Opportunities and Challenges to Innovation and Harmonization for Pharmaceutical Quality Manufacturing from Industry Perspective

Timothy Watson

Topics

- Review International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)
  - Explore the “score card” on ICH implementation and importance of harmonization
  - Review data output from the Control Strategy Harmonization data collection.

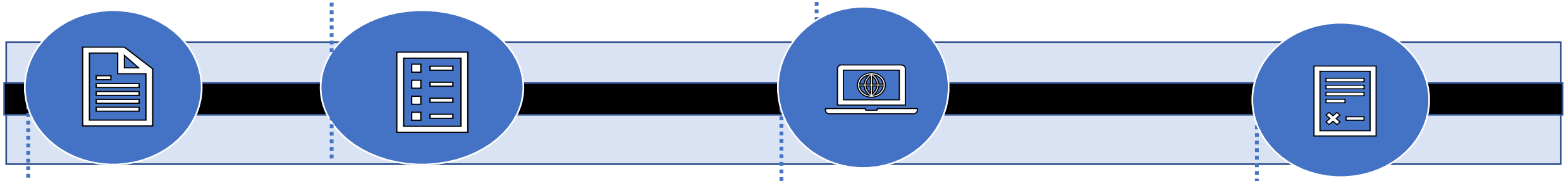
- Impact to Innovation

- Importance (opportunities?) of ICHQ12 with respect to global harmonization- can this help solve part of the challenges?
- Paper just published in ISPE PE; full data and analysis of all examples!

Background to formation of IQ Control Strategy Group

June 2018 P; R. Nosal, presents examples of divergence at ISPE- illustrating the difference in number of queries between agencies and the fact that only 20% are similar concerns

December 2018 P; T. Watson and R. Nosal present at FDA/ HC public forum and show multiple Pfizer examples. Prompts HC to ask if this is industry observed or just Pfizer.



Up to 2012

ICH Q8-Q11 implemented

Aug 2018 Publication
R. Nosal, F. Montgomery, T. Watson, J. Lepore
ICH guidelines Q8/11, Q9, and Q10 introduced risk-based approaches and enhanced scientific understanding as an opportunity to encourage continuous process improvement for pharmaceutical manufacturing

2019- IQ explores / proposes team

April 2020
IQ forms a Control Strategy Harmonization Group

IQ Control Strategy Global Harmonization WG

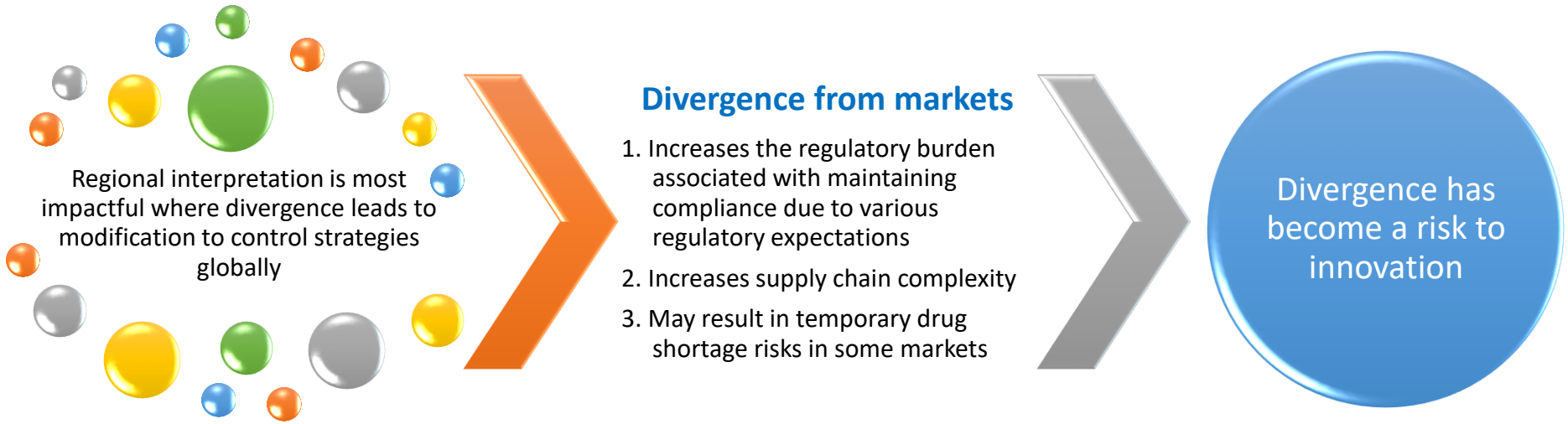
Tim Watson
Executive Director
Regulatory CMC
Pfizer

KeAndra Robinson
Sr. Manager Regulatory
CMC
Biogen

Greg Rullo
Sr. Director Regulatory CMC
AstraZeneca

Overview of the Working Group

- Regional interpretations of ICH guidance have resulted in different technical requirements and/or control strategies for each market posing significant challenges for a global industry.



- Industry develops a single core control strategy based on options outlined in ICH to supply the market globally. However, the same data sets are interpreted differently that result in diversion from control strategy.
- Applying country specific control strategies results in a customized Module 3 and this can delay patients' access to new medicines.
- In April 2020, the International Consortium Control Strategy Global Harmonization Working Group was formed to collect examples and to highlight harmonization and divergence in control strategies.
  - This working group has collected examples of harmonization challenges by both regulators and manufacturers, to facilitate opportunities for improved global harmonization that would advance manufacturing processes, innovative improvements, and enhance product quality.

14 Companies on the IQ team

Tim Watson (Chair), KeAndra Robinson (Co-Chair), Greg Rullo (Co-Chair)

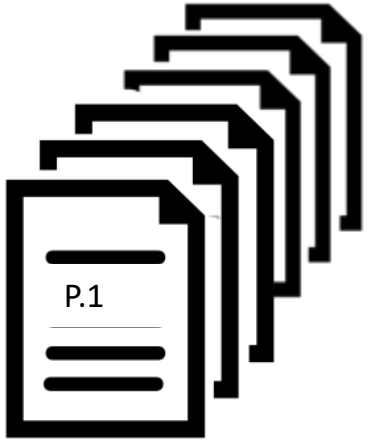
Definitions = Core Documents

Create Core Documents

A Core Document is a company's view of a document that complies with ICH requirements

Core Drug Substance Documents

Core Drug Product Documents



A complete set of "core" documents created for every Module 3 document

How Did the IQ Team collect data?

Company	Project Identifier Code	Year of submission	Country	Molecule (Synthetic or Biologic)	Dosage Form (Sterile or non-Sterile)	Describe Substance and Product manufacturing process (Design Space, PAR, combination)
Company 1	Company1_Drug 1	2014-2017	USA	Synthetic	non-Sterile	PAR
Company 1	Company1_Drug 1	2014-2017	EU	Synthetic	non-Sterile	PAR
Company 1	Company1_Drug 1	2014-2017	Canada	Synthetic	non-Sterile	PAR
Company 1	Company1_Drug 1	2014-2017	Japan	Synthetic	non-Sterile	PAR

Core Accepted S.2.2	Core Accepted S.2.3	Core Accepted S.2.4	Core Accepted S.4.1	Core Accepted S.7	Core Accepted P.3.2	Core Accepted P.3.3	Core Accepted P.3.4	Core Accepted P.5.1	Core Accepted P.8
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Yes = Team members identified the Core was accepted without modifications during submission review

Team members identified whether Core was accepted.

How often are core documents accepted?

Data assessment of Module 3 documents, that are key to control strategy, where **11 companies** submitted **112 marketing applications** in USA, EU, Japan and Canada.

	S.2.2	S.2.3	S.2.4	S.4.1	S.7	P.3.2	P.3.3	P.3.4	P.5.1	P.8	Average
Core Accepted	51%	52%	56%	43%	71%	79%	46%	59%	25%	62%	54%

Only a 54% chance core will be accepted

Acceptance Rates by Combined - Biologics - Synthetics

Total of **112** submissions from 11 companies.

Molecule Type	Submissions	S.2.2 Accepted	S.2.3 Accepted	S.2.4 Accepted	S.4.1 Accepted	S.7 Accepted	P.3.2 Accepted	P.3.3 Accepted	P.3.4 Accepted	P.5.1 Accepted	P8 Accepted	Likelihood of core Accepted
Combined	112	51%	52%	56%	43%	71%	79%	46%	59%	25%	62%	54%
Biologic	48	31%	54%	46%	29%	48%	85%	46%	54%	19%	46%	46%
Synthetic	64	66%	50%	64%	53%	88%	73%	47%	63%	30%	73%	61%

Very low acceptance rate for Biologics

Low acceptance rate of specifications regardless of Biologics or Synthetics

No significant difference in acceptance rate

Acceptance Rates by Country for Synthetics Only

IQ Working group on Specification harmonization should be able to provide more insight into low acceptance rate

Country	Submissions	S.2.2 Accepted	S.2.3 Accepted	S.2.4 Accepted	S.4.1 Accepted	S.7 Accepted	P.3.2 Accepted	P.3.3 Accepted	P.3.4 Accepted	P.5.1 Accepted	P.8 Accepted	Likelihood of core Accepted
USA	17	88%	88%	88%	65%	82%	88%	71%	71%	29%	76%	75%
Japan	12	50%	42%	50%	58%	92%	67%	50%	75%	17%	83%	58%
EU	19	42%	16%	26%	26%	84%	63%	37%	58%	21%	63%	44%
Canada	16	81%	56%	94%	69%	94%	75%	31%	50%	50%	75%	68%
	64	66%	50%	64%	53%	88%	73%	47%	63%	30%	73%	61%

Deep Dive needed to understand difference in acceptance rates between US , EU and Japan

Deep Dive needed to understand overall low acceptance rate, particularly in Canada

Acceptance Rates by Country for Biologics Only

Country	Submissions	S.2.2 Accepted	S.2.3 Accepted	S.2.4 Accepted	S.4.1 Accepted	S.7 Accepted	P.3.2 Accepted	P.3.3 Accepted	P.3.4 Accepted	P.5.1 Accepted	P.8 Accepted	Likelihood of core Accepted
USA	13	31%	38%	31%	31%	23%	85%	15%	31%	15%	31%	33%
Japan	5	0%	40%	60%	20%	40%	100%	40%	60%	20%	20%	40%
EU	16	25%	56%	38%	31%	56%	81%	63%	50%	13%	50%	46%
Canada	14	50%	71%	64%	29%	64%	86%	57%	79%	29%	64%	59%
	48	**31%**	54%	**46%**	**29%**	48%	85%	46%	54%	**19%**	46%	46%

Deep Dive needed to understand low acceptance rates

IQ Control Strategy Global Harmonization WG

Reasons for Non-Acceptance of 'Core' document reflect **fundamental differences.** Areas divergence include; but not limited to, the following:

- **Drug Substance Starting Material**
  - Identification & justification of API SM
  - Supplier information requirement
  - Changes to starting material requirement (solvents, reagents, synthesis)
- **Manufacturing Process Controls**
  - Setpoint parameters, NORs, PARs, design space
  - Manufacturing and controls details
  - Criticality of parameters
  - Process end points
  - In Process Controls for critical and noncritical parameters
  - Reprocessing requirements
  - Equipment list
  - Limited by batch records used in pivotal studies
- **Analytical Procedure/Validation**
  - Fate and purge
  - Intermediates
  - Forced degradation studies
  - Equipment Validation
- **Stability**
  - Country specific requirements
  - Defining API retest dates
  - Shelf-life
  - Batch selection and comparability
  - Post-approval protocol and commitments
  - Site specific requirements
- **Specification**
  - Degradation product
  - Impurities
  - Microbial limits
  - Enantiomeric Impurity
  - Dissolution
- **Drug-Device Combination**
  - Country specific requirements
  - Human factor studies
  - Evolving/Changing dose requirement

Fundamental differences that impact the global dossier and control strategy

Implications for the Future

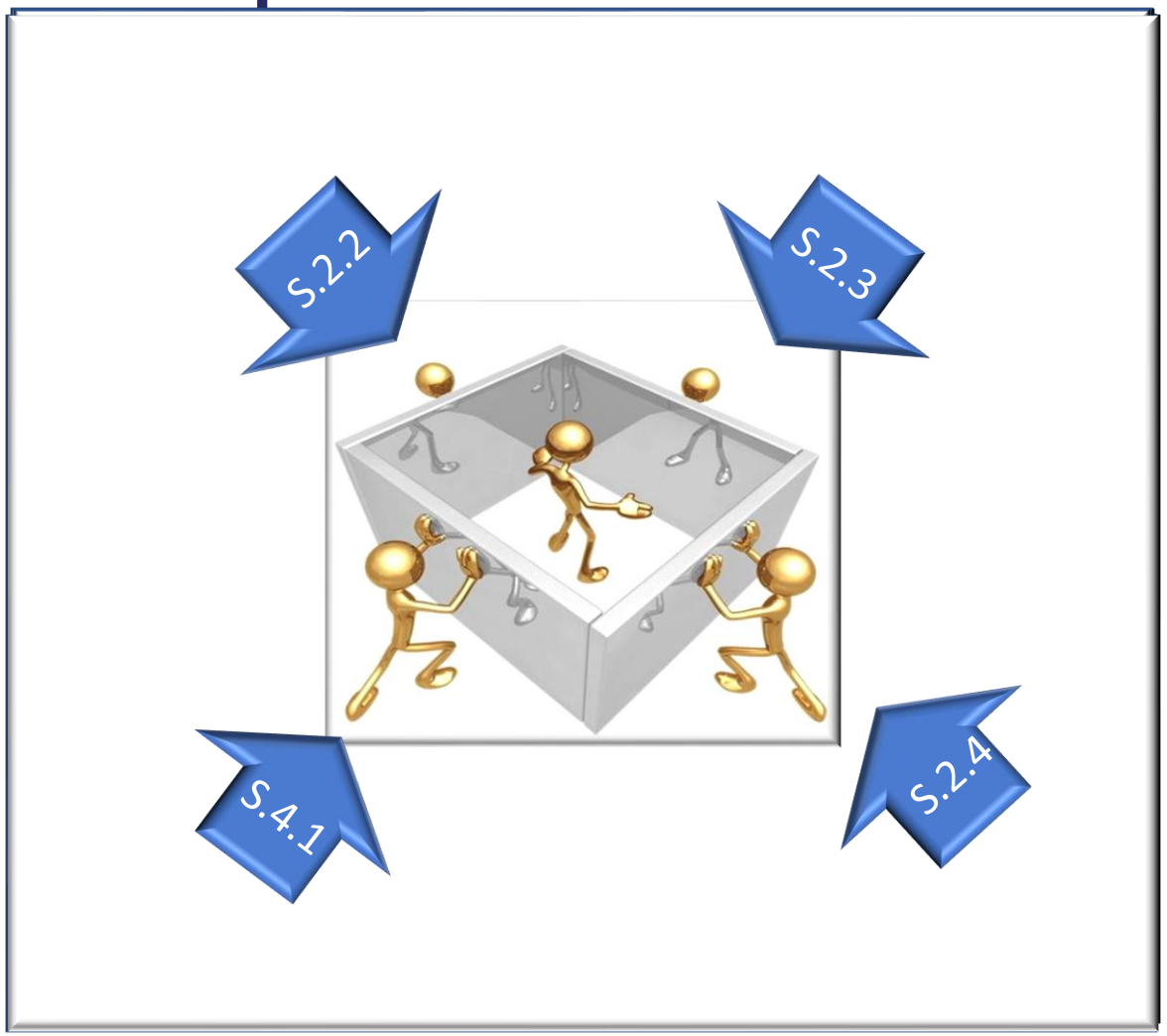
Core Document Acceptance Rate May Drop Significantly

- ICH Q8-Q11 are +10 years old; however, data shows growing divergence in control strategy requirements among established ICH Members.
- In addition, new ICH members/observers have unique and different control strategy requirements/expectations and the data from these countries are not included in the analysis.
- Newer ICH members can also be at different state of adoption, which creates additional divergence.
- Accelerated development and priority reviews often reveal additional and differing control strategy concerns
- New ICH guidance, Q12, may result in further divergence

Impact of Country Specific Requirements

Four key substance documents that constrain manufacturing flexibility S.2.2 + S.2.3 + S.2.4 + S.41	
S.2.2	3 versions
S.2.3	14 versions
S.2.4	3 versions
S.4.1	4 versions
Total	**24 versions**

Started with 4 documents and after global submissions now have 24 versions.



Country specific requirements constrain manufacturing, increase complexity and inhibit continuous improvement

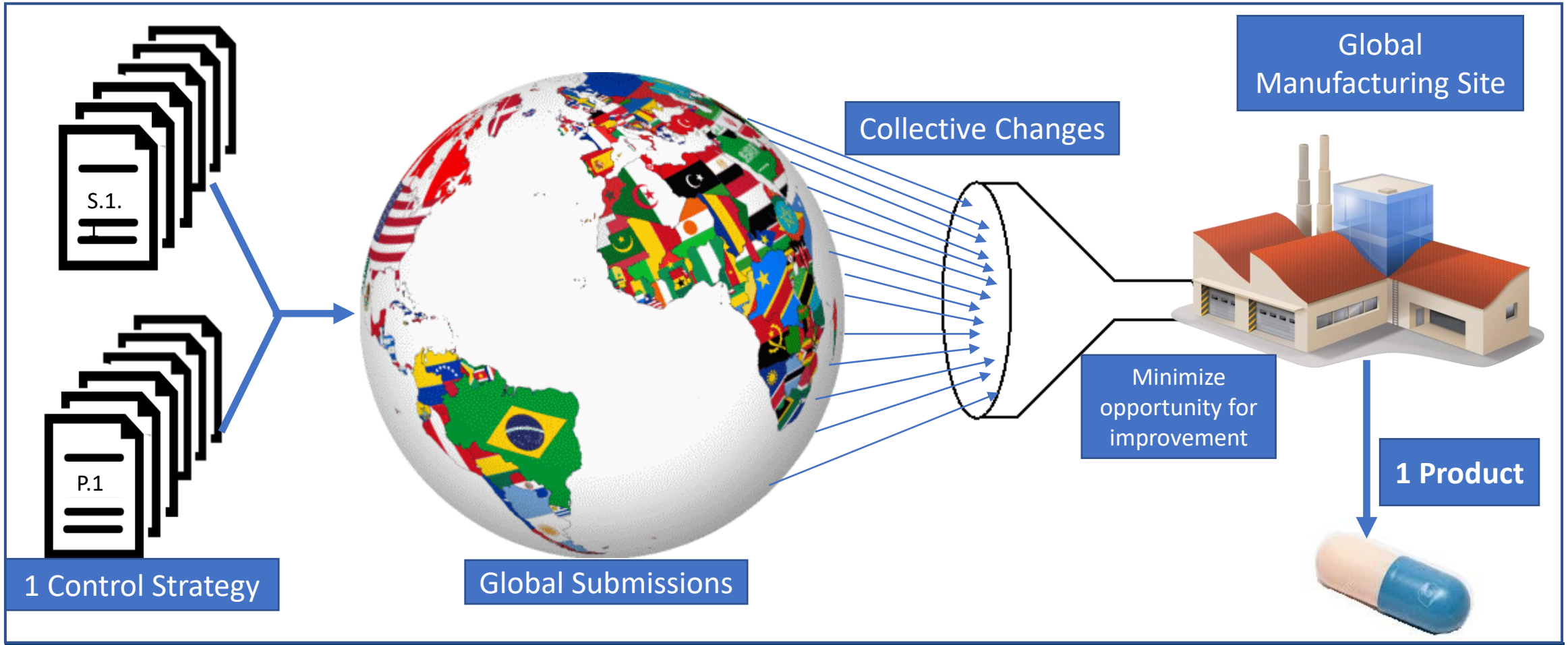
Is the Problem poor quality submissions?

- Is ~54% acceptance rate the result of industry asking for excessive flexibility in core?
- Consider the example below:
  - A roughly even distribution of synthetic submissions to US, EU, Japan and Canada.
  - US and Canada acceptance of 88% and 81% respectively.
  - Japan and EU acceptance rate was significantly lower at 50% and 42% respectively.
- What is the cause of differences and interpretation and implementation?

Conclusion: Industry and regulators need to work toward a common understanding of the appropriate submission content that is needed to support a control strategy.

Country	Submissions	S.2.2 Accepted
USA	17	88%
Japan	12	50%
EU	19	42%
Canada	16	81%
	64	66%

Any country can impact control strategy for the world



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

Harmonization and Impact to Innovation/ New technology

- What opportunities did the pandemic teach us? What can we learn to help innovation and new technology gain faster global acceptance?
- Industry can’t afford to advance new technology where there is risk for regions not accepting
- Case Studies- (for discussion)
  - Continuous Manufacturing
  - Co-crystals
  - Co-precipitates

Quality by Design and ICH Q12

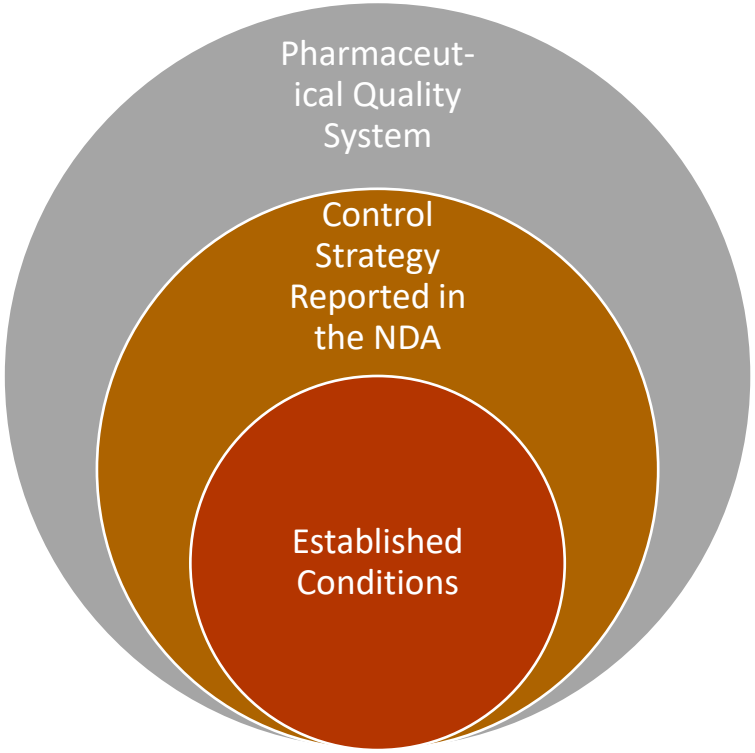
Quality by Design (QbD)	Science-driven, risk-based approach to expand product knowledge and process understanding Intended to serve as a foundation for and encourage continual improvement Increase assurance of quality for pharmaceutical products
The QbD approach	Prospectively characterizing quality risks 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

Identifying Established Conditions

PQS: All information related to manufacturing and testing of a product; includes facility, environmental controls, etc.

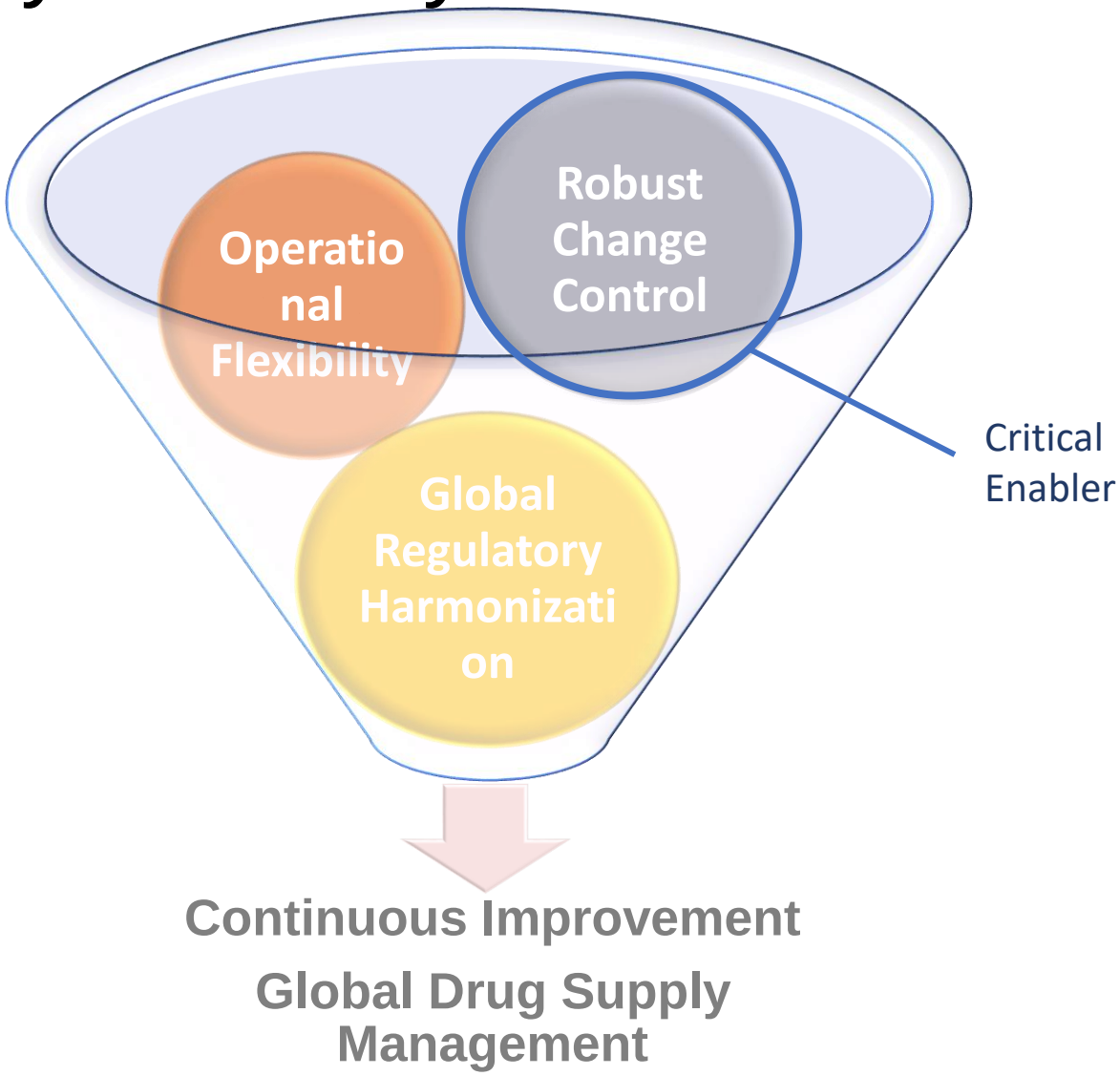
Control Strategy: reported in Module 3. Contains binding information on control strategy elements of product, process controls, etc. as well as supportive information.

Established Conditions: Legally binding information considered necessary to assure product quality. The Product Lifecycle Management Document (PLCM) serves as a central repository to provide transparency and facilitate strategic approaches to lifecycle management including regulatory assessment and inspection.



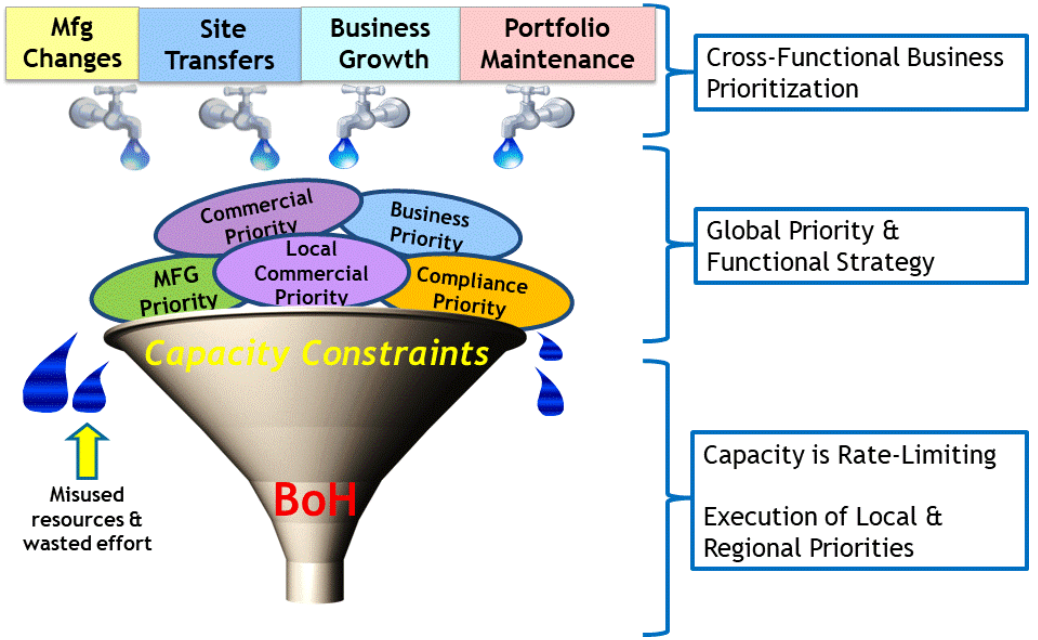
Operational and Regulatory Flexibility

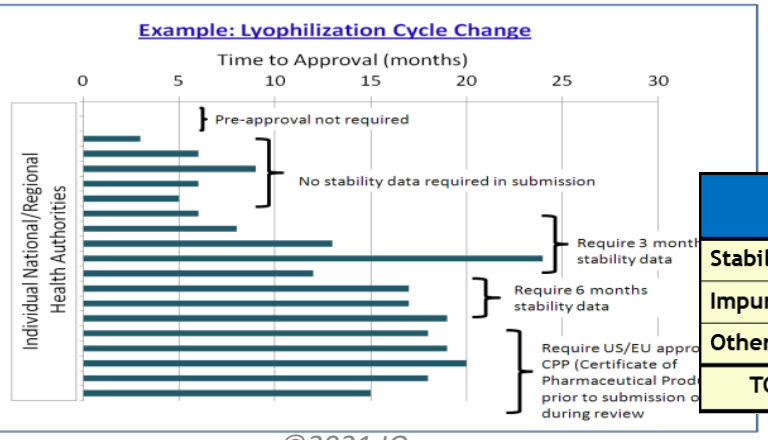
- Framework to facilitate the management of post-approval CMC changes
  - Increased product and process knowledge can contribute to reduced regulatory submissions
  - Enhanced ability to manage many CMC changes effectively under the PQS with less need for extensive regulatory oversight
- Operational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



COSTS FOR LACK OF ADHERENCE

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

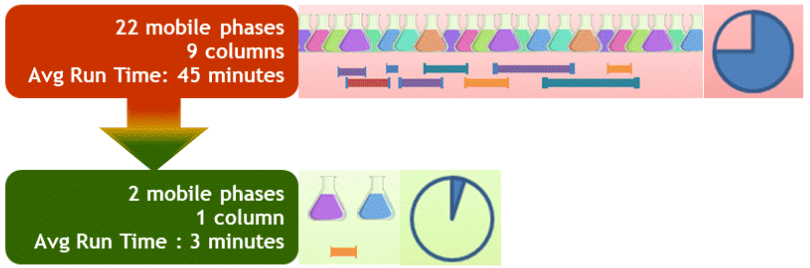




Post Approval Stability Commitments N=29	
Stability Issues	0/29
Costs/Commitment	$1.0M - $4.5M
Total Cost	~$81.2M

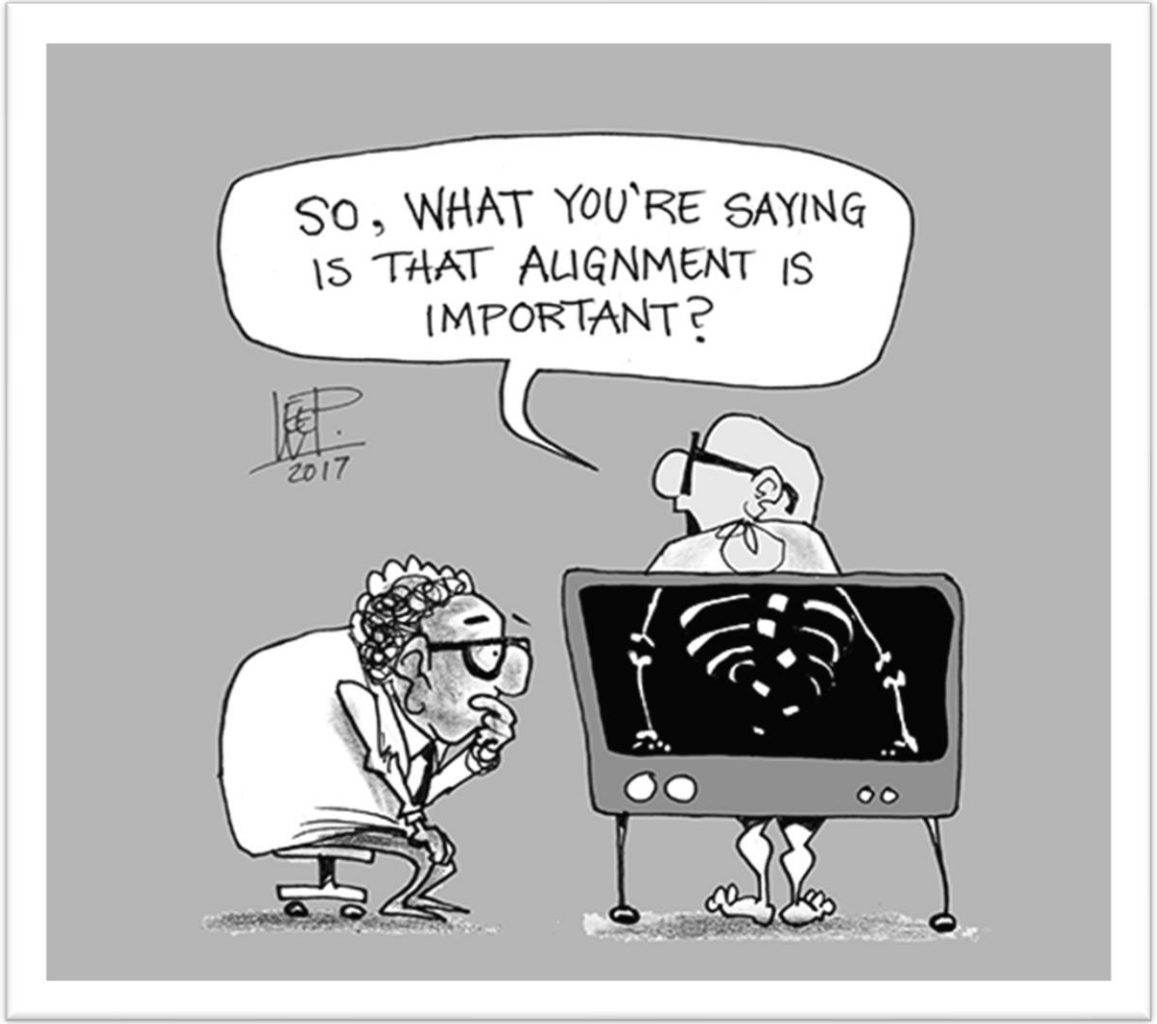
	Study Costs/ Product ($M)	Delayed Approval Costs/Product ($M)	Comments
Stability	0.25 - 1.50	2.0 - 5.0	Site specific & additional zones
Impurities	0.10 - 1.00	1.0 - 2.5	Mutagenic toxicology & reproductive testing
Other	0.05 - 1.25	0.5 - 1.5	Batch specific data & ancillary certifications
TOTAL	0.40 - 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!

OVERCOMING CHALLENGES TO CHANGE



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

Thank you!