

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



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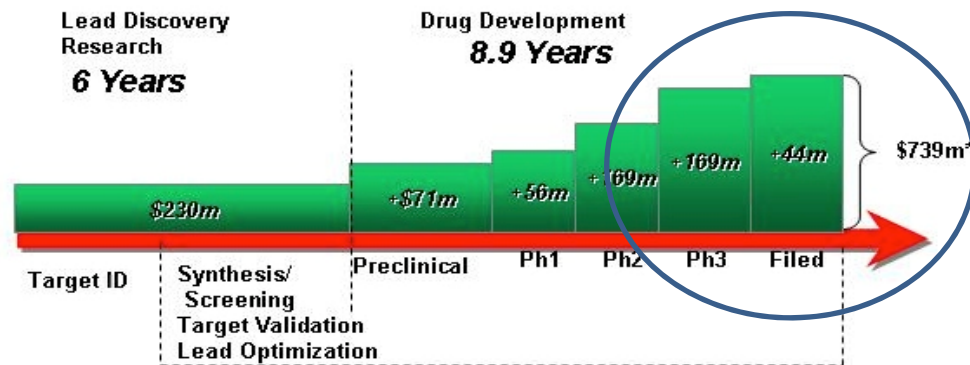
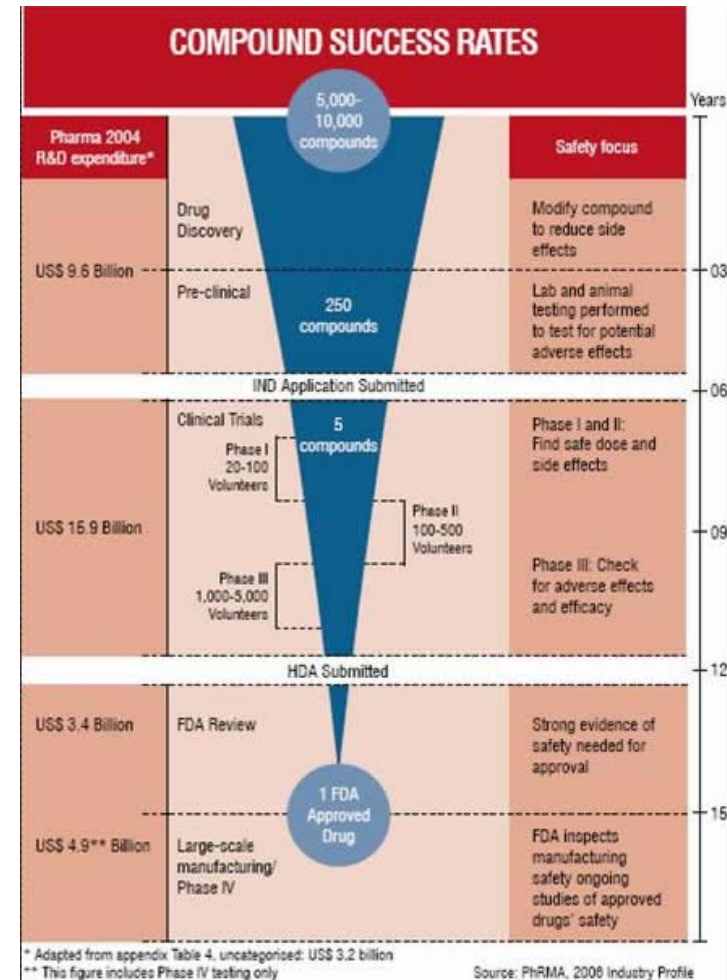
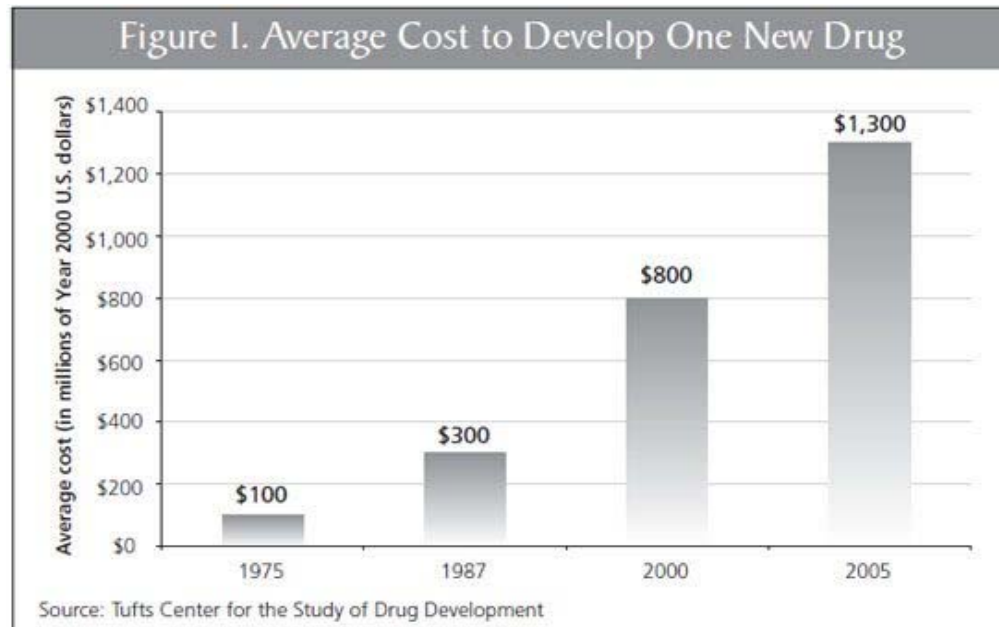


# ***Overview: From Threats to Therapies***

- *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*

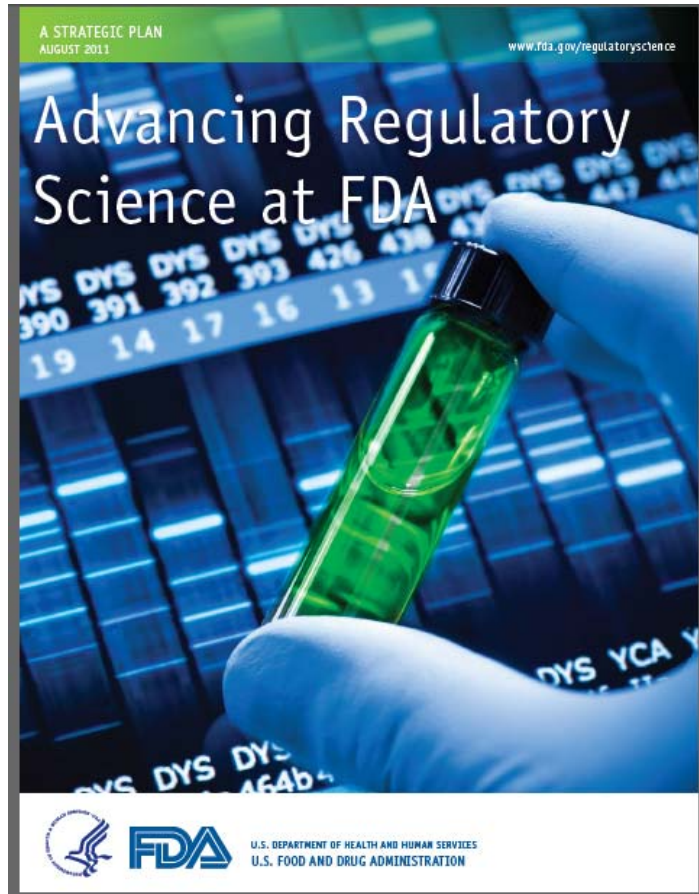
*Please note: presentation reflects personal opinions, not  
US policy*

# Costs gone wild: especially clinical development



\*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<sup>st</sup>-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



2014

to



FDA

# ***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



- *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?

## a) Successful Google ads

[Depression test](#)  
Take our quick, easy, and anonymous test to see if you have depression  
[www.moodmemos.com](http://www.moodmemos.com)

## Display network

Impressions: 4,739,517  
CTR: 0.35%  
Average CPC: \$0.13  
Conv. rate = 0.90%  
CPS = \$14.81

## Keyword search

Impressions: 1,248,583  
CTR: 6.02%  
Average CPC: \$0.09  
Conv. rate = 0.80%  
CPS = \$10.73  
Example keywords:  
depression test  
depression symptoms  
am I depressed

## b) Less successful Google ads

[Self help for depression](#)  
Feeling depressed and want to help yourself? Join the Mood Memos study  
[www.MoodMemos.com](http://www.MoodMemos.com)

Impressions: 83,998  
CTR: 0.13%  
Average CPC: \$0.25  
Conv. rate = 0%  
CPS = N/A

Impressions: 954  
CTR: 0.84%  
Average CPC: \$0.28  
Conv. rate = 0%  
CPS = N/A  
Example keywords:  
depression self help  
self help for depression

[Feeling down or low?](#)  
Want to improve your mental health? Join the free Mood Memos study  
[www.MoodMemos.com](http://www.MoodMemos.com)

Impressions: 12,171  
CTR: 0.07%  
Average CPC: \$1.96  
Conv. rate = 0%  
CPS = N/A

Impressions: 947  
CTR: 0.84%  
Average CPC: \$1.11  
Conv. rate = 0%  
CPS = N/A  
Example keywords:  
depression help  
help for depression



Impressions: 13,622  
CTR: 0.44%  
Average CPC: \$0.18  
Conv. rate = 1.67%  
CPS = \$10.65

## c) Facebook ads

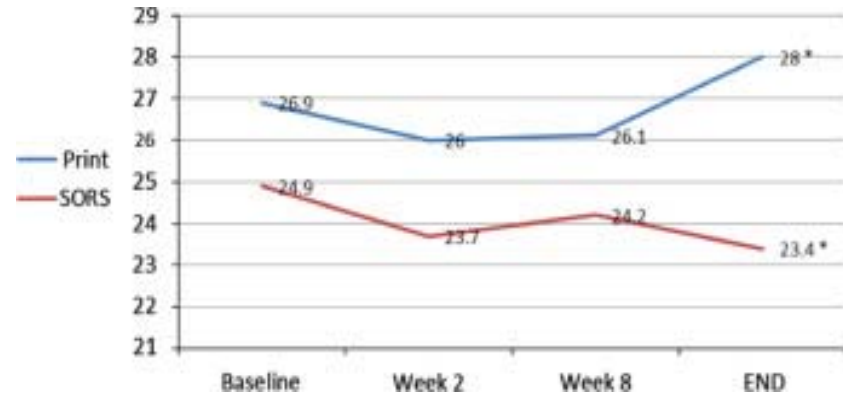
[Feeling blue?](#)  
moodmemos.com  
  
Want to help yourself feel better? Join the Mood Memos online study and you'll receive info and advice about depression by email.

Impressions: 340,406  
CTR: 0.026%  
Average CPC: \$0.69

[Depression test](#)  
moodmemos.com  
  
Take our quick and anonymous test to see if you have depression. Then sign up to the Mood Memos study for free help with depression.

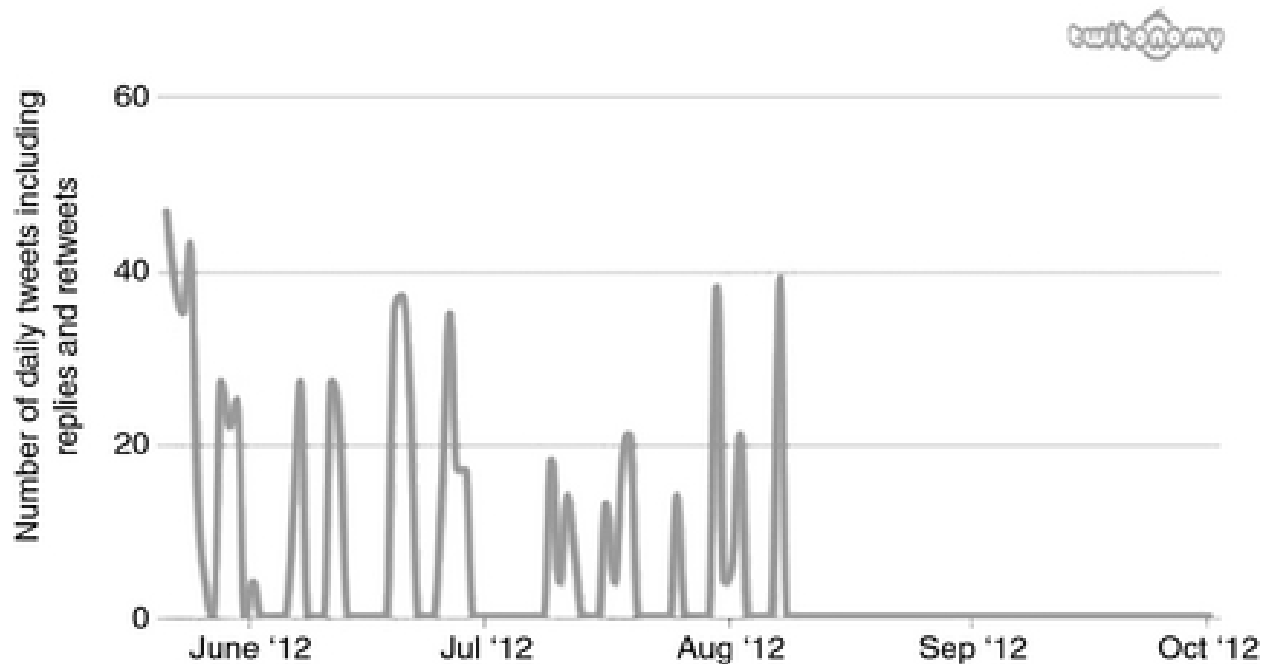
Impressions: 1,507,235  
CTR: 0.065%  
Average CPC: \$0.60

- “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)

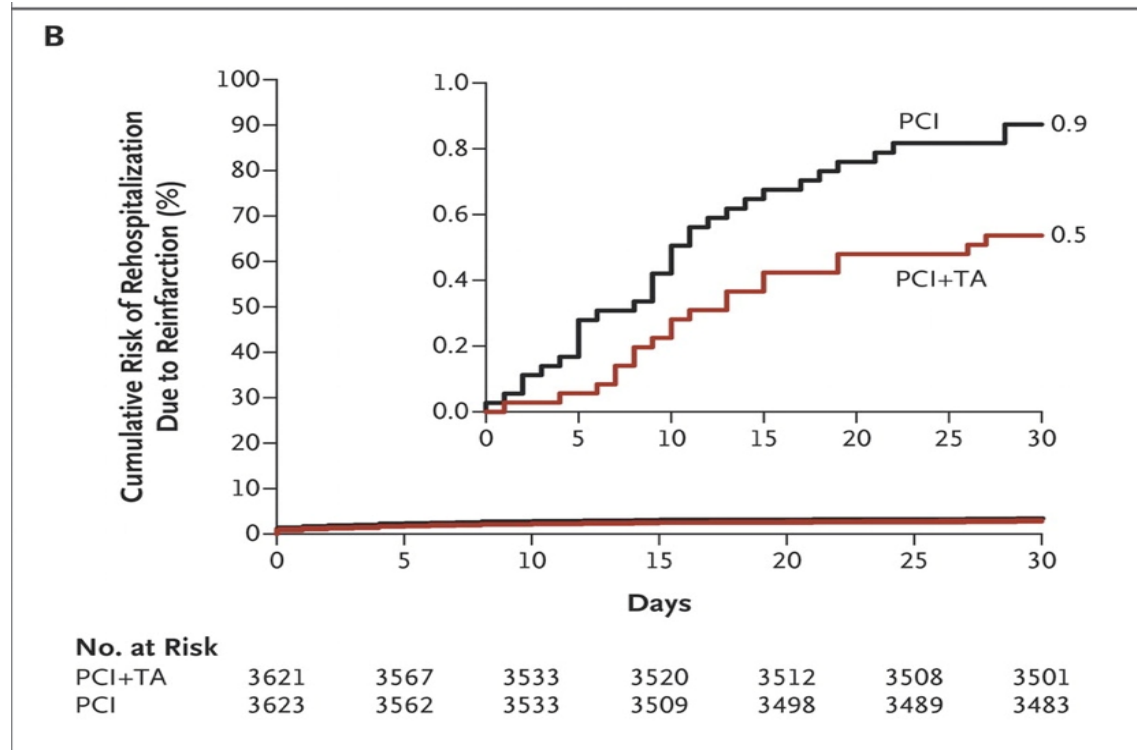
# Or Even Through Twitter?



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

[O'Connor A<sup>1</sup>](#), [Jackson L](#), [Goldsmith L](#), [Skirton H](#). Can I get a retweet please? Health research recruitment and the Twittersphere. [J Adv Nurs](#). 2014 Mar;70(3):599-609. doi: 10.1111/jan.12222. Epub 2013 Aug 4.

# 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 clopidogrel in the US, but better in 42 other countries!

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

*Differences in ASA Dose Used?*

		ASA ≤ 100		ASA ≥ 300	
		US	OUS	US	OUS
Primary	C	9.1% (24/263)	9.4% (699/7443)	7.7% (27/352)	16% (23/140)
	T	6.7% (19/284)	7.3% (546/7449)	12% (40/324)	20% (28/140)
CV Death	C	2.7% (7/263)	4.1% (302/7443)	1.7% (6/352)	7.1% (10/140)
	T	2.1% (6/284)	2.8% (209/7449)	3.7% (12/324)	7.9% (11/140)
NFMI	C	6.8% (18/263)	5.5% (413/7443)	5.7% (20/352)	10% (14/140)
	T	4.6% (13/284)	4.5% (335/7449)	9.6% (31/324)	14% (19/140)

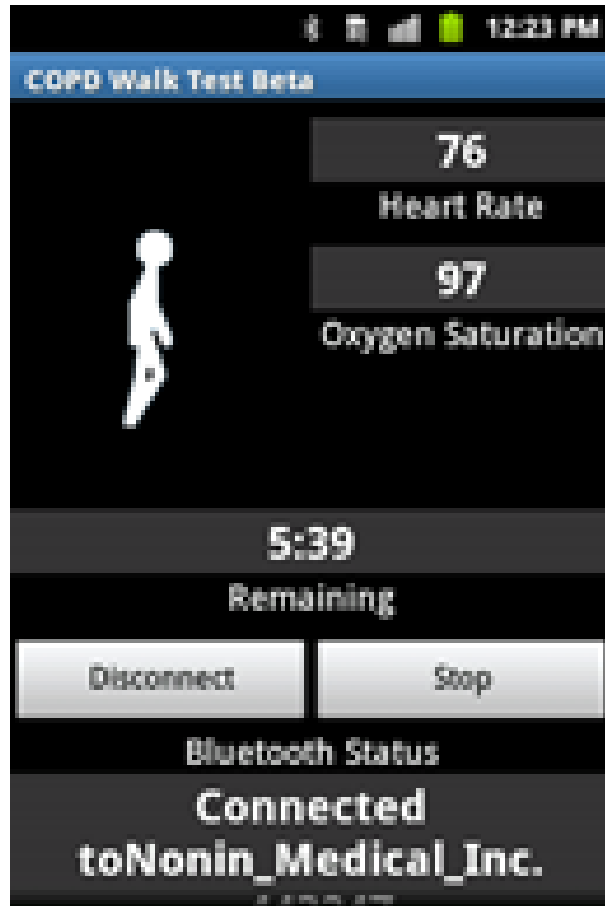
# New Approaches to Endpoints

- 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, O<sup>2</sup>



- 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*



**What's in the Pipeline?**

Check the progress and status of potential CF drugs and get details on clinical trials & news updates with a few clicks.

**LEARN MORE ▶**

The graphic features a vertical bar chart with seven horizontal bars of varying lengths and colors (green, orange, blue, blue, purple, green, red) on the left side.



**Help Find a Cure**

Enroll in a clinical trial and help develop new treatments for CF.

**LEARN MORE ▶**

The graphic features a portrait of a young woman with long brown hair on the left side.



- 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)
- <http://www.youtube.com/watch?v=F6nqcafmxBE>



# Globalization & supply chain challenges



**Tainted cough syrup kills 21 in Panama**  
CDC investigation traces mysterious deaths to industrial chemical

AP Associated Press  
updated 5:51 p.m. PT, Fri., Oct. 13, 2006

Most popular



November 26, 2008  
WORLD BRIEFING | AFRICA  
**Nigeria: Contaminated Medicine Blamed for Deaths**  
By NYT



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



INTERNATIONAL  
**Herald Tribune** | Asia & Pacific  
THE GLOBAL EDITION OF THE NEW YORK TIMES

China recalls infant formula

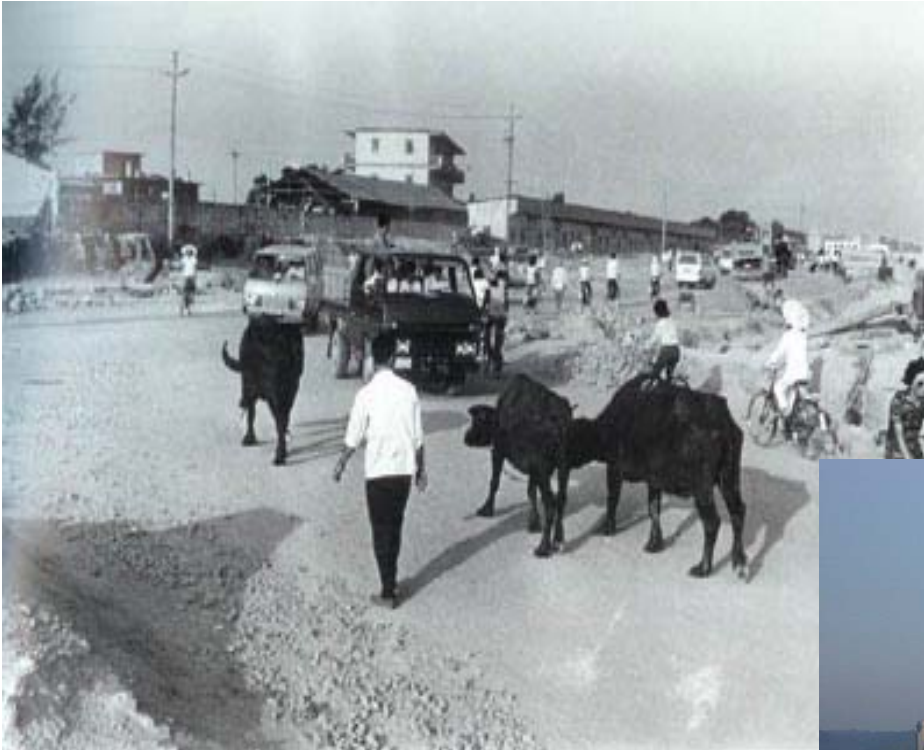
By Keith Bradsher

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*:  $\frac{3}{4}$  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

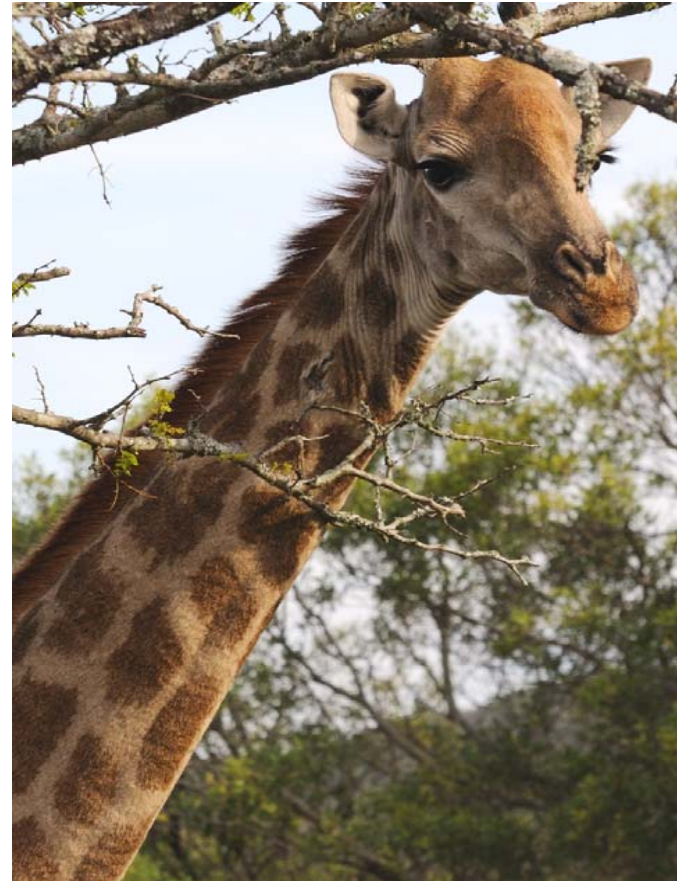
# Additional Approaches to Reduce R&D Costs & Speed Innovation

- 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!



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