The Future of Drug Development: Balancing Benefit and Risk

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Drug Development “Eras”

- Dawn of medicinal chemistry: decades pre- and post- 1900
- Early industrial phase: mid 1940’s onward
- Post 1962 amendments to the FD&C Act: formal clinical evaluation of performance
- Late 1980’s through early 2000s: the “go-go” years (blockbusters, high throughput screening)

Drug Development “Eras”

- ~2004-2010: Is this the end?
  - Drug safety problems
  - Recession; layoffs; pipeline problems
- Current era: Can precision medicine/specialty pharmaceuticals save the day?
- The future of drug development: what will happen next?

Forces Impacting Drug Development

- Science: the science has never been more promising; however—
  - Translational science academic enterprise is miniscule compared to basic science enterprise; this lopsided investment will increasingly cause problems as a bottleneck forms. Congress discussing explicitly involving FDA in this issue, e.g., “biomarker qualification” process, etc.
  - Lack of formal infrastructure for clinical evaluation has driven costs up exponentially; calls for more extensive evidence increase; something will have to give; no one “owns” this problem.

Forces Impacting Drug Development

- Costs: drugs costs a big theme in current presidential campaign
  - Higher deductible health care plans driving outrage; insured must bear a higher percentage of costs
  - Continued concern and misunderstanding of why US drugs prices are higher than elsewhere
  - Trend towards ever-increasing pricing for novel drugs not sustainable

Globalization

- New markets opening in emerging economies; new emerging threats needing solutions
- However, regulators world-wide also emerging, along with technology assessors who are looking for value, not just safety and efficacy
- Multiple requirements on firms, often slightly divergent
- Most obvious now in manufacturing sector, but also occurring in clinical development
- Increases costs and potential for error

Drug Development's Future Depends on Decisions Made in the Present

- Science
  - Collaboration on, and bolstering of, translational science
    - How will we move reductionist basic science evidence into integrated models of health and disease?
    - Pharmaceutical industry's individual drug development efforts are not an adequate vehicle
    - Consortia efforts are illustrating what needs to be done, but funding very shaky
    - Costs could be staggering unless new ways to develop the clinical associations can be developed
  - Construction of a new clinical evidence generation system
    - Use of trial networks, master protocols
    - Merging clinical research with clinical care in a meaningful way

Decisions: Costs—unlikely that society will tolerate unrestrained increases

- How to make drug development *more efficient?*
- Industry has been trying to do this for decades
- Rising costs driven by failure rate in the clinic
- Intra-company efforts unlikely to yield major gains; need collaborative efforts
  - Improve translational science
  - Modify clinical research enterprise
  - Improve manufacturing

Globalization

- Need to establish a goal of regulatory convergence
- No good reason for standards to differ in minor ways
- Manufacturing and inspectional standards may the first to be extensively harmonized
- FDA has entered into a mutual reliance initiative with the EU for GMP surveillance inspections

Changes in Drug Development Over Time

- Last almost 50 years: ever-increasing requirements and areas to study, first about efficacy and lately about safety
- Even if success rate were 100% after Phase 1, would still be a very expensive enterprise
- Ironically, the more we know about biology, the more it costs to develop a drug
- Will there be an inflection point in the next decade or so?

Drug Development over Time

- Current thrust of biomedical science is further splintering our understanding of human disease into smaller disease subgroups
- Drug developers have responded to these new targets with therapies tailored to subgroups—some of these therapies are greatly superior to existing approaches
- Time will tell if the success rate in development is significantly impacted
- But the impact on drug costs with large numbers of new agents targeting small subgroups of patients—may be problematic

Role of Regulation

- Since 1962, regulatory requirements have played a large role in bringing an evidence base to medical practice
- Rigorous evaluation embraced by the cardiology community
- However, you will face the issue of rare and ultra-rare disease subsets, as well as dealing with diseases that affect large percentages of the population
- How to implement flexibility in regulatory standards to deal with these increasingly disparate situations, has not been formally resolved

Benefit and Risk

- FDA has established and implemented a benefit/risk template in review
- Well accepted internally and by stakeholders
- However, most of these do not get at the actual tradeoffs
- Some quantitative benefit/risk assessments have been conducted internally, and some published, but much more needs to be done in this area
- Risks of uncertainty in effectiveness, and risks of “type 2” error, not usually addressed
- Current B/R template provides a good framework for the further work that needs to be done

The Patient's Voice

- Most B/R assessments historically, have been from a medical professional point of view
- Patients either not organized, or not asked
- Unsurprisingly, people suffering from a disease have often widely divergent opinions about B/R compared to people treating the disease
- FDA's "Voice of the Patient" meetings are eliciting important information about what matters to people; we need to formalize incorporation
- Increasingly, tech assessors will use this information to assess value, in payment decisions

Summary

- Future of drug development an open question
- Basic science very promising; translational apparatus challenging; regulatory environment (appropriately) demanding and financial prospects very worrisome
- Drug candidates will have to demonstrate substantial value to patients
- The process must become more efficient, or even fewer candidates will make it to evaluation


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