



U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.



FDA's Clinical Investigator Course

*Cosponsored by
FDA's Office of Critical Path Programs (OCPP)
and
The Clinical Trials Transformation Initiative (CTTI)*



FDA

U.S. Department of Health and Human Services

Food and Drug Administration





Medical Device Clinical Trials: An FDA Perspective

Bram Zuckerman, MD, FACC
Director
Division of Cardiovascular Devices
CDRH



U.S. Department of Health and Human Services

Food and Drug Administration



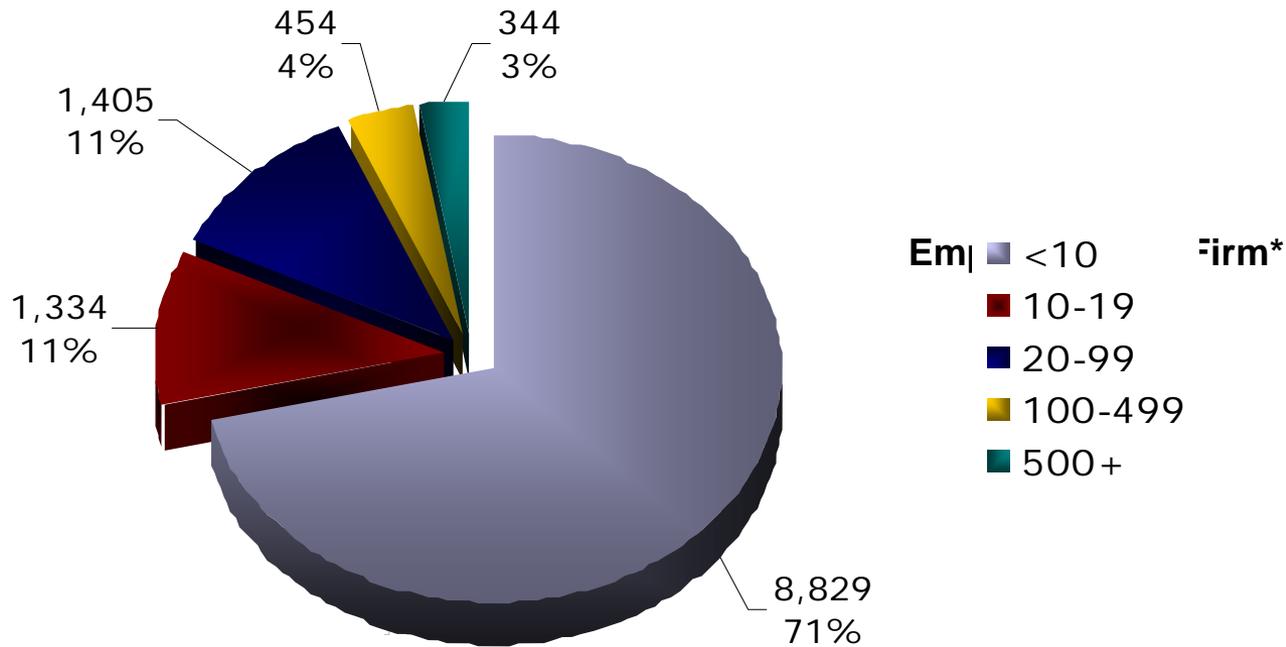


Today's Topics

1. Introduction
2. Premarket Device Trials
3. Off-Label Use

What does the U.S. medical device industry look like?

According to the US Census Bureau, there are over 12,000 **medical** device manufacturing firms in the US.*



* Source: Census Bureau, Number of Firms, Number of Establishments, Employment, and Annual Payroll by Employment Size of the Enterprise for the United States, All Industries 2005 using NAICS codes 339111, 339112, 339113, 339114, 339115, 339116, 334517, 334510, 325413 <http://www.census.gov/csd/susb/susb05.htm>

■■■ Medical Devices

The Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.

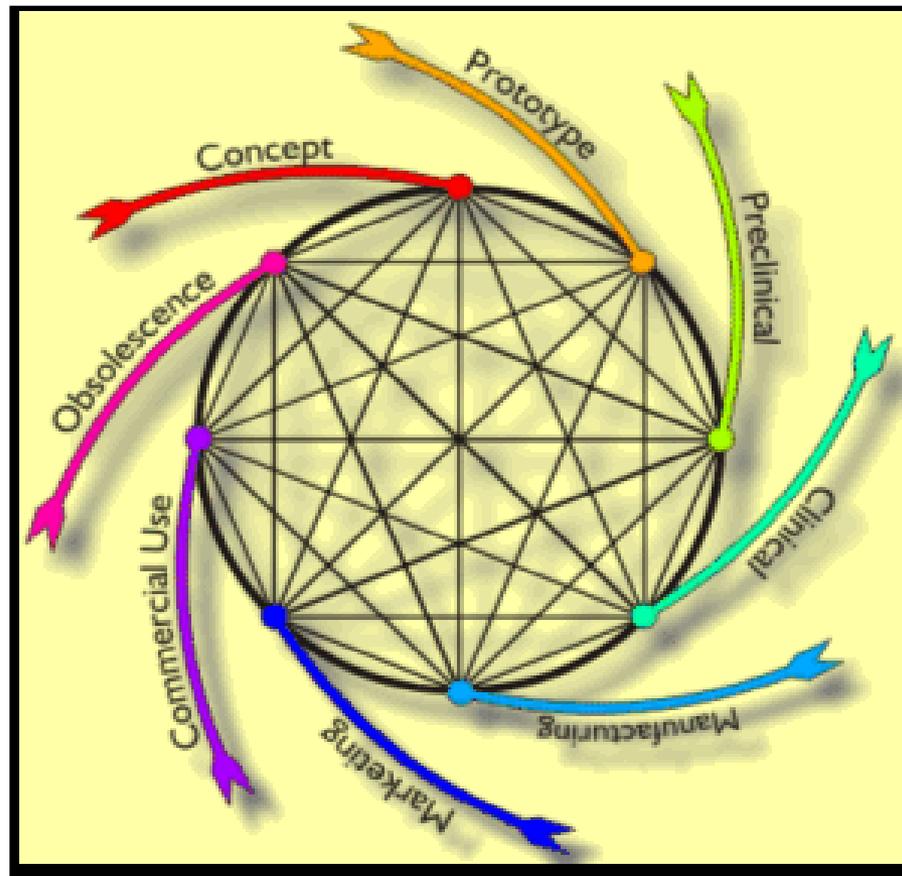
- **As simple as a tongue depressor or a thermometer**
- **As complex robotic surgery devices**



©2006 Intuitive Surgical, Inc.

■ ■ ■ The Total Product Life Cycle

- Regulation of device technologies requires a total product life cycle approach.



FDA

U.S. Department of Health and Human Services

Food and Drug Administration

■ ■ ■ Device vs. drug development

Developmental Feature	Device	Drug
Rate of technology change	High	Low
Ease of <i>in vitro</i> assessment	High	Low
Influence of physician technique on results	High	Low
Ease of blinding	Low	High
Definition of "Orphan" (number of patients)	4,000	200,000
Number of full scale studies usually required	1	2
Number of Regulatory Classes	3	1*

■■■ FDA Device Approval: Critical Issues

1. Pre-clinical Testing

- Are bench and animal studies acceptable?

2. Pivotal Trial

- Design: Minimize bias and confounding
- Execution: Minimize amount of missing data
- Analysis: Rule out chance (i.e., several prospectively chosen, clinically relevant hypotheses with plan for alpha allocation)
- Have clinically meaningful results been clearly demonstrated?

3. Manufacturing

- Can device be built safely for commercial distribution?

4. Is the Device Label truthful and accurate?



Analysis of Pivotal Device Trials

- Statistical significance is different from clinical significance
- There is no perfect device surrogate –
 - CDRH frequently deals with partial device surrogates
 - Understand their limitations
- Composite endpoints have limitations –
 - A combined endpoint needs to retain its interpretability
- The basic unit of analysis is the patient and not the device
- Advisory panels offer advice to the FDA in an open and transparent environment
- Totality of data in a device trial should indicate a beneficial risk/benefit ratio

■ ■ ■ Four Studies all with the same P - value

Number of Patients Receiving A and B	Proportion preferring A	P-Value
20	15:5	0.04
200	114:86	0.04
2,000	1,046:954	0.04
2,000,000	1,001,445:998,555	0.04



CDRH Case Study on Composite Endpoints

Cordis Checkmate Intracoronary Brachytherapy System

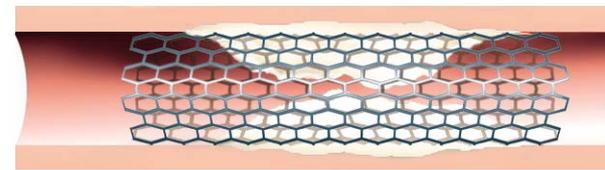
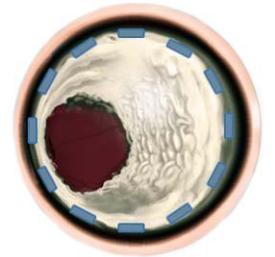
- Ref.
 - PMA SSED
 - Jan 25, 2001 NEJM Vol 344:
297-299

FDA Approval of Coronary-Artery
Brachytherapy



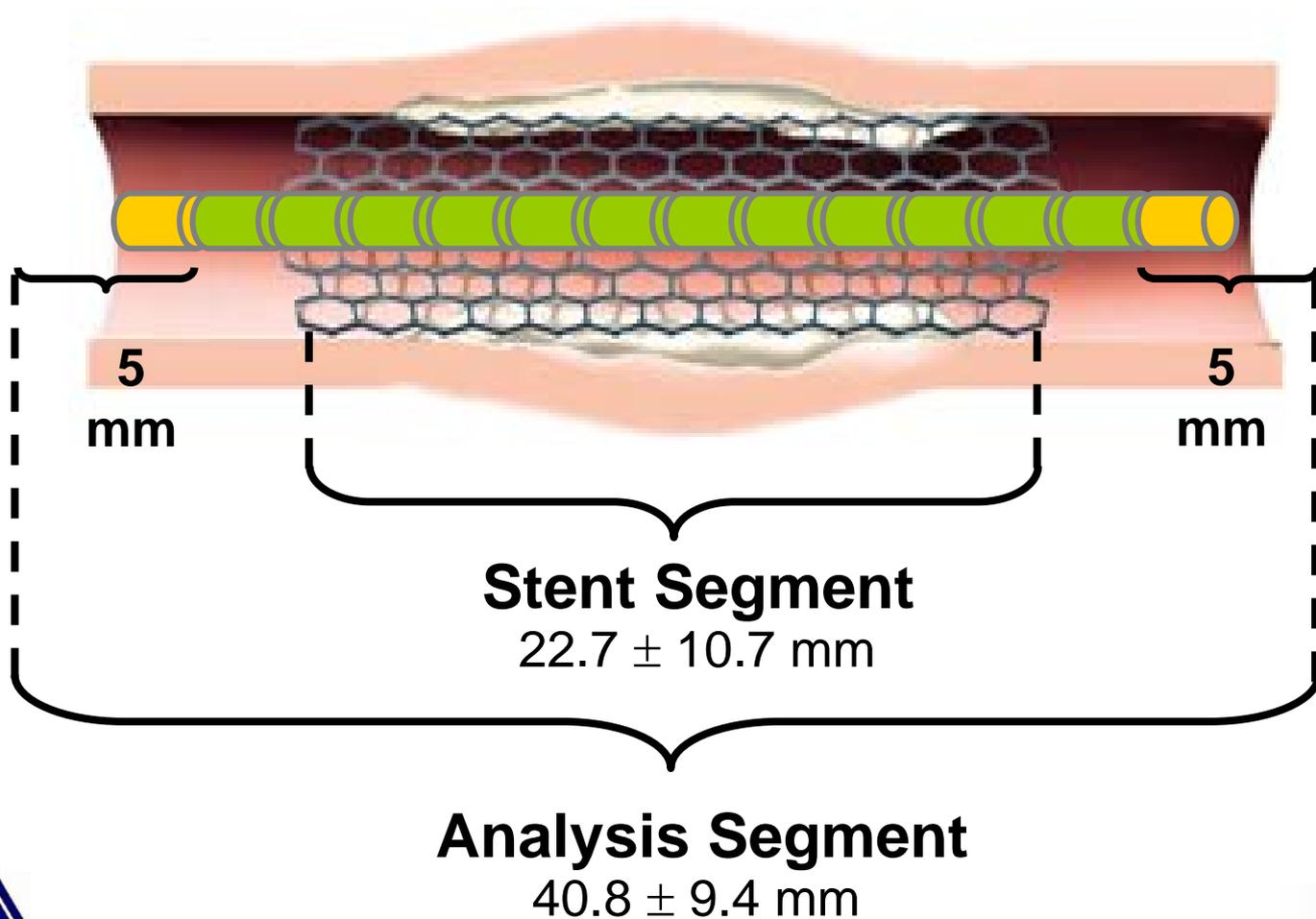
■■■ In-Stent Restenosis (2001)

- Over 725,000 percutaneous coronary interventions will be completed in the U.S. each year, of which > 80% will receive a new stent
 - Over 100,000 U.S. (20-40%) of patients will develop recurrent symptoms due to in-stent restenosis
 - Often no effective minimally
- therapies are available



In-Stent Restenosis

Intravascular Brachytherapy RX

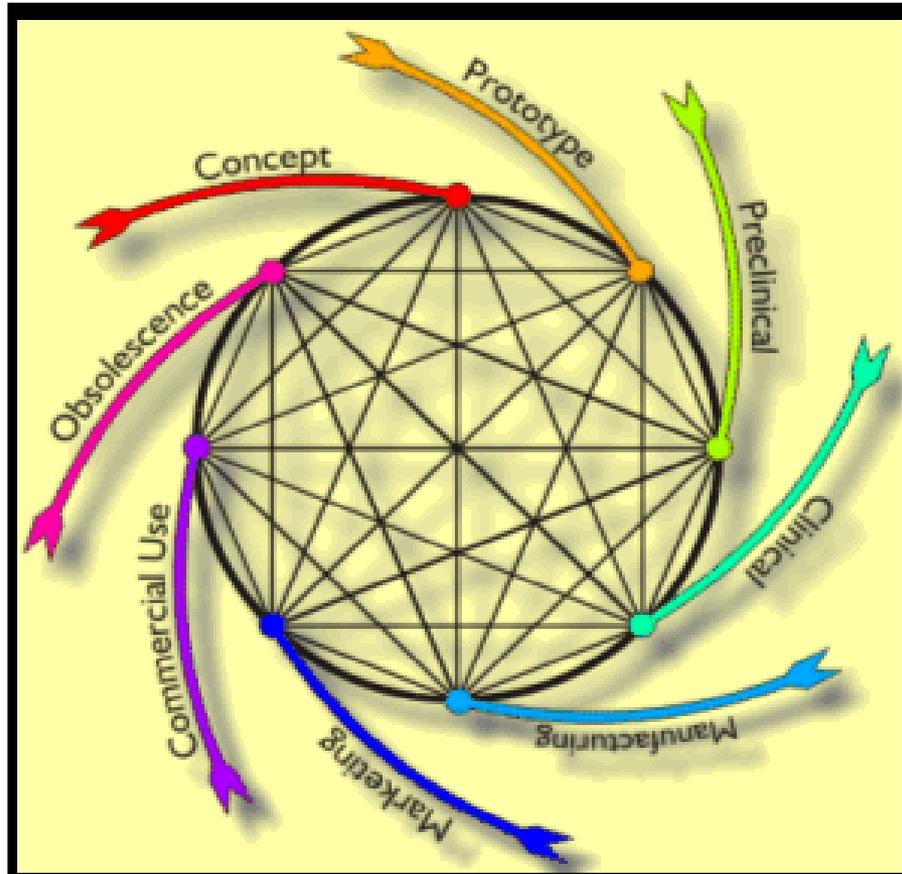


Cordis Gamma I Results

	IRT	PLACEBO	95% CI OF DIFFERENCE
9 Month MACE	28.2%	43.8%	(-27.3, -3.8%)
Death	3.1%	0.8%	(-1.1, 5.6%)
Myocardial Infarction	12.2%	6.6%	(-1.5, 12.7%)
--Q wave MI	5.3%	3.3%	(-3.0, 7.0%)
--Non Q wave MI	6.9%	3.3%	(-1.8, 8.9%)
Target Lesion Revascularization	24.4%	42.1%	(-29.2, -6.3%)

■ ■ ■ The Total Product Life Cycle

- Regulation of device technologies requires a total product life cycle approach.



FDA

U.S. Department of Health and Human Services

Food and Drug Administration



Striking the Right Balance Between Pre- and Postmarket Evaluation

- Use appropriate amount of pre-market data to make primary decisions about approvability of new devices (safety, effectiveness)
- Use postmarket data to
 - supplement our understanding about device and operator performance
 - identify device malfunctions and take corrective action as necessary
 - modify pre-market expectations for next generation devices.



Premarket Device Trials



U.S. Department of Health and Human Services

Food and Drug Administration





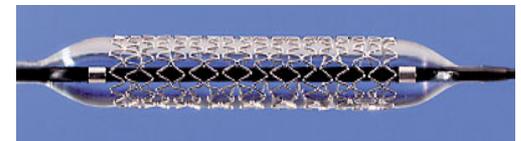
FDA's Approach to Medical Device Regulation

1. Base degree of control on risk
2. Weigh benefit vs. risk to determine safety and effectiveness
3. Use valid scientific evidence
4. Consider least burdensome means
5. Provide “reasonable assurance”

■ ■ ■ Device Classification

Medical Device Classes

- Class I
 - General Controls
 - Most exempt from premarket submission
- Class II
 - Special Controls
 - Premarket Notification [510(k)]
- Class III
 - Premarket Approval
 - Require Premarket Application [PMA]



Valid Scientific Evidence

21CFR860.7

Includes

- **Well-controlled investigations**
- **Partially controlled studies**
- **Studies and objective trials without matched controls**
- **Well-documented case histories**
- **Reports of significant human experience with a marketed device**

Does NOT include

- **Isolated case reports**
- **Random experience**
- **Reports lacking sufficient details**
- **Unsubstantiated opinions**



510(k)

Premarket Notification

- Substantial equivalence
- 10-15% require clinical data
- Performance testing
- Usually confirmatory
- Type of study dictated by:
 - Ability of bench and animal testing to answer questions
 - Amount of difference between subject device and predicate



PMA

Premarket Approval Application

- Establish safety and effectiveness
- Bench-Animal-Human
- Similar to NDA (New Drug Application)
- Clinical Studies
 - Reasonable assurance of safety & effectiveness



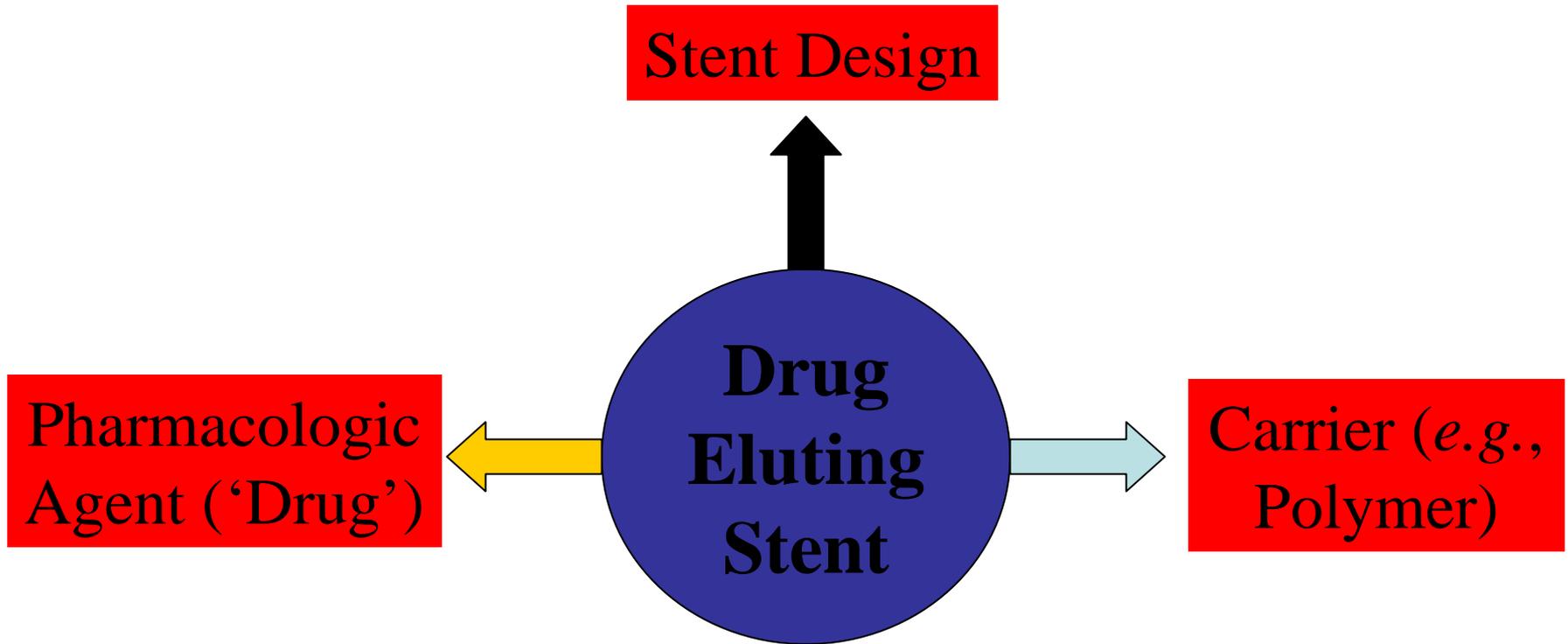
Investigational Device Exemption (IDE) Process

- Applies to significant risk studies
- Allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA
- Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices



Some challenges in the development of cardiovascular device trials

Device-specific challenges: Drug-eluting stents (DES)





Device-specific challenges

Clinical studies

	DES "A"	DES "B"	DES "C"
drug	NME	Approved for systemic indication	paclitaxel sirolimus
drug formulation	Novel drug formulation	Similar drug release profile (local/systemic)	Same drug formulation as approved DES
stent	New stent material	316L, CoCr, nitinol platform	Approved stent platform

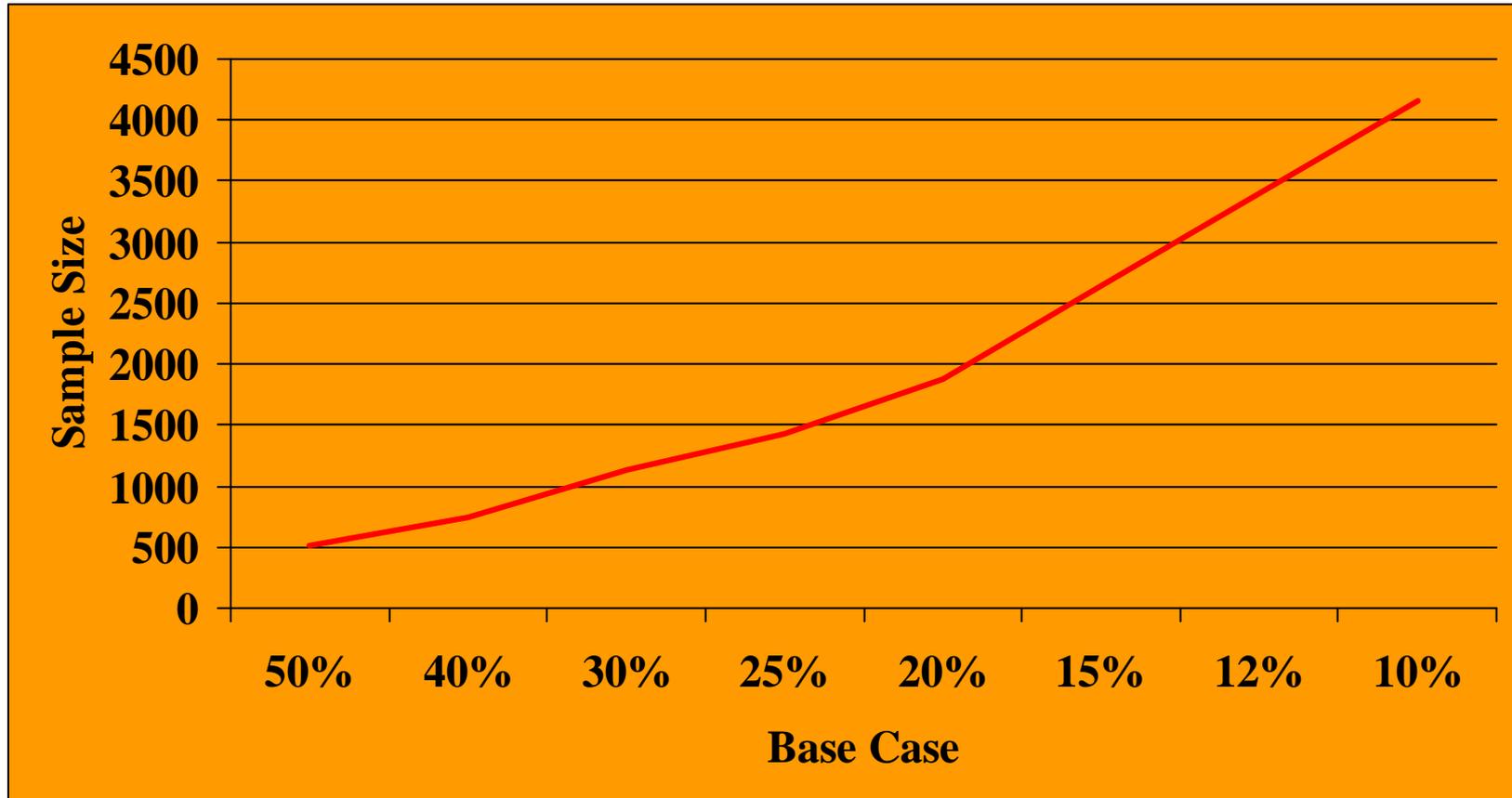


■■■ Evaluation of New Coronary Stents

One Size Does Not Fit All

- Randomized Control
- Nonrandomized Concurrent Control
- Historical control
- Operating Performance Characteristic (e.g., heart valve evaluation, LVAD BTT Trial)

Sample Size and the Binomial Distribution



Tx Effect = 25%, Power = 80%, Alpha error = 5%



Role of Bayesian Statistics in Medical Device Trials

- Combines information in the current trial with prior information accepted by the FDA: can be very useful in medical device clinical trials
- Not a substitute for poor trial design and/or execution
- Needs careful planning (prespecification of methods and validation of code is critical)
- Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials – 2006
- Examples: Circulatory Systems Advisory Panels (March 18, 2009; April 23, 2009; November 20, 2008)

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=705>



Off-Label Use



FDA

U.S. Department of Health and Human Services

Food and Drug Administration



■ ■ ■ After product approval...

What is “off-label use” according to the FDA?

- Use of a medical device for treatments other than for what the device was initially approved.
- Use not explicitly included in product labeling.
- Also referred to as “unlabeled,” “out-of-label,” “extra label” and “unapproved” use.

■ ■ ■ Off-label use

FDA concerns regarding off-label use:

- Off-label uses are not subject to a rigorous pre-market approval process.
- Off-label uses may diminish or eliminate the incentive to study or seek FDA approval for the indication for which the therapy is being used off-label.
- Adverse events associated with off-label use may not be captured and analyzed; patients not informed properly

Practice of Medicine and FDA

What is FDA's interpretation of "practice of medicine"?

- Discussing treatment with patient
- Using treatment on patient
- Discussing treatment with other physicians in course of professional activity

FDA does not regulate the practice of medicine (Sec 906, FDAMA)

Practice of Medicine and Physicians

- Recognition of the importance of evidence-based medicine and patient informed consent in guiding clinical decision-making.
- If physicians use a product for an indication not in the approved labeling, they have the responsibility to:
 - Be well-informed about the product
 - Base its use on firm scientific rationale and on sound medical evidence
 - Maintain records of the product's use and effects