The long-term solution for improving life science R&D effectiveness and efficiency: Counting bull's-eyes versus arrows missing the mark.

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A Eureka Moment

As an economist, I'm trained to decipher trends and theories. Yet, three years ago, I was presented with data that defied logic. At the age of 34 and with a white-blood count of 320,000/μL, (normal ranges are 3,000 to 10,000/μL) my twin brother, Bill, was diagnosed with acute myleoid leukemia. Cytogenetic testing revealed a rare chromosomal mutation only seen in a handful of patients. Following standard protocols, Bill had a less than 10% chance of five-year survival.

Bill was a sample of one. With limited information and no precedent, the clinical uncertainty was unfathomable. My father, a 30-year veteran of the pharmaceutical industry, knew Bill's treatment needed to be science-based. With his scientific acumen and my economic training, we armed ourselves with the latest tests and literature. Working with Bill's clinicians, we developed a treatment protocol that was data-driven from day one.

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This analytical approach resulted in an extremely effective and efficient process. Within three days, rather than the average six months, I was HLA-typed and identified as a fully-matched donor. Bill underwent induction chemotherapy and a round of consolidation therapy. A bone marrow transplant was scheduled so quickly, the hospital intake nurse teased that his application was mistyped.

At Bill's recent check-up at MD Anderson, his blood lines were 100% donor. His chances of a relapse have narrowed to 5-10%. Sadly, many patients have not fared as well. I hope Bill's picture on the "Wall of Fame" in the transplant wing will serve as a reminder that there are many others who yearn for progress and wait for a cure.

My brother's cure bolstered my faith in many ways, most notably in life science R&D. Undergoing this process, I couldn't help but think of the innovative health advancements that helped to save my brother. Remarkably, one of the drugs my father worked on early in his career, Vancomycin, saved my brother from fatal infection three times. Conversely, I couldn't help but fret about the industry's future. How would the legacy of the life sciences evolve?

I drew some fundamental conclusions that have become the foundation for a radically different approach to life science decision support:

- The naysayers are wrong. Drug development is not stuck in second gear. Basic research continues to be transformed by the convergence of genetics, computational technologies, and more efficient and precise instrumentation and methodologies.

- Exacerbated by a decade of consolidation, R&D leaders are forced to manage larger and more complex portfolios, spanning the full gamut of medicine.

- Information overload, in part a positive by-product of ever-expanding knowledge, is a rate-limiting factor that often stifles effective decision making.

- R&D effectiveness and efficiency will not improve with cost-cutting or jettisoning discovery. We must be more rigorous in assessing and advancing assets through clinical development.

- The industry must extract every ounce of value from data sources. Leaders must confront hard choices and make strategic decisions.

My brother and patients like him inspire our work at Lumleian. We provide life science leaders with the requisite scientific, clinical, regulatory, and commercial data analysis to make the most informed R&D investment decisions that benefit patients and investors alike. Our team of clinicians, scientists, and strategists provide objective and fact-based viewpoints on the relative attractiveness of portfolio assets, which enables life science leaders to make "apples to apples" comparisons across their portfolios.

Today, there are more than 3,000 compounds under development. Identifying the most attractive assets and developing the most beneficial therapies requires a data-driven strategy that moves beyond the practice of discharging too many aberrant arrows and ensures we hit the bull's-eye for patients and investors with precision aim and force. R&D leaders must over-emphasize the most promising assets in their portfolios with the greatest resources, both human and financial.

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An Inspiring Legacy

Over the last century, health advancements – largely developed by the life science industry – have transformed nearly every facet of human existence.

Increased Life Expectancy: Studies suggest that launches of new medicines contributed to a 40% increase in life expectancy from 1980 to 1999 across 52 countries.[i] Just a century ago, most Americans died by the age of 47. Today, life expectancy has nearly doubled to 78.7 years.[ii] Leading contributors include improved sanitation, antibiotics, vaccines, and preventative treatments for cardiovascular disease.

Just 60 years ago, there was only one treatment for a heart attack. Even President Eisenhower was prescribed six weeks of bed rest. In the last two decades, deaths from coronary artery disease have been reduced nearly 40% with prevention and treatment. Therapeutics and interventional treatments reduced heart attack deaths and heart failure by 45% from 1999 to 2005.[iii]

Improved Quality of Life: Many diseases that were once an imminent death sentence, such as AIDS, have been reduced to manageable, chronic conditions. We see, perhaps, the greatest benefits of life science innovation in developing nations.

With the introduction of highly active antiretroviral therapy (HAART) in 1995, deaths from AIDS have dropped by an astounding 78%.[iv] *More remarkably, recent studies demonstrate that early initiation of HAART reduces HIV transmission by 96%. In sub-Saharan Africa, where the crisis hits hardest today, the use of HAART is considered the first and still most effective prevention strategy, particularly in blocking mother-to-infant HIV transmission.*

Economic Growth: Economists Kevin Murphy and Robert Topel of the University of Chicago estimate that from 1970 to 2000, gains in life expectancy added about $3.2 trillion per year to national wealth with half of these gains due to progress against heart disease alone.[v] Their estimates suggest that prospective gains from a 10% reduction in all causes of mortality in the future would create $20 trillion dollars of economic value to current and future Americans.

Personalized Medicine: Many breakthrough advancements – targeted therapies, personalized medicine, and biomarkers – represent a fundamental change from treating the symptoms to treating the causes of disease with a greater focus on individual patients.

Substantial progress has been made in treating rare disorders and orphan diseases.

Hemophilia affects some 18,000 Americans. Isolation and purification of coagulation factors, coupled with recent breakthroughs in gene therapy, have substantially increased life expectancy from 11 years to more than 70 years.

In 2011, the FDA approved 35 new medicines, many of which were granted priority review status as serving a significant unmet medical need in the agency's judgment. Highlights include Adcetris, the first new drug for Hodgkin's lymphoma in 30 years; Benlysta, the first new drug for lupus in 50 years; Incivek and Victrelis for chronic Hepatitis C Virus; and Yervoy and Zelboraf to treat metastatic melanoma.

Daunting Challenges Present New Opportunities

Undoubtedly, past success contributes to the industry's current challenge and opportunity: innovation begets greater unmet need with increased life expectancy. In the shadow of remarkable progress, countless conditions await continued innovation to more broadly improve global health and reduce the human and economic tolls of, ironically, people living longer and healthier.

Growing Aging Populations and Disease Burdens: According to U.S. Census Bureau Projections, the number of people aged 65 and over is expected to rise from about 36 million today to about 70 million in 2030. An estimated 157 million Americans will suffer from chronic diseases in 2020, with one in four living with multiple chronic conditions. [vi] Many chronic diseases, including Parkinson's and Alzheimer's, still need effective treatments.

The Alzheimer's Association estimates that a new therapy that delays disease onset by five years could reduce new cases by 43% and save $447 billion a year by 2050.[vii]

> "PhRMA reports that only two to three out of every 10 approved medicines make back their investment."

Rising R&D Costs: Since the 1970's, research and development costs have increased 50-fold.[viii] According to PhRMA, to bring a single, new therapy from bench to market costs more than $1 billion.

Declining R&D Productivity: In 2010, America's biopharmaceutical companies invested a record $67.4 billion in research.[ix] Yet, this astronomical investment has resulted in relatively few new therapies versus recent history. There has been a 30-year decline in pharmaceutical industry productivity, as measured by new molecular entities per dollar spent on research and development.[x] As illustrated in *Figure 1*, this trend has not abated in the last decade.

Only about 15 of every 100 INDs filed are approved. From 2000-2009, 24 new drugs per year were approved, compared with 31 per year from 1990-1999. During the 2000 time-frame, the number of investigational new drugs and new drug application filings remained flat.[xi] PhRMA reports that only two to three out of every 10 approved medicines make back their investment.[xii]

Figure 1: Industry productivity continues to decline.

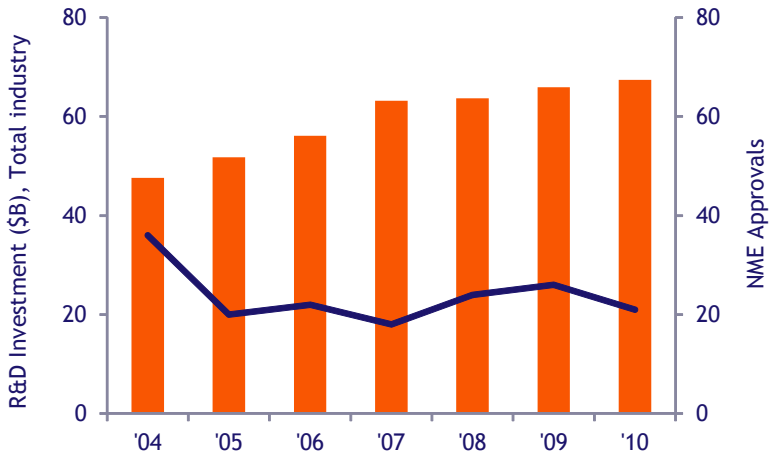
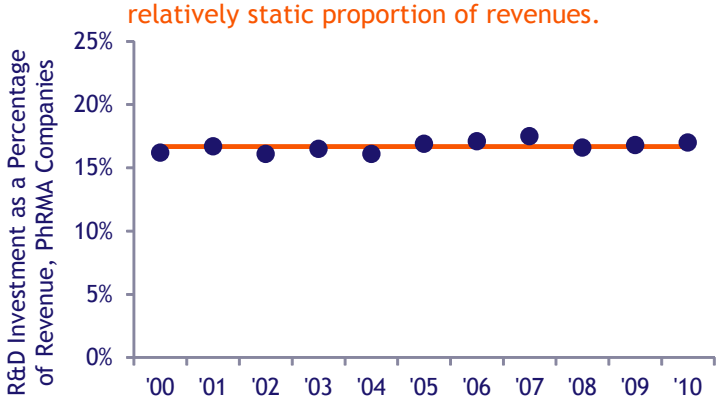


Figure 2: The industry's level of R&D investment is a relatively static proportion of revenues.



A recent study by the accountancy KPMG suggests that the internal rate of return for R&D investment has been nearly halved over the past twenty years from 17-18% in 1990 to less than 10% in 2010.[xiii] GlaxoSmithKline has made public its long-term target of a 14% return on R&D investment from a base of 11% in 2011. Assuming a 7-8% cost, a capital return of ~10% is relatively unattractive, especially considering the long development cycles and the disproportionate value "blockbusters" have on bio-pharma's value creation calculus.

Focusing on the Bull's-Eye

Similar to many business models, the dual goals of drug development are both altruistic and financial – to help patients and to provide investor return. R&D leaders take different approaches to achieve these objectives. Yet, some strategies blur the bull's-eye and take decision making off target.

Head in the Sand: Simply throwing money at research, bloating pipelines, and placating equity research analysts will not help patients, nor create long-term shareholder value. As illustrated in *Figure 2*, it is difficult to believe drug developers optimally allocate R&D resources if invariably the industry spends 16-17% of revenues on R&D. In this approach, revenue, not the viability of potential opportunities, dictates R&D investment.

> "The industry must prioritize and advance only those drugs most likely to succeed in clinical trials, regulatory submission, and the commercial market."

Flavor of the Month: Cost-cutting, offshoring externalization, and managing to the internal rate of return have a role to play in improving R&D productivity. Yet, each is a stop-gap solution.

To regain proper positioning and aim, R&D leaders must make strategic portfolio decisions based on rigorous and comprehensive analysis of all available data. To enhance productivity and bolster return, the industry must prioritize and advance only those drugs most likely to succeed in clinical trials, regulatory submission, and the commercial market. This presupposes that leaders have the requisite information to make "apples to apples" comparisons across drugs, and the support to make strategic decisions. The solution is better aim and more precise arrows being discharged. Every arrow must be viable and forcibly hit the bull's-eye.

Effective prioritization is made more challenging by a decade of industry consolidation; an overload of information absent insight; and incentives for discharging too many aberrant arrows. Under the premise that more discharged arrows is a viable strategy, inflated pipeline success stories give the false illusion of a bull's-eye. Realistically, regulators or physicians and payors dictate an arrow off mark.

Regulators effectively call off-mark drugs for which they don't believe the clinical benefit outweighs the risk to patients with a complete response letter or a restrictive label.

Payors and physicians call wide, poorly differentiated drugs. Lumleian's analysis of the industry's late-stage pipeline across major disease states suggests R&D investment is highly concentrated in select mechanisms of action.

It is very unlikely that multiple follow-on, but more costly drugs will hit the bull's-eye for payors and yield a commercial return on their R&D investment.

In the recent Forbes article, "Cancer Drug Targets: The March of the Lemmings", a similar analysis reached a parallel conclusion in oncology. Looking across all phases of development, >20% of oncology projects are concentrated in only eight targets: VEGF, PI3K, HER2, mTOR, c-KIT, cMET, EGFR, and PDGF.[xiv]

Lumleian's "Bull's-Eye" Approach

At Lumleian, we pursue a "**Bull's-Eye**" strategy to maximize the likelihood of success. Our process is based upon careful analysis and rigorous benchmarking to identify and advance viable assets that have the greatest potential to improve human health and achieve market success. Our data analysis provides the precise diligence and positioning to ensure proper aim. Our insight guides the draw and bolsters the discharge so clients hit the target, achieving their dual goals of benefiting patients and providing investor return.

Our team of 30+ clinicians and Ph.D scientists codify and validate next-generation scientific and clinical data using proprietary techniques. This information is updated in real time and maintained in a centralized knowledge management system. We constantly update our databases with the most current scientific, clinical, regulatory, and commercial data to ensure accuracy. We provide relevant "apples to apples" comparisons across disease states in two standardized offerings.

Disease State Primers: These comprehensive reports outline current and emerging disease and care paradigms, clinical pipelines and trial results, and the global commercial landscape.

Drug Development Benchmarks: These studies detail attrition, cycle-time and approval statistics; profile recent and ongoing clinical trial strategies across phases; and synthesize regulatory guidance across sponsors.

> "Lumleian helps life science leaders make better decisions for their scarce resources by objectively gathering and analysing all the facts: scientific, clinical, regulatory, and commercial."

On *Page 6*, we share the precise power of our "**Bull's-Eye**" strategy in a Rheumatoid Arthritis product decision "Go/No Go" case study.

Our mission at Lumleian parallels that of the life science industry - to ensure patients like my brother live longer, healthier lives. Collectively, we have decades of tremendous progress to illuminate our path and a moral responsibility to resolve the health challenges of the future.

By refining our aim, focusing on hitting the bull's-eye versus the number of aberrant arrows discharged, and using analytical and scientific diligence to drive decision making, we can improve R&D productivity, reignite innovation, and further our industry's impressive legacy of extending and enhancing human life.

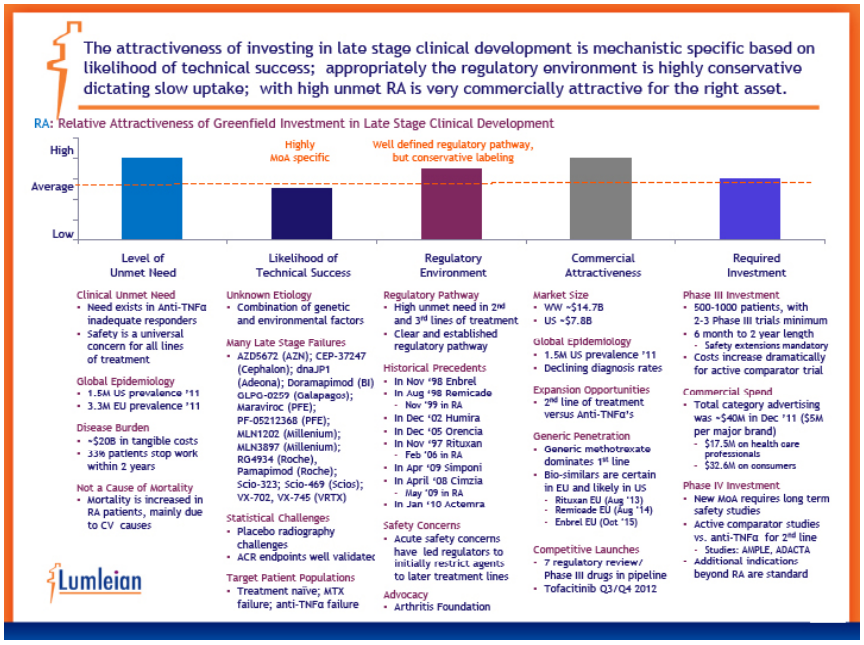
To learn more about Lumleian and to download a complimentary disease state primer, please visit **www.lumleian.com**.

Case Study - Defining the Bull's-Eyes for Rheumatoid Arthritis

The late stage pipeline is crowded as Lumleian validates 82 assets in active clinical development. Cytokine Inhibitors dominate: TNF, IL-6, IL-17 and GM-CSF are the main targets; next, Kinase Inhibitors with the most advanced targeting the JAK family, B Cells, T-Cells and the Complement are also important targets.

Given the plethora of assets, the majority of which will not re-coup their investment, it is important that R&D leaders apply a realistic set of criteria for advancing assets into phase III trials.

Lumleian argues standard criteria should apply across all disease states, including:
- Level of Unmet Need
- Likelihood of Technical Success
- Regulatory Environment
- Commercial Attractiveness
- Required Investment



The criteria most emphasized will vary across disease states and by asset. Lumleian defines realistic criteria in rheumatoid arthritis as follows:

Regulatory Bull's-Eye: Lumleian believes that regulatory precedent is clear as evidenced by Actemra's approval in 2010 and the recent advisory committee for tofacitinib. We believe the FDA sees substantial unmet need in 3rd line patients, (anti TNF alpha inadequate responders) to merit use of a new agent, but not in 2nd (methotrexate inadequate responders) or 1st lines (treatment naïve).

Sequentially, the agency may approve use in earlier treatment lines. To advance, an asset's return on investment should be attractive in this relatively smaller sub-set of the population, and not in the entire rheumatoid arthritis market.

Clinical Bull's-Eye: The high bar for efficacy in 2nd line patients as determined by ACR20 at 24 weeks is ~68% set by Orencia in the AIM study.[i] The standard of care Humira attained ~63% ACR20 at 24 weeks in the DE019 study.[ii] For safety, the bar is less than 15% of phase III study patients with serious adverse events at trial conclusion, excluding long-term safety extensions. Actemra attained 16% in its phase III program and Orencia attained 14% in its phase III program.

These are the same criteria with which payors make trade-off formulary decisions. For example, the National Institute for Clinical Evidence in the United Kingdom used similar logic in its February 2012 conclusion that the National Health Service offer Actemra based on a discounted patient access scheme.[iii]

Other recent approvals, Orencia and Simponi, are not recommended except in 3rd line patients. Fundamentally, payors are trading off clinical benefit with cost, and this is a relevant point of comparison.

Regarding oral formulations, everything else equal an oral formulation is preferential to a sub-cutaneous one. As the recent launches of Simponi and Cimzia illustrate, clinical differentiation trumps differentiated formulation. Both brands are reducing their sales force investment in the U.S. after less than three years on the market.

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Frank is the Founder of Lumleian and Director of Decision Science. Frank has over ten years of experience working with life science companies. He concurrently holds an appointment in the department of strategy at the Carroll School of Management, Boston College, where he teaches 'Strategic Issues in Pharma and Bio-Tech' to MBA students.

Prior to founding Lumleian, Frank was a director with Leerink Swann and a case team leader with Bain, where he gained substantial operational experience growing and operating a diverse set of businesses. Frank entered consulting after spending three years in the bio-pharmaceutical industry with Eli Lilly, supporting portfolio optimization and business unit strategic planning. Frank began his career as a quantitative risk analyst at BlackRock.

Frank earned a Ph.D. in econometrics from the Krannert School of Management at Purdue University, where his dissertation focused on applying game theory and statistical modeling to optimize pharmaceutical sales and marketing resources. Frank has a bachelor of arts in economics from Princeton University.

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[ix] PhRMA, R&D Investment by U.S. Biopharmaceutical Companies Reached Record Levels in 2010. 2011.

[x] Figure Source: Institute of Medicine. 2010. Extending the spectrum of precompetitive collaboration in oncology research: Workshop summary. Washington, DC: The National Academies Press.

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[xii] PhRMA, R&D Investment by U.S. Biopharmaceutical Companies Reached Record Levels in 2010. March, 2011.

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