Opportunity for New Paths to Accelerated Technology Implementation- *Global Challenge*

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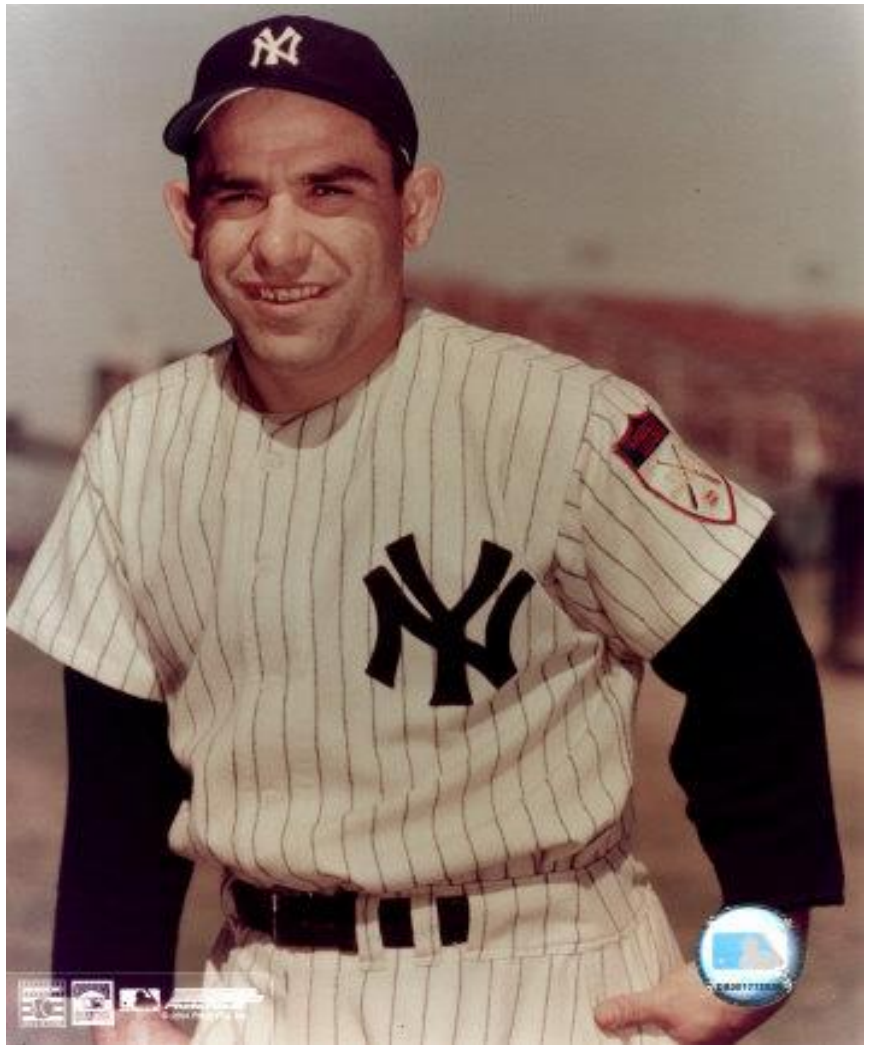
EXECUTION TO MEET GLOBAL OBLIGATIONS



"When you come to a fork in the road, take it."

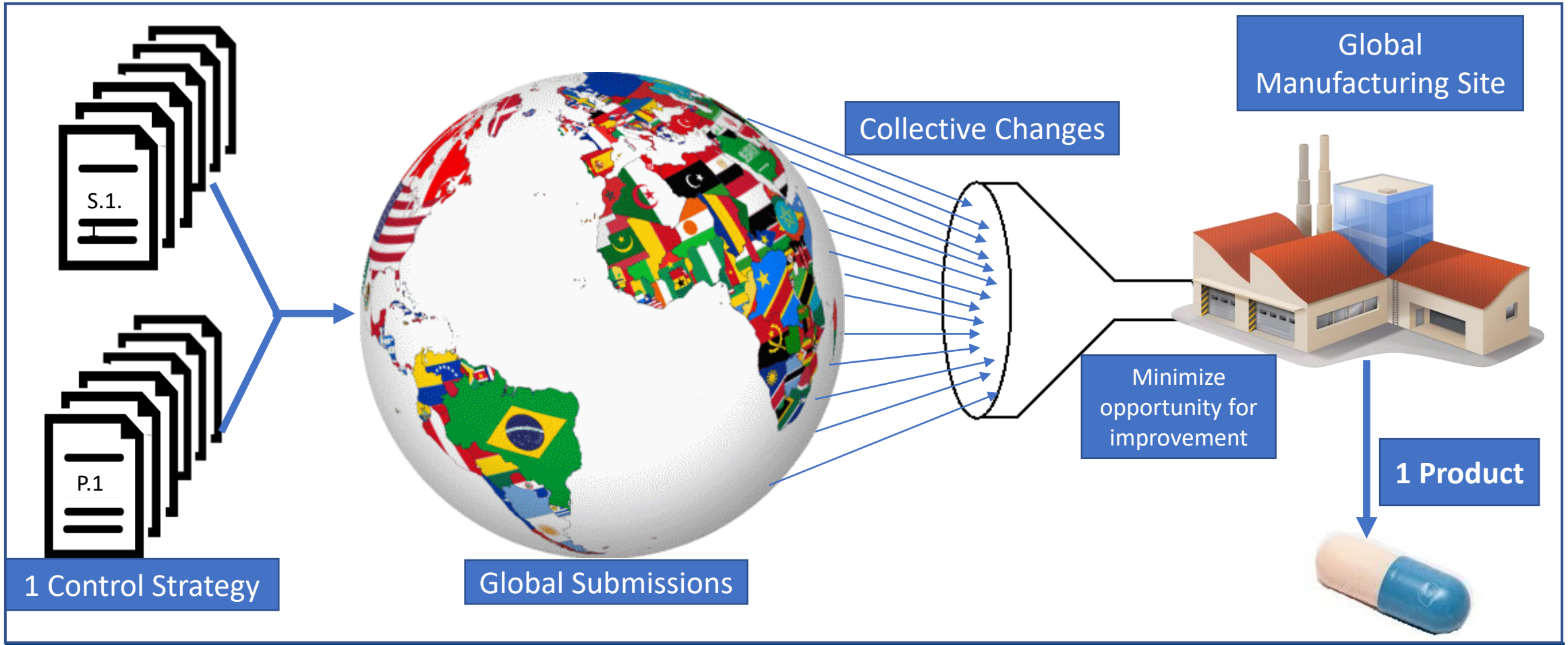
-Yogi Berra

American Philosopher (& baseball player)

Harmonization and Impact to Innovation/ New technology

- Industry can’t afford to advance new technology where there is risk for some regions not accepting (or different requirement)
- What opportunities did the pandemic teach us?
- What can we learn to help innovation and new technology gain faster global acceptance?

Any country can impact control strategy for the world



Shared Goal: Create incentives for rapid, continuous quality improvements and adequate supply to patients

New Technologies Examples

Continuous Manufacturing

Advantages: agility, efficiency, green chemistry, supply independence (replication)

Implementation: Has taken a long time, but now being implemented more and more. Why has it taken so long?

QbD

Advantages: enhanced understanding leading to more flexibility for continuous improvements

Implementation: Used internally, but regulatory divergence has reduced its use in registrations

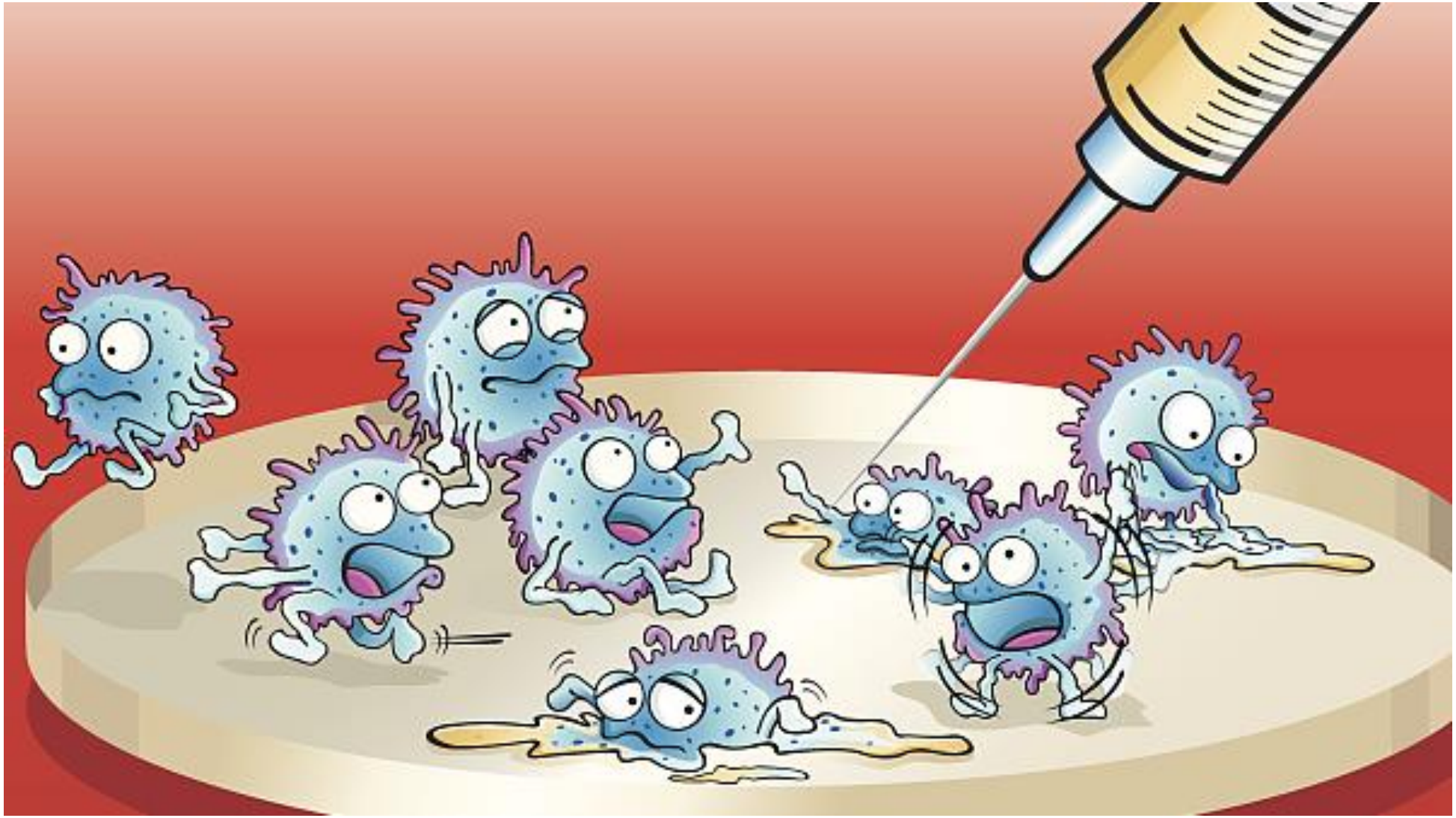
Co-processed APIs

Advantages: open the chemical space to DSs which historically could not lead to viable drug products

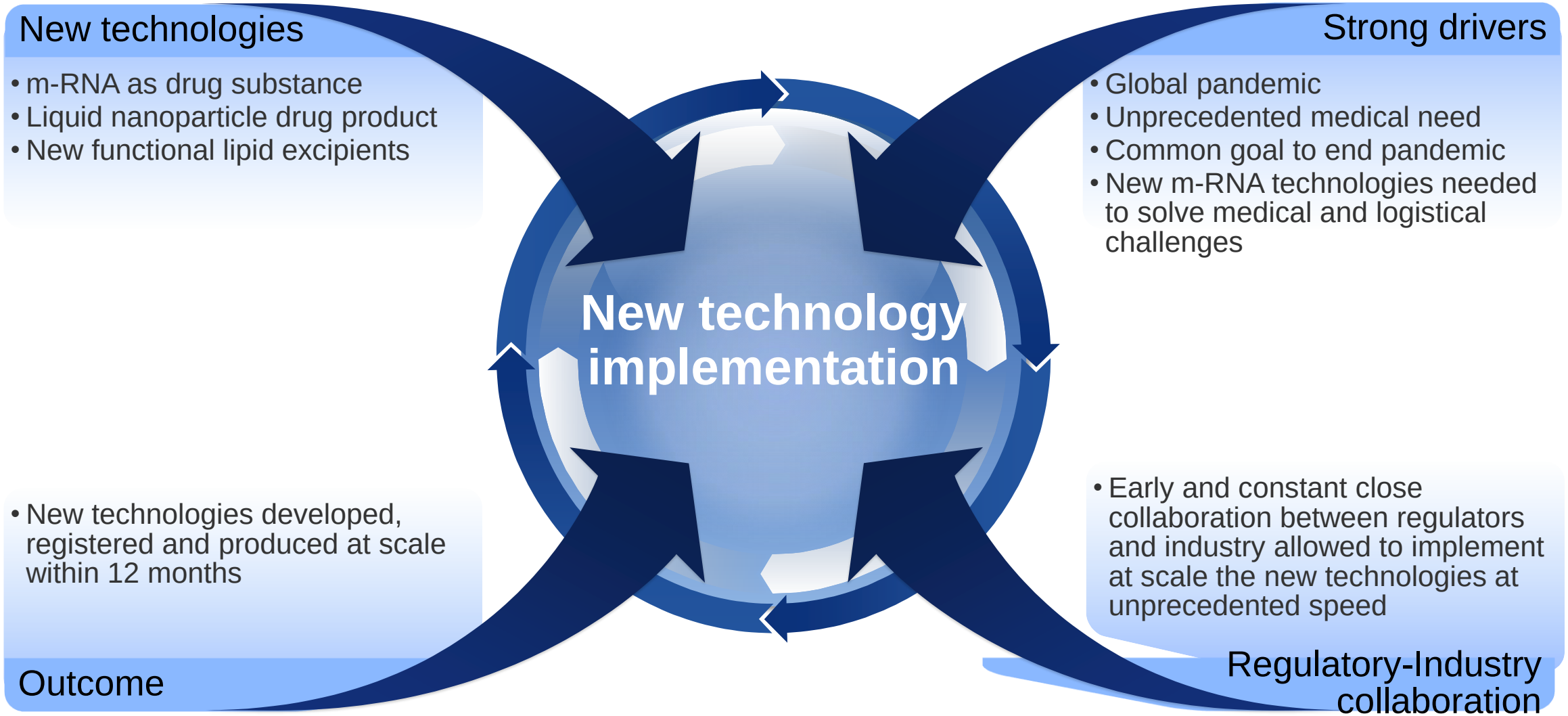
Implementation: To be discussed in this workshop!!

DS vs DP intermediate designation could hinder its implementation, especially if no global harmonised position is reached

VACCINE DEVELOPMENT PARADIGM SHIFT



m-RNA Vaccine Development



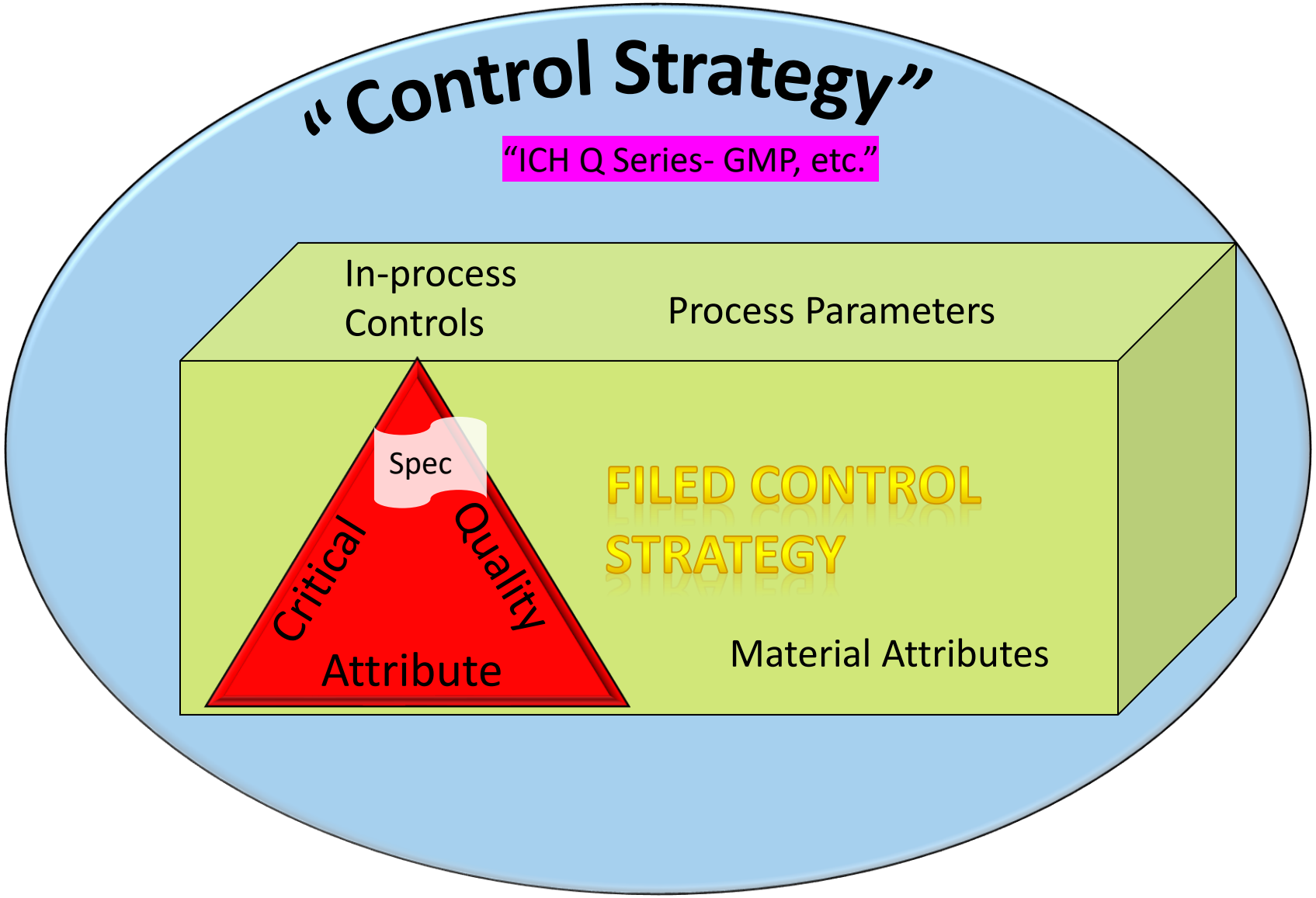
m-RNA Vaccine Learnings for other technology implementation

- New technologies can be developed, implemented and globally registered very quickly
- However this happened because significant investment was made at risk and because there was a strong partnership between regulators and industry and global regulatory alignment (at high level)
- Going forward, new technologies will be implemented faster if we can retain the strong regulator-industry partnership, ensure global alignment
- This regulatory certainty will enable large investments by industry and patients will benefit from new technologies

Food for thought during Workshop

- Why do we need new manufacturing technologies?
  - new manufacturing techs (continuous) to improve agility, efficiency, green chemistry, supply independence (replication)
  - new drug substance/product technologies (co-processed APIs) to open the chemical space to DSs which historically could not lead to viable drug products
- What are the barriers to new technologies:
  - Risk if using unproven technologies from scientific and business points of view
  - Need for capital investment
  - Risk of higher regulatory hurdle and global divergence.
  - Outcome of regulatory requirements could change the investment requirements drastically
- Positives about FDA engagement on new technologies
  - Unique agency that helps industry collaborate with FDA on new technologies
  - However, products are global and we need an aligned global regulatory position to really help accelerate the use of new technologies.

Coming together is a beginning; keeping together is progress; working together is success- Henry Ford


"Control Strategy"
"ICH Q Series- GMP, etc."
In-process Controls
Process Parameters
Spec
Critical
Quality
Attribute
FILED CONTROL STRATEGY
Material Attributes

FDA Industry Relationship; Opportunities for next decade

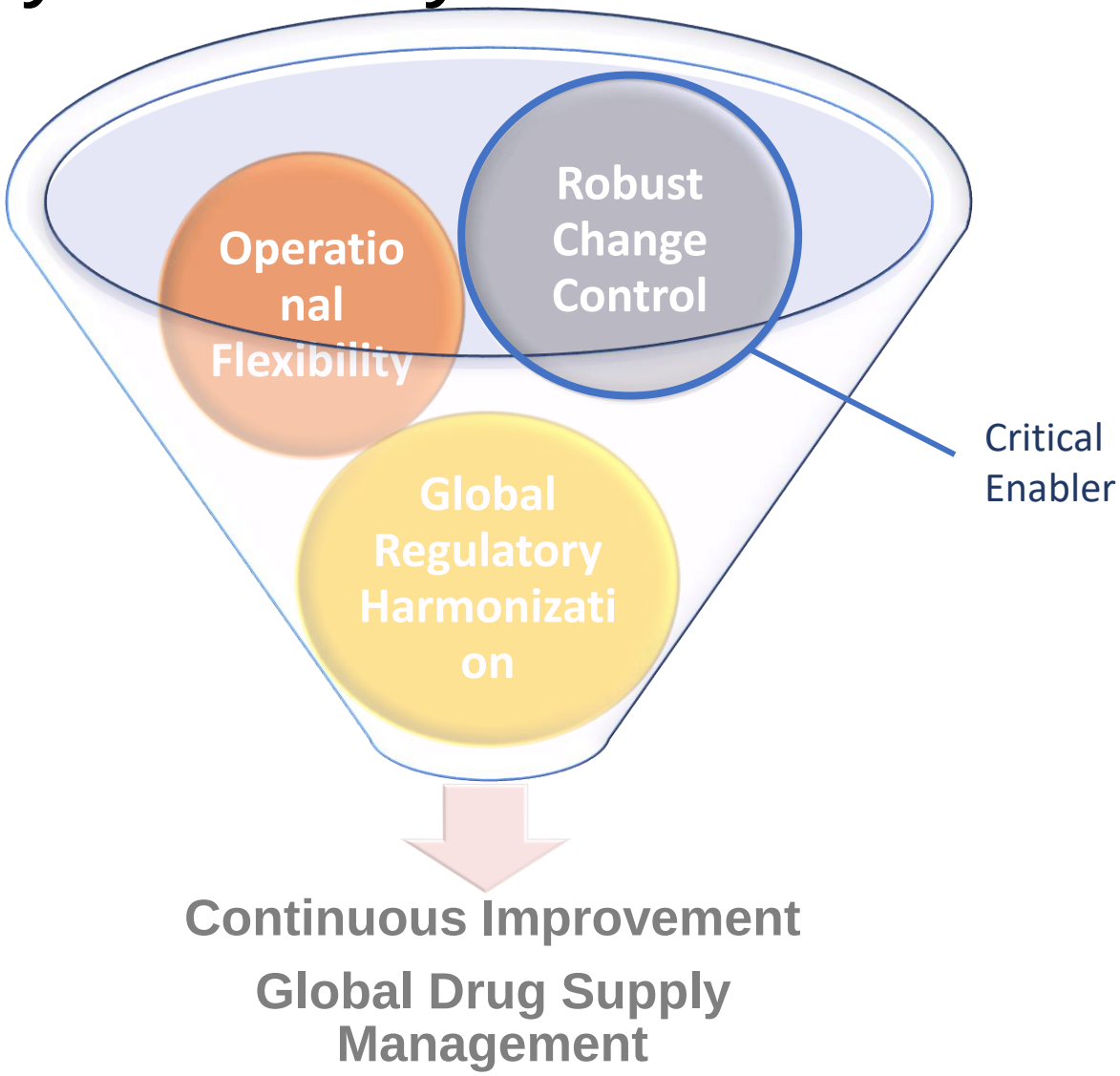
- Opportunities and Challenges
  - Global Harmonization remains a risk for expedited access of important medicines (US and ROW)
  - Divergence in the interpretation and implementation of ICH, regional regulations, and policies
  - Differences between regions in queries (types and number) and outcomes; different control strategy, expectations
  - Industry manufacture products for the world, not one market; thus is “limited” by the “lowest common denominator”.
  - Innovation, new technology, Lifecyle improvements are hampered by the global “bottleneck” (industry can’t afford a few markets special manufacturing)
  - The lack of global harmonization creates disincentives for new technology and manufacturing innovation
- How can the FDA relationship with Industry help
  - FDA is a global leader amongst regulatory agencies; very well respected
  - FDA can use its leadership platform to align global agencies; industry has struggled alone
  - FDA can help establish a global strategy to achieve “one control strategy” and faster adoption of new technology; industry can not do this alone
  - Build upon the success of the response to the COVID pandemic for rapid access, innovation and improved harmonization

Quality by Design and ICH Q12

Quality by Design (QbD)	Science-driven, risk-based approach to expand product knowledge and process understanding Intended to serve as a foundation for and encourage continual improvement Increase assurance of quality for pharmaceutical products
The QbD approach	Prospectively characterizing quality risks to patient safety and efficacy Developing an appropriate control strategy to mitigate those risks
Implementation of QbD to support regulatory applications	Incomplete No provisions for how post-approval changes would be acceptably submitted and effectively approved
ICH Q12	Regulatory mechanisms to simplify, enable and expedite post-approval variations Established Conditions (ECs) is an enabling mechanisms

Operational and Regulatory Flexibility

- Framework to facilitate the management of post-approval CMC changes
  - Increased product and process knowledge can contribute to reduced regulatory submissions
  - Enhanced ability to manage many CMC changes effectively under the PQS with less need for extensive regulatory oversight
- Operational and regulatory flexibility is subject to:
  - Product and process understanding (ICH Q8 and Q11)
  - Risk management principles (ICH Q9)
  - Effective PQS (ICH Q10)



Documentation and control strategy- barrier is higher for new technology- *"first to forgo will run a gauntlet"*

Current Paradigm

Sufficient dossier details (file more)

Lifecycle flexibility (file less)

Q12

Future Paradigm

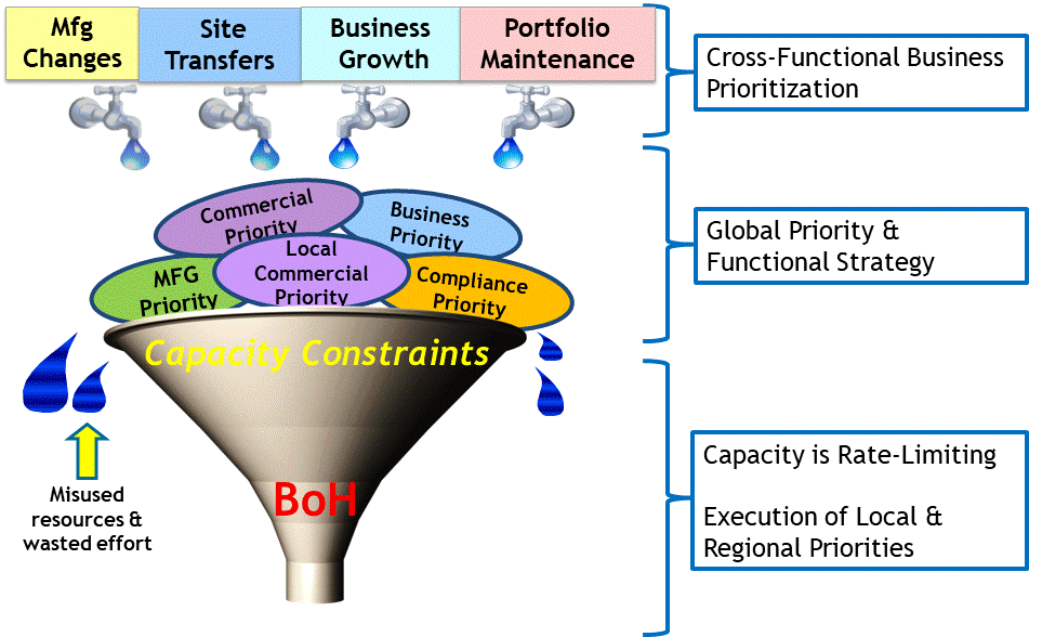
Sufficient dossier details

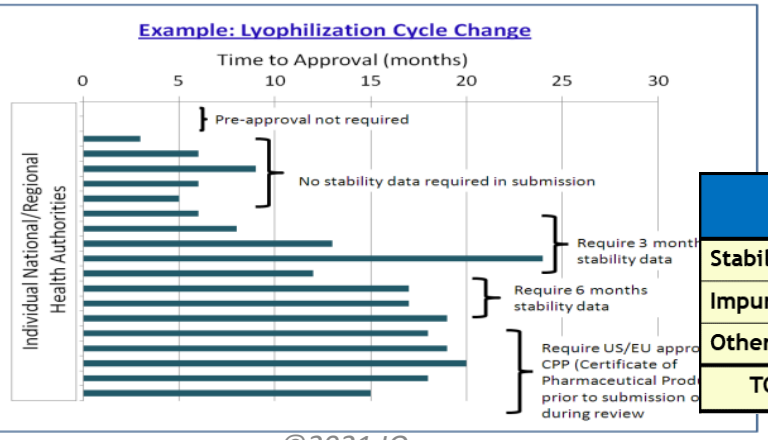
Lifecycle flexibility

Adapted from: Eli Zavialov, Janssen R&D, "First steps towards ICH Q12 Implementation" presented at ISPE Pharma Best Practices Webinar Series: Challenges and Successes of ICH Q12 Related Submissions, 17 February 2021.

COSTS

- Barrier to innovation & continual improvement
- Increased regulatory review & inspection burden
- Increased study & application costs
- Delayed approvals

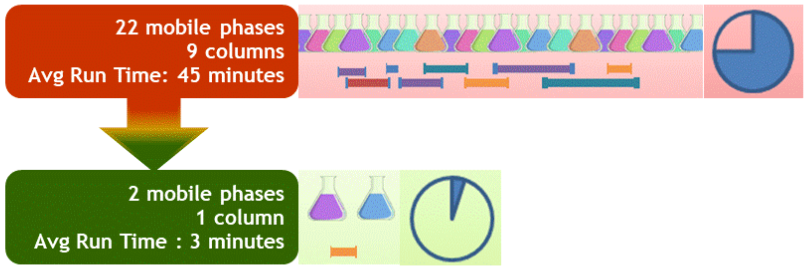




Post Approval Stability Commitments N=29	
Stability Issues	0/29
Costs/Commitment	$1.0M - $4.5M
Total Cost	~$81.2M

	Study Costs/ Product ($M)	Delayed Approval Costs/Product ($M)	Comments
Stability	0.25 - 1.50	2.0 - 5.0	Site specific & additional zones
Impurities	0.10 - 1.00	1.0 - 2.5	Mutagenic toxicology & reproductive testing
Other	0.05 - 1.25	0.5 - 1.5	Batch specific data & ancillary certifications
TOTAL	0.40 - 3.30	3.5 - 9.0	Estimated costs based on random assessment of New & PAC submissions since 2010 - total of ~130,000 submissions

Consolidation of testing methods for a range of different products among 20 different APIs to optimize operations using a single "always on" method



- These products are sold in 174 countries
- Implementation requires changing 6364 National Licenses!

Acknowledgments

- Olivier Dirat
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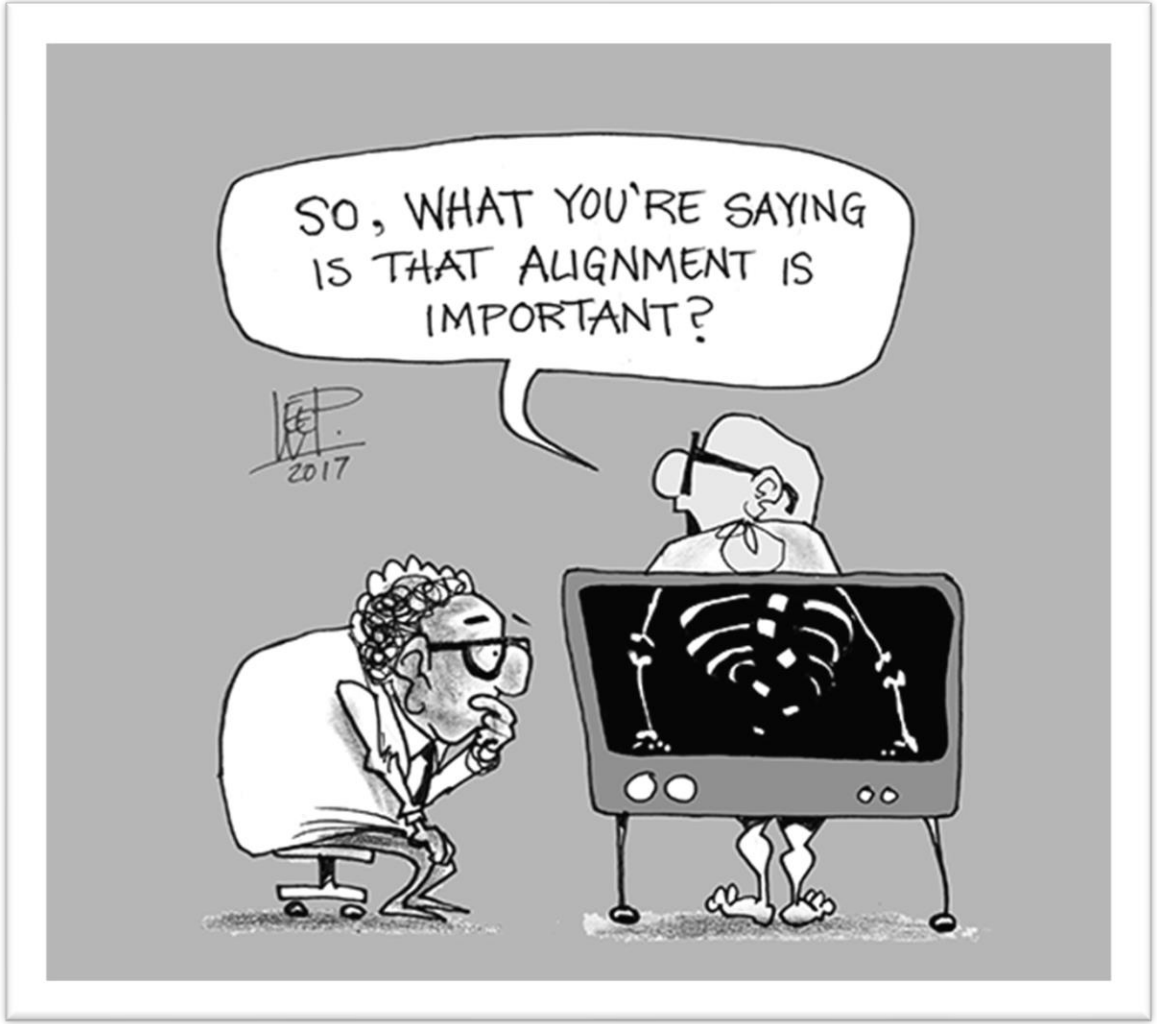
- IQ

OVERCOMING CHALLENGES TO CHANGE



- Consistent understanding of ICH expectations/implementation industry and regulators
- Joint engagement with regulatory agency
- Mutual recognition

Thank you!