Regulatory Science: Challenges & Opportunities in Product Development and Public Health

Jesse L. Goodman, MD, MPH

Director, Center on Medical Product Access, Safety and Stewardship,
Professor of Medicine and Attending Physician Georgetown University
and VA Medical Centers

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Overview: From Threats to Therapies

• The Product Development Ecosystem: Can it become more connected and efficient?

• Regulatory Science and its Role:
  – Reduce uncertainties for new/emerging technologies
  – Improve prediction and determination of safety and efficacy

• FDA’s Strategic Plan: Overview & exploration of selected opportunities

Please note: presentation reflects personal opinions, not US policy
Costs gone wild: especially clinical development

Figure I. Average Cost to Develop One New Drug

Source: Tufts Center for the Study of Drug Development

*Lehman Brothers, 1997; ** Tufts CSDD
FDA Strategic Plan for *Regulatory Science*

- FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need

- 21\textsuperscript{st}-century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community
Regulatory Science: Then and Now

1906 to 2014
FDA Strategic Priority Areas

1. Transform toxicology (ex: human on chip)
2. Stimulate *Innovation in clinical trials* and personalized medicine
3. New approaches to improve *Product manufacturing and quality* (ex: new rapid sterility assays)
4. Readiness to Evaluate *Innovative/ emerging technologies*
5. Harness diverse *Data* to improve health outcomes
6. Facilitate Development of Medical Countermeasures (MCM) to protect U.S. & global health and security
7. Strengthen social and behavioral science to help consumers and professionals make informed decisions
Clinical Trials: New Approaches

• Patient recruitment: New technologies/social capital for
• Study designs: Adaptive/iterative
• Bigger OR smaller studies

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• Large simple trials – when “simple” is to focus on collecting only key data, i.e. major safety / efficacy endpoints
Clinical trials: New Approaches (continued)

• *Point of care (health care)/community trials:*
  – Trial entry and consent at Point of Care by Electronic Monitoring remote
  – and to various degree, clinical follow up, data access, imaging etc.

• *Smaller trials:*
  – Smaller is cheaper
  – The bigger the response rate/difference, the smaller the trial
  – Especially useful for rare diseases/patient subtypes
  – May also consider in phased development with initial narrow studies/approvals – *e.g. oncology approvals for targeted therapies*
Recruit subjects online?

- “Study website received visits from 94,808 individuals over the 14-month recruitment period. The recruitment target was reached with 1699 individuals signing up to the trial and 1326 fully enrolling...at a cost of $12 per participant.”  
  *J Med Internet Res.* 2013 Feb 12;15(2) recruitment to a depression prevention intervention

- But patients recruited through internet may be different! Ex differing response to Rx:

  - “Digital divide”: More income & race disparity of internet vs. cellular access
  - Patient groups/networks also have been quite effective(e.g. Michael J. Fox)
Or Even Through Twitter?

A researcher tweeted 749 times over 4 months(!) – this approach led to 529 people taking an online survey about needs of older mothers

Large Simple Trial at Point of Care

Patient enrollment & efficient collection of major outcomes of interest through national registries
Clinical Trials: Globalization

• Multiregional trials can speed recruitment & lower cost
• Potential caveats:
  – Population differences can result in “non-representativeness”
  – Special challenges from differences in:
    • Disease diagnosis, severity, co-morbidities
    • Access + other aspects/standards of care, non-medical care
    • Host genetic and other pharmacologic/physiologic factors
    • Health literacy, ethics, culture, economic well-being, perceptions -- compliance differences
• Difficulty determining whether outcome differences among regions detected in a trial are real vs. random
• The best approach is to design studies & analyses up front to reduce/account for such factors
Why did ticagrelor - to prevent thrombosis - look worse than clopidigrel in the US, but better in 42 other countries!

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n/N)</th>
<th>Clopidogrel (n/N)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=18,624</td>
<td>9.8% (864/9333)</td>
<td>11.7% (1014/9291)</td>
<td>0.84 (0.77, 0.93)</td>
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<tr>
<td>Non-US</td>
<td></td>
<td></td>
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<tr>
<td>n=17,211</td>
<td>9.6% (780/8626)</td>
<td>11.8% (947/8585)</td>
<td>0.81 (0.74, 0.90)</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n=1,413</td>
<td>12.6% (84/707)</td>
<td>10.1% (67/706)</td>
<td>1.27 (0.92, 1.75)</td>
</tr>
</tbody>
</table>

**Differences in ASA Dose Used?**

<table>
<thead>
<tr>
<th></th>
<th>ASA ≤ 100</th>
<th>ASA ≥ 300</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>OUS</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>9.1% (24/263)</td>
<td>9.4% (699/7443)</td>
</tr>
<tr>
<td>T</td>
<td>6.7% (19/284)</td>
<td>7.3% (546/7449)</td>
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<tr>
<td>CV Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2.7% (7/263)</td>
<td>4.1% (302/7443)</td>
</tr>
<tr>
<td>T</td>
<td>2.1% (6/284)</td>
<td>2.8% (209/7449)</td>
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<td>NFMI</td>
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<td>C</td>
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<td>5.5% (413/7443)</td>
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<tr>
<td>T</td>
<td>4.6% (13/284)</td>
<td>4.5% (335/7449)</td>
</tr>
</tbody>
</table>
New Approaches to Endpoints

• Biomarkers, imaging and other more proximate predictors of clinical outcome
• Patient reported outcomes
• Remote directly measured/monitored responses/outcomes

but

• Like any measurements, new approaches must be validated
Monitor gait with cell phone? – and/or HR, BP, O²

• Determine what people with chronic disease are actually doing and what happens while doing it
• Or help people walk better and do more
• Or monitor pregnancy*

GaitTrack: Health Monitoring of Body Motion from Spatio-Temporal Parameters of Simple Smart Phones Qian Cheng; Conference on Bioinformatics, Computational Biology and Biomedical Informatics, Health Informatics Symposium, Sep 2013
Beyond technology: The Power of Patients

- Helped fund discovery and development of ivacaftor (Kalydeco™), approved 2012 for CF patients with rare G551D mutation, and lumacaftor (~ $75m investment in partnership with Vertex)

- 6/2014: clinical trial results reported that ivacaftor in combination with lumacaftor yield significant improvements in patients with 2 copies of the common F508del mutation (~ 50% of CF)

  - [video](http://www.youtube.com/watch?v=F6ngcafMxBE)
Globalization & supply chain challenges

The New York Times
November 26, 2008
WORLD BRIEFING | AFRICA
Nigeria: Contaminated Medicine Blamed for Deaths
By NYT

The New York Times
May 7, 2007
80 children die in Haiti due to contaminated glycerin in acetaminophen syrup

The New York Times

Heparin Contamination May Have Been Deliberate, F.D.A. Says

China recalls infant formula
By Keith Bradsher
Published: September 12, 2008
The Supply Chain: Increasingly Vulnerable?

• Much competition based primarily on cost:
  – challenging investment in modernization
  – resulting in concentration to few suppliers

• Globalization:
  – increasingly complex
  – less redundant and more vulnerable supply chains, for
    drugs 40% and for API 80% is non-US manufactured
  – similarly >50% of devices now imported

• *US DOC study*: ¾ of the manufacturers of products deemed
  critical were found to depend on non-US source
Old Shenzhen, China (early 1980s)

New Shenzhen
Keeping Global Supply Chain Safe

• Pay for and compete on quality, not just price
• Enhance global footprint and collaboration in regulation - backed by trade/economic policies
• Build global regulatory capacity
• Clarity, awareness and enhancement of manufacturer responsibility/accountability for suppliers
• Better science for manufacturing, testing and risk analytics
• Better monitoring
• Define products essential for core health system and for emergency response needed to support society for defined time period as part of critical infrastructure
  • For these critical products, consider steps such as increased diversity of suppliers, maintaining inventory, or building domestic/regional manufacturing capacity
Emerging Public Health Threats: overdue attention to antimicrobial resistance

• Incentives for industry and venture capital:
  – Must be collaboratively developed
  – Willingness to pay well for real advances but also linked to phased, appropriate promotion and use

• Legislative/Regulatory approaches:
  – GAIN Act – 5 years additional exclusivity, eligibility for fast track and priority review
  – Explicit authorization for limited population antibiotic development pathway/trials
  – Encourage new approaches/trial designs focused on resistant organisms
  – Presidential Order of 9/18 creates new Cabinet level task force, supports stewardship, calls for investment in drug development, diagnostic prize, and global engagement
Emerging Diseases: A Pressing Need for Global Clinical Trial Preparedness and Capacity

• Emerging infections and public health emergencies pose a global threat but are often initially rare or limited geographic distributions, e.g. H5N1/ MERS
• They often arise where the economy, health systems and clinical trial capabilities are deficient, witness Ebola
• Unlike most pharmaceutical studies, research must be rapidly mobilized for results to matter
• Must incorporate scientific & ethical principles in conduct, communicating knowns & unknowns
• Must engage and build trust with affected communities
• Long term investment in infrastructure and investigators needed
Harness data, yes….but drowning in it is not just possible: it’s happening
Problems with Our Sea of Data

• We know the promise – biomarkers, use of EHR for safety/ efficacy
  BUT...
• “Men have become the tools of their tools” – Thoreau 1854
• We have become both enamored of and overwhelmed by the data and its complexity
• Data itself does not equate with knowledge or understanding
• Multiple analyses will yield results and associations of p<0.5 that make no sense, which has an opportunity cost in distracting from true issues and findings
• The art of recognizing & asking questions is in danger of being lost
AND
• Conversely, we are confronted with continuing failures to predict, see or recognize real findings
Big Data: Needed Course Corrections

• Teams are critical but cannot solve all the problems of extreme data and specialization

• We also need to
  – Ensure career paths not just for specialists,
  – But also for generalists and people with feet in more than one discipline (e.g. medicine, informatics, anthropology...)
  – Leadership that balances the emphasis on tool and data driven science vs. science driven tools and data

• And educational systems and workplaces that reward human contact, including with those different from us
Additional Approaches to Reduce R&D Costs & Speed Innovation

- Enhanced post-approval capacity to detect problems quickly (better, faster, bigger data)
- Can enable earlier approval for unmet needs
- Tie and speed reimbursement and special benefits in regulatory pathways toward products addressing truly unmet needs and clinically significant treatment effects
  - For example, *breakthrough therapy designation* provides intense and high-level regulatory engagement where preliminary clinical data show benefit
Toward a Bright Future

- Regulatory science is critical to provide tools needed to speed innovative products to patients, safely and efficiently
- The work is too complex for any one party or sector and requires global engagement
- Collaborative approaches are essential for success

Thanks!

jesse.goodman@georgetown.edu