Career in Pharmaceutical Industry:

Exciting, Challenging and Rewarding

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BASS XIX

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- Chrissie Fletcher, Kevin Carroll, Greg Campbell and Ivan Chan for citing some of their past presentation materials.

We Reap What We Sow

- Sow a thought, reap an action;
- Sow an action, reap a habit;
- Sow a habit, reap a character;
- Sow a character, reap a destiny.
- We are what we repeatedly do.
- Excellence is not an act, but a habit.

Source: Author Unknown.

Outline

- Evolving role of statisticians in the pharma industry
- Statistical science has come a long way in supporting product development
- A scientifically exciting time
- Preparing ourselves for a career in pharmaceutical industry
- Professional development and volunteering
- The fourth hurdle and the changing environment
- Moving forward

The Ten Greatest Public Health Achievements of the 20th Century in US

- **Vaccination**
- Motor-vehicle safety
- Safer workplaces
- **Control of infectious diseases**
- **Decline in deaths from coronary heart disease and stroke**
- Safer and healthier foods
- Healthier mothers and babies
- Family planning
- Fluoridation of drinking water
- Recognition of tobacco use as a heath hazard

CDC (US) Morbidity and Mortality Weekly Report. (1999) 48:1141.

Evolving Role of Statisticians

Little Use of Statistics ==>

"Required" Use of Clin Statistics ==>

Tactical Use of Statistics ==>

Strategic Use of Statistics & "**Statistical Thinking**"

1955 2012 and beyond

Industry Perspective: “Then”

- Statisticians were hired to get things through the regulatory agency (mostly in the US).
- Statisticians were “number crunchers” to get analyses done.
- Statisticians blessed clinical trial designs with minimal intellectual participation except sample size.
- Statisticians focused on trials and manufacturing.
- There was very little statistical input outside of “the necessary”, low involvement in non-clinical areas.
- Statisticians played a secondary role.

Statistician's Role: Now

- Full and equal partner with basic, clinical & regulatory scientists as articulated in the ICH-E9 document.
- Focus on experimental design *and* development strategy.
- Application of statistical thinking throughout the life cycle of a pharmaceutical product.
- Parallel development in other disciplines such as biomarker development, Pharmacometrics, genomics, data mining, predictive modeling, epidemiology, safety signal detection and risk management has expanded statistician's contributions.

Our Contributions Are Many

BASS XIX: Examples of topics covered

- Model-based drug development: design and analysis
- Bayesian approach in phase 1 dosing finding, adaptive allocation and evidence synthesis
- Comparative effectiveness analysis
- Safety assessment in clinical trials
- Safety surveillance using clinical trial data and observational healthcare data
- Quantification and communication of benefit and risk in the pre- and post-approval arena
- Propensity score matching in clinical trials
- Multiple comparisons

An Exciting Time Scientifically

- The entire human genome (over 3 billion base pairs) was successfully sequenced in July 2000, 10 years after a commitment to a public-private collaborative effort.
- In late April 2009, CDC was able to sequence the genome of the new H1N1 flu virus, leading to the rapid development H1N1 flu vaccine.
- More treatments are targeted for patient subgroups, with oncology leading the way.

Targeted Cancer Therapies (TCT)

- Drugs or other substances that block the growth and spread of cancer by interfering with specific molecules (**targets**) involved in tumor growth and progression.
- Some TCTs do NOT require diagnostic tests.
  - Rituximab (Rituxan) - multiple B-cell lymphomas
  - Sunitinib (Sutent) - renal cell carcinoma
- Many TCTs require diagnostic tests.
  - Tamoxifen (Noveldex) - breast cancer
  - Trastuzumab (Herceptin) - breast cancer
  - Imatinib (Gleevec) - chronic myeloid leukemia
  - Cetuximab (Erbitux), panitumumab (Vectibix) - colorectal cancer
  - Crizotinib (Xalkori), NSCLC
  - Vemurafenib (Zelboraf), melanoma

Source: NCI and FDA websites.

Personalized Medicines,

Targeted Therapies,

Beacons of Hope for Patients.

FDA/CDRH Approved Several MIAs

- An In Vitro Diagnostic MIA (Multivariate Index Analysis) is a device that:
  - Combines the values of multiple variables to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease. *Source: FDA/CDRH IVDMIA Draft Guidance (July, 2007)*.

- The GeneSearch BLN (Breast Lymph Node) assay was approved (July 2007) for rapid detection of clinically relevant metastases to nearby lymph nodes based on 70-gene signature in sentinel lymph nodes tissues removed during surgery. It helps guide surgeons to decide whether to excise additional lymph nodes during the same surgery.

Personalized Medicines *(Source: Kevin Carroll, 2011).*

The right treatment at the right dose for the right person at the right time for the right outcome

Expectations raised for:

Safer, 'More Effective' Drugs: No more 'one-size-fits-all' drugs. New drugs will be safe and effective for specific populations

Faster Developments at Less Cost and Less Risk: Speedier clinical trials based on high 'responder' populations, higher R&D success rates and lower overall development costs.

Cost-Effective Healthcare: Reduced costs, due to avoidance of futile treatments in large populations who do not benefit, reimbursement challenges reduced

Critical Questions

- How sure are we that the defined subgroup will benefit to a greater extent, or the remaining subgroup will not benefit at all or derive minimum benefit?
- Is the subgroup identified through an exploratory analysis of a study demonstrating no overall treatment effect?
- If a subgroup is defined by a molecular target, do we have a reliable test with acceptable specificity and sensitivity to identity the subgroup?
- Often, the real danger is we think we know the answer before we have the data; or the data we rely on are flawed.

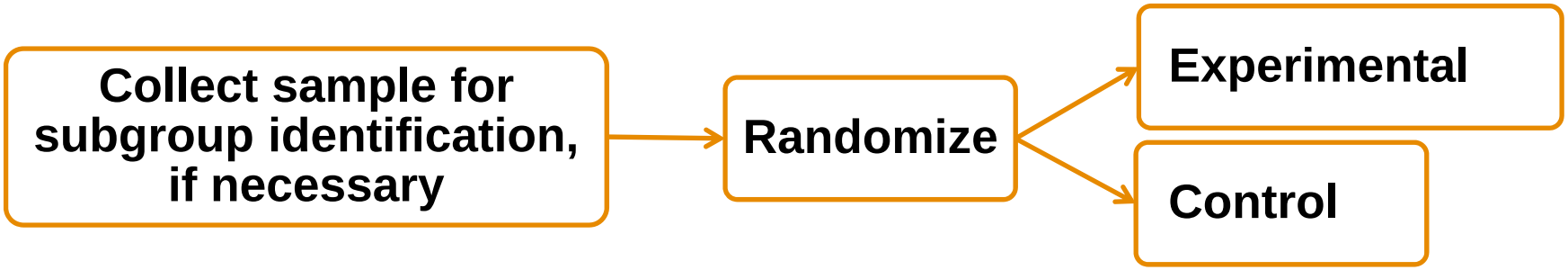
Source: Kevin Carroll (2011), modified.

The Story of Tarenflurbil

- Tarenflurbil is a selective $A\beta_{42}$–lowering agent that has been shown in vitro and in vivo to reduce $A\beta_{42}$ production in favour of less toxic forms of $A\beta$.
- A Phase 2 trial (12 month DB treatment with 12-month extension) enrolled 210 patients between 3 Nov 2003 and 24 April 2006 in 31 sites in Canada and UK. The study included two doses (400 vs 800 mg) and placebo.
- A phase 3 study (800 mg vs placebo) began on Feb 21 2005 at 133 sites in US. The study initially enrolled both mild and moderate AD patients. After analysis of phase 2 data indicated that patients with mild AD responded better, enrolment was restricted to mild patients only.
- Efficacy results in 1684 mild AD patients were flat.

Sources: Wilcock et al, Neurology, 2008; Green et al, JAMA, 2009.

Randomize-all Design



- **Pros:**
  - **Able to estimate the benefit and risk of experimental treatment vs. control in each subgroup.**
- **Cons:**
  - **The subgroups of interest need to be similarly prevalent, or the targeted subgroup needs to be more prevalent**
  - **For molecular target, biomarker status for some patients may be missing due to sample or assay problems**

Adaptations for All-comers Design

- Adaptive Selection Design
  - Enroll all comers to start with; select a subgroup based on an interim analysis and limit future enrollment to the subgroup.
- Adaptive Signature Design
  - Enroll all comers; use 0.04 to test for all patients or use the first half to search for the subgroup most likely to benefit and test this subgroup using the second half at the 0.01 level (Freidlin and Simon, 2005).
- Biomarker Adaptive Threshold Design
  - Assay is ready for use except for the cutoff (Jiang, 2007).

Phase 0 Trials

Characteristics of these trials

- Interrogate and refine a target or biomarker assay for drug effect in a limited number of subjects, using procedures developed and validated in preclinical models.
- Minimize the human toxicity exposure through the use of subclinical dose that reduce the chance of adverse reactions to human volunteers and patients.
- Eliminate the number of toxicity studies in animals.
- Avoid scale-up process since the amount of drug needed for the trial could be supplied by laboratory procedures.
- Experience so far suggested achieving objectives without compromising patient safety.

Opportunities for Statisticians

- Methods to support all aspects of personalized medicine including biomarkers and subgroup strategy
- Strategy for global product development
- Adaptive strategies at the program level
- Strategies to better retain patients in our trials
- Prevention and disease modifying trial designs
- Statistical support behind biosimilar regulations
- Standards for accessing and analyzing electronic health records for effectiveness and safety
- A common framework for benefit/risk assessment

Be a 21st Century Pharma Statistician

- Being technically smart is not enough:
  - Understand the broad clinical, regulatory and public-health context
  - Communicate statistical strengths and weaknesses
- Proactive, not passive:
  - Design: Options available, decision analysis
  - Execution: Quality control and risk mitigation
  - Analysis: Planned and unplanned, strengths/weaknesses
  - Interpretation: Pre-planned or data-driven
  - Presentations/Publications: Keeping audience in mind.

Statistics is a Collaborative Science!!

Personal Strategy

- Continue to broaden our non-statistical knowledge base and keep our mind open – we don't know as much as we think we do.
- Have a positive attitude – do what we can, with what we have, wherever we are.
- Remember that respect and trust are something we need to earn ourselves.
- Learn the power of networking as our work environment becomes increasingly virtual.
- Join professional organizations. Volunteer and take advantage of opportunities, big and small, to build leadership qualities.

Leadership Qualities

- Ability to let go off the small stuff and focus on the big picture.
- A restless discontent with the status quo.
- Effective communications – the power of open, frequent, candid communication.
- Healthy appreciation for creativity and innovation.
- Leadership by actions – People listen to what we do.
- Respect for diversity and open to different opinions.
- Willingness to see things as they are, not as what we wish them to be.
- Wisdom to know when to step in and when to get out of the way.

Career Success Factors in Business

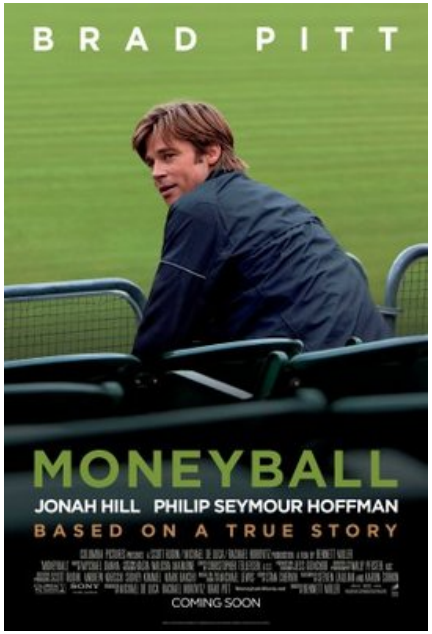
- 2012 ASA President Bob Rodriguez convened a "Career Success Factors Working Group", led by Bob Starbuck. The group identified the following four success factors:
  - **Presentation skills**
  - **Influence skills**
  - **Personality training and team building**
  - **Career planning**

Source: BOD Meeting Highlights, AMSTAT News, May 2012

It Takes All of Us

To build a successful team that delivers, we need all types of talents.

- Innovator
- Connector
- Mover
- Fixer
- Closer



We Need Professional Societies

Professional Societies (e.g. ASA, DIA, SCT, ENAR, ISI)

- Confirm our identity.
- Serve as our voice.
- Provide a forum for us to connect with others beyond geographic proximity.

Professional Societies Need Us

- General Powell: “Organization doesn’t really accomplish anything... Endeavors succeed or fail because of the people involved”
- Professional societies are nothing but a collection of individuals.
- Size matters. Size allows a society to better serve its member by combining resources, forces and talents.
- There is strength in numbers; size matters.

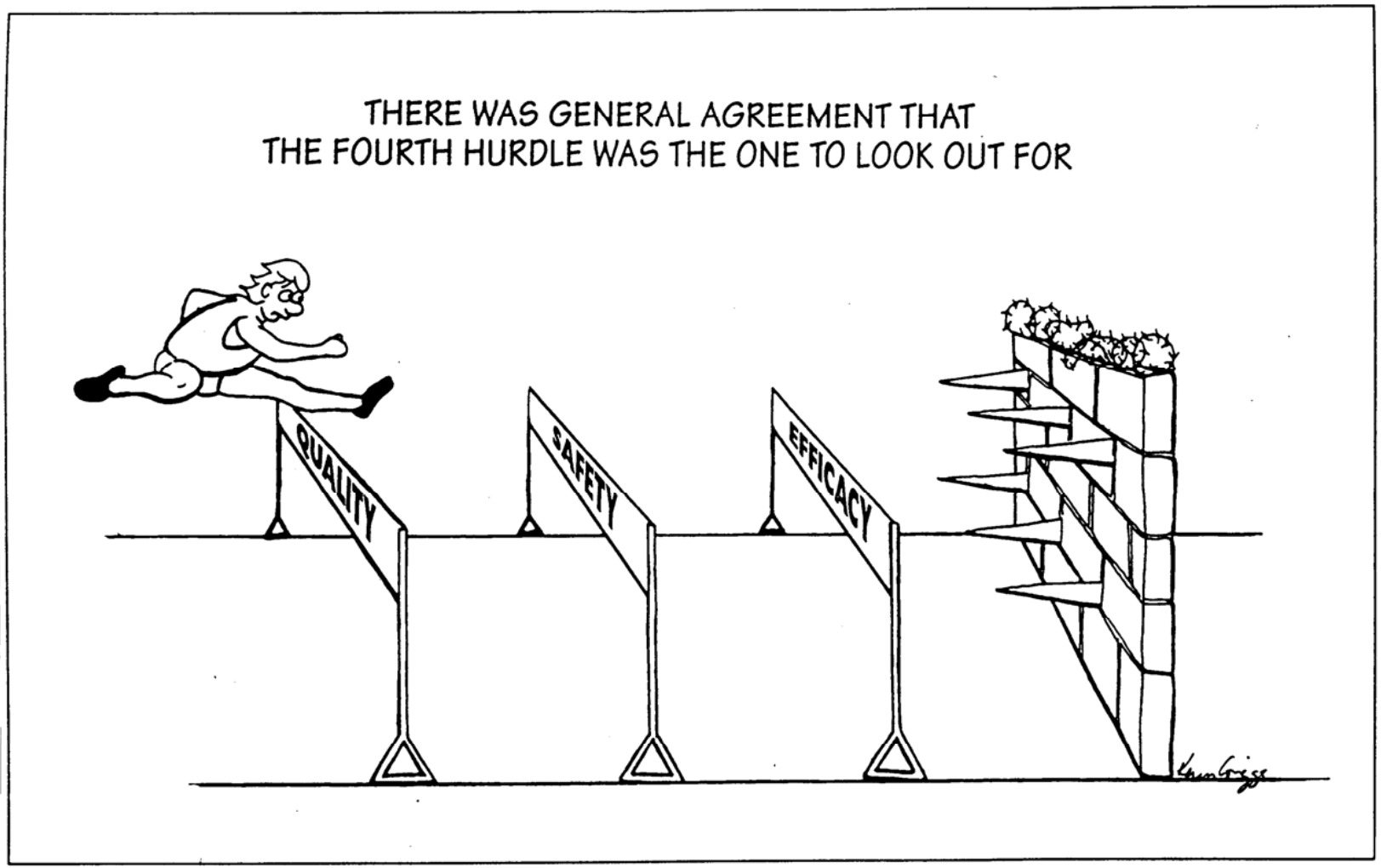
My Involvement with ASA

- Southwest Michigan Chapter president
- Program Chair of Biopharmaceutical Section
- Committee on Fellows
- ASA Board, Vice President
- Accreditation Committee
- 175th Anniversary Steering Committee
- *Running for ASA President-elect on the 2013 ballot*

How I Benefited from Volunteering

- Allowed me to be part of something bigger than myself.
- Introduced me to many statisticians. Some of them are leaders of our profession and became my role models.
- Offered me the opportunities to grow and to influence outside of the work environment.
- Made me realize that “Passion makes career and volunteering builds character”.

The Fourth Hurdle



Source: Chrissie Fletcher

What Is the Fourth Hurdle?

- Health Technology Assessment?
- Comparative Effectiveness?
- Risk/benefit Assessment?
- Other Factors
  - An increasingly more risk-averse society
  - An increasing number of parents refusing vaccination for their children
  - Financially strained healthcare systems, worsened by a global economic slowdown.
  - Increasing # of governments override patents on HIV medications, allowing generics to be produced locally.

Germany's New Law – AMNOG

- Starting Jan 2011, a sponsor of a new (non-orphan) drug has to submit proof of added value relative to a comparator following marketing authorization, preferably in a randomized controlled trial, for reimbursement negotiation.
- The comparator will be chosen by the reimbursement-decision body.
- Evidence on relative effectiveness should be based on relevant patient endpoints such as mortality, morbidity/complications and quality of life. Surrogate endpoints are not enough.
- Subpopulations are routinely examined.
- Level of reimbursement depends directly on the proof of added value.

Challenges We Are Facing

- The desired comparator at the point of reimbursement discussion may not be the one chosen at the design stage.
- Preferred endpoints to measure patient outcome may not be the primary endpoints for marketing authorization decision. The study may not be adequately powered for these endpoints.
- Subpopulations have reduced sample size and thus reduced precision for inference.
- Sampling variation means that some of the subpopulations will report a lower observed clinical benefit.
- France appears to move in a similar direction as Germany.

Our External Stakeholders

- Health care providers
- Patient care givers
- Regulators
- Journal editors
- Shareholders
- Health care payers

- And most importantly - **THE PATIENTS**

Calls for Open Clinical Trial Data

- Doshi P, Jefferson T, Del Mar C (2012) The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med 9(4). (April 10, 2012)
- Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G (2012) Open Clinical Trial Data for All? A View from Regulators. PLoS Med 9(4). (April 10. 2012)
- Open access (to patient-level data) could lead to public-health benefits by additional independent analysis and the development of predictive models using patient-level data. However, standards are necessary to protect personal data and overcome the risks of unprincipled use of data or poor quality in analysis.

A Sponsor's Response

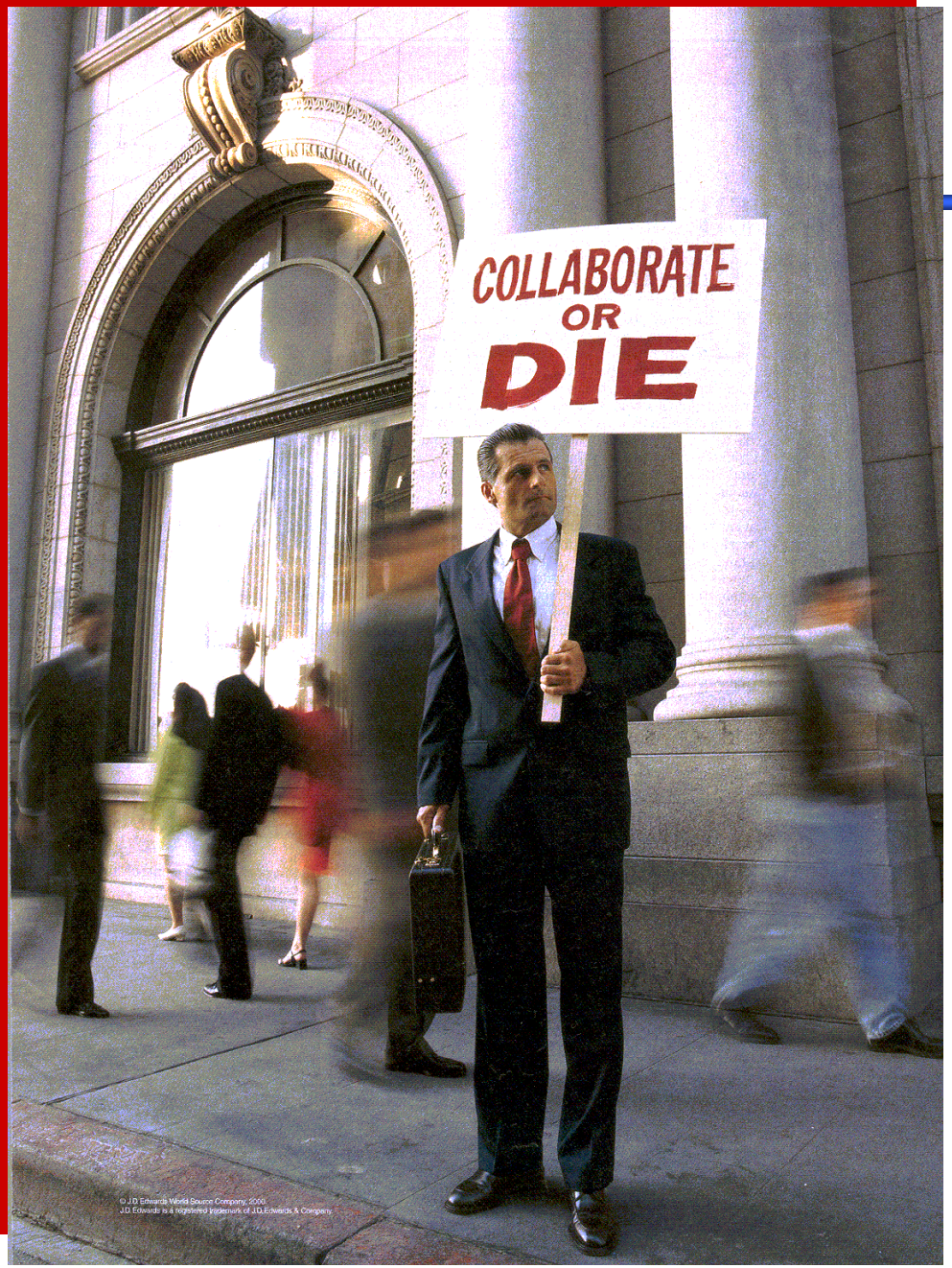
- GSK announced on Oct 11th 2012 initiatives to further advance openness and collaboration.
- One initiative is to create a system that will enable researchers to access the detailed anonymised patient-level data that sit behind the results of clinical trials of approved medicines and discontinued investigational medicines by GSK. To ensure that data will be used for valid scientific endeavour, researchers will submit requests which will be reviewed for scientific merit by an independent panel of experts and, where approved, access will be granted via a secure web site.
- This new step goes beyond granting data access to authors of publications on pharma-sponsored trials.

Develop Partnerships & Collaborations

- Foster partnerships among academia, industry and government.
- Reasons:
  - Solve complex problems by sharing resources and knowledge
  - Integrate ideas and increase credibility through peer review
  - Create solutions to account for differing perspectives
- Belief:
  - Working together is more effective than working in isolation

TransCelebrate BioPharma Inc

- Sept 19 2012 – Ten leading biopharmaceutical companies announced the formation of a non-profit organization to accelerate the development and delivery of new medicines for patients.
- Companies realize the importance to join forces to address longstanding challenges in new drug development.
- Participating companies agree to share meaningful information and expertise in the pre-competitive arena. Clinical trial execution is an initial area of focus.
- This is the largest ever collaboration of this kind.

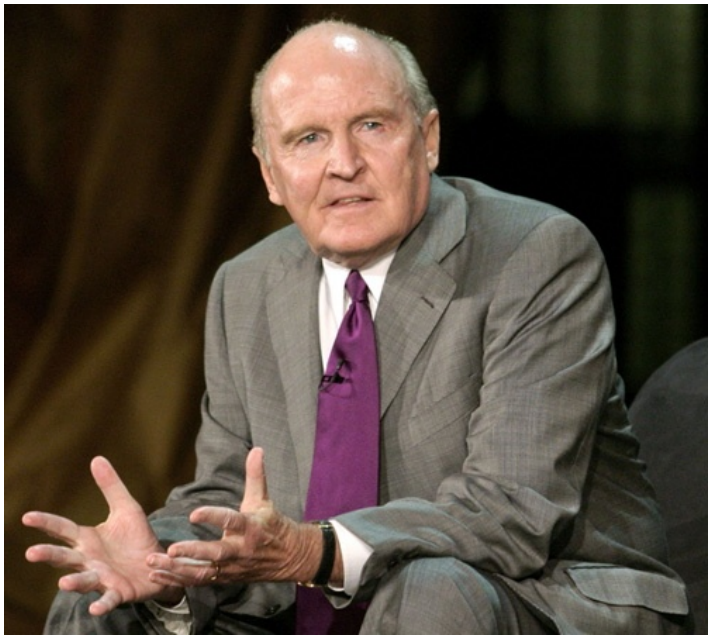


Source:

A.G. Edwards advertisement

“When the rate of change internally is less than the rate of change externally, you are living on borrowed time.”

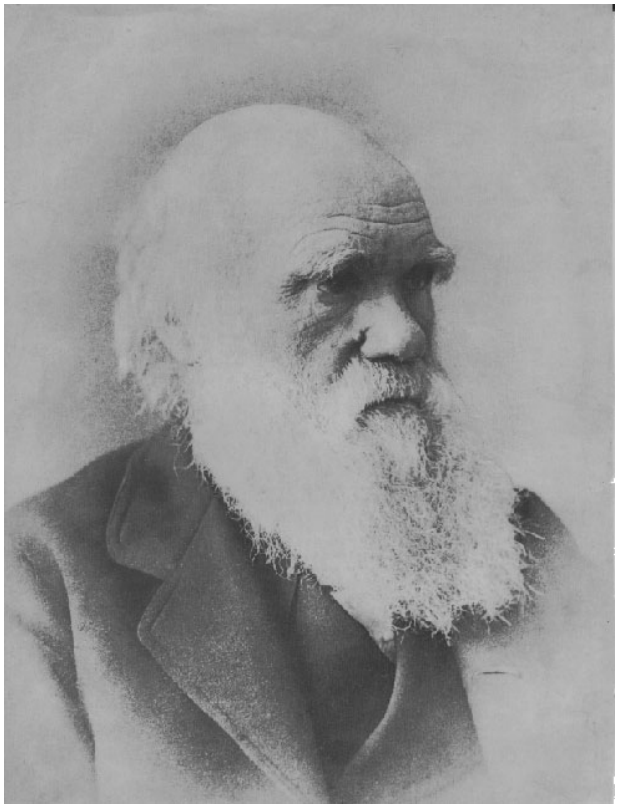
- Jack Welch



Business Model in Pharmaceutical Industry

- Acquisitions and mergers will continue.
- There will be more co-development programs among industry partners to share risk and rewards.
- Business consolidation will continue in favor of more outsourcing.

It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change.



Charles Darwin

On the Origin of Species*

1859

***On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life.**

Develop Tolerance for Change

- Expect change at professional (career), project, and organizational level. Consider a secondment and learn additional (non-statistical) skills.
- Develop a greater tolerance for changes in the game plan, for mid-course corrections, for raw surprise.
- Allow a little more confusion in our lives. Be willing to feel our way and take some risks.
- The best insurance against change tomorrow is our effort to develop ourselves today.

Job Opportunities in Healthcare Industry

- Many important areas such as safety, comparative effectiveness, cost effectiveness, electronic health records will need quantitative scientists.
- Many of the opportunities for statisticians may not be the traditional clinical or preclinical roles. They may involve real world data such as claims data or electronic health records in patient outcome research.
- The changing environment requires an agile and responsive mind.
- The healthcare industry will continue to be a great place to build a career for innovative statisticians with an entrepreneur spirit and collaborative attitude.

Moving Forward

- An exciting time for quantitative scientists.
- Business model will continue to evolve in response to the scientific, financial and commercial environment.
- Outsourcing models will propel in-house pharmaceutical statisticians toward more strategic activities.
- Public and government will continue to demand safe and affordable medicines that are of value to patients.
- Statisticians need to learn to extract knowledge from data and effectively communicate it to stakeholders.
- With quantitative skills and agile mind, statisticians will enjoy a rewarding career in the 21st century pharmaceutical industry.

Our Career Is a Marathon

- Maintain a proper balance between professional pursuit and personal happiness and well-being. The balance is necessary to sustain our performance at the peak efficiency.
- We need to keep both our body and mind fit in this race.

And Remember

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- Sow an action, reap a habit;
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