



# Interesting Times: The Challenges of Drug Development in 2007

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*May you live in interesting times;*

*May you come to the attention of those in authority;*

*May you find what you are looking for.*

-Attributed to Ernest Bramah

## US panel backs young adult antidepressant warning

Thursday 14 Dec 2006

In Interests of Patient Safety, Pfizer Stops All Torcetrapib Clinical Trials; Company Has Notified FDA and is in the Process of Notifying All Clinical Investigators and Other Regulatory Authorities - Dec 2, 2006

Last night, [ABC News](#) carried a [report that teen suicide has](#)

[increased since the Black Box](#) [Warning](#) was labeled for anti-depressants. It is very unpleasant

[Pfizer to lay off 10,000, close plants in cost-cutting moves](#) [news](#) - Eye on FDA, 6 Feb 2007

Tuesday 23 Jan 2007

## Eli Lilly stops trial of brain cancer drug

Friday 22 Dec 2006

Merck profit falls, hurt by charges, generic Zocor

Wednesday 31 Jan 2007

Genentech cancer drug shows no significant benefit

Monday 08 Jan 2007

Parkinson's drugs can cause heart damage?

Thursday 04 Jan 2007

## FDA Proposes Tougher Warnings on Painkillers

Wednesday 20 Dec 2006

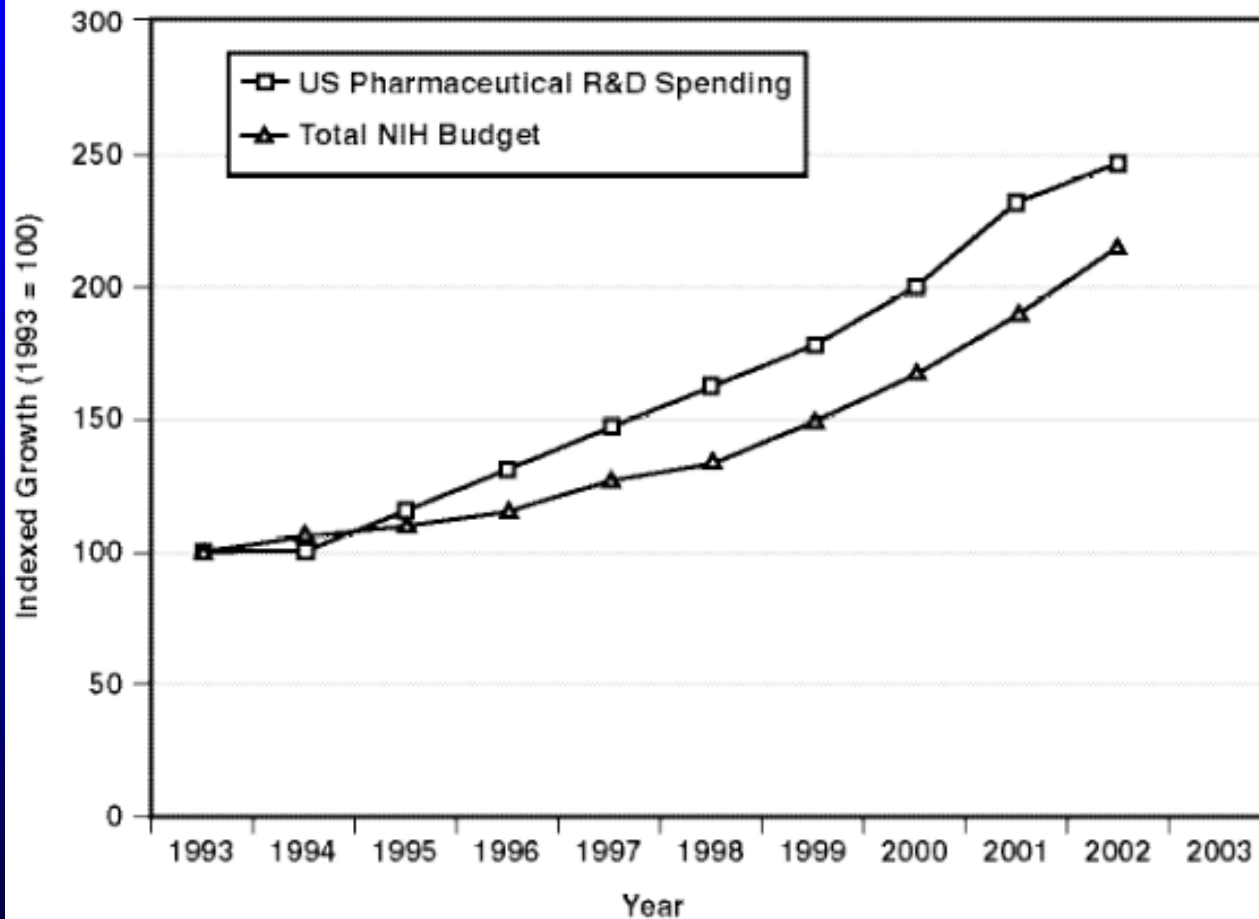
Warning Is Issued On Drug Rituxan Following Deaths

Tuesday 19 Dec 2006



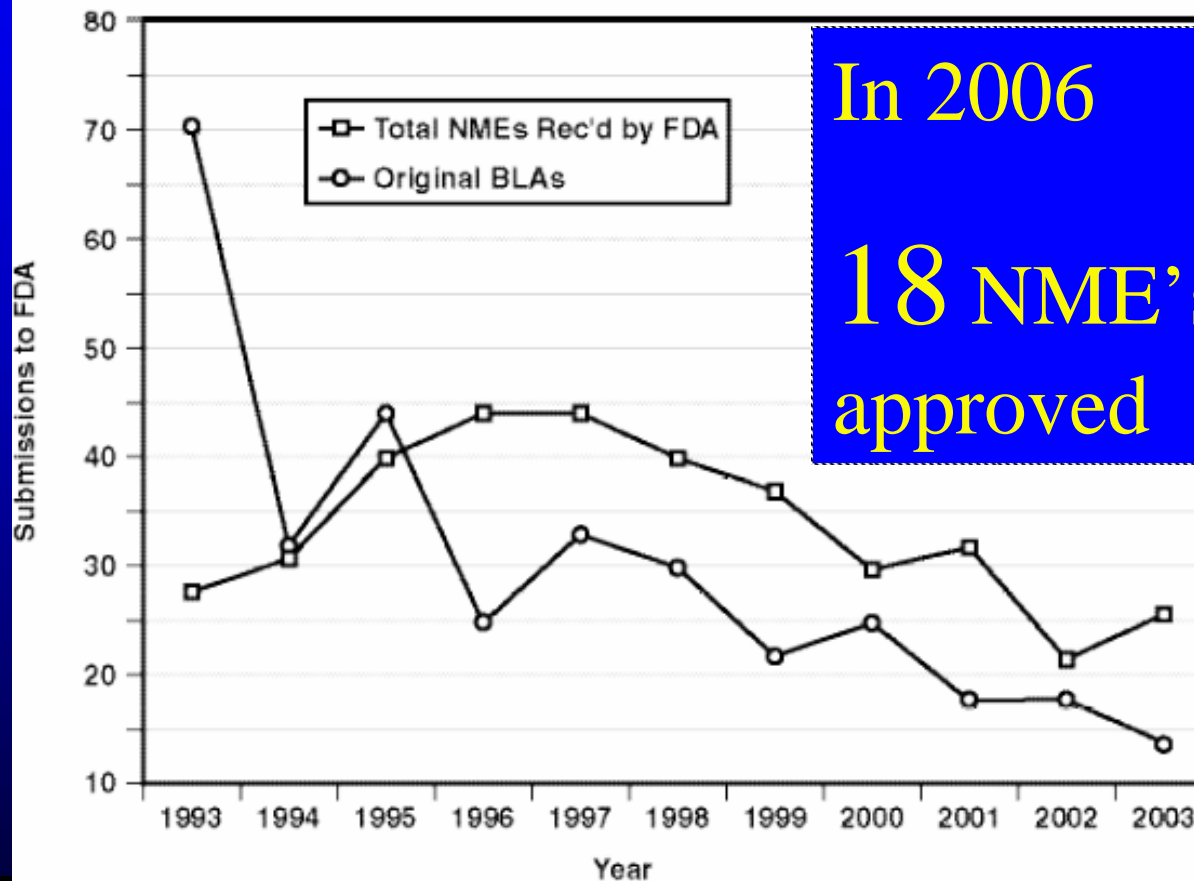
# Spending is going up....

Figure 1: 10-Year Trends in Biomedical Research Spending



# Submissions are going down...

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA

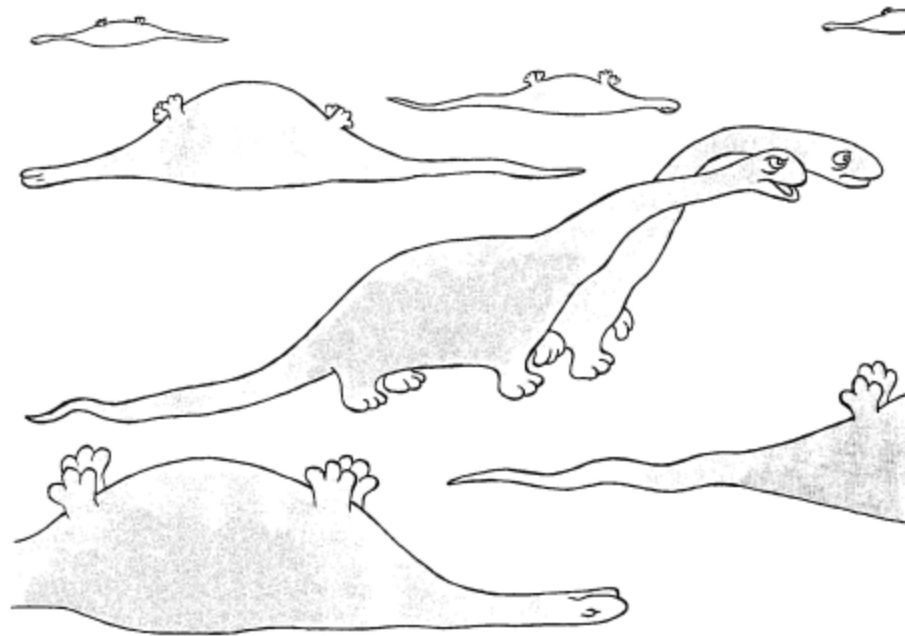


In 2006

18 NME's  
approved

# Interes\$ting Time\$

- Current cost estimates of bring a medication to market : \$ 0.8 – 1.7 *billion*
- Less than 20% of new molecular entities make it to the NDA stage
- High rate of failure in Phase 3
  - Can be devastating for companies and for whole areas of clinical research, e.g., antibiotics



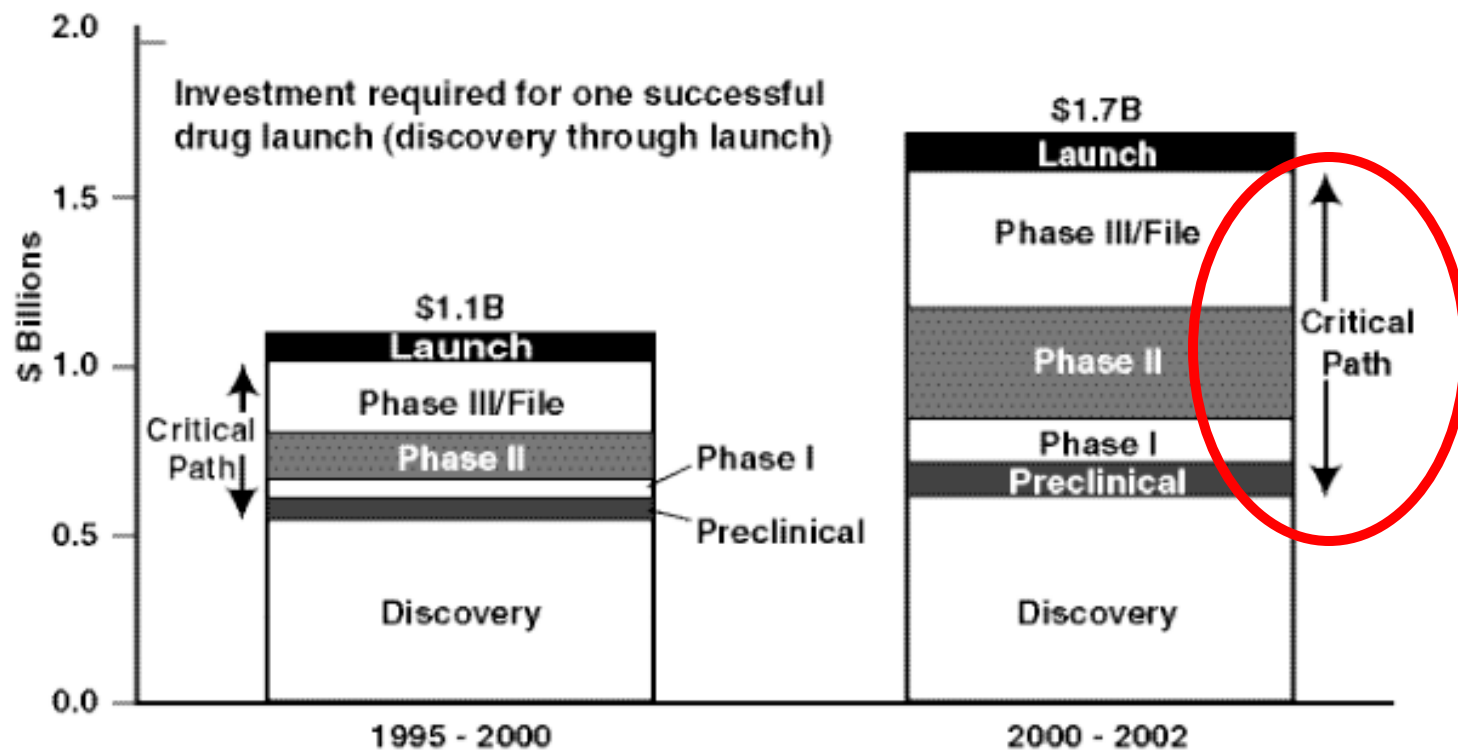
*“Frankly, I don’t like the way things are going.”*

# The Critical Path

- Recent advances in basic science have not yet led to an commensurate improvement in candidate selection
  - Gap between basic research and clinical research is widening
- We are screening more candidates, but the capacity/ability to turn these into drugs has not increased
- Reasons (?)
  - Current high throughput screening of candidates is reductionistic (gene-pathway level)
  - Does not necessarily reflect the pathophysiology at the whole organism

# The Critical Path

- What we are (perhaps) finding is that this simple view of human disease does not live up to our expectations
- A drug entering Phase 1 has no more chance of success than one that entered Phase 1 in **1985**
- Current chance of success for a compound beginning Phase 1 - **8%**



“I am increasingly fearful that much of the hyped promise is illusory.”

-David Horrobin, on pharmacogenomics

“Although big advances do and will continue to occur, their impact on the art and practice of medicine is usually incremental.”

Glassman and Sun, on Biotechnology



# Other reasons why it's getting tougher

- We must do many studies today that we never had to even 20 years ago
  - Drug Interaction studies – now essential
    - Can't "label" our way out of difficulties today
    - Hope/plan for "clean" compounds, but that is difficult
  - QTc studies
    - Must be performed on ALL compounds
    - Very expensive

# When drugs go bad...

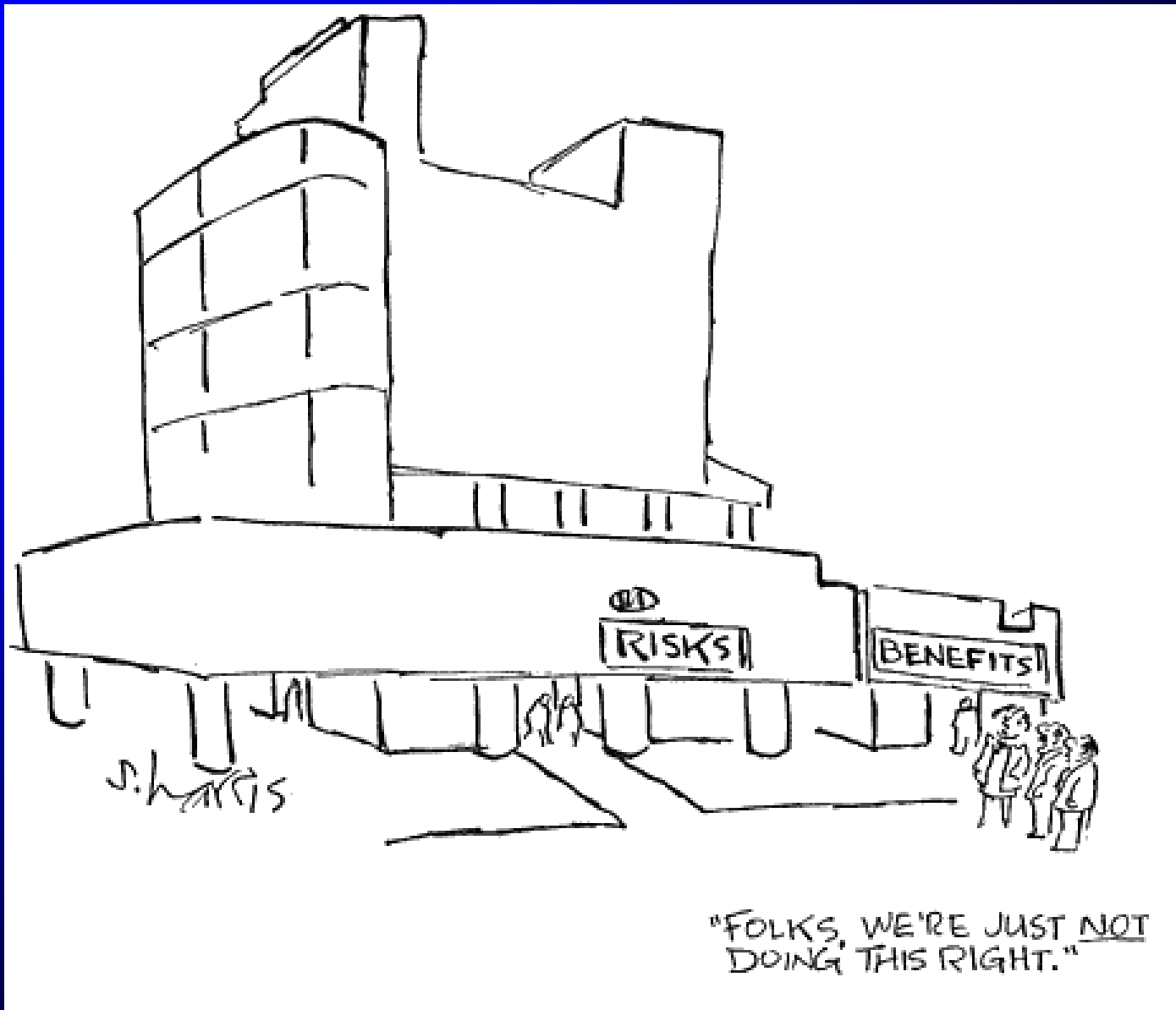
- Current ways of assessing toxicity are decades old, empiric and not very informative
  - OK for ensuring safety of short-term exposure, but abysmal for long-term dosing
- Safety problems that occur at a low frequency are usually uncovered during Phase 3 or post-marketing, with predictable (bad) results
  - Troglitazone, Rofecoxib, Torecetrapib
- This epidemiological way of studying drug safety is rapidly becoming untenable
  - Expensive
  - Exposes too many patients to potential risk
  - Leads to the poor image of pharmaceutical industry



## Examples of Drugs Removed Due to Toxicity 1993-2005

Fenfluramine	(Pondimin <sup>®</sup> )	1973-1997 (24)
Terfenadine	(Seldane <sup>®</sup> )	1985-1998 (13)
Astemizole	(Hismanal <sup>®</sup> )	1988-1997 (9)
Cisapride	(Propulsid <sup>®</sup> )	1993-2000 (7)
Grepafloxacin	(Raxar <sup>®</sup> )	1997-1999 (2)
Cerivastatin	(Baycol <sup>®</sup> )	1997-2001 (4)
Troglitazone	(Rezulin <sup>®</sup> )	1997-2000 (3)
Rofecoxib	(Vioxx <sup>®</sup> )	1999-2004 (5)

**Average = 6.6 years**



# What Needs to be Done – FDA's View

- Critical Path Research (March 2004)
- Develop new scientific tools that will make the development process more efficient and predictable
- These tools include
  - Biomarkers
  - Disease models
  - New clinical trial endpoints
  - New safety assessment tools

# What FDA is doing about the problem

- Concentrating on two areas
  - Biomarker Development (safety/efficacy)
  - Streamlining Clinical Trials
- Other areas of interest
  - Bioinformatics
  - Manufacturing
  - Antibiotics/bioterrorism
  - Pediatrics

# C-Path Institute

**C-Path is an independent non-profit institute that serves as a “trusted third party” enabling scientists from the FDA, academia and industry to work together for the public good.**

- **Founded by FDA, University of Arizona and Stanford Research Institute**
- **No drug company funding**
- **Mission is to develop tools to streamline drug development**
- **Variety of projects underway currently**

# NIH is also getting involved...

- Roadmap for Medical Research
  - “A series of far-reaching initiatives designed to transform the nation’s medical research capabilities and speed the movement of scientific discoveries from the bench to the bedside.”
- Clinical Translational Science Awards (CTSA) – designed to energize translational research at major centers

# How's all this working out?

- Too soon to tell BUT
- All is not well at the FDA...
  - (IMO) has been without a strong leader for >15 years
  - Extremely risk-adverse due to political climate
  - Woefully under-funded
- We need a strong FDA, not a weak and political FDA, which is what we have now
- The nature of change involve risk-taking, so I see progress here to be slow at best
- Last C-Path newsletter update – winter 2006



*"I thought he would run all sorts of scientific tests."*

# What all this means for you

- Crisis = Opportunity
- Still a shortage of trained scientists
- Job security is not what it once was, but Pharma is more stable than most industries
- With change of one kind or another, how best to prepare (and manage) a career in the pharmaceutical industry?

People who ask our advice almost never take it. Yet we should never refuse to give it, upon request, for it often helps us to see our own way more clearly.

Brendan Francis

Please give me some good advice in your next letter. I promise not to follow it.

Edna St. Vincent Millay, *Letters*

*US poet (1892 - 1950)*

# Actively Manage Your Career

- Fact: you will be employed for 20-30 years
- Fact: Most of what you know in your field (if you graduate today) will be substantially altered/changed in 5 years
- Fact: In industry, doing your job will NOT keep you on the cutting edge
  - If you do your job well (and that's all you do) you will find that you are significantly behind in 5-10 years
- Just doing your job well also will NOT get you promoted
  - Industry as well as government

# What to Do

- The first 18 months, learn your job. After that...
- Each year, set some goals around learning some new skills that will keep you out in front
  - Measurable, do-able and realistic
- Set some time aside each week to work on these – reading, (gasp!) studying, whatever
  - ***Training courses do not count***
- Look for ways to use these new skills in your job
- Rigorously self-assess each year

# Communication

- To get ahead in industry, you must be able to convey your ideas clear and succinctly in both the spoken and written word
- Get as much practice as you can presenting in front of others, especially, if you are not comfortable in front of an audience
- Writing – very important ; poor writing can stall your career

# What Else to Do

- Keep up with the literature
  - Read one journal each month, “scan” 3-5 others of interest
- Join a professional organization that suits *your* needs
- Become *active* in that organization
  - Networking possibilities
  - Opportunities for presenting

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***"Learning is not compulsory.... neither is survival"***

W. Edwards Deming

