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FUTURE OF ADMET SYMPOSIUM

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Alternate Paradigms to Pharmaceutical Product Development

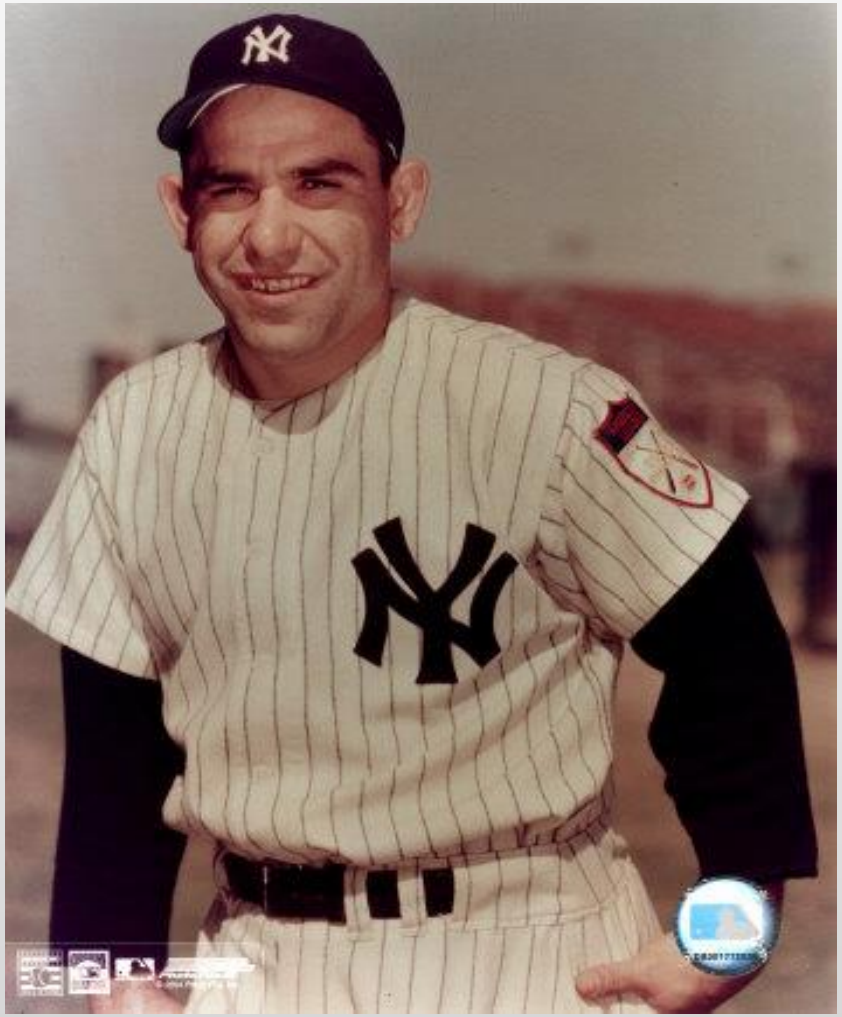
Roger Nosal

Roger Nosal PharmaCMC
Regulatory Consultants, LLC
rogernosal@outlook.com
+1 860 625 1072

Chair, ISPE *Enabling Global Pharmaceutical Innovation*

Head of Regulatory Strategy
Your Needs. Our Focus.
rnosal@ngtbiopharmaconsultants.com

AMERICAN PHILOSOPHER & BASEBALL PLAYER



"It's tough to make predications….especially about the future."

-Yogi Berra

ABSTRACT

The development of pharmaceutical products, in particular, the transition from late discovery research to initiation of human clinical studies, has adhered to relatively standard scientific & regulatory expectations for the last 40 years. The threshold for a new medicinal entity is demonstration of requisite safety & viable pharmacological activity to effectively justify administration to humans. These criteria tenaciously rely on surrogate animal studies but do not guarantee human efficacy. Expanding toxicological databases & the emergence of increasingly robust pharmacokinetic/ pharmacodynamic models offer the prospect of improving human, *in vivo* predictability.

Perhaps more significantly, opportunities to accelerate product development have emerged from recent experience in response to the COVID-19 pandemic. While alternative approaches did not preclude the need for compelling & robust demonstration of product quality, safety or efficacy, they did establish groundbreaking development & regulatory paradigms that expedited global access to COVID-19 vaccines.

This presentation focuses on how leveraging the paradigms from the pandemic experience, in conjunction with steadily improving preclinical models & digital data can expedite the pharmaceutical development timeline.

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- *WHAT DID WE LEARN FROM THE PANDEMIC & ARE WE AT A CROSSROADS?*
- *WHAT DOES THE NEW DEVELOPMENT PARADIGM LOOK LIKE?*

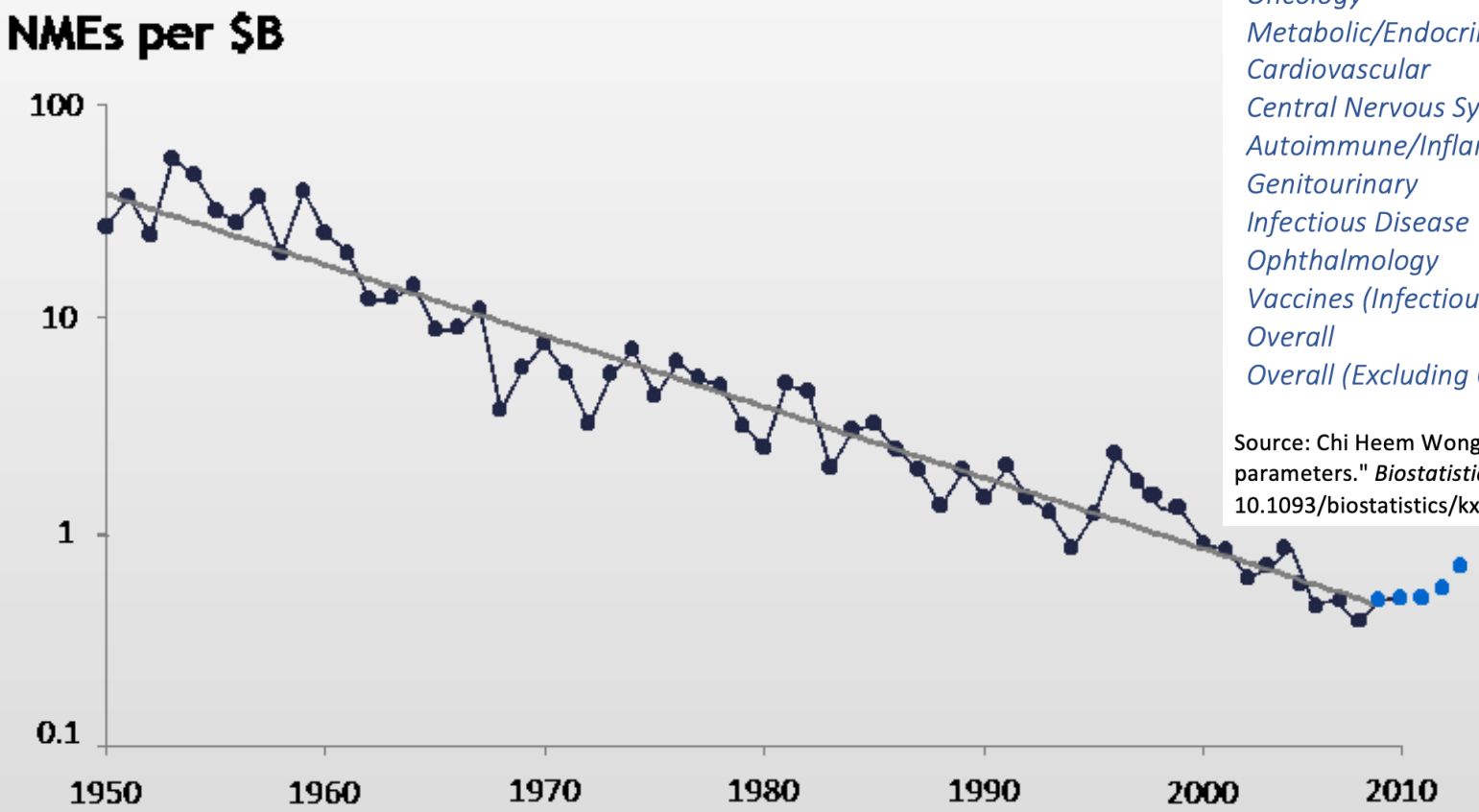
SO WHAT'S THE PROBLEM?

PRODUCT DEVELOPMENT CHALLENGE

- The POS of a molecule entering the clinic becoming a new medicine remains very low **<1/10,000: ~96% Failure Rate**
- Some have said that the business model is unsustainable
- Regulators have responded with 'innovation agendas' but…
- ….cost-ineffective drug regulation exists and may stifle innovation
- All companies are engaged in efforts to reduce unit costs and improve cycle times (ie, acceleration strategies)
- Most companies have developed strategies to help 'pick the winners' and price 'insensitive' portfolios (e.g., oncology, rare diseases, precision therapeutics, etc.)
- Some companies are developing automation and artificial intelligence approaches to improve probability of success and increase efficiency.

PROBABILITY OF SUCCESS - EROOM'S LAW*

*Moore's Law: The # of circuits in a silicon computer chips doubles every 2 years.



Probability of Success[2] by Clinical Trial Phase and Therapeutic Area

	P1 to P2	*P2 to P3*	*P3 to Approval*	*Overall*
Oncology	57.6	32.7	35.5	3.4
Metabolic/Endocrinology	76.2	59.7	51.6	19.6
Cardiovascular	73.3	65.7	62.2	25.5
Central Nervous System	73.2	51.9	51.1	15.0
Autoimmune/Inflammation	69.8	45.7	63.7	15.1
Genitourinary	68.7	57.1	66.5	21.6
Infectious Disease	70.1	58.3	75.3	25.2
Ophthalmology	87.1	60.7	74.9	32.6
Vaccines (Infectious Disease)	76.8	58.2	85.4	33.4
Overall	66.4	48.6	59.0	13.8
Overall (Excluding Oncology)	73.0	55.7	63.6	20.9

Source: Chi Heem Wong, Kien Wei Siah, Andrew W Lo. "Estimation of clinical trial success rates and related parameters." *Biostatistics* 20(2): April 2019, Pages 273-286. Published online: 31 January 2018. DOI: 10.1093/biostatistics/kxx069

Productivity (drugs/dollar) = Time x Cost x Probability of Success (POS)

Source: Bernstein Research "The Long View - R&D Productivity" (September 30, 2010), EvaluatePharma, BCG addition since 2010

NEW DRUG APPROVAL COST

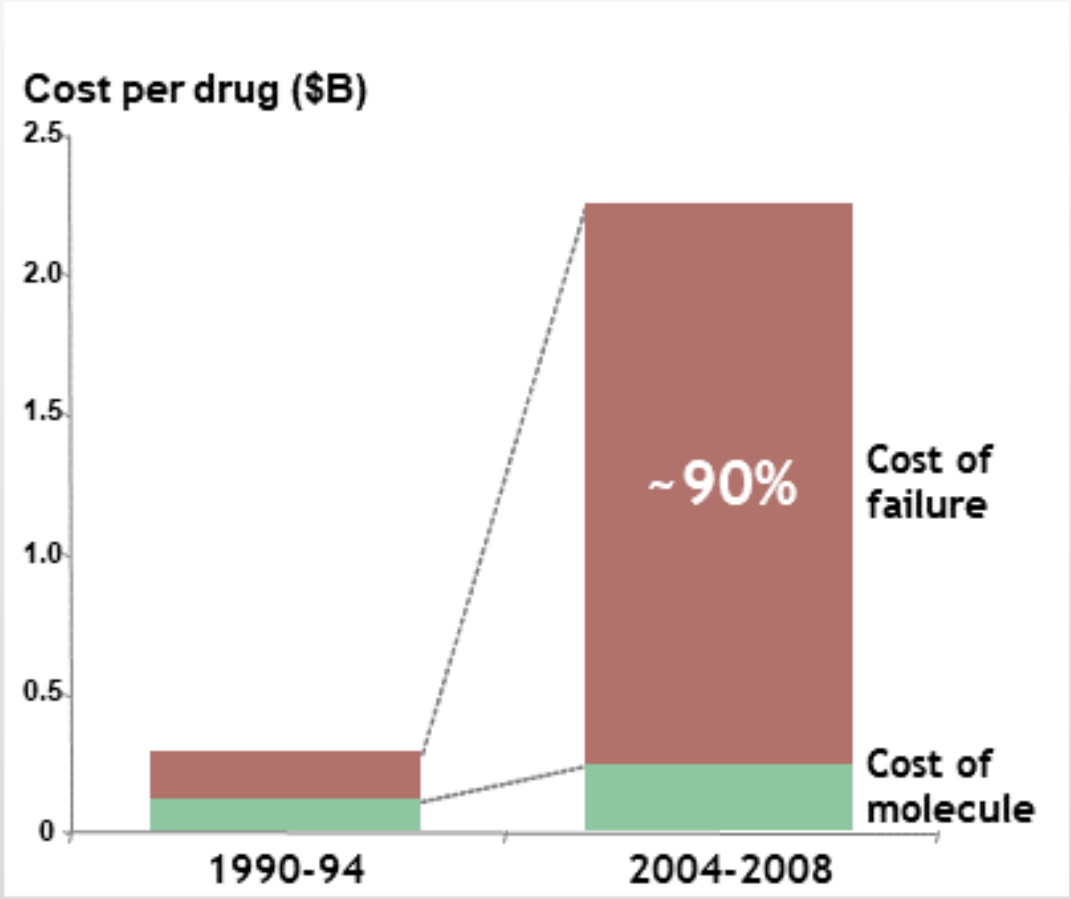
Tufts University CSDD top-line findings estimate R&D costs to develop an approved new drug are $1.4B - $2.9B, depending on cost basis. Summary cost figures include:

- $1.4B out-of-pocket cost/approved new drug
- Equivalent to $2.9B on a capitalized basis
- Cost of failure (drug program terminations)
- Data reflect a ~9% annual inflation-adjusted growth rate compare to estimates from 1990's

Major drivers cited for increasing R&D cost:

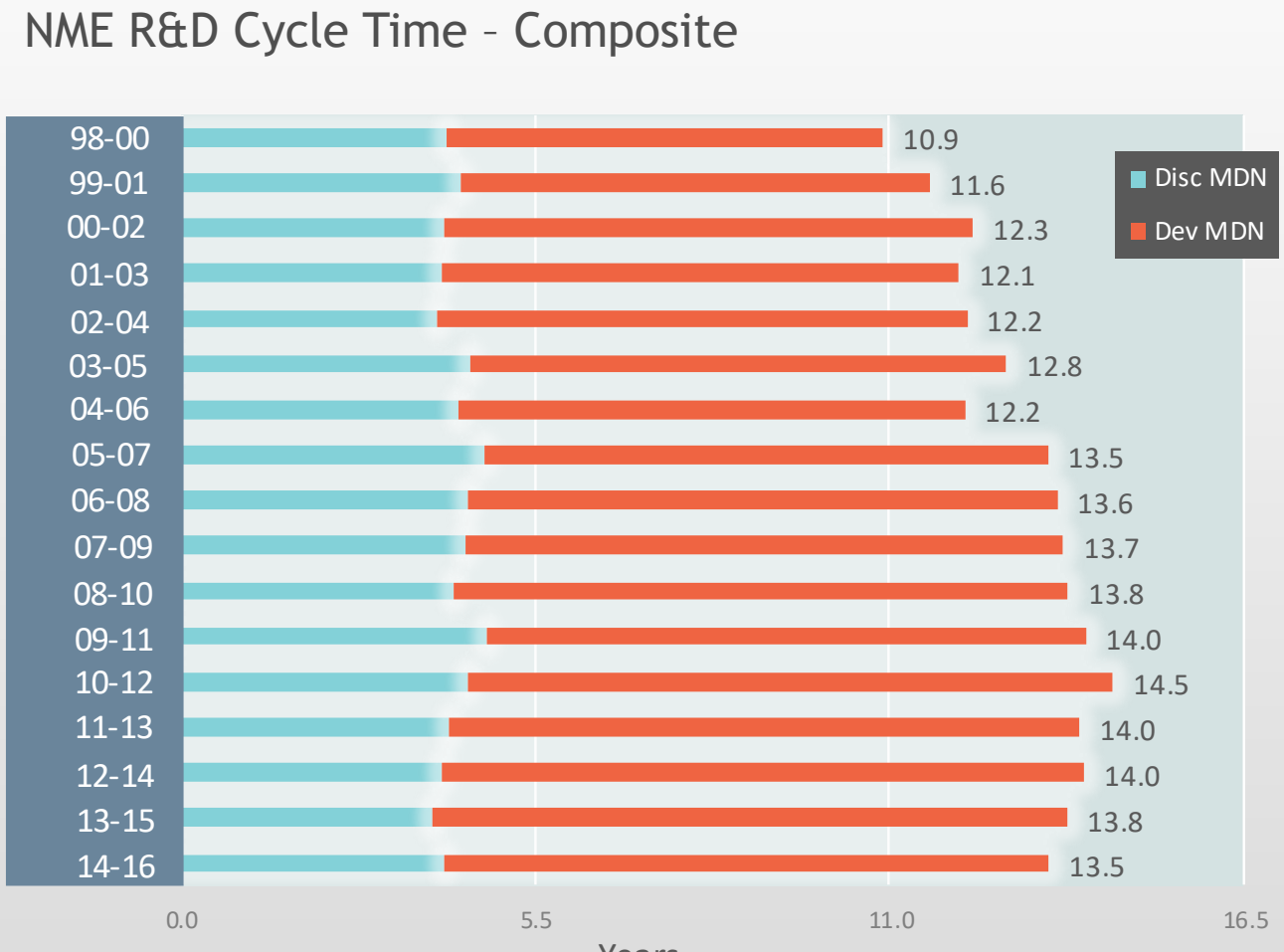
- Increasing clinical costs (direct investment)
- Decline in clinical success rates (cost of failure)

... main contributor to productivity change



Sources: Dimasi et al. Journal of Health Economics 2016:47:20-33
Pammoli et al. Nature Reviews Drug Discovery 2011: June issue. BCG adaptation courtesy of M Ringel.

MEDIAN DISCOVERY-TO-APPROVAL TIME = ~13-14 YRS



NME R&D Composite Cycle Time: Target Identification through First Approval in a Major Market

Median durations in Discovery & Development are approximately 4 & 9 years, respectively:

- Discovery cycle time (~4 years) includes all stages following target identification; assay development, screening and optimization
- Development cycle time (~9 years) includes all phases preclinical through registration

Source: Pharmaceutical Benchmarking Forum (PBF) R&D General Metrics Study public release materials, September 2017. Median cycle time performance among 13 of the top 20 international biopharmaceutical companies as measured by annual human health R&D investment and revenue. NME = New Molecular Entity

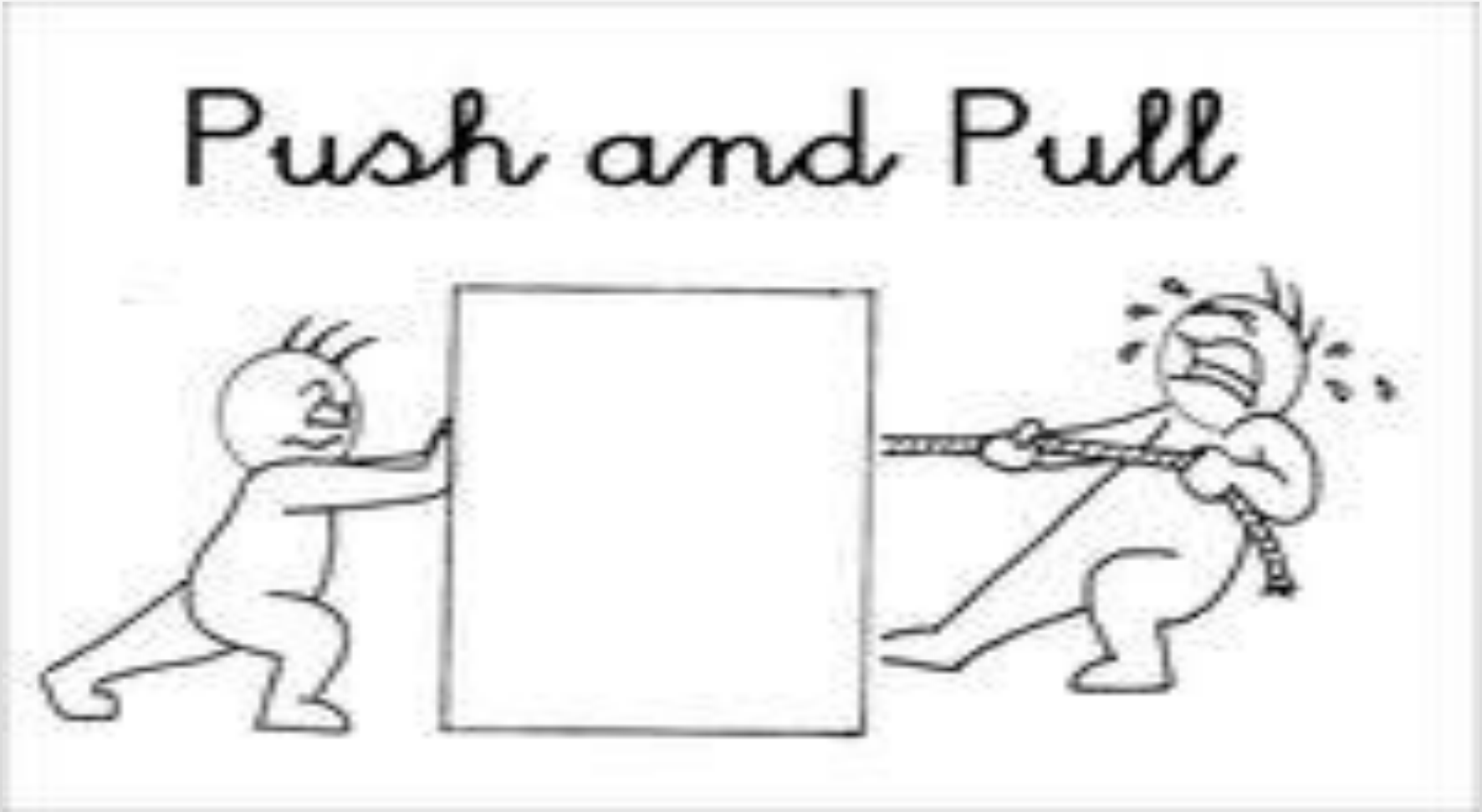
MEANWHILE . . .

Keeping Pace w/Evolving Diseases?

- Vaccines – Proliferation of variants & mutations
- Inflammatory/Oncology Diseases – Multiple competing mechanisms of action demand increased complexity in drug & clinical design
- Infectious Disease – Rate of resistance to ciprofloxacin used to treat urinary tract infections varied from 8.4% to 92.9% for E. coli & from 4.1% to 79.4% for Klebsiella pneumoniae globally*
- Malaria - A mosquito has a 6 week lifespan during which to evolve while it takes >10 years to design, develop, test & produce a new drug to combat malaria.

*WHO Global Antimicrobial Resistance & Use Surveillance System

WHAT DID WE LEARN FROM THE PANDEMIC & ARE WE AT A CROSSROADS?



BENEFIT/RISK

FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine

Action Follows Thorough Evaluation of Available Safety, Effectiveness, and Manufacturing Quality Information by FDA Career Scientists, Input from Independent Experts

On May 10, 2021, the FDA ex
Pfizer-BioNTech COVID-19 Va
of age. The emergency use a
Vaccine to be distributed in

"While not an FDA approval, today's emergency use authorization of the Pfizer-BioNTech COVID-19 Vaccine holds the promise to alter the course of this pandemic in the United States. With science guiding our decision-making, the available safety and effectiveness data support the authorization of the Pfizer-BioNTech COVID-19 Vaccine because the vaccine's known and potential benefits clearly outweigh its known and potential risks."

Peter Marks, M.D., Ph.D., Director, FDA/CBER

COVID-19 VX REGULATORY EXPECTATIONS

- The requirements & regulatory expectations for demonstrating appropriate product quality assurance are no different for *Early Access Approaches* than for conventional regulatory applications.
- The difference is balancing appropriate benefit/risk to defer data that confirms requisite quality assurance
  - ❑ Establish reliable provisional criteria
  - ❑ Commit to post authorization/approval obligations
- Flexibility is predicated on transparent communication & direct & frequent engagement between sponsor & regulator

OPPORTUNITY

The delivery of COVID-19 vaccines could not have been effectively achieved without the following paradigm shifts:

- Parallel rather than sequential product & process development;
- Full transparency & a balance of flexibility in regulatory expectations & processes including confirmation of manufacturing consistency & quality through post authorization obligations & commitments;
- Mutual, risk-based reliance among regulatory authorities globally.

REGULATORY PROGRESS?

Amending the U.S. Federal Food, Drug, and Cosmetic Act, originally passed in 1938, *FDA Modernization Act 2.0* eliminates the requirement of testing drug candidates on animals before human trials.

FDA: Animal Testing No Longer Mandatory before Human Trials

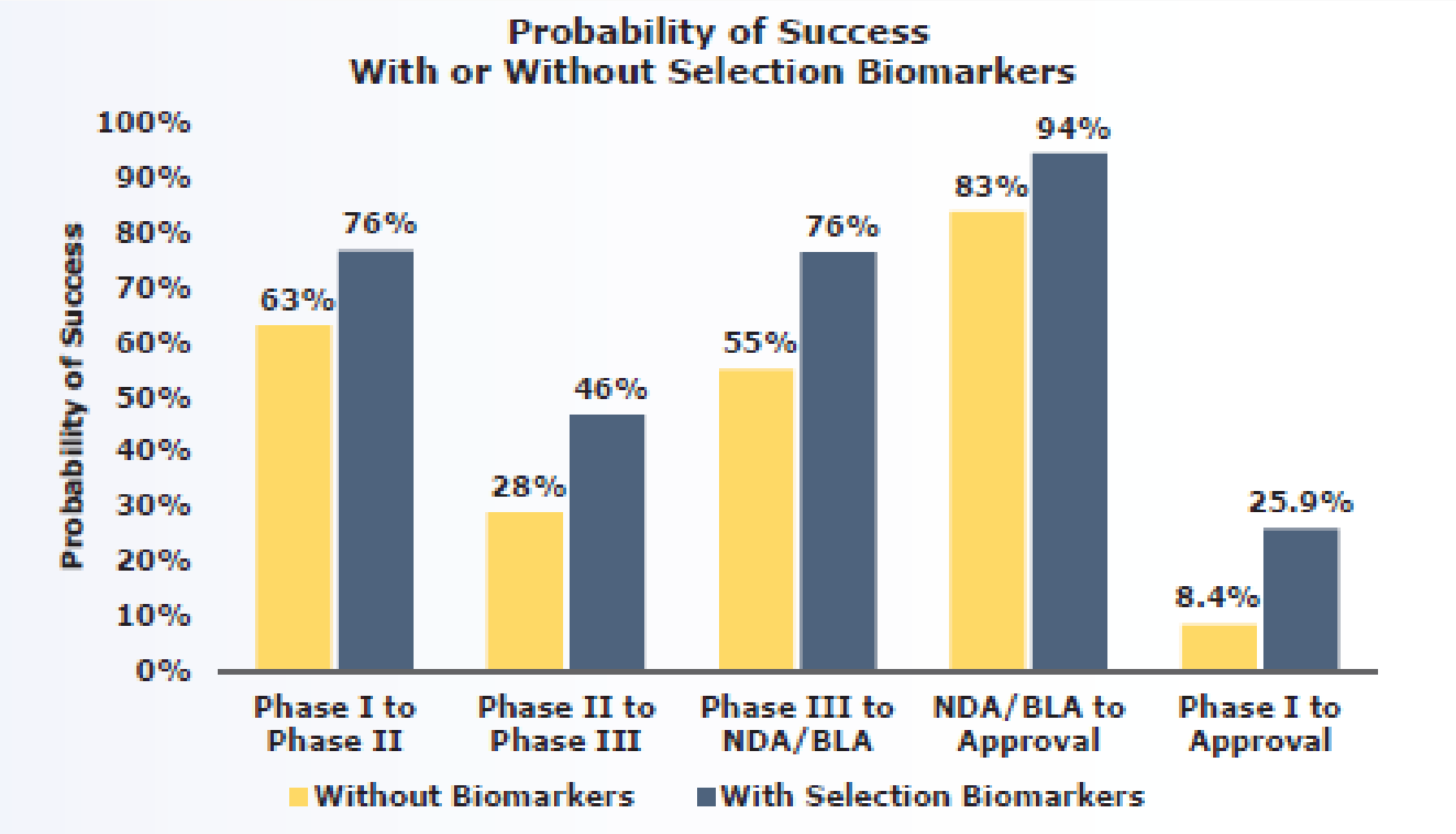
Some researchers & companies have already adopted effective alternative drug-testing methods like computer modeling, organs-on-a-chip, & thumb-sized microchips, but limitations are debatable among the scientific community.

FDA: Provisions Mandating explicit guidance in support of advanced manufacturing technology

MODELS CAN COMPRESS PRECLINICAL DEVELOPMENT TIME

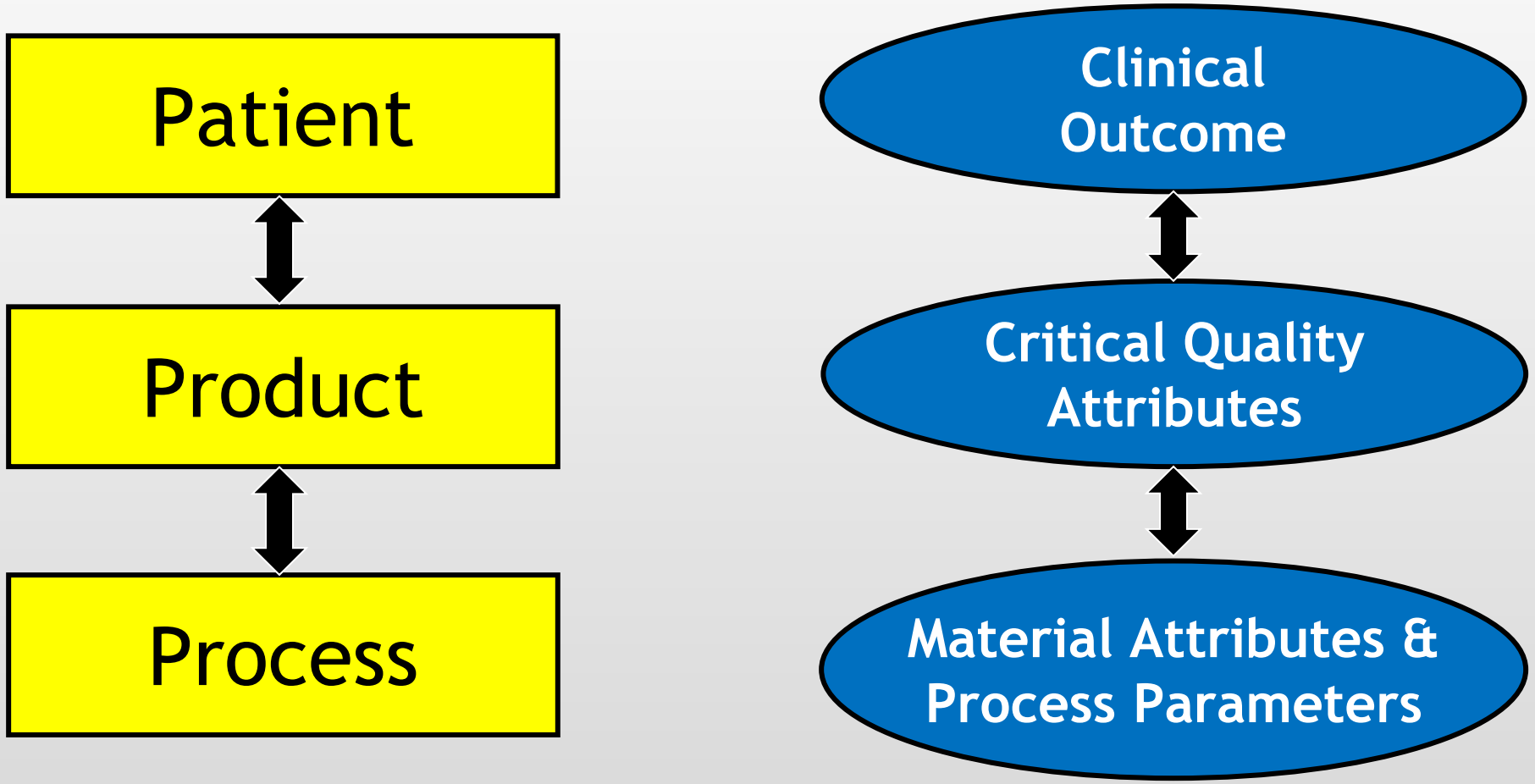
- Several *Approved*, in vitro pharmacology models, PK/PD, demonstrate more robust human *in vivo* predictability relative to surrogate animal models
- Gastroplus™ demonstrates surrogate GI Transit performance
- In silico DEREK Nexus®/SARAH/TOPKAT computational models provide robust comparability of SAR for toxicology thresholds
- Predictive permeability assays, i.e., CACO-2 measure drug absorption

BIOMARKERS PROVIDE AN ADVANTAGE



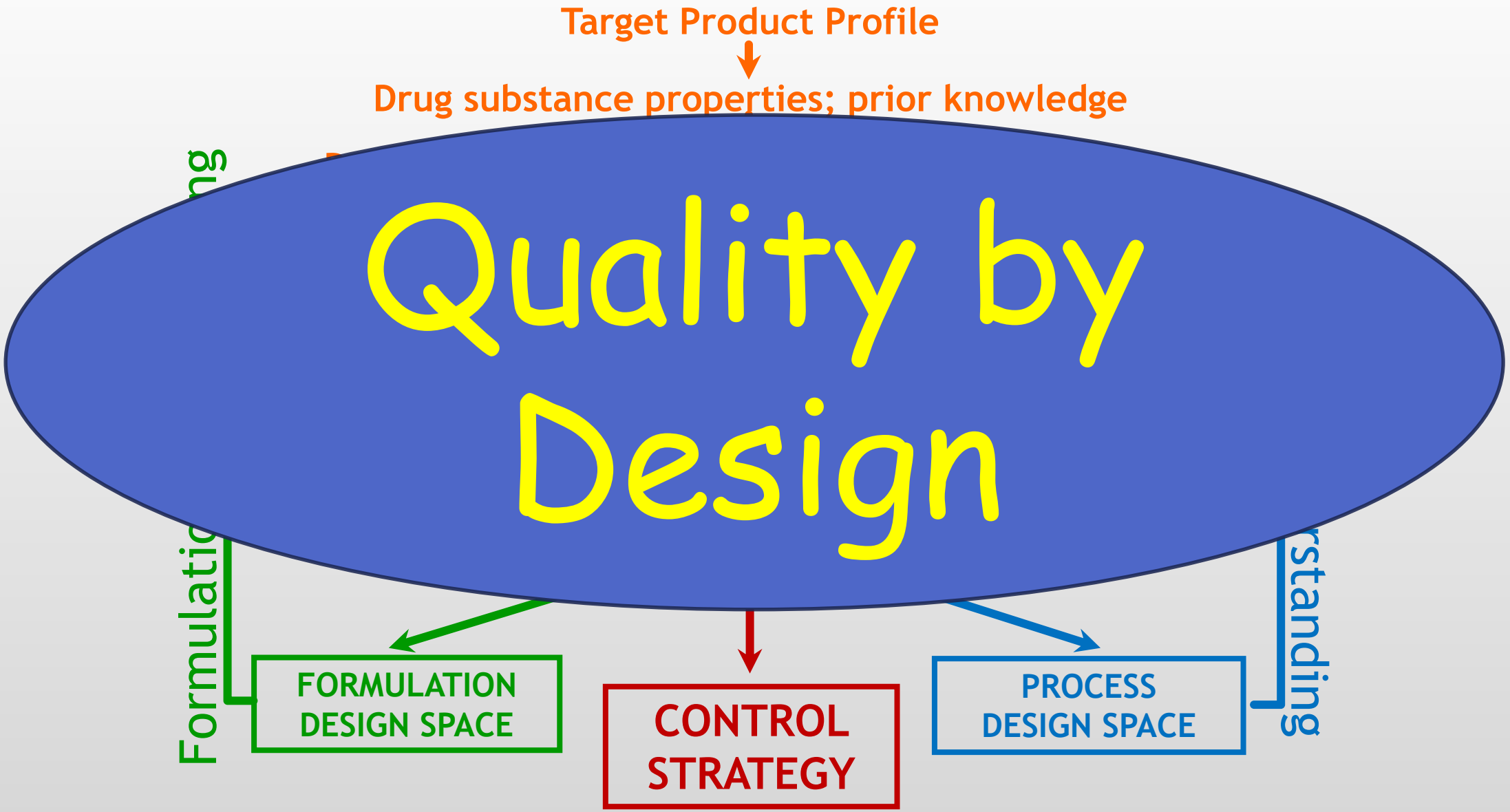
https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

PATIENT CENTRIC DEVELOPMENT PARADIGM



John Jenkins, DIA Washington, DC, 2010

A PROSPECTIVE APPROACH TO DEVELOPMENT



EfPIA Working Group, 2005

WHAT DOES THE NEW DEVELOPMENT PARADIGM LOOK LIKE?

CONVENTIONAL DEVELOPMENT APPROACH

Product Knowledge – Incremental & Sequential

NEW DEVELOPMENT PARADIGM

Product Development to Enable Registration & Commercialization

Product Development to Enable Clinical Studies

Product Knowledge – Parallel Development

DEVELOPMENT TIME

ASPIRATIONS FOR INNOVATIONS IN PHARMACEUTICAL MANUFACTURING

Pharmaceutical Industry

- Improve productivity & reduce costs
- Reduce quality issues
- Global regulatory convergence, i.e., Mutual Reliance/ Recognition
- Improve quality assurance
- Increase flexibility to accelerate
- Improve regulatory collaboration & reduce punitive oversight
- Introduce incentives to innovate old & Gx products
- Automate

Regulatory Authorities

- Resolve quality issues
- Improve quality assurance
- Establish quality mfg. maturity
- Focus on product reliability & sustainability
- Create agile & flexible mfg.
- Provide regional adaptable technology
- Integrate mfg. redundancy
- Leverage ICH

Patients

- Provide consistent product quality
- Reduce costs
- Improve quality assurance
- Improve convenience for administration compliance

BIG HAIRY AUDACIOUS GOAL

- President Kennedy's 1961 famous declaration: "*This nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to earth.*" (NASA. *A President Issues NASA's First Historic Challenge*)

- SpaceX's goal to "*enable human exploration and settlement of Mars.*" (SpaceX. *Mars & Beyond*)

- Meta, BHAGs include to "*make the world more open and connected*" and "*give everyone the power to share anything with anyone.*" (META. *Our Mission*)

- Google wants to "*organize the world's information and make it universally accessible and useful.*" (Google. Think with Google. *The Eight Pillars of Innovation*)

BHAG is from the 1994 book *Built to Last: Successful Habits of Visionary Companies* by Jim Collins and Jerry Porras.

PUSH/PULL = PARADIGM SHIFT

The PUSH

- Increase use of *in silico* models & predictive assays
- Invest in development of Biomarkers
- Adopt prospective QbD approach to product development
- Leverage Real World Evidence (where applicable)

The PULL

- Parallel rather than sequential development
- Collaboration among developers & with regulatory authorities & government agencies
- Consistent, reliable & robust product quality assurance provides opportunities for negotiable regulatory flexibility - commitments.
- Mutual Reliance/Recognition aligns regulatory authorities & expedites delivery to patients globally.

THE DESIRED STATE FOR PROCESS DEVELOPMENT

- Leverage Prior Knowledge & Experience
- Emphasize Control Strategy

A planned set of controls derived from current product & process understanding that assures process performance & product quality.

Get your process & methods under control, by demonstrating understanding & control when producing your product

A specification, by itself is NOT a control. It confirms control.

ICH Q10

FDA

PhRMA

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
PhRMA = Pharmaceutical Research & Manufacturers of America

PRODUCT DEVELOPMENT *BY DESIGN*

Start with the Patient	• Understand patient needs – TARGET PRODUCT PROFILE • Understand the process – *Does it deliver what the patient needs?*
Assess materials & process risks to quality	• Understand criteria (CQAs) needed to assure product quality • Process understanding (Not all 'critical parameters' carry equal risk)
Determine location for optimal control	• Differentiate CPP/change management based on residual risk • Control inputs, parameters, IPCs, outputs OR a mix
Determine which risks require a test	• *How does process deal with risks to quality – ENHANCED knowledge?* • *What needs to be controlled to assure quality for the patient?*
Develop analytics to monitor quality risks	*Can Control Strategy provide a measure of product performance?*
Establish specification for critical controls	• Test method + acceptance criterion OR • Rationale for how CQA is controlled w/o testing

REGULATION HAS AN IMPACT ON DEVELOPMENT

- Upsides
  - Precedented Standards (ICH S/E/Q)
  - Incentives (exclusivity, vouchers, accelerated & expedited review, etc.)
  - Prescriber, Patients, Consumer trust
- Downsides
  - Regulatory barriers to entry (cost, time, portfolio decisions)
  - Inertia & precedent can limit flexibility and progress
  - Limit communication of valid medical information
  - Non-value added regulatory requirements
  - Duplication & divergence of regulatory requirements globally

REGULATORY STRATEGY – *WHAT, HOW & WHY*

- Regulations & guidelines define ***WHAT*** is expected in regulatory applications
- Regulators worry about ***WHAT*** is approved & ***HOW*** it will change over the lifecycle of a product
- Sponsor is responsible for effectively describing ***HOW*** regulatory expectations have been addressed & ***WHY*** data & risk assessments substantiate how those expectations will be addressed through the product lifecycle

SUMMARY

- Drug Development is expensive
- Cost of failure has biggest impact on productivity
- Embrace BHAG - Bold Initiatives to introduce alternative approaches & evidence sources, i.e., in silico modeling, predictive assays, RWE, etc.
- The pandemic introduced opportunities to expedite development & regulatory approval
- Industry drug development portfolios have & will continue to evolve to align with economic & regulatory incentives.

Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has.

- Margaret Mead,
Cultural Anthropologist