Center for Drug Evaluation and Research (CDER)

The US Regulator's Decision-Making Context

Janet Woodcock, M.D.

- **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
- From D.A. Tobbell, "Allied Against Reform: Pharmaceutical Industry-Academic Physician Relations in the United States, 1945-1970" Bull Hist Med, 2008, 82:878-912.
- 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

Policy and Decision-Making

- **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**

Essential Point

- **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

Guidance Documents

- **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

Medicine

- **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