Drug Discovery, Development and Commercialization, 2013

Industry Considerations with Phase III Clinical Trials

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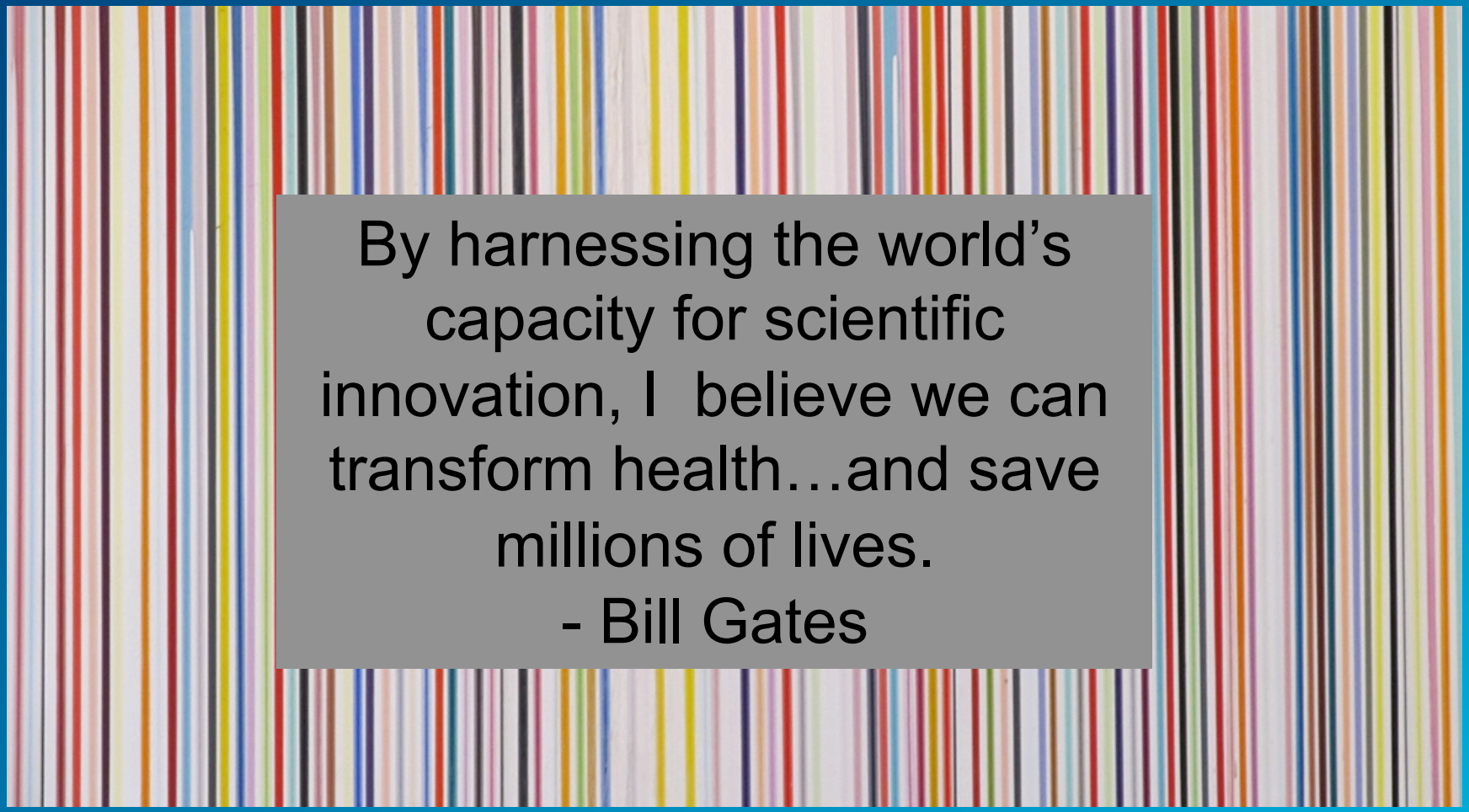
Objectives/Outline

- Discuss the value of medical research
- Analyze study design choices for a Phase III trial
- Assess the pros and cons of current and potential new ways of completing Phase III trials
- *Differentiate between the types and reasons for different types of NDA submissions and approvals*
- *Evaluate various reasons for implementation of post marketing studies*
- *Describe the major laws affecting drug approval and promotion*

What is the goal of medical research?

What are the benefits of global research?

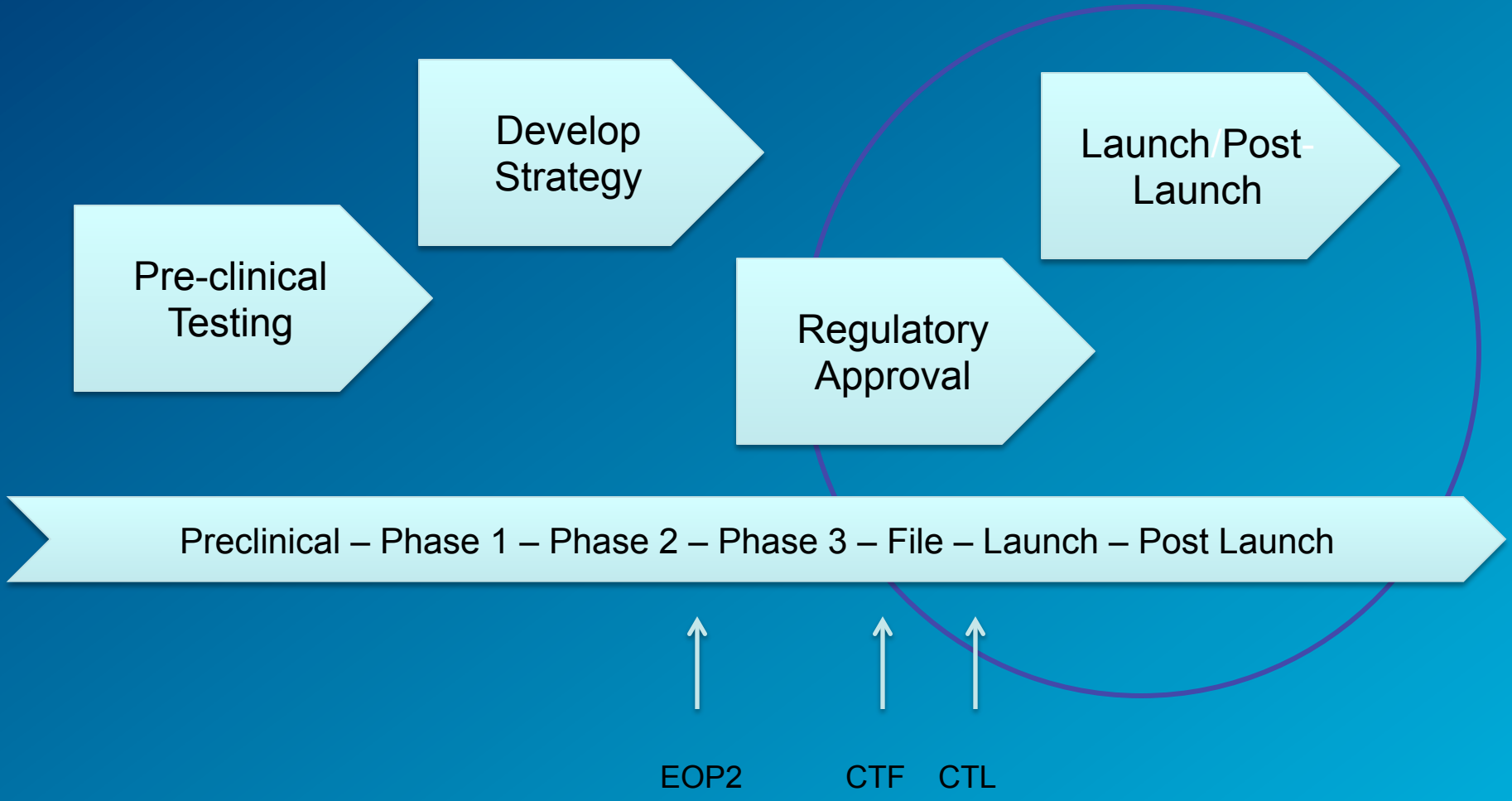


What is the value of medical research?

- What is the Total Burden of Chronic Disease to US Economy?
- Who funds most of the life science research?
- What is the impact for disease prevention and treatment?
- Will this information change pharmaceutical and biotechnology research?

Total Burden = treatment expenditures + lost economic output
http://www.milkeninstitute.org/pdf/USChamberLifeSciencesApril2009.pdf

Commercialization Process



EOP2 - End of Phase 2 CTF - Commit to File CTL - Commit to Launch

Pines and Pines. A Practical Guide to Food and Drug Law and Regulation.

Strategic Decisions are Critical

End of Phase 2 Meeting

Type of Communication	Timing	Expected Outcomes
End of Phase 2 Meeting	After Phase 1 and 2 trials complete Before Phase 3 trials	Discuss Phase 3 Clinical Trials Agree on Primary Endpoints Identify/Address Safety Issues Identify/Address Scientific Issues

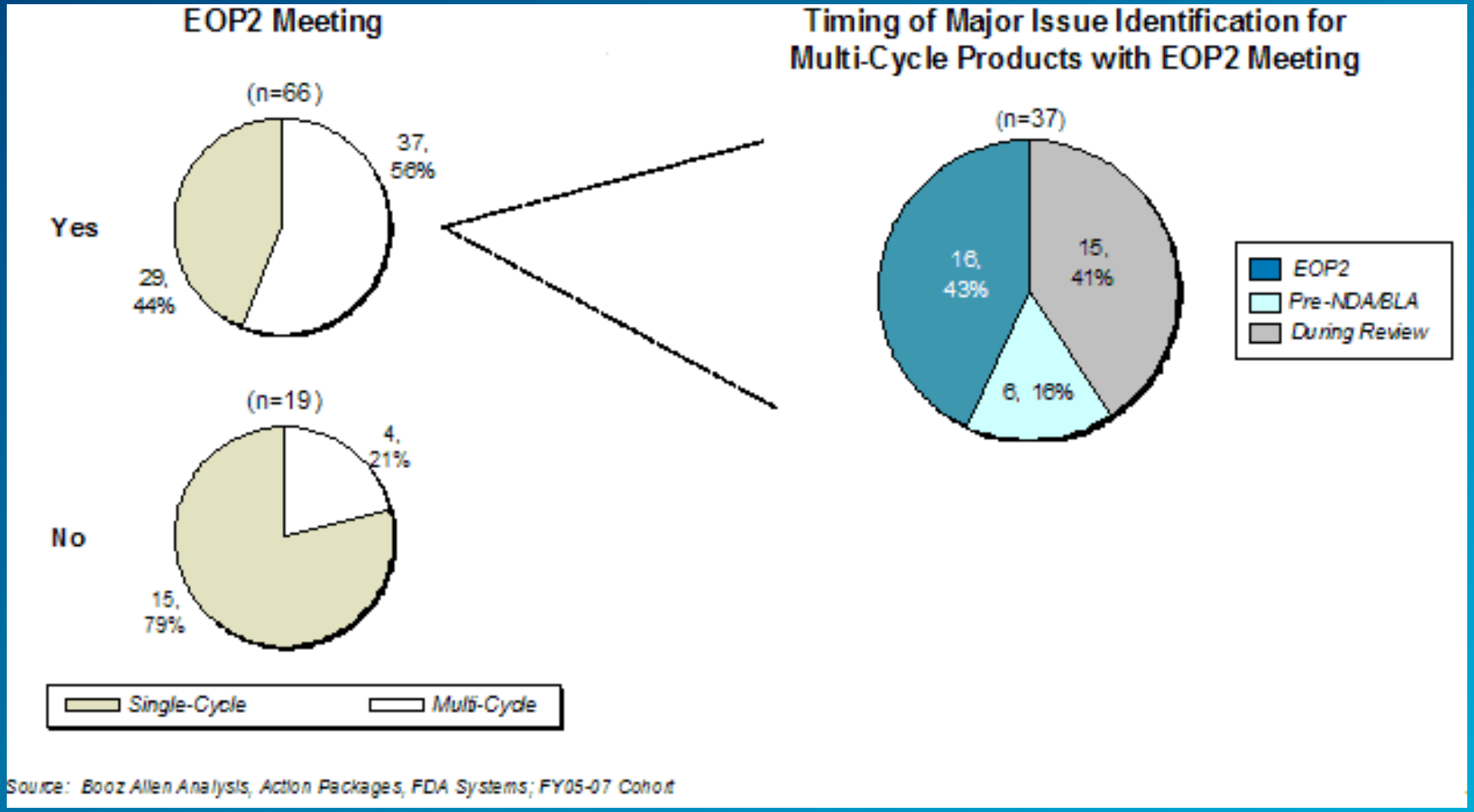
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127153.htm
Assessed January 2012

What is the Process for an End of Phase 2 Meeting?

- Submit Meeting Request
- Schedule Meeting
- Submit Briefing Document
- Preliminary Response
- Hold Meeting
- Meeting Minutes

FOOD AND DRUG ADMINISTRATION MODERIZATION ACT OF 1997 (FDAMA)

Does having an EOP2 meeting affect approval rates?



http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127153.htm
Accessed February 2012

Can decisions from end of phase II meetings be altered?

- Yes
  - Written consent of the sponsor
  - Via a written decision identifying a substantial scientific issue “essential to determining the safety or effectiveness of the drug” that would have not otherwise have been addressed.

What are Design Features of a Phase III Trial?

- Goal: Collect data in diseased population needed to meet the safety and efficacy standards required for FDA approval or label extension[1]
- Characteristics can include:
  - Large Scale
  - Multi-Center
  - Performed in Final Dosage Form
  - Controlled
  - Typically Non-Inferiority Design
  - Typically 2-3 Year Duration
  - Study Endpoints

1. Pines and Pines. A Practical Guide to Food and Drug Law and Regulation.

Study Design

- Non-inferiority trials are designed to show the product is not clinically inferior to the comparative agent.[1]
- Equivalence trials are designed to show any difference between products is not clinically important.[1]
- Superiority trials are designed to show the product is better than the comparative agent.[1]

1. US Guidance for Industry Statistical Principles for Clinical Trials, September 1998 Guidance to Industry- Providing Clinical Evidence for Effectiveness for Human Drug and Biological Products

Considerations on Patient Populations: Special Populations

Drugs should be studied in all age groups for which they will have significant utility

Guidance for Industry: Study of Drugs Likely to be used in the Elderly; E7 Studies in Support of Special Populations: Geriatrics; Guidance to Industry for Clinical Evaluation of Drugs in Infants and Children

Data Safety and Monitoring

- Monitor trial progress and conduct
- Consider participant safety
- Adverse event reporting
- Assure data accuracy
- Ensure compliance
- Required for Phase III trials

Guidance for Industry: Establishment and Operation of Clinical Trials Data Monitoring Committees; www.nlm.nih.gov

What are some challenges with executing trials?

- 64% would deviate protocol to improve medical care
- 83% agreed research protocols should be used as guidelines only
- 90% felt it was ok to disregard minor entry criteria if there was patient benefit
- 55% agreed to not offering trials to eligible patients
- 22% reported enrolling the ineligible patient.
- 52% participated in trials they felt treatments weren't in the patient's best interest

Survey of 744 investigators evaluating the ethical conflict between research interests and clinical interests Charles W. Lidz, Paul S. Appelbaum, Steven Joffe, Karen Albert, Jill Rosenbaum, and Lorna Simon, "Competing Commitments in Clinical Trials," IRB:Ethics & Human Research 31, no. 5 (2009):1-6

CMC Development Phase 3

- CMC development continues in parallel with the clinical development during phase 3 studies
- The CMC safety information provided to support phase 3 studies should focus on the information that is warranted in maintaining the continued safety of the patients enrolled in these studies
- During or before phase 3, CMC safety information that has previously been submitted to the IND may have changed and, consequently, should be updated as required under § 312.31.7

Why is Study Design and Execution so Important?

Pina KR and Pines WL. A Practical Guide to Food and Drug Law and Regulation. Second Edition. 2002

What Makes a Study Adequate and Well Controlled?

- Clear and measurable objectives
- Designed for a valid comparison
- Designed to minimize bias
- Designed with well defined and reliable measures
- Analysis is appropriate

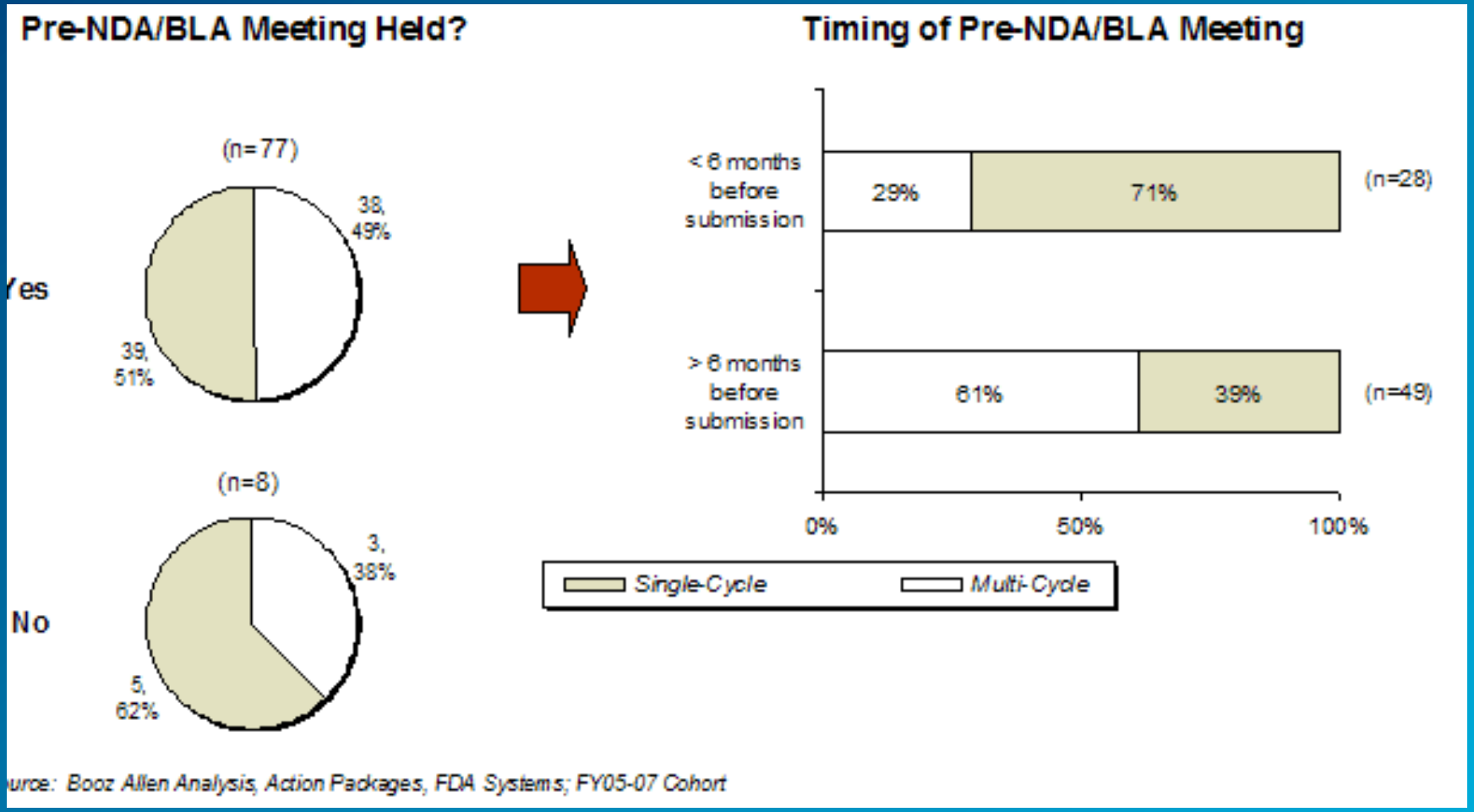
21 CFR 314.126; Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products. May 1998; FDA Drug Study Design – Information Sheet available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm

Pre-NDA/BLA Meeting

Type of Communication	Timing	Expected Outcomes
Pre-NDA/BLA Meeting	After trials to be part of filing are complete Before submission of NDA/BLA	Agree upon: Data presentation Label Format Index Statistical Analysis Discuss submission process Discuss potential filing issues

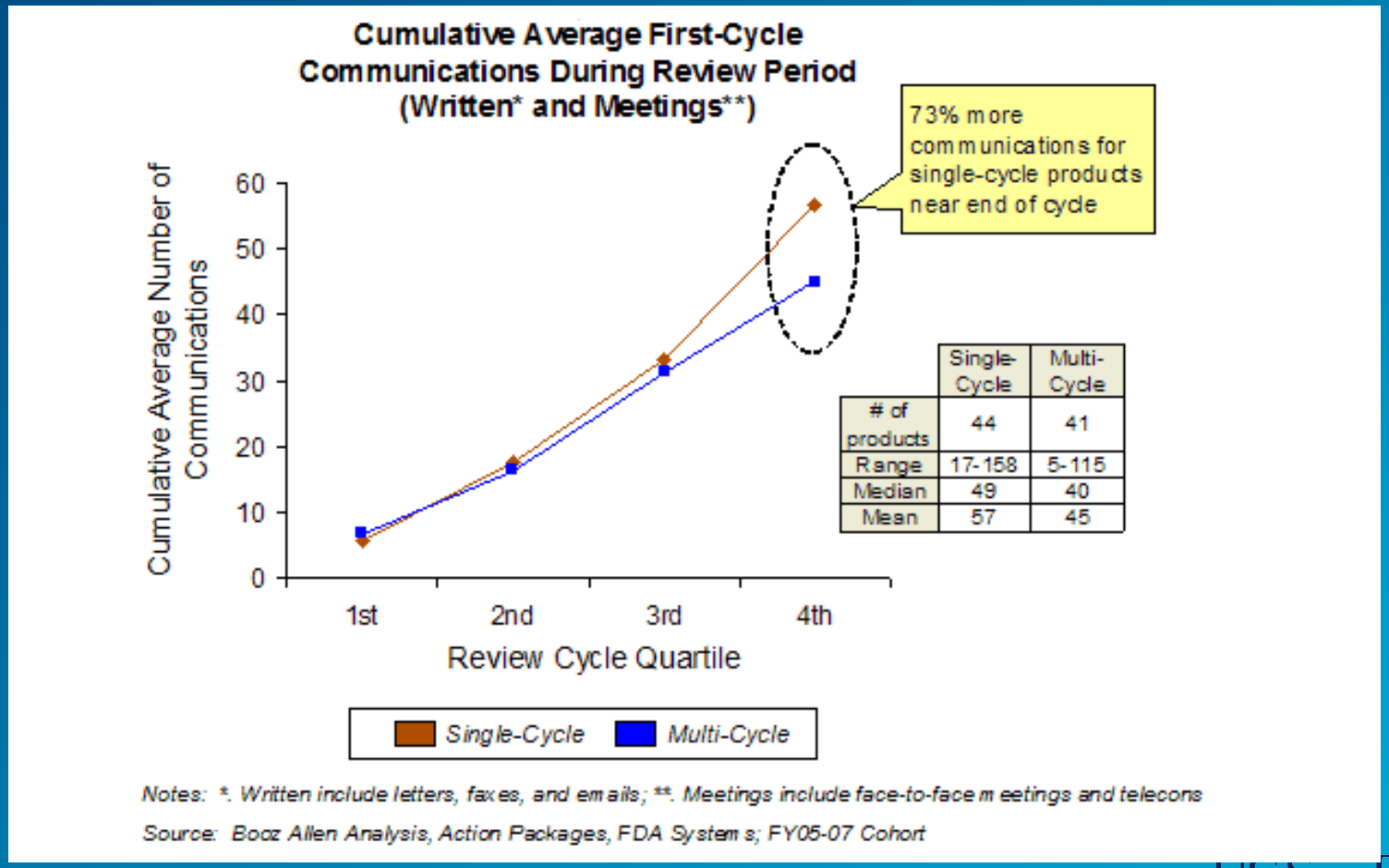
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127153.htm
Assessed January 2013

Effect of Pre-BLA Meetings on Approval Rates



http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127153.htm
Accessed February 2012

Assessment of Having A Pre-NDA/BLA and EOP2 meeting



	Single-Cycle	Multi-Cycle
# of products	44	41
Range	17-158	5-115
Median	49	40
Mean	57	45

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127153.htm
Accessed February 2012

Other Factors in Bringing a Drug to Market

What Are the Costs to Consider?

- Manufacturing the drug(s) tested
- Trial designers and administrators salaries
- Consultants or Contractors
  - Contract Research Organization (CRO)
  - Site Management Organization (CMO)
- Study materials and shipping
- Investigators and their staffs
- Communication with investigators
- Investigator training meetings
- Costs incurred by investigators
- Patient payments

Common Causes of Study Delays

- Contracts and budgeting
- Patient recruitment
- Protocol finalization
- Legal review
- IRB review

Source: Farfel and Neuer. Faster Start Up and Reduced Cost through the Use of Clinical Document Exchange Portals. Center Watch Survey 2009. http://www.intralinks.com/articles/wp_faster_study_startup.pdf

Improving Efficiencies in Trial Design

- Analytical Efficiencies
- Randomized Clinical Design vs. Pragmatic Clinical Trials
- Integrative Design
  - Can be used to evaluate dose-response and time-response behavior of safety and efficacy endpoints

Orloff J, et al. Nature Reviews 2009; 8:949-957
Luce BR, et al. Annals Intern Med. 2009; 151:206-209

Pros /Cons for Running Trials in Developed vs. Developing Countries

- **Discussion**:
  - What are some benefits of trials in developed countries? Undeveloped countries?
  - What are some potential limitations of trials in developed countries? Undeveloped countries?
  - How would you weigh these pros and cons?
  - When would you feel the benefits outweigh the limitations? Why?
  - What are potential solutions to overcome the limitations?

Garnier, JP. Rebuilding the R&D Engine in Big Pharma. Harvard Business Review May 2008: 1-8
Glickman SW, et al. NEJM 2009. 360;8:816-823. Alliance for Case Studies for Global Health.
www.casestudiesforglobalhealth.org. E5: Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data.
21 CFR §312.120, 314.10 • §314.126

Foreign Clinical Data Use Considerations

- Study design applicable to US population
- Relevant to US medical practice
- Qualified clinical investigators
- Appropriate data validation
- Conformance with ethical principles
- Demonstrate effectiveness
- Adequate and well well-controlled studies
- International consensus on assessment?

21 CFR §312.120, 314.10 • §314.126

Foreign Clinical Data Use Considerations

- Efficacy differences?
- Immunogenicity differences?
- Case definition difference?
- Standard of care difference?
- Schedule changes?
- Safety monitoring and reporting?

21 CFR §312.120, 314.10 • §314.126

Drug Approval Requirements

- Effective by parameters measured
- Reasonably safe
- Adequate manufacturing controls
- Labeling must meet Applicable statutory and regulatory requirements

How Did FDA Gain Authority in Drug Regulation?

Precipitating Factor	Law	Effect of Law
Sulfanilamide Elixir containing diethelye glycol as solvent results in 107 deaths	Federal Food Drug and Cosmetic Act of 1938	Goal: Drug must be safe prior to marketing Why Key?: Established regulation process
Sleeping pill thalidomide found to cause birth defects	1962 Kefauver-Harris Amendments	Goal: Drug must be effective and safe Why Key?: Established advertising of prescription medications authority
	Food & Drug Administration Modernization Act (FDAMA) of 1997	Why Key?: Allows regulation of unapproved used of approved drugs

New Drug Application (NDA)

- Preparation of the NDA
- Pre-NDA meeting with FDA
  - Goal: ensure the application will contain the required data
- Submission of NDA
  - Received: NDA arrived at FDA
  - Filed: Formally accepted for review
  - Refuse to File

CFR Title 21 Part 314

New Drug Application Contents

- Pre-clinical data
- Human pharmacokinetic and bioavailability data
- Clinical Data
- Proposed Manufacturing, Processing and Packaging methods
- Description of the drug product and drug substance
- List of all patents
- Proposed drug labeling
- Summary of application concluding with risks and benefits of drug

21 CFR 314

Refuse to File (RTF)

- The FDA can refuse a file for reasons including:
  - Incomplete application
  - Fails to make required certifications
- Common reasons for refuses to file (RTF) include
  - Omission of a required section
  - Clear failure to include appropriate evidence of effectiveness
  - Omission of critical data, information or analyses needed to evaluate safety or effectiveness
  - Failure to provide adequate directions for use.
- RTF are more common with ANDAs because they do not usually involve a pre-application meeting.

Advisory Committees

- These Committees:
  - May review drug clinical studies
  - May review proposed labeling
  - Will respond and vote on questions
  - May provide recommendations on issues related to the drug's approval
- Recommendations provided are not binding
- The FDA must make a final decision or explain why no decision has been made within 90 days of advisory meeting

FDAMA,
Guidance to Industry on Development and Use of Risk Minimization Action Plans

Historic Drug Approval Timelines

Year	Priority		Standard	
	Number Approved	Median FDA Review Time (months)	Number Approved	Median FDA Review Time (months)
1993	13	13.9	12	27.2
1994	13	15.0	9	22.2
1995	9	6.0	19	15.9
1996	18	7.7	35	14.6
1997	9	6.4	30	14.4
1998	16	6.2	14	12.3
1999	19	6.3	16	14.0
2000	9	6.0	18	15.4
2001	7	6.0	17	15.7
2002	7	13.8	10	12.5
2003	9	6.7	12	13.8

www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm

Types of Approval

- *Standard Review*
  - Offer minor improvement over existing marketed therapies
  - NDA review goal is *ten-months*
- *Priority Review*
  - Offer major advances in treatment, or provide a treatment where no adequate therapy exists
  - Can apply to drugs used to treat serious diseases and to drugs for less serious illnesses
  - NDA review goal is *six months*

www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm

PDFUA Performance Goals

ORIGINAL and RESUBMITTED NDAs/BLAs and Efficacy Supplements:

SUBMISSION COHORT	STANDARD	PRIORITY
Original Applications	90% IN 10 MO	90% IN 6 MO
Class 1 Resubmissions	90% IN 2 MO	90% IN 2 MO
Class 2 Resubmissions	90% IN 6 MO	90% IN 6 MO
Original Efficacy Supplements	90% IN 10 MO	90% IN 6 MO
Class 1 Resubmitted Efficacy Supplements	90% IN 2 MO	90% IN 2 MO
Class 2	90% IN 6 MO	90% IN 6 MO

MANUFACTURING SUPPLEMENTS

FY 2008-2012	90% IN 6 MO	90% IN 4 MO

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm

Fast Track Approvals

- Facilitate the development, and expedite the review of drugs to treat serious diseases **AND** fill an unmet medical need
  - *Serious:* impact on survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one
  - *Unmet Medical Need:* providing a therapy where none exists or providing a therapy which may be potentially superior to existing therapy

www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm

Accelerated Approval

- Instituted in 1992
- Faster approval of drugs to treat serious diseases that fill an unmet medical need
- Based on a surrogate endpoint
- Full approval once confirmatory trial shows that the drug provides a clinical benefit

www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm

Post Approval Activities

- FDA continues to evaluate safety and efficacy
  - Evaluation of lot release
  - Adverse event reporting
  - Post-marketing studies
  - Monitoring of promotional materials

Phase IV Studies

- Post-Marketing Studies
  - Can be initiated by the sponsor
    - Effectiveness in widespread population
    - Therapeutic Usefulness of Drug
    - New Uses/Abuses of Drug
    - Defects in Manufacturing Processes
  - Regulatory authority
    - May be condition of approval (FDAMA)
    - Pharmacovigilance (safety surveillance)
    - Facilitate FDA post-approval monitoring

1. 2006 FDA report to Congress
2. http://www.medicalnewstoday.com/articles/162928.php, 2009 FDA study by Booz Allen Hamilton for Congress

Types of Phase IV Studies

Phase IV, Postmarketing Clinical Trials are of several types:

1. Additional studies to elucidate the incidence of adverse reactions, to explore a specific pharmacologic effect, or to obtain more information of a circumscribed nature.

2. Large scale, long-term studies to determine the effect of a drug on morbidity and mortality.

3. Additional clinical trials similar to those in Phase III, to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data which would ordinarily be obtained before marketing.

4. Clinical trials in a patient population not adequately studied in the premarketing phase, e.g., children.

5. Clinical trials for an indication for which it is presumed that the drug, once available, will be used.

Guidance for Industry: Considerations for the Clinical Evaluation of Drugs

Choosing a Study Design

Study Type	Characteristics
Case Control Studies	Observational. Measures **prevalence of risk factors** in group with and without a disease Useful in rare disease or diseases with a long interval between event and outcome Can NOT be used to determine incident of an event Are usually, but not always retrospective
Cross Sectional Studies	Observational Measure event differences at a given point in time, or provide a "snapshot" Can provide information on **disease prevalence**
Cohort Study	Observational Measures the **incidence (rate) of an event/disease**, relative risk or excessive risk populations Are usually, but not always prospective
Randomized Controlled Trials	Experimental A form of cohort study, strongest study design required to test for statistical significance Are usually prospective, but can have retrospective components

http://www.stacommunications.com/journals/pdfs/cpm/cpmwinter03/phasefour.pdf

ClinicalTrials.gov

- Public information about on-going clinical trials
- Interventional and Observational studies
- FDA 2007; mandatory registration of clinical studies
- Penalties for non-registration

Supplemental NDA

- Post Marketing Changes to Approved Application must be done by submission of a supplemental NDA.
- These come in three categories each with their own requirements and timelines:
  - Prior Approval Supplement
  - Change Being Effected
  - Annual Report

Prior Approval Supplement (PAS)

- Major Change to Label
- Changes requiring PAS include, but are not limited to:
  - Changes in the qualitative or quantitative formulation
  - Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency
  - Changes in the source material or cell line
  - Establishment of a new master cell bank or seed
  - Changes which may affect product sterility assurance

21CFR601.12

Change Being Effected (CBE)

- Sponsor must submit a supplement to its NDA 30 days prior to planned use
- Evidence of causal association with contraindications, warnings, precautions, or adverse reactions
- Any change in the product, production process, quality controls, equipment, facilities, that may affect the identity, strength, quality, purity, or potency of the product

21 C.F.R. §314.70(c)(6)(iii).
Federal Register at 73 Fed. Reg. 2848 (FDA Jan. 16, 2008))

Supplemental NDA Annual Report

- Editorial or minor changes in labeling.
- Submitted each year within 60 days of the product approval anniversary date
- Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product

21 C.F.R. §314.70(c)

Withdrawal of an NDA

- Why?
  - Serious problems with the drug or its application
  - New clinical evidence shows not safe under approved conditions
  - New clinical evidence shows not effective
  - False or misleading labeling
  - Inadequate quality and purity assurances
- FDA rarely invokes this statutory authority to withdrawal NDAs.

Physician Labeling Rule

- Physician Labeling Rule
  - Applies to prescription drug products
  - Part of larger initiative to reduce medical errors
  - Improvements to Label
    - Highlights Section
    - Index
    - Revised Content and Layout
    - Prioritization of Safety information
  - Went into effect June 30, 2006
    - Implementation over seven years
    - Not all drugs require formatting change

http://www.fda.gov/cder/regulatory/physLABEL/physLabel_qa.htm#changing. Assessed May 5, 2009. 21 CFR 201.57(a),(c)
http://www.spfiles.com/pipeg-intron.pdf; http://www.aranesp.com/pdf/aranesp_pi.pdf

What is Drug Promotion?

- Activities aimed at providing:
  - Product information
  - Education on product use
  - Education on product payment
  - Product differentiation

Pina KR and Pines WL. A Practical Guide to Food and Drug Law and Regulation. Second Edition. 2002

Promotional Labeling

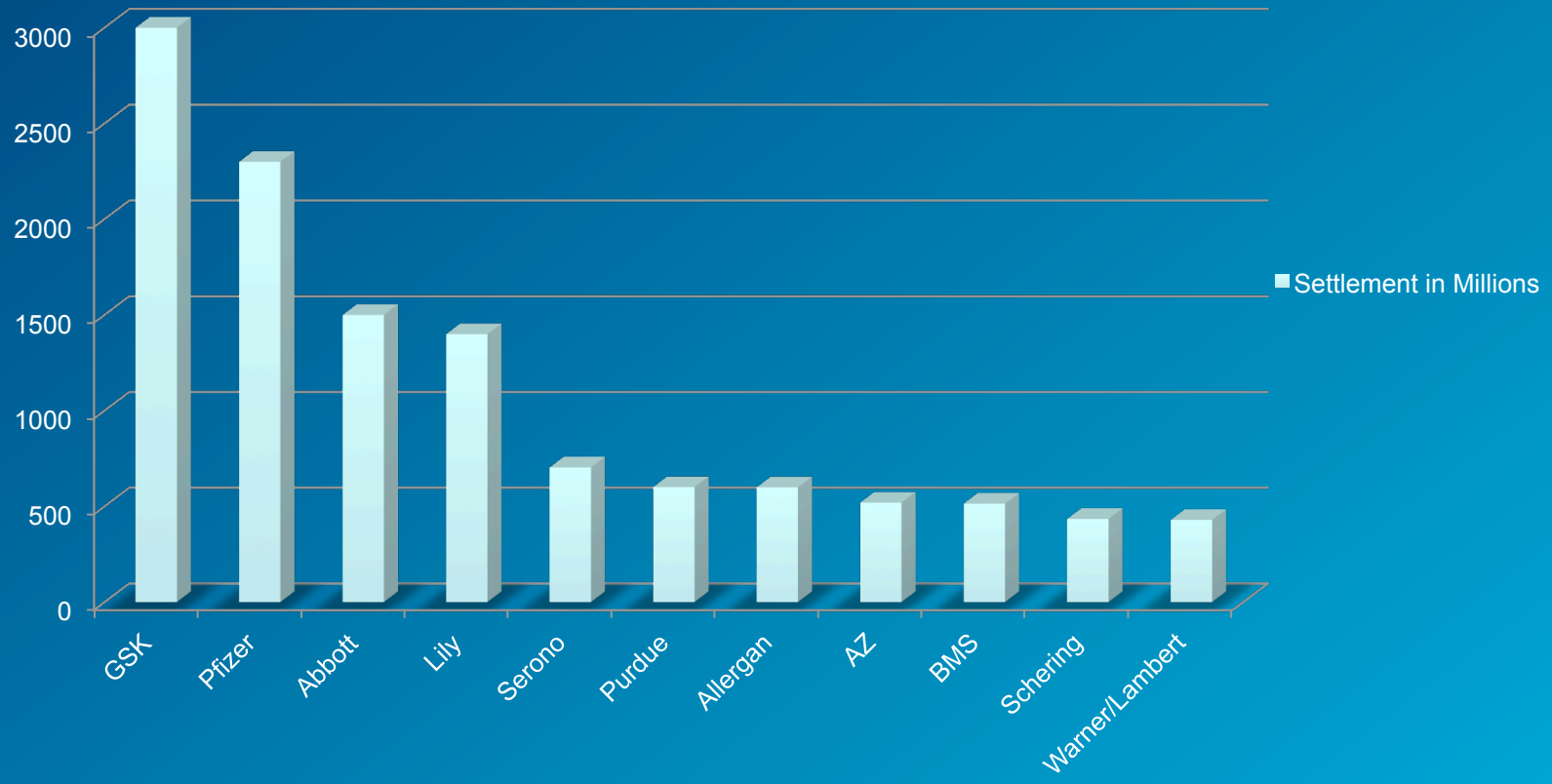
http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm082284.htm Assessed February 2013

What is Considered a Promotional Violation?

- Omission/minimization of risk information
- “Off-Label” Use
- Unsubstantiated claims
- Omission of material fact
- Omission of adequate directions for use
- Reminder ad violation

21 CFR 202.1

Eleven of the Top Off-Label Promotion Settlements*



*As of July 2012
Information from Department of Justice Website.

UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences

Questions?

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Is Increasing Spend the Answer?

- **Discussion**:
  - What are potential reasons for exponential increases in spend resulting in the same number of drug approvals between 1980 and 2006?
  - How would you recommend redesigning the organization and why?
    - Do you agree with GSK's model? Why or Why not?
  - Can more innovation occur with empowerment of the researchers? Why or Why not?

Garnier, JP. Rebuilding the R&D Engine in Big Pharma. Harvard Business Review May 2008: 1-8