices. *Surgery* **128**:379-385.

Prentice's Criteria for Validation of a Surrogate: Mathematical Formulation

For surrogate S, true endpoint T and treatment Z

1. $f(S|Z)$ is not $f(S)$
2. $f(T|Z)$ is not $f(T)$
3. $f(T|S)$ is not $f(T)$
4. $f(T|S,Z) = f(T|S)$

Prentice (1989) *Stat in Med* as in Burzykowski, Molenberghs, Buyse (2005). *The Evaluation of Surrogate Endpoints*

Prentice Criteria

- The four elements of the Prentice criteria are difficult to achieve simultaneously. The fourth one in particular implies that the entire treatment effect on T is captured by S (100% explained).
- There is nothing in the criteria that prevents one from going from a binary true endpoint to a continuous surrogate.

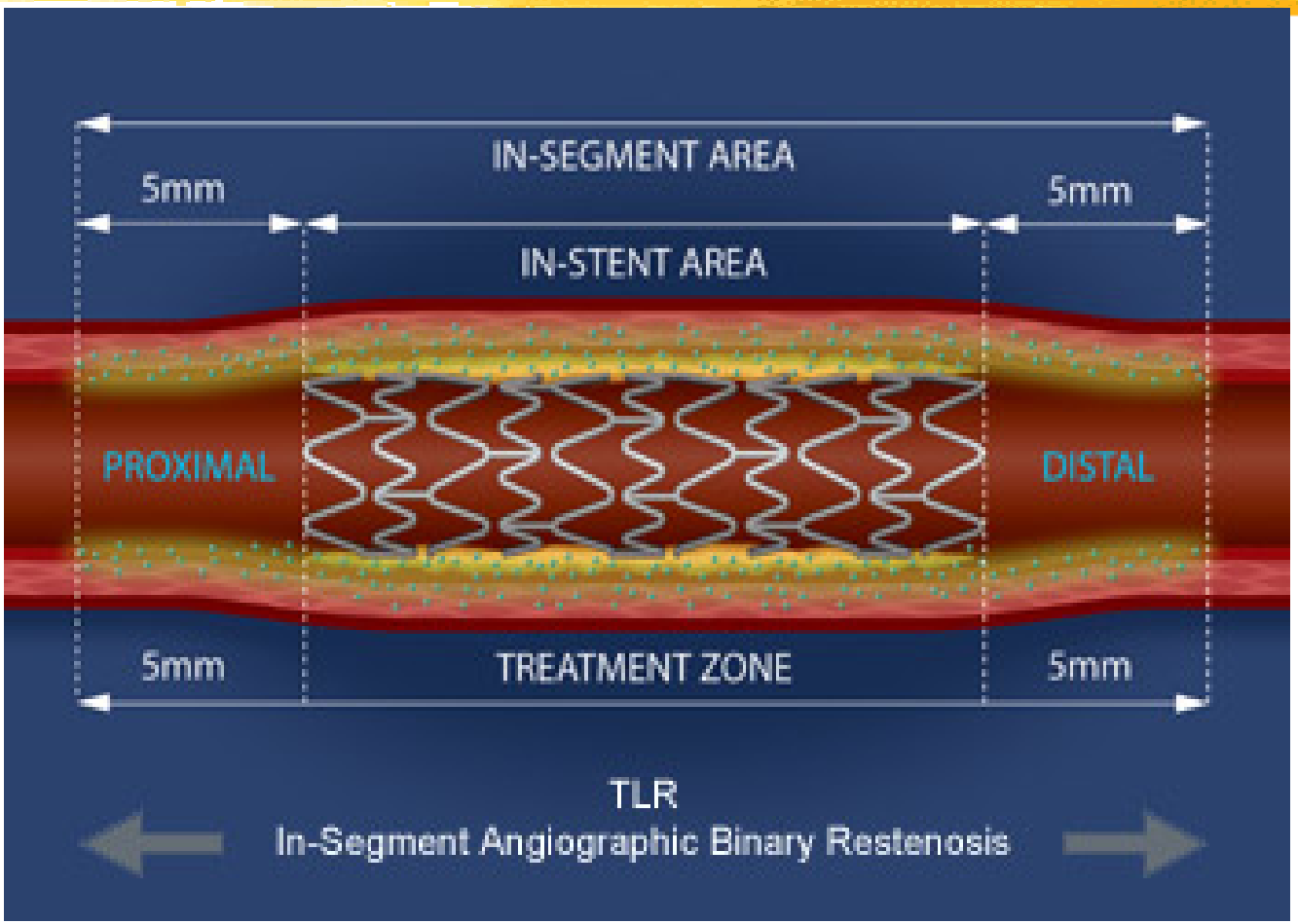
Drug-Eluting Coronary Stents

- Drug-eluting stents have dramatically reduced the restenosis rate compared to BM stents.
- Target Lesion Revascularization (TLR) is often the ultimate (true) endpoint of interest at 9 months. TLR is any repeat percutaneous intervention of the target lesion or bypass surgery of the target lesion.
- Surrogate candidate: Late luminal loss is the difference in millimeters between the diameter of a stented segment post-procedure compared with the follow-up angiogram at 6 or 9 months, a continuous measure.

Validation vs. Qualification of Surrogates

- Prentice criteria are most difficult to achieve.
- Is the surrogate “reasonably likely to predict clinical benefit”?
- How much does knowledge of the surrogate contribute to the prediction of the primary endpoint?
- Assoc. Comm. Janet Woodcock refers to the “qualification” of surrogates

Drug-Eluting Stent



Types of Late Loss in DES

- Late Loss in-stent—late loss within the length of the stent
- Late Loss in-segment—late loss within the stent plus 5 mm on either side
- Late Loss can be measured either in mm or as a percentage of the (expanded) blood vessel lumen diameter immediately after a stent procedure. This latter is referred to as Percent Diameter Stenosis (%DS).

Late Loss

- This variable Late Loss (LL) does not save time since the angiography is at virtually the same time as TLR.
- The interest in LL is related to sample size reduction associated with the use of a continuous as opposed to a binary outcome.
- There is a possible concern about the measurement error since LL relies on two angiographies at two time points and the associated diameter measurements.
- There have now been a number of randomized trials involving drug-eluting stents.

Why LL May be Plausible as a Surrogate

- The main reason to do TLR is that there is evidence that there has been narrowing, and this is confirmed with imaging. So in a study in which every patient undergoes angiography at 6 or 9 months, the result could be the decision to do TLR. It is unusual to do such imaging in the real world without some clinical symptoms.
- In short, it could be directly in the causal pathway.

Late Loss and TLR

- When restenosis hits 50% or more most interventionalists agree to reintervene.
- lLogistic regression and ROC methods are beig used to investigate the relationship of LL compared to TLR.
- At this point, FDA has not agreed to the general acceptance of LL or %DS as a surrogate for TLR.

Intermediate Temporal Endpoints

- An intermediate endpoints is identified by Temple (JAMA, 1999) as a clinical endpoint but not the true (ultimate) one.
- Here an intermediate temporal endpoint is the true (ultimate) endpoint but at an earlier time point.
- One example Age-Related Macular Degeneration (Buyse et al, 2000) where 6-month visual acuity is used as an intermediate temporal endpoint for the true endpoint namely one-year visual acuity.

Orthopedic Example

- Use 12-month success on a spinal fixation device as the temporal intermediate endpoint of the ultimate (true) endpoint of 2-year success.
- A patient can go from success to failure or failure to success.
- Useful in adaptive designs (Bayesian or frequentist)
- Such models could be used to investigate whether 12-month success is a reasonable surrogate for 24-month success. However no such surrogate has as yet been established.

FDA Critical Path Opportunities List

Advancing Innovative Trial Designs

- 34. Design of Active Controlled Trials
- 35. Enrichment Designs
- 36. Use of Prior Experience or Accumulated Information in Trial Design
- 37. Development of Best Practices for Handling Missing Data
- 39. Analysis of Multiple Endpoints

http://www.fda.gov/oc/iniatitives/criticalpath/reports/opp_list.pdf

FDA's Critical Path Medical Device Opportunities List

- #1 Biomarker Qualification
  - One of five questions is "What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy?"
- #6 Surrogates Outcomes for Cardiovascular Drug Eluting Stents
- #23 Imaging Biomarkers in Cardiovascular Disease

http://www.fda.gov/oc/iniatitives/criticalpath/reports/opp_list.pdf

Conclusion

- The statistical worlds of the pharmaceutical industry and the device industry are growing ever closer, with combination products such as drug eluting stents and also with combination of diagnostics and drugs in pharmacogenomics.
- Statistical issues that confront medical devices are challenging and exciting.


PIONEERS IN CONSUMER PROTECTION
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Center for Devices and Radiological Health
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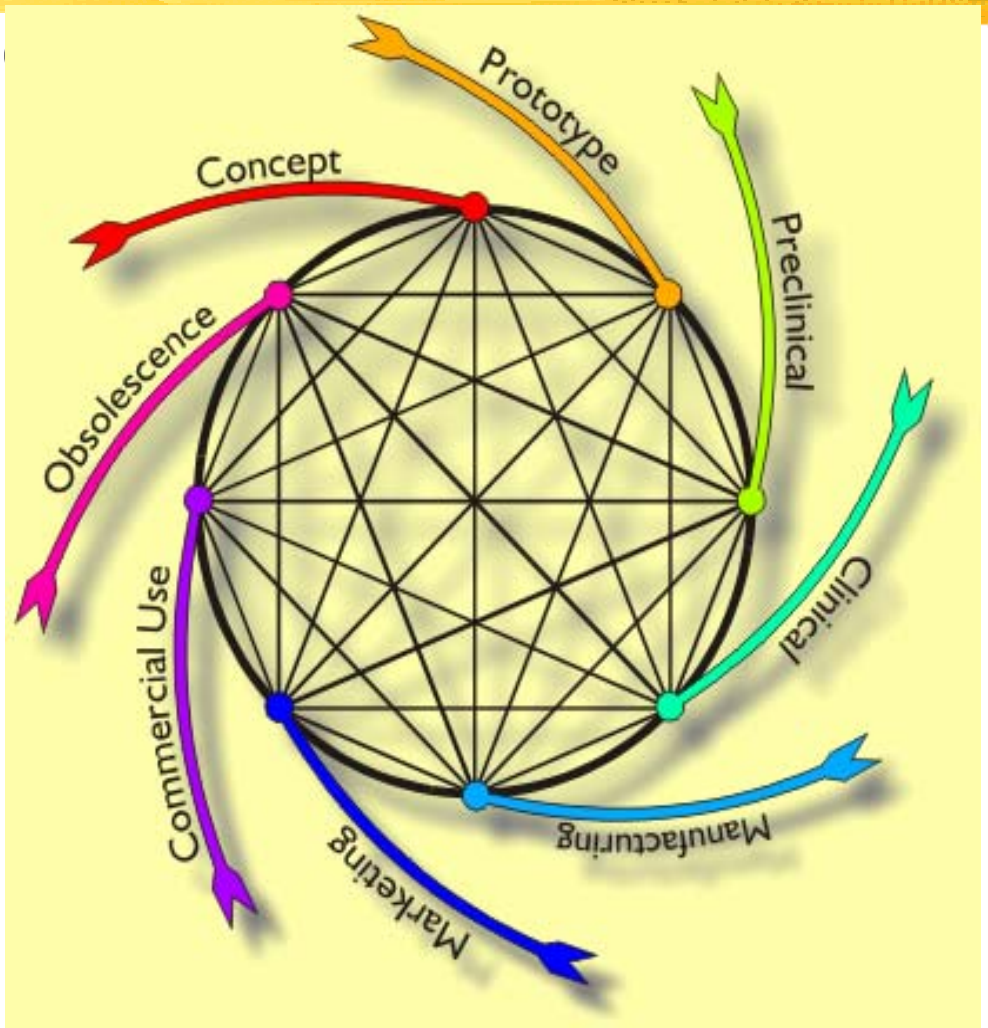
Total Product Life Cycle (TPLC) for Devic



"Ensuring the Health of the Public Throughout the Total Product Lifecycle . . . It's Everybody's Business"

CDRH's Vision of the Pipeline