# 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

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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

# 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
- 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.
- 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

# 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 (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 trans-dermal 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 turndowns 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 rigorous manner, given that there is a spectrum of opinions and 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

# (Politics)

- 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