

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**



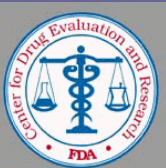
It Starts with the Law

- **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**



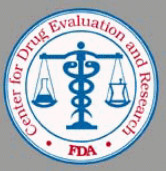
After Law Passage: Action at the Agency Level

- **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”**



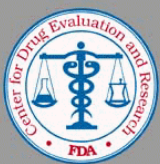
Establishing Regulations

- **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**



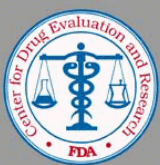
Essential Point

- **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



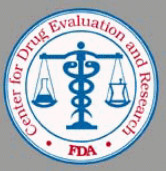
Medicine

- **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 made 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**



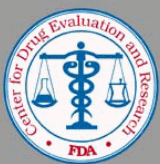
Examples

- **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**

