The US Regulator’s Decision-Making Context

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• Decision Making in Drug Regulation: Intersection of Law, Policy, Science, Medicine and Social Values
It Starts with the Law

- Regulation is the result of laws that limit the actions/speech of some parties (usually over their objections) to achieve a common good
  - Regulatory laws are compromises
- Examples
  - Financial market regulation
  - Environmental regulation
Making Food and Drug Law: A Hundred Years of Legal History

- Long and colorful history
- Regulatory law changes usually precipitated by tragedies
- “Sausage-making”: a series of compromises
- Generally opposed by:
  - Manufacturers
  - Medical profession
  - Libertarians
  - In some cases, pharmacy community
Regulatory Evolution: the First Fifty Years Focused on Safety

- **103 years ago, Pure Food and Drug Act passed**
  - Truth in drug labeling
  - Banned adulteration; USP/NF standards

- **1938 Amendments**
  - NDA to prove safety
  - Complete listing of ingredients
  - Authorized inspections

- **1951 Durham-Humphrey**
  - What constitutes a prescription
  - Who decides
The Stage is Set for Reform

- “Public and Congress... increasingly disillusioned with the pharmaceutical industry”
- “Several new drugs... found to cause adverse reactions”
- Industry’s advertising practices, its high profits, and the high cost of prescription drugs ... under fire”
- Physicians ...”joined in criticizing drug advertising as excessive, misleading and...inaccurate” “frustrated by the hard selling pharmaceutical sales representatives”
- “Health care costs ... a subject of scrutiny in Congress and the press”
The Stage is Set for Reform

- Various parties warn about “the impending socialization of medicine”
- An Advisory Committee evaluating the Agency “emphasized the FDA’s inadequate budget and lack of scientific prowess and called for a three to fourfold increase in the Agency’s budget and the addition of a thousand new field inspectors”
Déjà Vu

- Era described: the 1950’s: these struggles led to 1962 amendments
- There are enduring themes in drug regulation
When a New Law is Passed

• Result of compromises, usually broad strokes, frequently unclear, devil is in the details

• One of the roles of the Federal Courts: interpret the law
  – Build up a series of precedents: “case law”
  – May be appealed

• Numerous drug law controversies have gone to the Supreme Court
After Law Passage: Action at the Agency Level

- Write “implementing” regulations

- Extensive administrative process: “notice and comment rulemaking”
  - Interpret law at more detailed level
  - Paperwork Reduction Act requirements
  - Economic analysis
Other Agency Level Actions

- Agency may be dealing with a specific health related regulatory problem
- May seek to use existing law to deal with it
- May issue regulations that interpret law to cover situation (pediatrics)
- Similar in the minds of some to “judicial activism”
Establishing Regulations

- Once final, have force of law
- Frequently challenged in court
- Court rulings add to the case law
- These establish the framework within which drug regulation can operate on a day-to-day basis
• FDA then makes a series of regulatory decisions based on law and regulations: these establish our policy
• Decisions may be challenged in court and litigated
• Legal standard (for us): decisions cannot be “arbitrary and capricious”, i.e., they must reflect a consistent policy, otherwise they are not fair
• We cannot make ad hoc or one-off decisions based on how we feel about a particular matter; our decisions must be fair and thus consistent, not arbitrary and capricious; they must be within a policy framework
So What About Guidance?

- Our regulatory world is very complex
- Regulations at a high level
- Need more detailed interpretation but want flexibility to evolve with science and technology changes
- Guidance
  - Not binding
  - Explain reasoning, general approach, details
Where we are making decisions on a case by case basis stakeholders have to deduce our policy from what they know about the decisions; like reading tea leaves.

Guidances make the policies available to all.

Technical guidance the same; rather than explain 1:1, give general advice.
Science and Medicine

• How are these different?
• Science: driven by scientific method
  – Cornerstone is experimental verification and reproducibility (Galileo)
  – Results in facts we can all agree upon
• Medicine: still very much an art
  – Gap between evidence and how medicine is practiced
  – Drug regulation must intersect with the realities with real world practice
• One of the triumphs of FDA drug regulation is its contribution to evidence-based medicine
• Not that much evidence out there except that required by FDA
• However, HUGE uncertainties
  – Who prescribes and uses what medicines for what purposes?
  – What are the actual outcomes of drug use in the real world? (comparative effectiveness)
Science and Medicine: Use of Medicines in Health Care

- Intersection of behavioral/social science and biomedical science
- Great complexity and uncertainty poorly studied and understood
- We make predictions about drug performance based on clinical trials
- Our evaluation has been somewhat lacking in social science perspective
- CE: hopefully new era (Sentinel)
Regulatory Decision-Making Framework

- Our decisions are our “case law”
- Each decision is make either in the context of established policy (i.e., allowable impurity level) or establishes new policy
- Science—which is a system for established, agreed-upon experimentally based facts—cannot make decisions
Framework for Regulatory Decision-Making

- Law and regulations establish “hard boundaries”
- Within these lines, there is much discretion
- Where facts of science are clear, can establish new policy in straightforward fashion
- Often remaining uncertainties are HUGE: judgment and values come into play
Role of Judgment and Values in Drug Regulation

- **Judgment**: how does this decision comport with established policies and legal interpretation?
  - Big picture impact
  - Effect on OTHER decisions

- **Values**: what each individual weighs most strongly (wide differences here)

- The more uncertainty, the greater the play of judgment/values
Examples

• Acetaminophen

• Progressive multifocal leukoencephalopathy
Need for (Semi)Quantitative Benefit Risk Analysis

• Complexity and uncertainty mean that many scientific or medical issues are being debated
• Benefit-risk framework—wherein a common understanding of the facts can be written down—can greatly inform the debate
• Provide a basis for recording the precedent or judgment—another form of regulator’s case law
Need for Semi-Quantitative Benefit Risk Framework

• Besides Enumerating what is known about benefits and risks, can write down weights or values assigned to various potential outcomes and also to the degree of uncertainty that exists.
• Provide transparency about basis for differing recommendations made on the same set of facts.
• Provide clarity about how decision made.
Summary

• Law and regulations set framework
• Science provides available facts
• Regulatory decisions must demonstrate consistent policy: not be arbitrary and capricious
• Areas of uncertainty create need for judgment and amplify impact of individual values
• Writing these down in a benefit risk framework can clarify complex decision making