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Drugs, Vaccines, and Devices
Public Health, Private Industry and the Limits of Regulation

Symposium on Risks Posed by New Biomedical Technologies

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Public Concerns about Products

- Lack of important on-label information
  - Inadequate safety testing, resulting in patients injuries and product withdrawals
  - No “real world efficacy” and comparisons with other options
  - Subpopulation gaps
    (pediatrics, geriatrics, women, racial and ethnic groups)
- Off-label promotion and use
  - Little or no safety or effectiveness data

Public Concerns about Priorities

- New products not really important
  - "Me-too" drugs, not true innovations
  - Drugs for "lifestyles", not for saving lives
- Neglect of prevention (vaccines) and cures
- Industry driven by marketing, not science
  - Research for new uses (or ad claims)
  - R&D spending about 1/2 of marketing and administration budget
  - "Creation of diseases" through marketing

Public Preferences

- Safe products
  - Either zero risk or a well-defined safety profile
  - No more surprises
- High value products
  - Life saving or extending
  - Disease preventing
- Low cost products
  (for users and insurers)
- Evidence-based comparative choices

Our Model for Development of New Biomedical Technologies

- Responsibility for basic medical research lies with government researchers, academia, and charities
- Responsibility for product development lies with the private sector
  - Decentralized decision-making
  - Reliance on profit incentives to raise capital for R&D
- Responsibility for the safety and effectiveness of technology development and transfer lies with regulatory agencies

Classic View of Regulation

- Regulators (*e.g.,* FDA) are to enforce rules
  - Enforcement tools are primary coercive (*e.g.,* civil and criminal penalties, prohibitory injunctions)
  - Tools are "sticks" which offer no incentive other than the avoidance of pain and loss
- Regulators are not to tell industry what to do, only what ***not*** to do

Better View of Regulation

- Regulators and regulatory schemes can provide incentives to encourage research in certain directions or on certain issues
  - Regulators have discretion within parameters
  - Statutory authority is essential for other incentives
- BUT, incentives remain constrained and impose limits on what regulation can accomplish

Discretionary Options for Regulators

- Create incentives by giving favored treatment to desired products
- Examples
  1. Prioritize applications for review
  2. Provide guidance on pathway to approval
  3. Permit approval on less-than-complete data, with post-approval studies
  4. Improve scientific basis for decisions

(1) Prioritized Application Process

- FDA began for drugs in early 1980s
  - Classified depending on predicted therapeutic contribution compared to existing therapies
    - More important drugs got higher priority
    - Not limited to life-saving drugs
  - Best case: AZT for AIDS (1987)
- Prescription Drug User Fee Act (PDUFA) legislation (1992-2007)
  - Two classes (priority and non-priority)
  - Shorter review deadlines for priority (6 vs. 10 months)
- Congressional ratification of “fast track” (1997)

(2) Guidelines to Expedite Development

- Begun in 1970s by FDA for drugs and devices
  - No overt priority scheme obvious, but clear hints
- Major leap forward with AIDS and cancer products starting in late 1980s
  - Surrogate endpoints
  - Trial design to reduce or eliminate placebos
- Expanded greatly under PDUFA
  - More resources to produce
  - Wider dissemination via Internet

(3) Accelerated Approval with Subsequent Studies

(slide 1 of 3)

- First use was in 1969 with levodopa
- Concept
  - Approve only based on short-term safety and efficacy
  - Defer other questions to post-approval
    (*e.g.,* long-term safety, subpopulation studies)
- Limited to drugs providing meaningful improvement over existing therapies for serious or life-threatening diseases

(3) Accelerated Approval with Subsequent Studies

(slide 2 of 3)

- Generally requires post-approval studies to confirm effectiveness (if based on endpoint other than mortality or irreversible morbidity) and safety
  - Can include subpopulations, other stages of disease, concomitant drug, improved dosing regimens
- FDA can impose restrictions on clinical use, pre-clear marketing materials, and expedite withdrawal of product if it proves unsafe or ineffective

(3) Accelerated Approval with Subsequent Studies
(slide 3 of 3)

- Problems encountered by FDA and industry
  - Not all studies requested by FDA are meritorious, scientifically feasible, or even ethical
    - Lack of consistent standards or procedural safeguards
  - Inability of FDA to track commitments
  - Lack of effective enforcement tools for failure to do studies
    - Withdrawal of valuable product unrealistic

(4) Improving Scientific Basis for Decisions

- FDA believes current requirements are becoming obsolete in light of new genomic information and tools
  - Biomarkers for potential effectiveness, safety risks
  - Surrogate endpoints in lieu of full trials
- FDA intends its new Critical Path Initiative to accelerate identification, validation, and implementation of new tools

Observations on Discretionary Options of Regulatory Agencies

- Limited (even marginal) influence on economic incentives
- Cannot exclude or ignore disfavored products altogether
- Constrained by political acceptability
  - Rapid approval or conditional approval is fine, until it proves to have been a mistake in a specific case

Statutory Schemes to Provide Regulatory Incentives

- Focused directly on increasing financial rewards for favored products
- Not part of patent laws
  - Not subject to requirements for patentability
  - Not enforced by civil actions in court
- Part of regulatory process
  - Implemented by regulators

Examples of Statutory Schemes to Provide Regulatory Incentives

1. Orphan Drug Act (1983)
   - Limited to drugs with potential use <200,000/year
   - FDA may not approve the same drug for same use for 7 years after 1st approved
   - Only available if product is approved
   - Runs concurrently with any patent protection (*i.e.,* not limited to unpatentable products)

Examples of Statutory Schemes to Provide Regulatory Incentives

2. Hatch-Waxman Act (1984)
   - Available for all "new chemical entities" without preference for any type of product or therapeutic contribution
   - FDA may not approve "abbreviated" application for same drug for 5 years after 1st approved
     (of for new use of a drug for 3 years after 1st approved for that use)
   - Runs concurrently with any patent protection

Examples of Statutory Schemes to Provide Regulatory Incentives

3. Hatch-Waxman Act (1984)
   - Available for a generic copy of an innovator, if the innovator's patent exclusivity is successfully defeated or evaded
     - Incentive here is to bring generic competition to the market as early as possible
   - FDA may not approve 2nd "abbreviated" application for same drug for 180 days after 1st approved and can enter the market

Examples of Statutory Schemes to Provide Regulatory Incentives

4. Pediatric Exclusivity Provisions (1997)
   - Available for any drug which is tested in response to FDA request to determine safety and effectiveness in one or more of four sub-adult populations
     - No requirement that drug be safe or effective, only that its safety and efficacy be determined
   - Delays the date on which FDA may first approve a competing application by 6 months
     - Thus, extends exclusivity periods under Orphan Drug Act and Hatch-Waxman

Observations on Statutory Schemes for Regulatory Incentives

- Can be very potent
  - But, as with patents, ultimate value depends on actual market for product protected
- No necessary correlation between the cost (or risk) to gain the financial incentive and its economic value
  - Can create political controversies
- The rewards are not always available

Authority to Compel Specific Research: Introduction

- The two categories discussed so far have dealt with incentives to encourage the direction of research
- The critical question, now, is whether regulators can order that certain research be done?
  - Bear in mind, violation of an order can result in civil or criminal sanctions under the overall regulatory scheme

Implicit Authority to Compel Specific Research (slide 1 of 2)

- FDA rules require "adequate directions" in labeling for all "intended uses"
- Manufacturers required to assess safety and effectiveness for high-risk populations covered by approved use
  - Geriatrics
  - Women generally, and of child-bearing potential in particular

Implicit Authority to Compel Specific Research (slide 2 of 2)

- In mid-1990s, FDA attempted to adopt regulations to compel manufacturers to perform studies in children, if they were subject to the disease covered by the approved labeling occurred
  - 4 tiers (neonates, toddlers, pre-adolescent, and adolescent)
  - Could require new dosage forms
- Regulation invalidated on judicial review

Statutory Authority to Compel Specific Research

- In 2002, Congress empowered FDA to order manufacturer of a specific drug to conduct studies to determine whether it is safe and effective in children
  - Applies only to uses approved for adults that occur in a substantial number of children
  - Does not supersede pediatric exclusivity
  - Elaborate process before order becomes effective

Authority to Compel Research regarding Off-Label Uses

- FDA historically said that if a product was used "off-label," the manufacturer either had to get the use "on-label" or take steps to stop it
  - Rarely if ever used to compel off-label research

Observations on Authority to Compel Specific Research

- Legal uncertainty exists whether FDA's authority to require "adequate directions for use" extends to being able to order studies for subpopulations covered by the approved (on-label) use
- No case law regarding off-label use area
- Congressional enactment was narrowly tailored and replete with procedural requirements

The Limits of Regulation

- Generally, regulators are not empowered to control the direction of development for biomedical products
  - Manufacturer selects the uses it intends
  - Regulators can provide incentives to influence the selection process, but ultimately cannot veto the outcome
  - Once use is selected, regulators can influence the subpopulations within that use to be studied (but extent of power is unclear)

Should Regulators Have More Power?

- Public policy makers have several alternatives to affect the direction of biomedical research and development
  - Command-and-control regulation
  - Indirect incentives
    (market exclusivities, tax credits)
  - Direct incentives
    (contracts to develop or purchase specific products)
  - Internal R&D
    (use government laboratories)

What Powers Should Regulators Have?

- Who selects the products or targets to be given priority?
  - Different diseases have different constituencies
  - Social objectives may not match available scientific knowledge
- Is development in other areas to be forbidden?
- Who must do the development work in target areas?
  - What options do the affected private parties have?
- What degree of coercion can be applied?

Conclusion

- The authority of regulators in limited for good reasons
  - Decentralized decision making serves both democratic and free market values
  - Command-and-control is not well-equipped to bring out investment or assure vigorous work
- To get the kind of products the public wants, policy makers should not look to increasing regulatory powers