Managing a Complex Medical/Legal/Scientific Organization for the Public Benefit

Janet Woodcock M.D.
Director, CDER, FDA
Agenda

• Nature of the drug regulatory enterprise: role of law, regulations, medicine, science, (politics)
• Underlying controversies
• Current set of priorities
• Role of science
• Importance of management
  – Governance
  – Execution
• 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
Impetus 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”
Arguments over 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
• Similar drama occurred 2001-2007
• 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 (explicit discussion of some societal tradeoffs, not well received usually by scientific staff)
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

• FDA 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?

• The drug regulatory world is very complex
• Regulations are 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

- When FDA makes decisions on a case-by-case basis stakeholders have to deduce 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; many unknowns
  – Drug regulation must intersect with the realities of 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 (esp. in US):

- Who prescribes and uses what medicines for what purposes?
- What are the actual outcomes of drug use in the real world?
- Many of these hard to predict at time of original drug approval.
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
- FDA must make predictions about drug performance based on clinical trials
- This evaluation has not been well informed by the social sciences
Regulatory Decision-Making Framework

• FDA decisions are its “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 Decision Analysis

• Complexity and uncertainty mean that many scientific or medical issues are debated
• Analysis of benefits and harms—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 Decision Analysis

• Besides enumerating what is known about benefits and harms, 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
Role of Patient Input: Neglected up Until Recently (Medical Paternalism)

- What is the burden of disease?
- What are acceptable tradeoffs between benefits and various harms?
- What are the perceived benefits and liabilities of existing interventions?
- How to weight the benefits and side effects of the investigational therapy from the patient standpoint?
- How do patients view remaining uncertainties?
Role of Patient Input

• FDA’s judgments should robustly reflect patient viewpoint
• People with the disease will have a range of approaches to desired benefits and tradeoffs
• Ways to allow autonomy of choice while respecting the needs of more conservative individuals is challenging for FDA, since individual benefit/risk discussion occurs between provider and patient
• Next wave of legislation (“21st Century Cures”, PDUFA) will probably reflect these positions
SCOPE OF DRUG REGULATION
CDER has Multiple Important Priorities

• Diverse stakeholders: all have expectations that their priorities will be addressed (promptly!)
• Congress has provided ongoing priorities in Statutory form: FDAAA, FDASIA, DQSA, Sunscreen Innovation Act, appropriations bill language
• Operation of four user fee programs with multiple ongoing goal commitments
• All relate to underlying mission of ensuring an accessible supply of safe and effective drugs, and preventing introduction of unsafe, ineffective or counterfeit drugs
Front Burner Priorities

• Implement new (and clarified) statutory provisions on drug compounding (Janet Axelrad, lead)
• Meet GDUFA review goals that went into effect 10/1/14 and continue to reduce pending applications (≈ 3000 applications) (Cook Uhl, OGD lead)
• Continue standup of Office of Generic Drugs “super office”, (OGD lead)
• Stand up Office of Pharmaceutical Quality (Implementation team, lead)
• Implement and continue to develop PAG agreements with ORA (Andy Kish, CDER lead)
• Implement new process, data and document management IT system (OBI lead)
Front Burner Priorities

- Respond as needed and participate as requested in “21st Century Cures” legislative activities (Bob Guidos, lead)
- Rapidly re-evaluate our regulation of drug advertising and promotion in light of current jurisprudence around the 1st Amendment (CDER OMP, OCC, OC OP lead)
- Execute immediate actions required by Sunscreen Innovation Act; develop longer-term implementation plan (Theresa Michele, lead)
- Respond to Ebola outbreak (Ed Cox, lead)
- Issue final guidance(s) on abuse-deterrent opioid formulations (working group lead)
- Improve staffing:
  - More than 600 staff vacancies
  - Recruiting for multiple executive positions
Scientific Needs Related to Priorities

- **Opioids**
  - Developing framework for testing new formulations that purport to be abuse-deterrent
  - Initially, laboratory testing and “liking” studies
  - On market—epidemiology of abuse

- **Sunscreens**
  - Studies to determine effect of formulation change on transdermal absorption (published)
  - Understanding the toxicology of “endocrine disruption”

- **Compounding**
  - Crafting requirements for aseptic processors for “outsourcers”

- **Ebola**
  - Trial designs for new therapeutics (recent NEJM perspective)
Important Priorities (in no order)

- Develop new “Sentinel” network (OMP lead)
  - Reagan-Udall Foundation IMEDS program for methodologic research
- Continue to refine drug safety program (from FDAAA, Terry Toigo, lead)
  - Risk management and risk communication
- Implement biosimilars program (Leah Christl, lead)
  - Protein analytics and clinical pharmacology
- Implement statutory provisions related to the drug supply chain and “track and trace” (Ilisa Bernstein, OC, lead)
- Continue to work on Drug Label Improvement Initiative (OMP lead)
- Continue to work on new scenarios for Over-the-Counter drugs (OMP lead)
  - Probably could use some social science expertise!
Important Priorities

• Post routine demographic information about development programs for newly approved drugs (John Whyte, lead)
• Develop a strategic plan for managing drug imports (TJ Christl, lead)
• Continue to refine policies around personalized medicine (OTS, OND leads)
  – Recent scientific workshop on this topic
• Continue to develop policy approach to development of antimicrobials for drug-resistant organisms (antimicrobial task force lead)
  – Clinical methodologic science
Important Priorities

• Evaluate the impact of “Breakthrough Therapy” designation program (Medical Policy Council lead with OSP)
• Additional programs agreed to under PDUFA V
  – Patient reported outcomes
• Continue work on streamlining clinical trials (OMP lead)
  – Working with CTTI, Transcelerate, etc.
• Evaluate approaches for additional indications for targeted cancer therapies (Oncology Office lead)
  – Many new cancer therapies will be effective for subgroups, often rare subgroups, of different histological tumor types
• Evaluate the impact of requiring CV safety studies for certain chronic indications, e.g., diabetes and obesity (OND lead)
Important Priorities

• Make significant progress on FDA-EU mutual reliance initiative (with GO, Dara Corrigan, lead)
• Continue to push standards development and standarized electronic submissions (Mary Ann Slack, lead)
• Continue to conduct, and assess impact of, patient-focused drug development meetings (OSP lead)
• Continue pilot of semi-quantitative benefit-risk assessment template and evaluate it (Patrick Frey, OSP, lead)
• Refine approach to PRO development (beginning to implement refined approach to biomarker qualification process)
• Issue important drug development guidances (OND)
  – Draft on Duchenne Muscular Dystrophy
  – Final on approaches to pre-dementia Alzheimer’s
Important Priorities

• Advance progress of the more than 20 consortia CDER is collaborating with (OTS lead)
  – For example, potential CNS toxicity of anesthetics in infants
• Develop new sustainable model for ICH (T Mullin, lead)
• Work on ways to get drugs not supported by PREA/BPCA studied in children (OTS and Lynn Yao, OND)
• Develop implementation plan and training for pregnancy/lactation label rule (Maternal health staff)
• Further develop use of Bayesian statistics, adaptive designs, modeling approaches, etc. for difficult drug evaluation issues (Lisa LaVange, lead)
• Ones I can’t talk about (because they are pre-decisional, under review, etc.)
Continuing Priorities

• These have been previous high priorities and they are continuing to perform well:
  – PDUFA process: meeting the goals
  – FOI : Reducing the backlog in the face of a higher request rate
  – Advisors and Consultants: holding AC meetings
  – OSE operations: multiple safety functions
  – CDER research functions: well-organized, integrated with regulatory staff, and productive
Important Administrative/Managerial Priorities

- Re-evaluate CDER governance system (ongoing, Mary Beth Clarke, lead)
- Develop a more mature quality management system (JW lead)
- Refine time reporting system (OSP lead)
- Fully implement new training model (Kathy Hanson, DTD, lead)
- Build in-house OD capacity; continue OD efforts in new OGD and OPQ (Kathy Hanson)
- Continue to look at root causes for Employee Viewpoint Survey Results lowest scores (CDER generally gets excellent scores overall in this survey) (OEP, lead)
OPQ: New Surveillance Function

- Seeks to identify quality status of all facilities manufacturing drugs for US market
- “Pharmaceutical Platform” IT system will support: links ORA and CDER databases
- Integrate intelligence from many sources: applications, inspections, “quality metrics”
- New quantitative template for inspections being developed by ORA and CDER—scoring system to include “exceeding” minimal expectations as well as not meeting. Risk based.
- Surveillance Office will integrate all the info in a risk model to target inspections
New Surveillance Function: Quality Metrics

• Intend to collect well-understood metrics from facilities regarding state of quality
• Metrics widely used in quality management in most large-scale manufacturing sectors
• Often combined in “dashboard” to alert management to impending problems
• Takes time to understand metrics and make sure they represent the same measure across various groups; pilots ongoing
Safety Functions

• New Sentinel Network
  – New contract completed for Sentinel Network (no longer “mini”)
  – Currently contains data from 178 million lives
  – Need to institutionalize system as a standard tool in marketed drug safety evaluation
  – Methodologic research also being carried out by IMEDs (PP Partnership via Reagan-Udall Foundation)

• Refining approach to REMS, etc.
  – Policy, evaluation, and management efforts
“Drug Snapshots”: Demographic Information on Development Programs

- Commitment in Action Plan from FDASIA 507
- Post info on participation in trials by sex, race, age and ethnicity
- Posted pilot group of certain NMEs from 2014; opened docket and seeking comments on presentation of data
- Not as easy as it looks!!
- Low representation of certain racial/ethic groups in trials: multiple factors contribute
- How much is enough??
“Personalized Medicine” Policies

• CDER is approving significant number of “targeted therapies”
• These drugs target pathways or specific genetic mutations and thus are less disease-specific
• Target populations tend to be narrow sub-populations of specific diseases; and developers then seek to get additional indications
• Efficacy requirements for these additional “small slices” are under consideration. Have used case-by-case evaluation up to now, but broader policy development is needed
• Workshop 12/12/14 at White Oak on this topic
Streamlining Clinical Trials: Multiple Projects Ongoing

- Collaboration with CTTI on trial innovation
- Use of new IT
  - Use of personal devices for patient input
  - Use of telemedicine in clinical trials
- “Monitoring and Data Cleaning Practices”:
  - Traditional monitoring may not be most effective way of ensuring data quality: building quality in; developing risk-based approaches, and focusing on the most important data points may provide better quality
Evaluation of Breakthrough Therapy Designation Program

• Pace of submissions and designations continue
• Initial evaluation of 1st two years conducted by OSP
• Surveyed medical staff; did not survey industry
• We seek both process and content improvements
• Industry input will be helpful in determining the value of the program: did it help and, if so, how was the designation helpful? Evaluation will be done under contract.
Evaluation of Breakthrough Drug Program

- Clearly, for some new drugs, designation accelerated availability to patients
- Lack of clarity for industry leads to many requests that are not on the mark
- Large volume of turn downs increases workload for medical review staff, without any payoff
- We are working to streamline process for requests that clearly don’t qualify
“Patient-focused” Drug Development

• We understand that people with chronic diseases are “experts” in that disease, as far as the symptoms and the impact on QOL, and what might be acceptable tradeoffs
  – On risk
  – On uncertainty
• How to meaningfully collect that knowledge, in a rigorous manner, given that there is a spectrum of opinions and a spectrum of disease burden in any given disease?
• How to do this for the many thousands of diseases?
Importance of Good Management

• In addition to these priority initiatives and other initiatives, CDER has a large volume of work that must be accomplished every day: we are a production shop.

• Tens of thousands of decisions made yearly on INDs, applications and supplements; thousands of meetings with industry; more than 50 guidances and multiple regulations published; FOI work (over 3000 requests in 2014); AC’s; import decisions; drug safety communications; underlying drug safety evaluation activities; evaluation of inspection results; compliance and enforcement actions; and scientific activities, to name just a few.

• Ensuring that all this gets done, well and efficiently, requires engaged staff members who feel supported and listened to by leadership, careful process and quality management, and high-quality IT support.
Importance of Good Management

• Many of our stakeholders have policy priorities and do not understand how critical good management is to making things happen; seems to be a general problem in government

• It is feasible to handle a handful of initiatives through an informal process, but not hundreds, while at the same time managing the ongoing workload

• CDER’s “lean team” assists with process improvement throughout the Center

• We have a plan for implementing modern IT process and data support: accomplishing these longer-term goals will be key to sustaining our success
Congress and various administrations increasingly involved
  – In specific policies
  – In specific product decisions (very problematic)
Lack of formal rules of engagement means that each new administration creates its own interface, and Congress has multiple modes
For over 20 years, I’ve generally reported directly to a political appointee
General political turbulence impacts Agency functioning
Summary

• Successful drug regulation requires that FDA perform at a high level in
  – Science
  – Law
  – Medicine
  – Policy
  – Management and execution
  – Political and stakeholder engagement