COMPARATIVE ASSESSMENT FOR MEDICATIONS AND DEVICES: APPLES AND ORANGES?

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Outline

- Comparative effectiveness: US regulatory history and definitions
- US device and drug approval regulations
- Barriers between regulatory approval and evaluating comparative effectiveness
  - Apples version: drugs
  - Oranges version: devices

Legislative History

- Several attempts to fund CER since the early 1990s
  - Annual federal funding has generally been less than the cost of one large oncology trial
- Prior legislative attempts disrupted by claims it would lead to government interference in “decisions between a doctor and a patient”
  - Opponents less forthcoming about real motives

Comparative Effectiveness Funding
American Recovery and Reinvestment Act

- $400 million to the Office of the NIH Director
  - Discretion to distribute across agencies
- $400 million to Secretary of Health and Human Services
  - Research comparing clinical outcomes, effectiveness, and appropriateness of interventions used to prevent, diagnose, or treat diseases
  - Develop clinical registries, clinical data networks, and other electronic health data that can be used to generate or obtain outcomes data
- $300 million to AHRQ
  - Build on its existing collaborative and transparent Effective Health Care program.

Institute of Medicine

- ARRA legislation calls on the IOM to
  - Define “comparative effectiveness”
  - Identify research priorities
  - Report due June 30, 2009

CBO Definition

- Comparative effectiveness is a rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy. The analysis may focus only on the relative medical benefits and risks of each option, or it may also weigh both the costs and the benefits of those options.

FDA Definition of a Drug? Section 201(g) of the FD&C Act

a) Articles Recognized in the Official United States Pharmacopoeia, or Official National Formulary, or Any Supplement to Any of Them

b) Articles Intended for Use in the Diagnosis, Cure, Mitigation, Treatment, or Prevention of Disease in Man or Other Animals

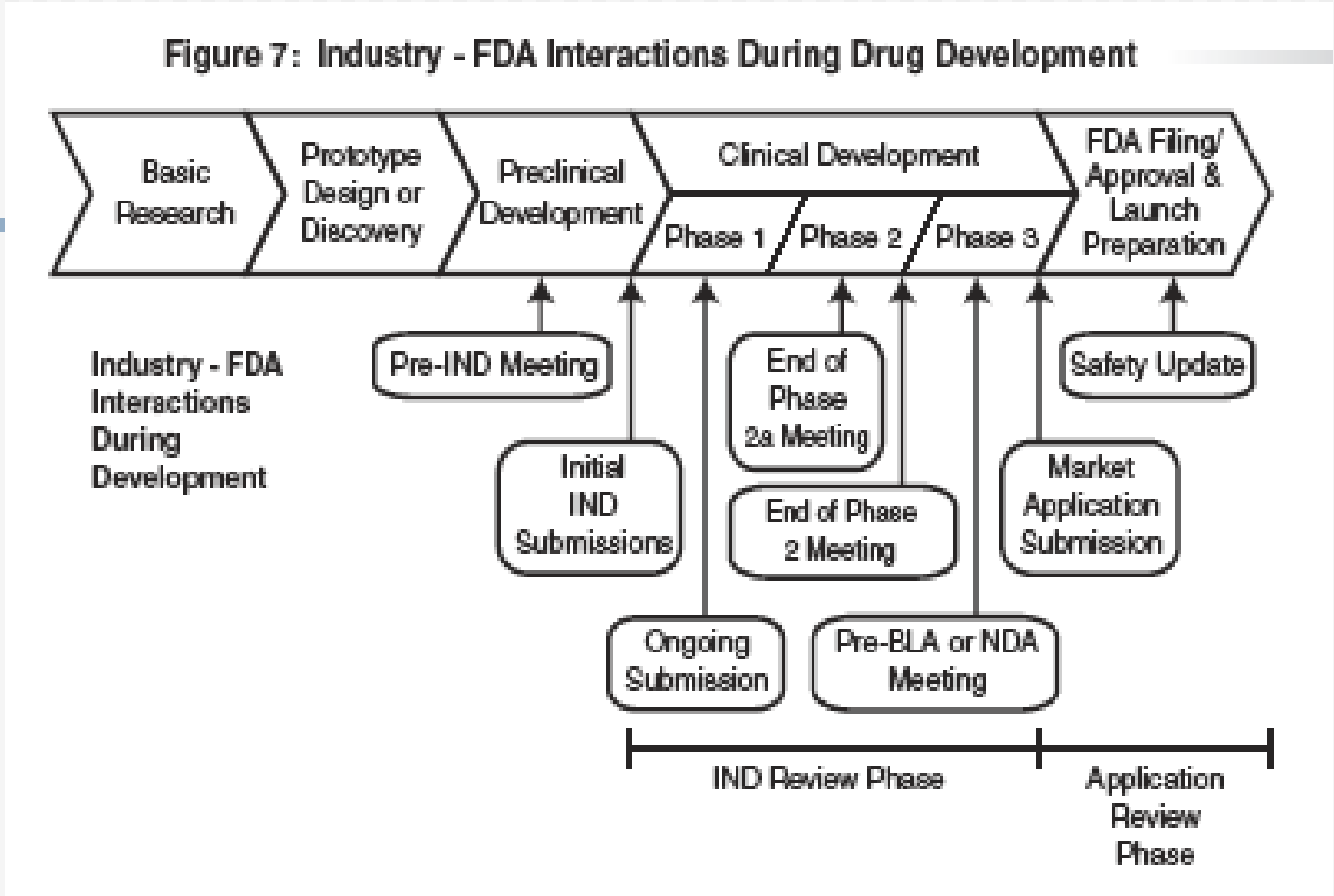
c) Articles (Other Than Food) Intended to Affect the Structure or Any Function of the Body of Man or Other Animals

Drug Labeling and Promotion

- Label Limited to Proven Efficacy and Safety
- Promotions Generally Limited to Proven Efficacy
- Physicians may prescribe “off label” but companies cannot promote off label use

Clinical Trials

- Phase I
  - What are the side effects?
  - Is it safe enough to test?
- Phase II
  - Does it work at all?
  - What is the dosage range?
- Phase III
  - Is it better than placebo?
  - Is it better than other treatments?
  - What are the side-effects?



FDA Initiative: Innovation vs Stagnation - Challenge & Opportunity on the Critical Path to New Medical Products, March 2004

Drug Approval Process is Protracted and Costly

- 8-10 years from idea to approval
- Manufacturer pays the FDA for its review
- $800,000,000 for R&D, trials, and fees

FDA Definition of a Medical Device - Section 201(h) of the FD&C Act

- Diagnosis, cure, mitigation, treatment or prevention of disease or condition
- Affects the structure or function of the body
- Does not achieve intended use through chemical reaction
- Is not metabolized to achieve effect

Classification System / Risk Categorization

- Class I
  - *General Controls*
- Class II
  - *General Controls and*
  - *Special Controls*
- Class III
  - *General Controls*
  - *Premarket Approval*

Risk

Low

Medium

High

Premarket Notification 510(k) (21 CFR Part 807)

- Marketing Clearance Process
- No form - Application submitted at least 90 days before marketing.
- Demonstration of Substantial Equivalence (SE) to legally marketed device in U.S.
- SE means **“As safe and as effective”**

510(k) Device User Fees and Review Time

- For fiscal year 2009 (October 1, 2008 through September 30, 2009), the fee for a 510(k) review is the following in U.S. Dollars:
- **Standard Fee $3,693**
- ***Small Business Fee $1,847**
  - ***** ***(≤$100 million in gross receipts or sales)***
- 90% of 510(k) application reviews completed within 90 days

Premarket Approval (PMA) (21 CFR Part 814)

- Only applies to Class III devices
- Device found **Not** “substantially equivalent” to existing device
- Proof of “reasonable assurance” of safety and effectiveness

PMA Device User Fees and Review Time

- For fiscal year 2009 (October 1, 2008 through September 30, 2009), the fee for a PMA review is the following in U.S. Dollars:
- **Standard Fee $200,725**
- **Small Business Fee for <u>First</u> Application**
  - ***≤$30 million in gross receipts or sales – ……..Fee is Waived***
  - ***≤$100 million in gross receipts or sale -……$50,181***
- Average review time 335 days

Problems with Drug Regulations from CER Perspective

- Trial based evaluation of safety & efficacy vs. population-based safety and effectiveness
  - Care settings
  - Patient characteristics (“selected” vs. “real world”)
  - Endpoints (intermediate vs. final, clinical vs. pt. oriented)
  - Underpowered for many safety endpoints
- Comparator for FDA approval usually is not the standard of care
  - Placebo
  - Pharma selected “weak” competitor

Problems with Device Regulations from CER Perspective are More Basic

- FDA rarely asks for evidence from randomized, controlled studies
  - 510(k): 98% of new devices approved this way
    - Controlled trials RARE
    - If all that has been established is “substantial equivalence” to a predicate device, what evidence exists that warrants use?
  - PMA: 2% of new device approvals
    - Controlled trials not required, occasionally done
    - Randomization and blinding RARE
    - Endpoints often focus on analytical validity (e.g., sensitivity, specificity)
- FDA regulations do not address the issue of operator skill as a factor influencing device effectiveness
  - Example: bovine pericardium approved for lung volume reduction surgery
  - Initial mortality CMS patients: 25%; NHLBI trial mortality ~ 5%

“Valid” CER Endpoints: An Ongoing Controversy for Drugs and Devices

- Intermediate measures vs. definitive outcomes
  - e.g., tumor response vs. survival
- Patient Oriented Outcomes
  - Symptoms vs. functional status vs. QOL
- Caregiver burden
- Workplace productivity
- Cost-effectiveness

Summary

- Drugs (Apples)
  - Drug development is very costly and time consuming
  - FDA process tells us:
    - That it works in idealized settings
    - Little about effectiveness/safety in clinical practice
    - Very little about effectiveness/safety vs. best standard care
- Devices (Oranges)
  - Device development can be inexpensive and quick
  - FDA approval generally does not allow decision makers to answer “Does it work?” from the perspective of clinical utility
    - Safety even less so due to operator issues
  - Special limitations for CER: blinding, randomization