Post Approval Changes & Product Lifecycle Management

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Emma Ramnarine
Sr. Director, Head Global Analytical Science & Technology
Genentech/Roche

Globalization vs. Nationalization

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Companies are globalized

Ideally: one product
for one world

Regulatory approvals are nationalized*

Reality: one product
with 100+ approvals

*Note: or regionalized (e.g. EU)

Change is Inevitable

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Managing change is a necessity post first approval of the product

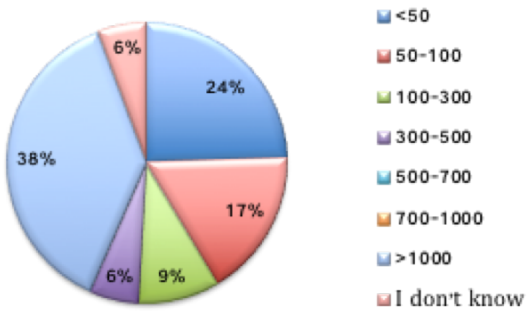
- Product & process knowledge grows
- New technologies emerge
- Industry practices change
- Regulatory requirements evolve
- Supply chain and suppliers change

Managing change is a regulatory expectation

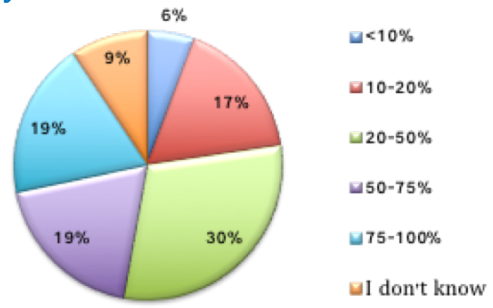
"Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of product and process knowledge" (EU GMPs, Part I, Chapter 1)

Post Approval Change Activities – 2017 PDA Survey

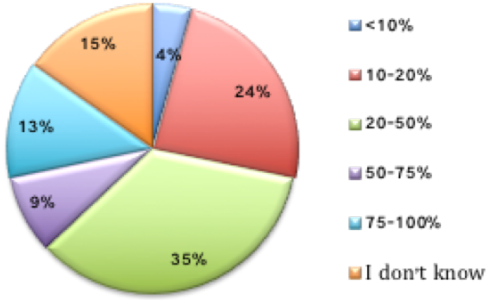
How many PACs, not including submissions, does your company typically process in a given year?



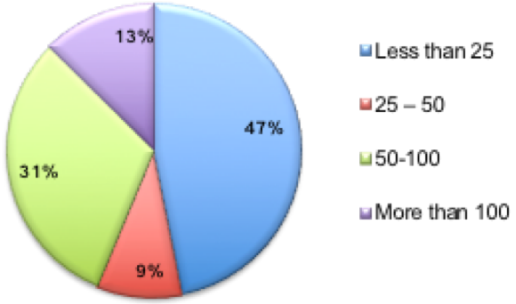
How many PACs require submission to a health authority?



Of those regulatory relevant changes, how many changes were considered moderate to major (i.e. Type 2, PAS, CBE-30)?

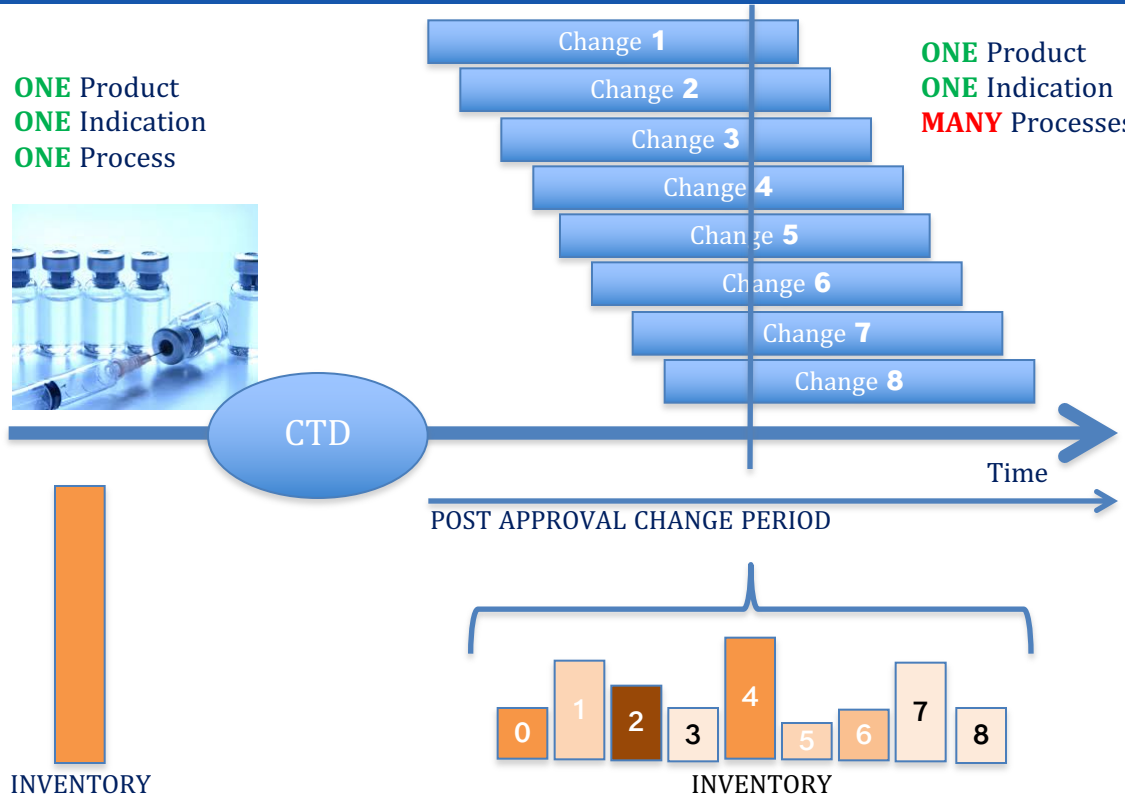


In how many different countries do you typically file changes?



Post Approval Change Complexity

ONE Product
ONE Indication
ONE Process



ONE Product
ONE Indication
MANY Processes

Consequence

Logistics challenge →

- less ability to act on change in demand for one version → shortage
- risk of errors made

The above is greatly simplified. In reality, changes are counted in the hundreds every year for a full product portfolio.

Post Approval Change Activities – 2017 PDA Survey

Why does your company make PACs?

Answer Options	Response Percent	Response Count
Process improvements	89%	40
Expansion/reduction of manufacturing capacity	76%	34
Manufacturing site changes	73%	33
Upgrade or replacement of obsolete equipment	71%	32
Tech transfer	69%	31
Specification/testing change	69%	31
Raw material replacement	64%	29
Regulatory commitment	60%	27
Introduction of innovative technologies	60%	27
Compliance to new regulations	53%	24
Product-related change (e.g., combination product, new formulation)	47%	21
Other (please specify)	4%	2

Others Specified:

- Analytical methods upgrades
- Change in QC reference standards

Post Approval Change Paradox – A "Wicked Problem"

The cGMPs require facilities and processes to be **current**	*yet*	Even simple PACs take **up to 5 years** for global approval to make facility/process current
Improvements are intended to **reduce risks**	*yet*	Long PAC approval timelines **delay risk reduction**
Improvements intended to **assure better availability** of drug products	*yet*	Long PAC approval timelines **hinder availability**
Changes in high tech industries usually happens in **months**	*yet*	In the pharma industry changes are measured in **years**

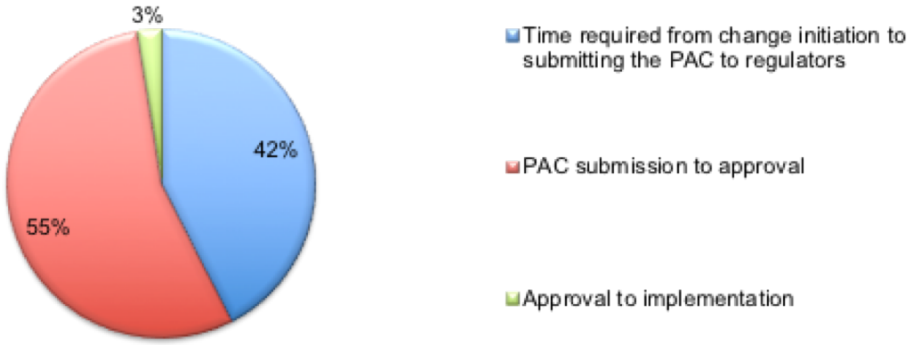
"Wicked Problem" Characteristics

- Difficult to clearly define
- Many interdependencies and often multi-causal
- Attempts to address the problem often leads to unforeseen consequences
- Often not stable
- Usually no clear solution
- Socially complex
- Rarely is the responsibility of one stakeholder only
- Solutions involve changing behaviors
- Some characterized by chronic policy failure

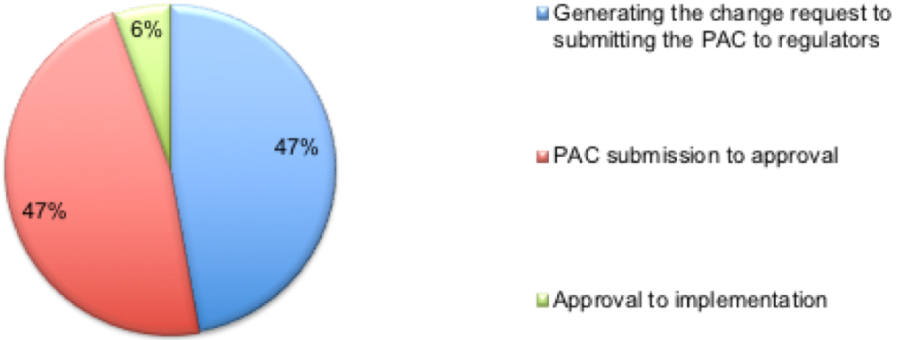
Source: Vinther, A., Drug Shortage is a "Wicked Problem ", PDA Letter May 2016

Post Approval Change Activities – 2017 PDA Survey

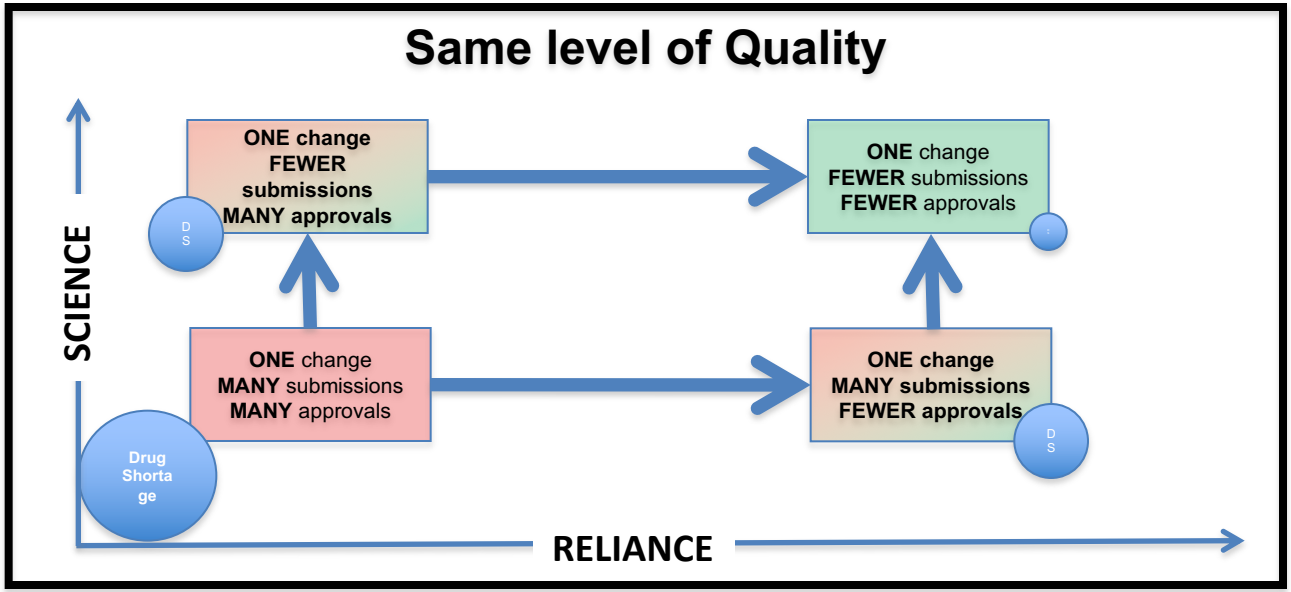
Which step is the most unpredictable for your Major changes?



Which step is the most unpredictable for your Moderate changes?

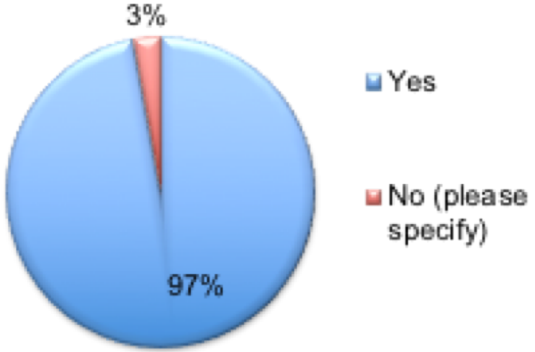


Industry and Regulators Working Together

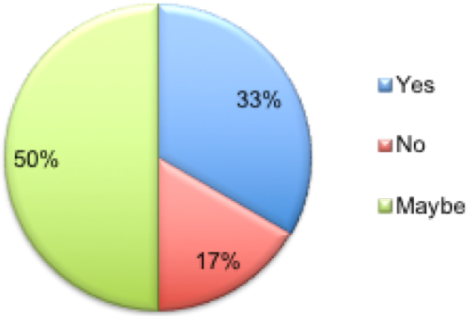


Post Approval Change Activities – 2017 PDA Survey

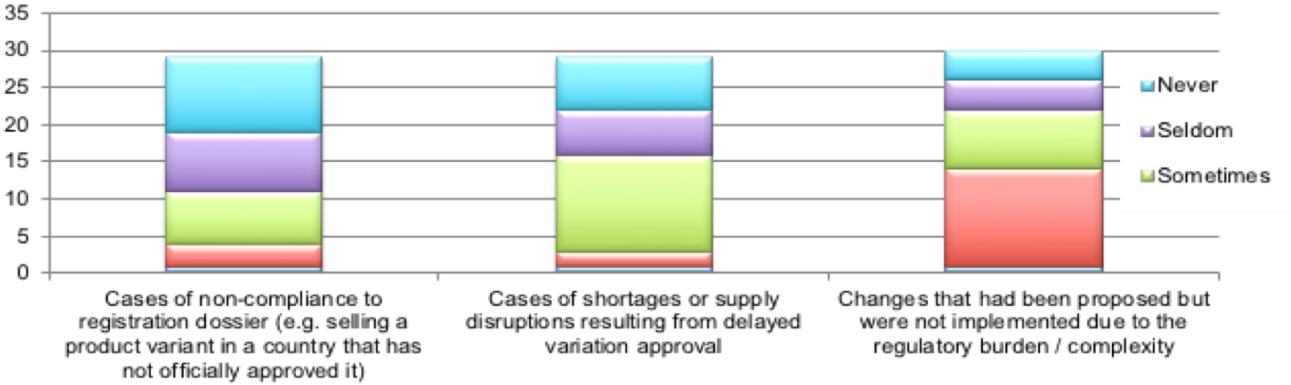
Do you think the current PAC process hinders technology progress?



Do you believe ICHQ12 can reduce the current regulatory burden related to PAC?



How frequently did you experience each of the following situations in the last 5 years:



Product Lifecycle

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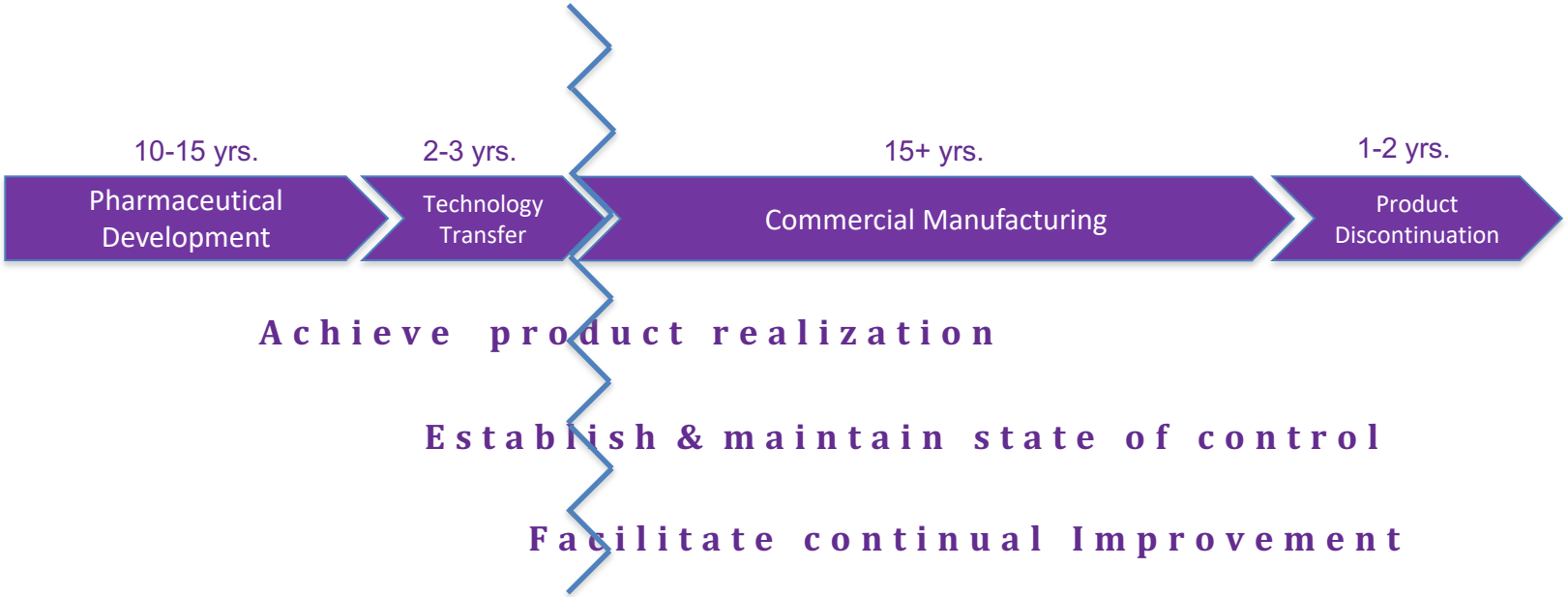
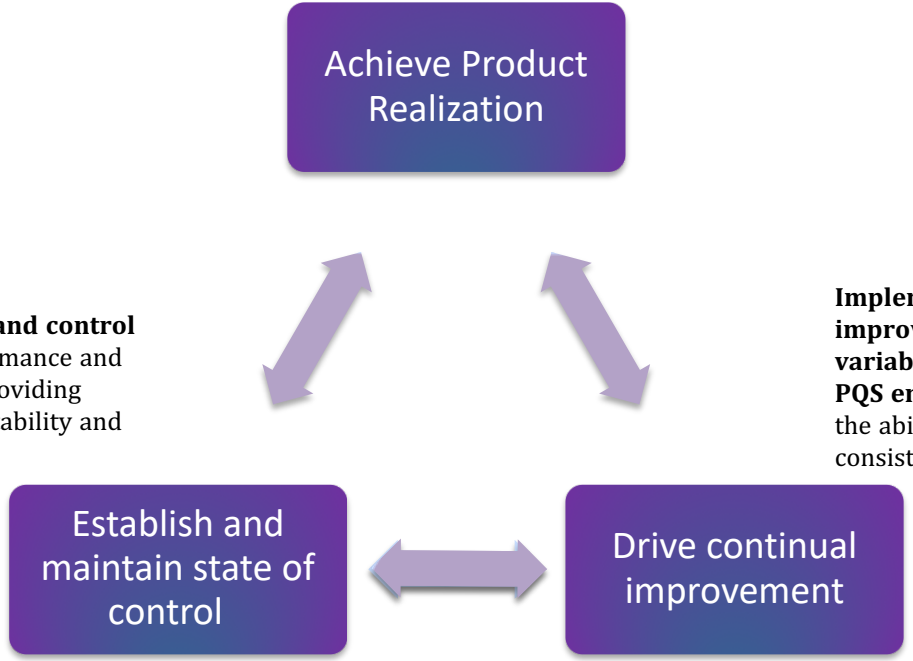
All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q8(R2))



ICH Q10 Objectives

Deliver products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers



Use **effective monitoring and control systems** for process performance and product quality, thereby providing assurance of continued suitability and capability of processes.

Implement appropriate product quality **improvements**, process improvements, **variability reduction**, **innovations** and **PQS enhancements**, thereby increasing the ability to fulfil quality needs consistently

The Life of a Product is Dynamic

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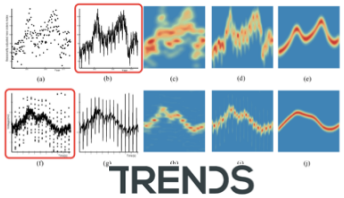
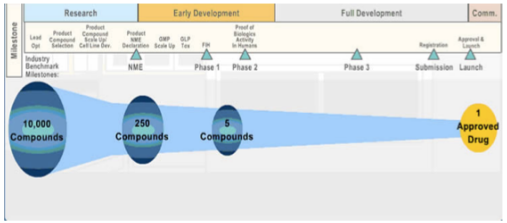
QTPP
CQAs
CPPs

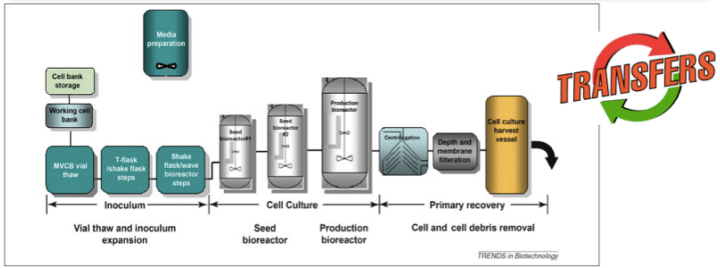


Evolution of Control Strategy

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation



Initial product & process knowledge - few batches



New product & process knowledge (changes in CQAs & CPPs) - many batches

Product Lifecycle Management is Essential…..

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Question is how much of it is reactive vs. proactive

- Are post approval changes/transfers planned?
- Feedback/feedforward
  - Is product and process monitoring in place?
  - Do the control strategy and CAPA system facilitate timely feedback/feedforward?
  - How are outcomes of Annual Product Review and Management Review managed?
- How is continual improvement and innovation achieved?

Managing Knowledge as Part of the Product Lifecycle

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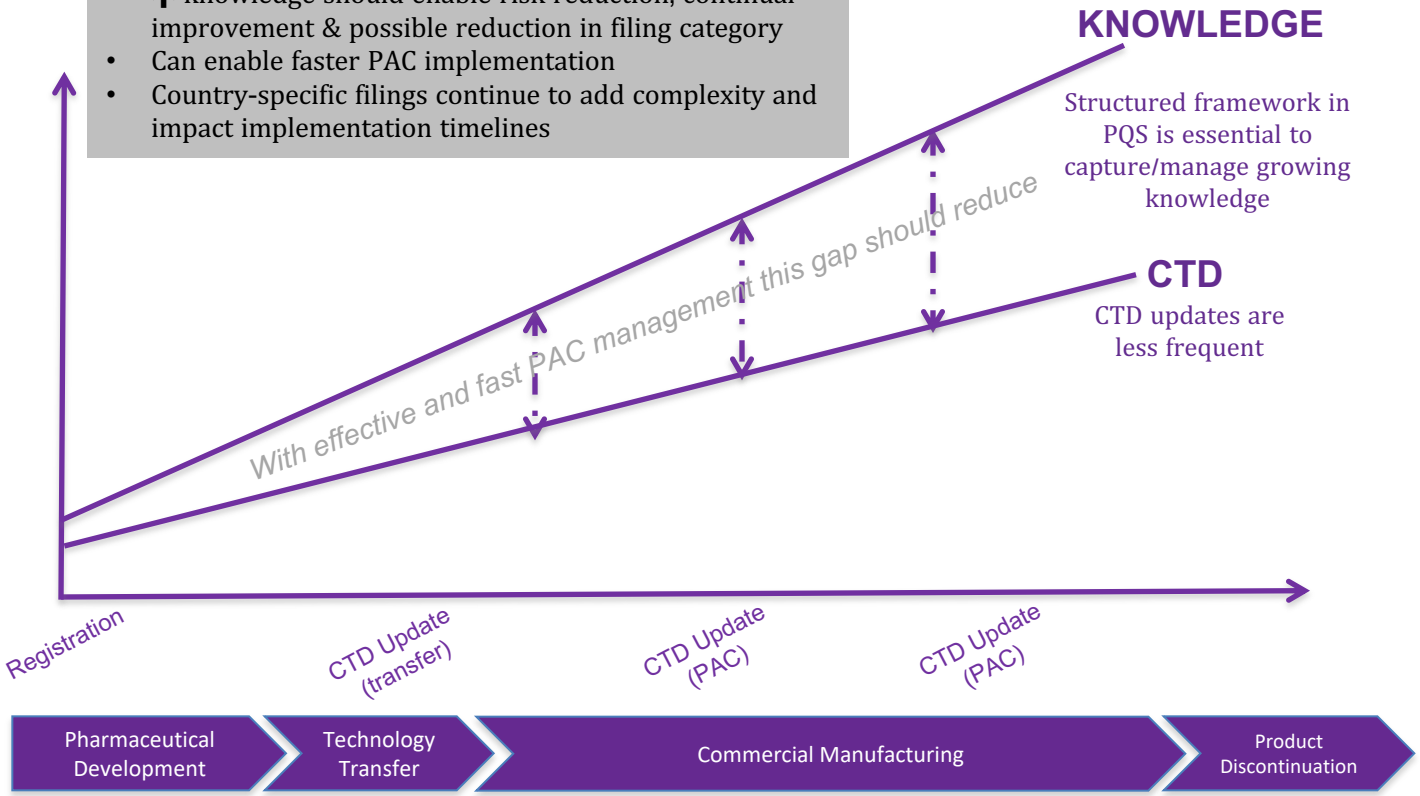
- ↑ knowledge should enable risk reduction, continual improvement & possible reduction in filing category
- Can enable faster PAC implementation
- Country-specific filings continue to add complexity and impact implementation timelines



Product Lifecycle Management Strategy

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A product's lifecycle management strategy describes how the overall product lifecycle will be managed within the company's PQS to ensure that the relevant quality requirements and processes are implemented and maintained according to any global or regional regulatory commitments and the company's PQS

Holistic

Proactive

Global

Solutions, Product Lifecycle Management Plan

Roche

Objectives of LCM

- Achieve product realization
- Establish and maintain a state of control
- Facilitate continual improvement

Elements of Lifecycle Management

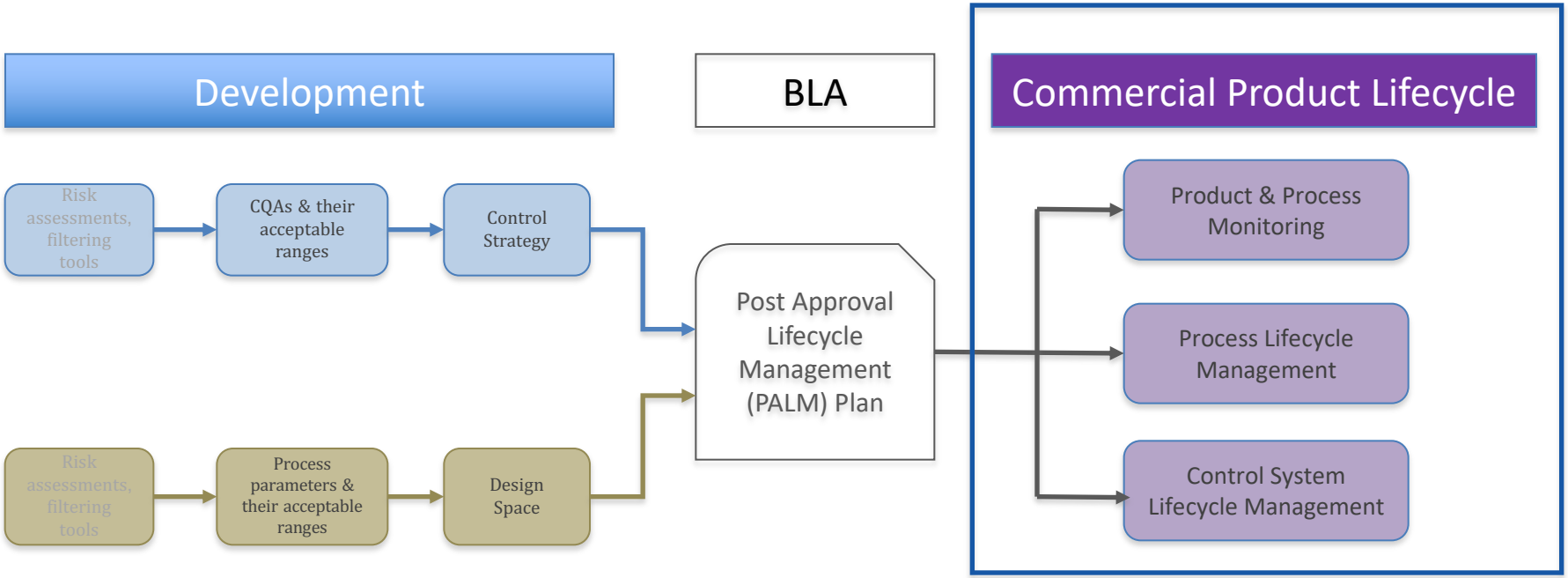
- Product Established Conditions (EC) incl. Control Strategy Summary
- Planned Post-Approval Changes
- Summary of how product lifecycle will be managed in the PQS
  - Managing Product & Process Knowledge During the Commercial Lifecycle
    - *Product & Process Monitoring*
    - *Annual Product Review (APR)*
    - *Post-marketing Surveillance and Pharmacovigilance*
  - Control System Management
  - Managing PACs in the PQS

Note: Additional elements to consider
Supply strategy
Drug shortage prevention plan

Source: PDA Points to Consider: Technical Product Lifecycle Management; *PDA J Pharm Sci and Tech*, 2017, 71 163-169
www.pda.org/pac

Post Approval Lifecycle Management Plan (Roche)

- The Post Approval Lifecycle Management (PALM) Plan links development and commercial phase of a product
- Been in place for the last several years (prior to ICH Q12 concepts)
- Roche's PALM Plan will evolve to further integrate ICH Q12 concepts



Elements of Roche's PALM Plan

The PALM Plan is a regulatory agreement between Roche and the Health Authorities that specifies how Roche will

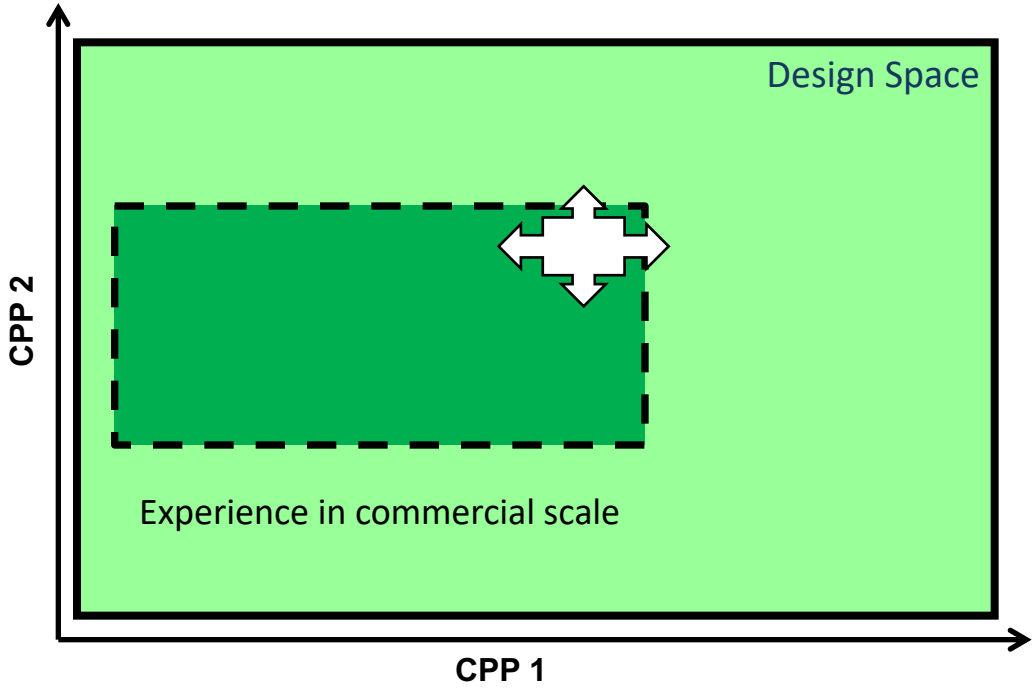
- **Monitor** the process and product quality attributes to ensure they remain within a controlled state post-approval
- **Manage changes** to process parameters within the design space
- **Update the control system** as necessary based on further process and product knowledge

Within the Quality System, elements of the PALM plan are described in the

- **Process Monitoring and Trending Protocol**
- **Manufacturing Process Specification** (MPS)

Where Design Space is Defined

- Acceptable region for CPPs and non-CPPs (multivariate ranges)
- Derived from small scale models; extends commercial scale experience
- Movement within Design Space does not require HA approval



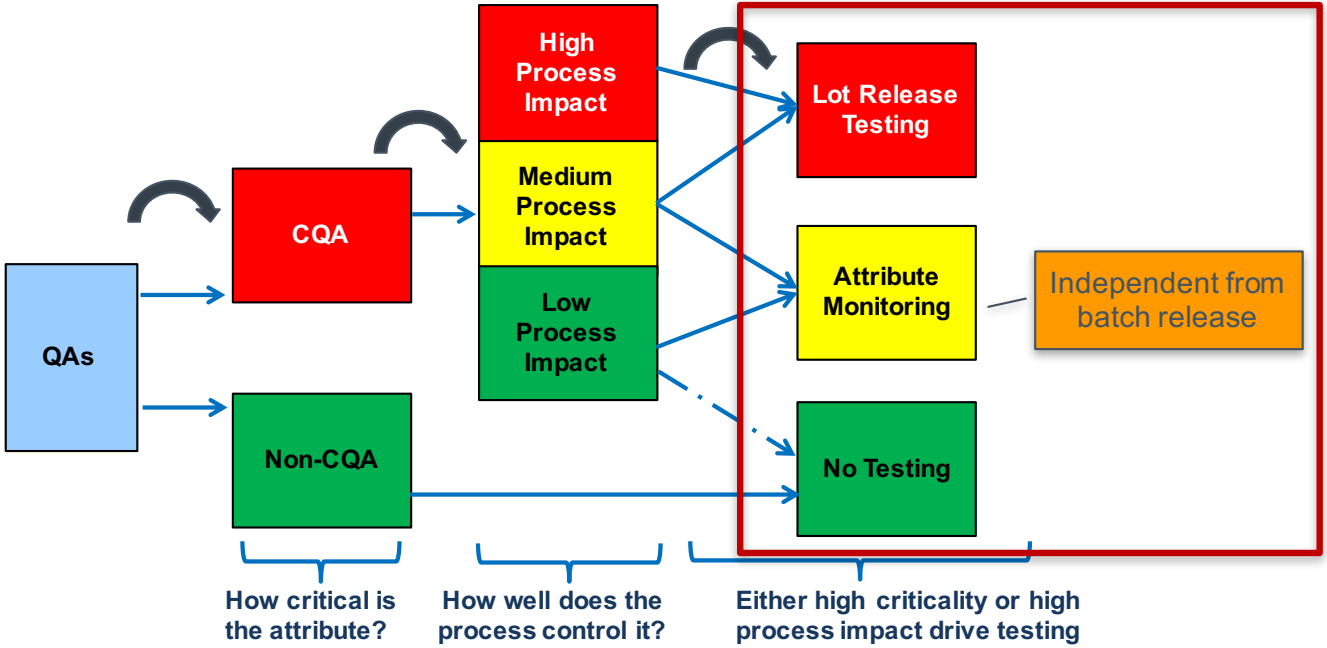
Where Design Space is Filed - Product X FDA Approval Letter

Roche

Upon review of the supporting data, the design space as proposed in BLA xxxx was found to be acceptable. The Agency would like to reiterate that in addition to the information described in the application, it is our expectation that plans for implementation of the design space for the commercial process are documented within the firm's Quality System. Such quality systems may include plans for handling movements within the design space (e.g., change control procedures, plans for updating batch records). In accordance with ICH Q8(R2), while the Agency does not expect any regulatory notification for movements within the design space, any other changes in the manufacturing, testing, packaging, or labeling or manufacturing facilities for Product X will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

The Control Strategy is a Risk Management Strategy

Fundamental QbD principles and risk assessments are used to ensure consistent design of robust manufacturing processes and Control Strategies



Example Summary of Testing Strategy in PALM Plan

Attribute	Drug Substance[a]					Drug Product[a]			
	Control System Testing			Monitoring	Considered for Stability in Comparability Exercises	Control System Testing		Monitoring	Considered for Stability in Comparability Exercises
	Batch Release	Release Relevant In-Process Control	Stability			Batch Release	Stability		
Product-Related Variants									
CQA 1	X		X			X	X		
CQA 2	X				X			C	X
CQA 3…	X								
Glycosylation Variants									
CQA n…	X								
CQA n+1…				C					
Process-Related Impurities									
CQA m	X								
CQA m+1				P					
CQA m+2…				C					
…						…			

[a] X = test is performed; C = continual monitoring; P = periodic monitoring.

Monitoring Frequencies:

Continual: each batch

Periodic: 1 out of 4 batches

Frequency can be adapted during product lifecyle as knowledge increases

CQA Changes Handled Restrictively

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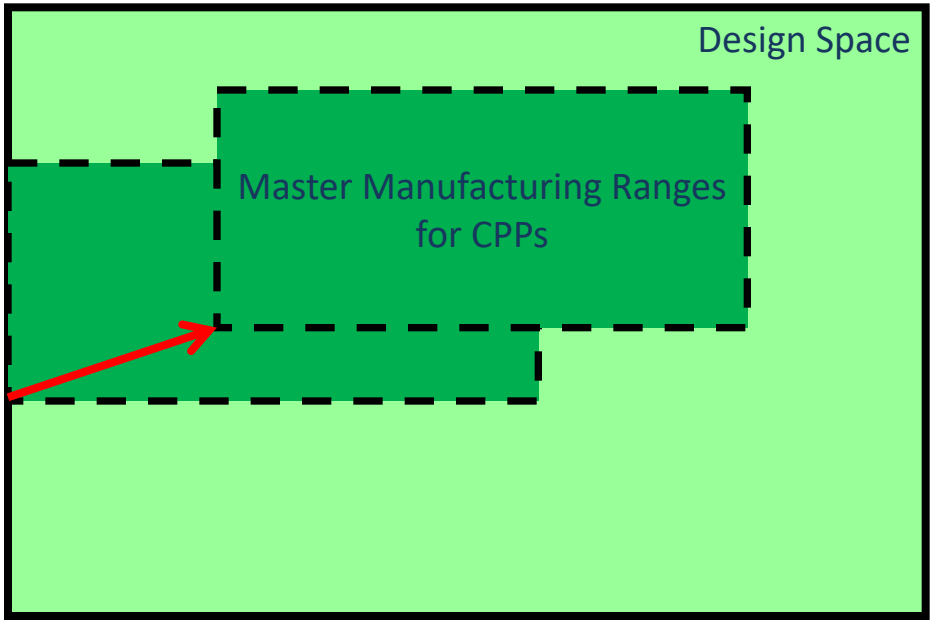
- New CQAs require HA approval
- Changes in Control System requires HA approval
- Changes in testing frequency for additional monitoring attributes do not require HA approval
  - After initial phase (i.e. 30 data points) downgrade from «continual» to «periodic» (i.e. 1 out of 4) or from periodic to «1 per batch» possible
- Always in internal change control

Where Design Space is Filed : Process Parameter Changes



- All changes to (non) CPPs are handled in the PQS
- Changes **to** Design Space must be notified to Health Authority
- No HA notification for changes **within** Design Space; these require assessments as described in PALM-plan
  - Level of post-implementation is dependent on level of risk and the potential to impact relevant CQAs
- Need to consult PALM plan (formally via MPS) as part of regular change procedure

Product X PALM Plan - CQA Change Control

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Table 4 Lifecycle Management of Quality Attributes

Type of Change	Approach	CQA and Non-CQA
Change in control system testing strategy	Manage in quality system	Yes
	Health Authority approval required	Yes (US: CBE-30 or PAS)
Change in testing frequency of additional monitoring attribute after initial data set is complete	Manage in quality system	Yes
	Health Authority approval required	No[a]
Change in criticality designation (new CQAs and upgrades of non-CQAs to CQAs)	Manage in quality system	Yes
	Health Authority approval required	Yes (US: CBE-30)
Downgrades from CQAs to non-CQAs	Manage in quality system	Yes
	Health Authority approval required	No[a] (US: reported in AR)

AR = US Annual Report; CBE-30 = change being effected in 30 days; CQA = Critical Quality Attribute; PAS = prior-approval supplement.

[a] Can be verified during inspection.

Product X PALM Plan - Process Parameter Change Control

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Table 5 Lifecycle Management of Process Parameters of the Design Space

Type of Change	Approach	CPPs and non-CPPs
Change to a process parameter target or target range within design space	Manage in quality system	Yes
	Health Authority approval required	No[a]
Change to a process parameter target or target range outside of design space	Manage in quality system	Yes
	Health Authority approval required	Yes (US: CBE-30 or PAS)
Reclassification of process parameters that lead to a change of the design space or the control strategy / Identification of a new CPP previously not part of the design space	Manage in quality system	Yes
	Health Authority approval required	Yes (US: CBE-30 or PAS)
Reclassification of process parameters that do not lead to a change of the design space or the control strategy	Manage in quality system	Yes
	Health Authority approval required	No[a] (US: reported in AR)

AR = US Annual Report; CBE-30 = change being effected in 30 days; CPP = Critical Process Parameter; PAS = prior-approval supplement.

[a] Can be verified during inspection.

Change management includes assessment against ranges in risk assessments, PC/PV or development studies; impact on quality and regulatory relevance is assessed

All changes to (non) CPPs are handled in the PQS

Solutions, Effective PQS for Post Approval Changes

Annex 1

"Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles"

"Opportunity to optimize science- and risk-based post approval change processes to maximize benefits from innovation and continual improvement"

ICH Q10

June 2008

The Right Quality Culture

Change Management

- Fully integrated Q9 principles, clear risk based PAC plans
- Alignment of risk assessments between company and regulators

CAPA

- Integrate knowledge from deviations, trends and complaint/recall incidents in risk based PAC plans
- Monitor PAC effectiveness

Internal Audit

- Assess effectiveness of risk based decision making for PAC management

Process Performance & Product Quality Monitoring

- Early and proactive detection of control drifts, variability, trends, adverse events/complaints
- Drive continuous improvement

Outsourcing

- PQS effectiveness should be assessed for each CMO/Supplier
- Clear agreement between CMO/Supplier and MAH for PAC notification and management

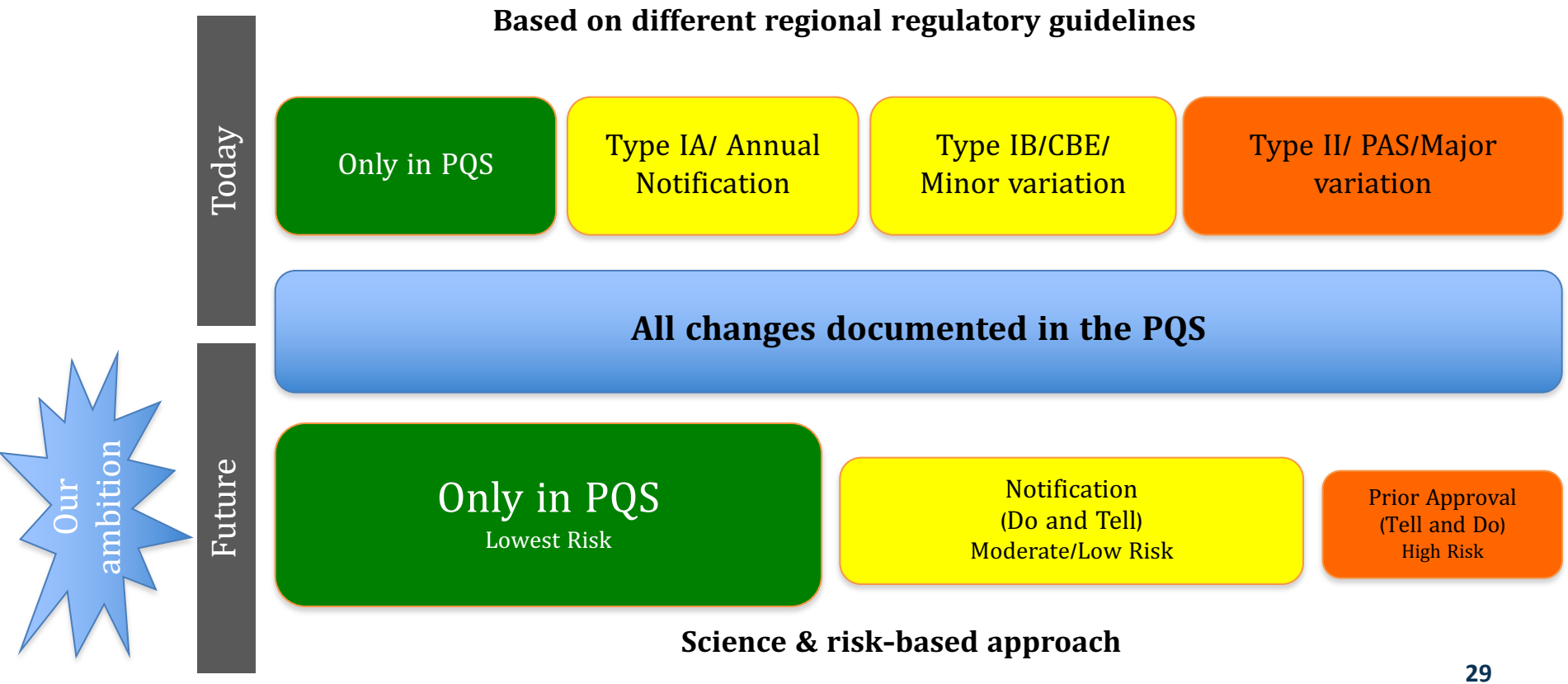
Management Review

- Risk based decision making on product, process and quality system performance metrics

Integrated Quality Risk Management & Knowledge Management

PtC PQS, www.pda.org/pac

Solutions, Moving to Science and Risk-Based PAC Management



Solutions, Regulatory Complexity

> 99 %*

So in reality risk-based PAC management doesn't exist

- Consistent regulatory reporting levels and reporting requirements
- Agreed to (shorter) timelines for PAC approvals
- Less percentage of prior approval PACs by accepting science and risk-based company assessments (ICH Q9 principles)
- Regulatory convergence

….& ultimately simple global regulations & faster PAC approvals

* Success rate for prior approval PACs in survey

Summary

Roche

Product/ process knowledge evolves; **post approval changes are inevitable**.

A **LCM strategy** can enable the MAH to manage a product **holistically, prospectively, and globally** to accomplish Q10 objectives

The LCM strategy can serve as an excellent communication mechanism to **proactively engage HAs, build trust**.

Expedite review and implementation of planned PACs through a knowledge- and risk-based foundation

An **effective PQS** is essential for establishing and executing the LCM strategy

Connecting People, Science & Regulation ®

- ✓ Call For Action PDA Letter January 2016
- ✓ Points to Consider
  - ✓ Lifecycle Management
  - ✓ Effective PQS for Management of PACs (& article)
  - – QRM and Knowledge Management for PACs
- ✓ Industry Survey
- Technical Report: Post Approval Change Implementation for Biologics and Pharmaceutical Drugs
- Global Post Approval Change Management Protocol Library of Examples
- Workshops, Trainings, Tools & Templates

Find much more on www.pda.org/PAC

It’s time to shift the dialog

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Acknowledgements

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- PDA PAC iAMSM Task Force

Contact

eramnar@gene.com
@emma_ramnarine

Doing now what patients need next