

Q1 Productions

Lifecycle Management: Updates and Insight on Post-Approval Changes and PAC iAM Activities

July 25th, 2017

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Globalization vs. Nationalization

Companies are globalized



Ideally: one product
for one world

Regulatory approvals are nationalized*



Reality: one product
with 100+ approvals

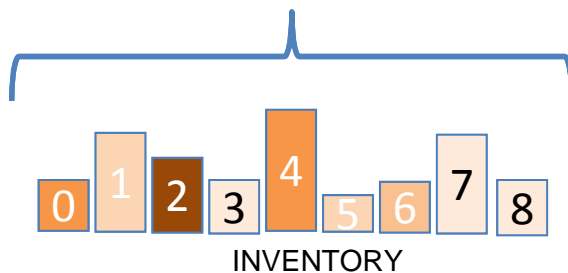
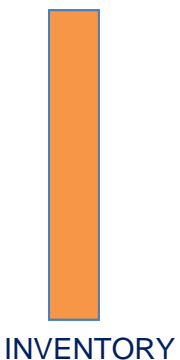
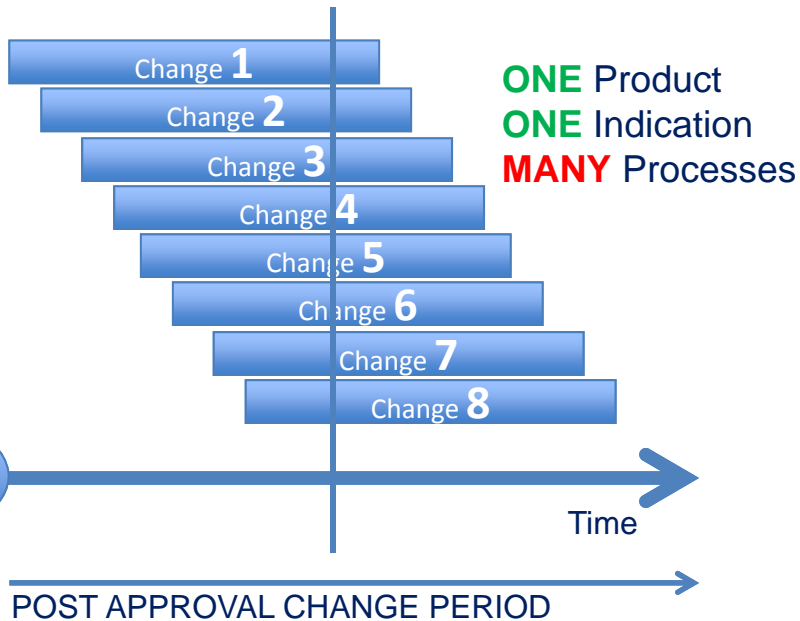
*Note: or regionalized (e.g. EU)

Post Approval Change, explained

ONE Product
ONE Indication
ONE Process



CTD



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 actuality, changes are counted in the thousands every year for a full product portfolio.

About PDA

- Global organization with >10,000 individual members
- Connecting People, Science and Regulation
- Committed to developing scientifically sound, practical technical information and expertise to advance pharmaceutical and biopharmaceutical manufacturing science and regulation so members can better serve patients.
- www.pda.org

PDA PAC iAMsm Deliverables

- ✓ Call For Action PDA Letter January 2016
- ✓ Points to Consider
 - ✓ Lifecycle Management
 - ✓ Effective PQS for Management of PACs
 - 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
 - Science and Risk Based Approaches to Technical Change Management – Sept 13-14, 2017 – Washington, DC
- Website for PAC iAMsm pda.org/PAC

Mission: Identify, assess and address current barriers to implementation of PACs that are intended to ensure continued operations, drive innovation and continual improvement

The Post Approval Change Paradox



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

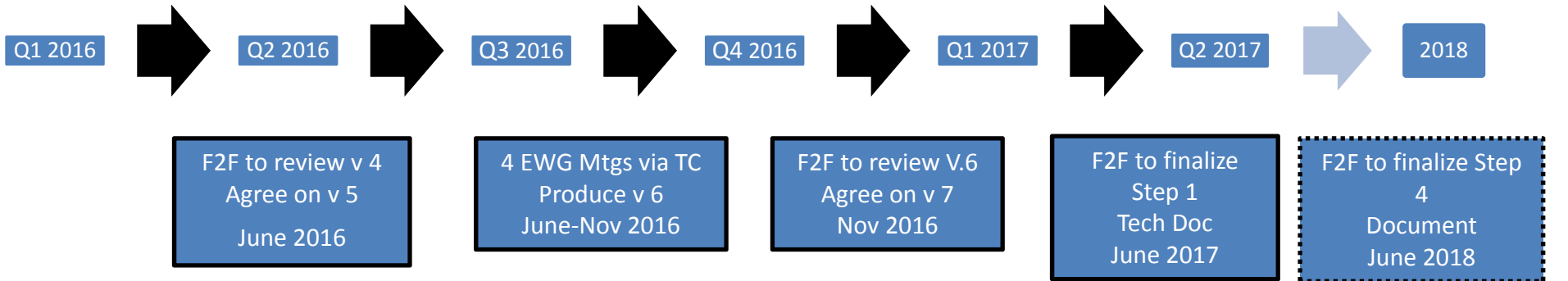
What are the Intentions of Q12?

- Reduce unnecessary cost and time burdens on industry and regulators, while assuring that patients reliably have access to high quality therapies
 - Realize benefit from application of current and innovative manufacturing technologies on a timely basis
- Enable and encourage increased transparency
 - between industry and regulators
 - between MAH and (contract) manufacturers
 - between reviewers and inspectors

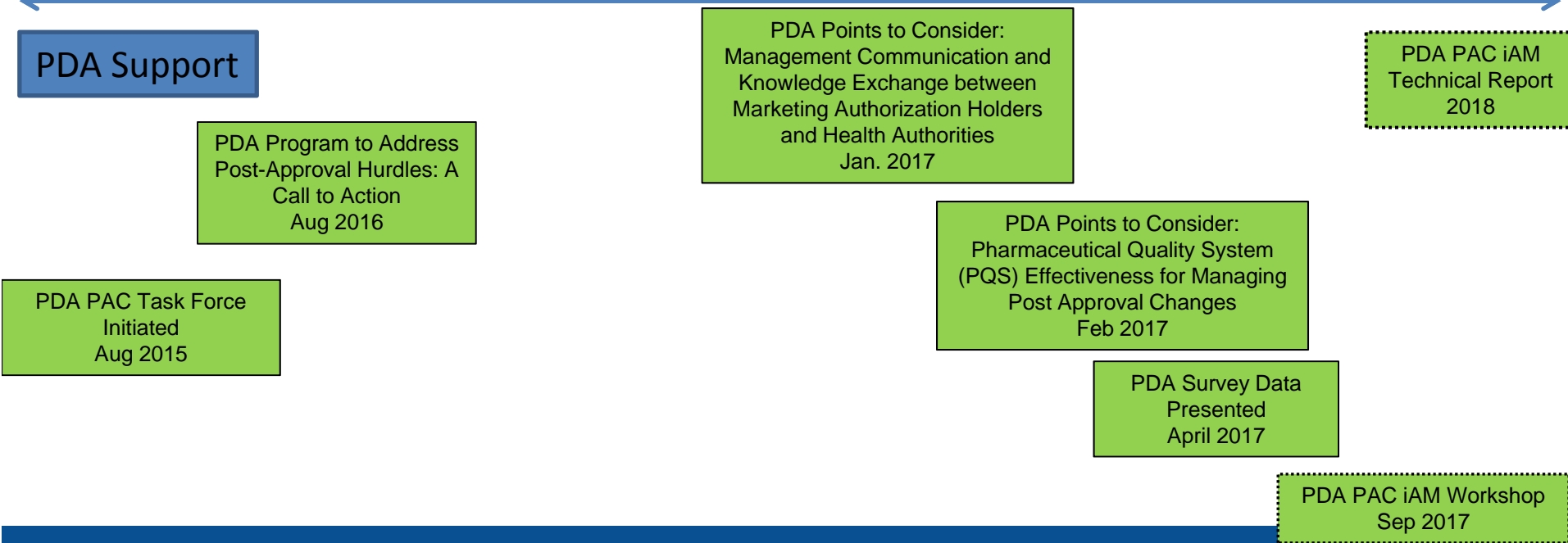
ICH Q12 Timeline



ICH Activities



PDA Support



Product Specific Lifecycle Management Strategy (PSLCM)



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

Focus & Contribution from PDA

- Expand LCM discussion from managing PACs to a much broader conversation about LCM elements and the importance of Knowledge Management

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

PDA Points to Consider: Technical Product Lifecycle Management

Communication and Knowledge Exchange between Marketing Authorization Holders and Health Authorities



- A product's lifecycle management strategy describes how the overall product lifecycle will be managed in the company's PQS. It provides a foundation for risk-based quality and regulatory decisions.
 - These objectives have been put forward and are supported by ICH Guidelines Q8(R2), Q9, Q10, and Q11 (4,5,6).
- Documenting the lifecycle management strategy can provide visibility to health authorities to improve planning and may be leveraged to hold proactive discussion to potentially reduce reporting categories
- **The Points to Consider paper provides the elements of a Lifecycle Management Strategy – and the potential benefits**
 - Established Conditions (including control strategy summary)
 - Planned Post Approval Changes
 - Summary of how Product Lifecycle is Managed in the PQS
 - Quality Culture
- By sharing the lifecycle management, including significant changes planned and their interdependencies, the MAH builds a mutual understanding with health authorities

Established Conditions, explained

- Legally binding information (or approved matters) considered necessary to assure product quality
- Contained in a regulatory submission, submitted by the applicant, and approved, as necessary, by the regulatory authority.
- May be specifically proposed in a submission or they may be implicit based on existing regulation and guidance.
- Any change to Established Conditions necessitates a submission to the regulatory authority

Focus & Contribution from PDA

- Dialog on convergence of health authorities on “global” set of Established Conditions (via ICH and WHO) per product
- Increased product/process understanding and risk management to help shift Established Conditions changes from “tell & do” to “do & tell”

Reporting Categorization of Changes

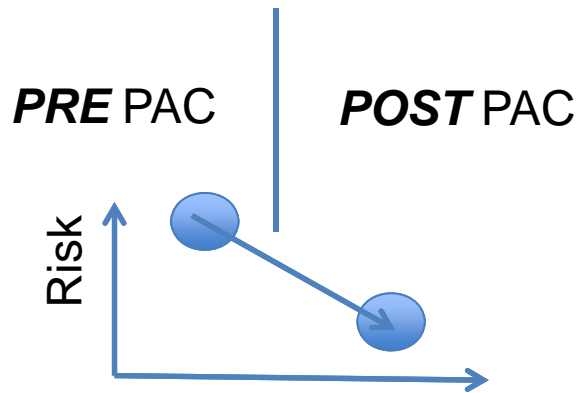
- **Prior-approval:** Changes with sufficient risk; require regulatory authority review and approval.
- **Notification:** Moderate to low risk changes may not require prior approval; generally require less information to support the change. Communicated to regulatory authority formally within a defined time period after implementation.
- The lowest risk changes are only managed and documented within the PQS and not reported; may be assessed on inspection.

Focus & Contribution from PDA

- How to apply QRM for effective change categorization
- Focus risk scope as: impact to product quality, efficacy, and/or patient safety
- Global alignment on PAC categorization
- Allow more changes in the PQS based on risk level; reduce number of prior approval changes
- Changing the mindset to allow faster implementation when PACs result in lower risk

Changes to Established Conditions can be 'Tell and Do' or 'Do & Tell'

If.....

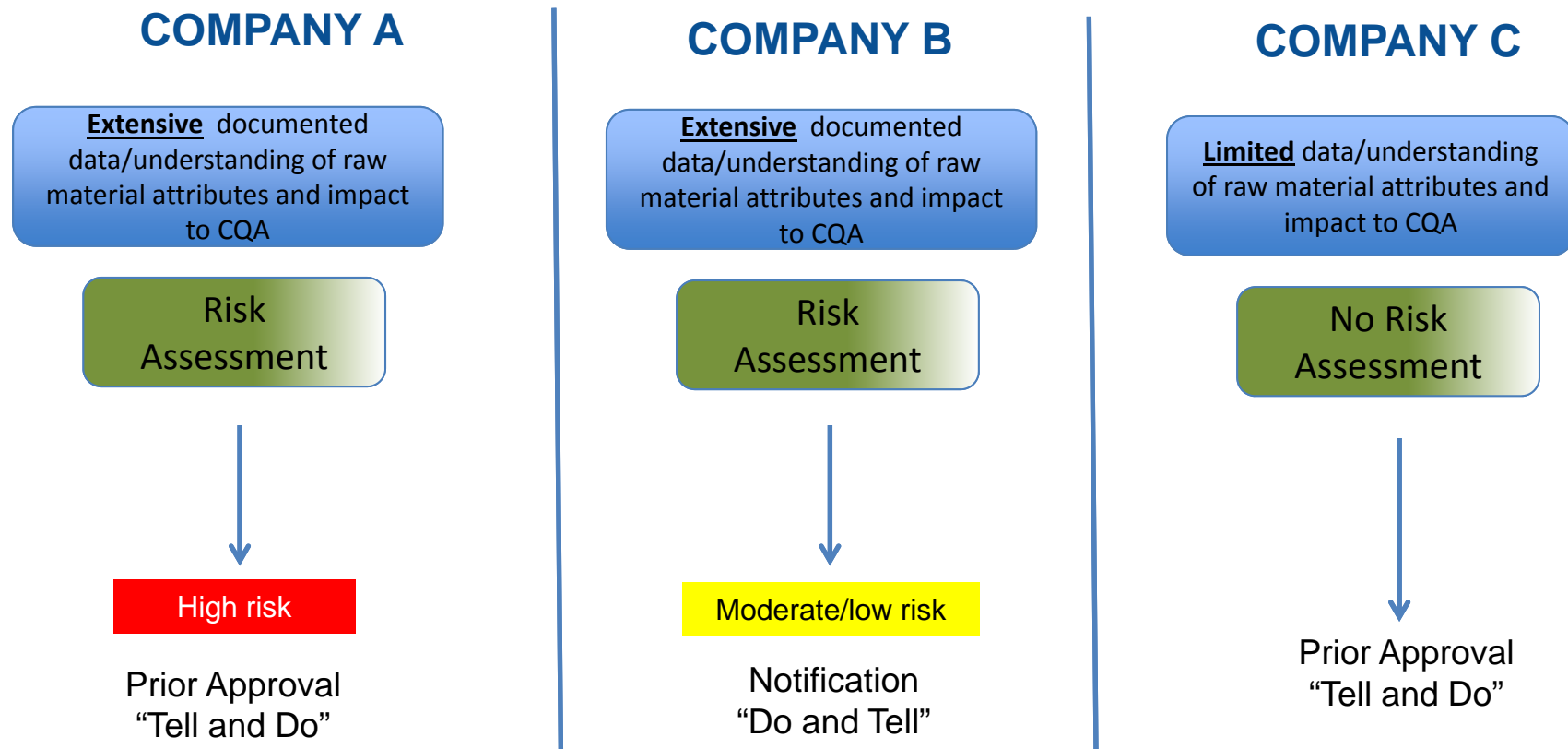


Then.....

Implement change as 'Do & Tell' even for Established Conditions

The company must have an effective PQS (including risk and knowledge management) for managing PACs

Change in a starting raw material (can impact a CQA)



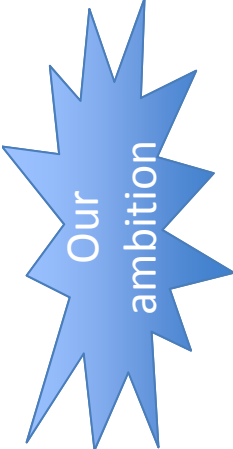
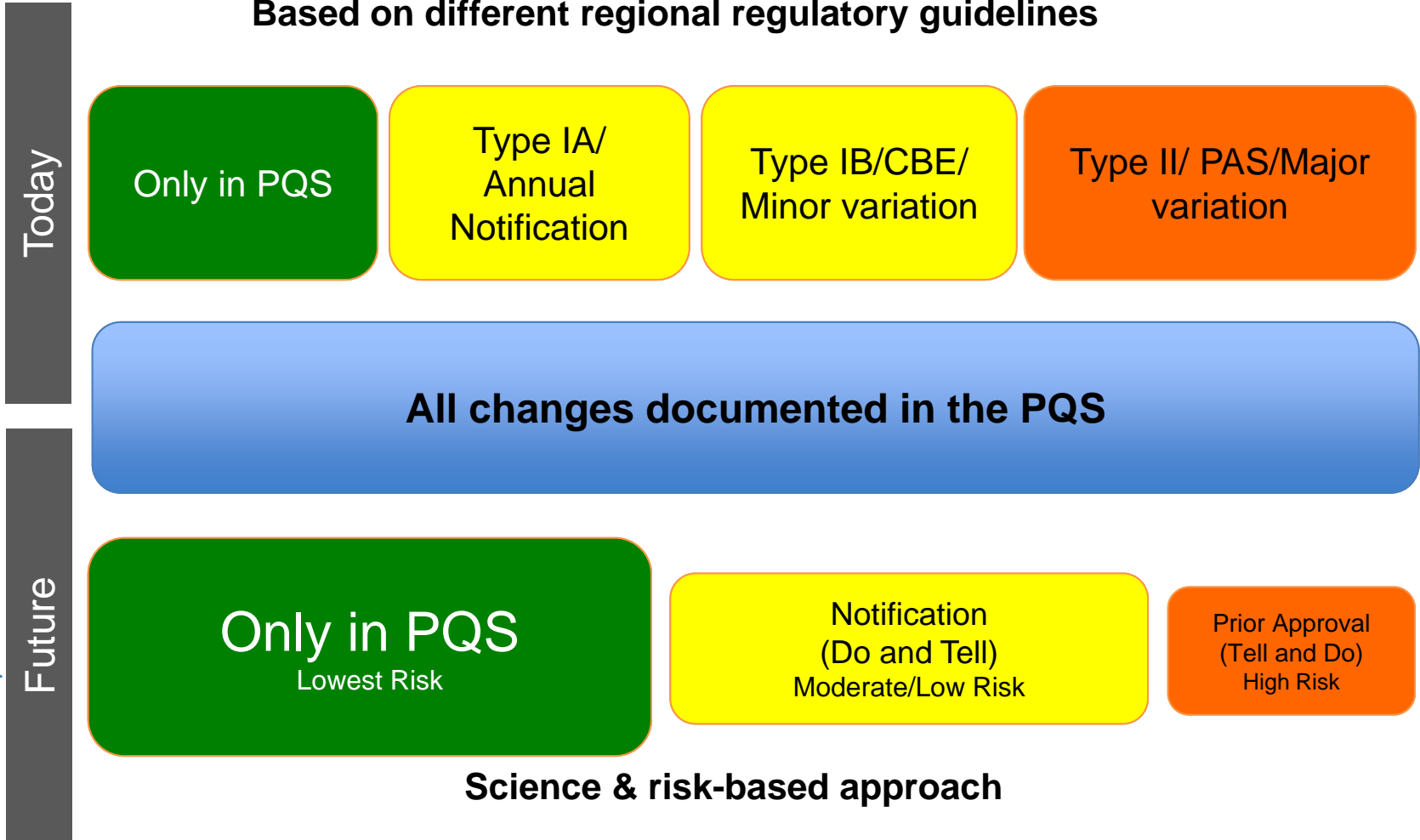
The same PAC will have different regulatory flexibility depending on knowledge and risk as well as whether or not the Company has an effective PQS for managing PACs

- Implementation of an effective PQS is essential for a company to achieve product realization, establish and maintain a state of control, and facilitate continual improvement
- When changes are made during the commercial life of a product, an effective PQS, product and process understanding, and use of quality risk management should ensure that product quality, patient safety, and adequate supply to patients are maintained
 - This, according to ICH Q10 – Annex 1, should provide companies the opportunity to manage post-approval changes (PAC) with reduced regulatory oversight
- **The Points to Consider paper is a step-by-step guide for implementing an effective PQS for managing PACs** – and is a direct continuation of ICH Q10
- Objective is to advise companies and regulators to take advantage of ICH Q10, Annex 1
- Focuses on
 - Management Responsibilities
 - PQS Elements: Process Performance and Product Quality Monitoring System, CAPA System, Change Management System, Management review of process and product quality
 - Enablers: QRM & Knowledge Management
 - Quality Culture

Moving to Science & Risk-Based PAC Management



Based on different regional regulatory guidelines

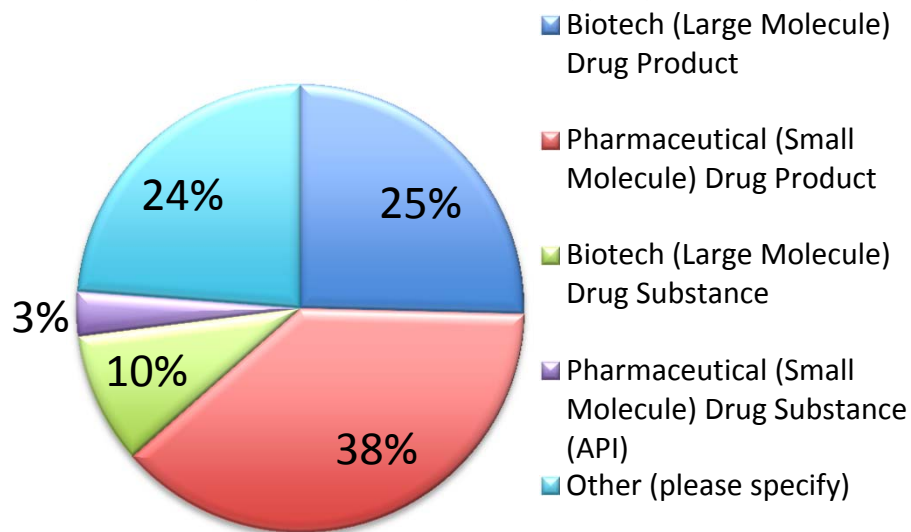


PDA PAC iAM Survey Results

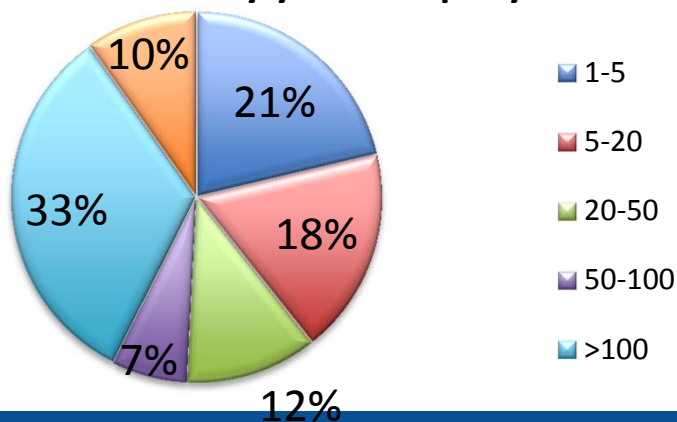
Survey Demographics



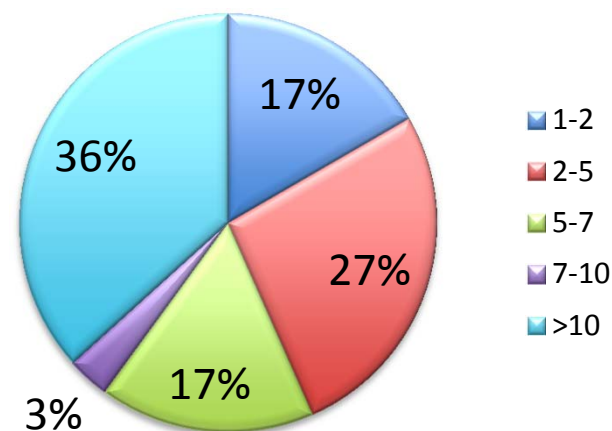
3. Please select the primary product type you are responsible for:



4. How many different products approved by global regulators are distributed by your company?



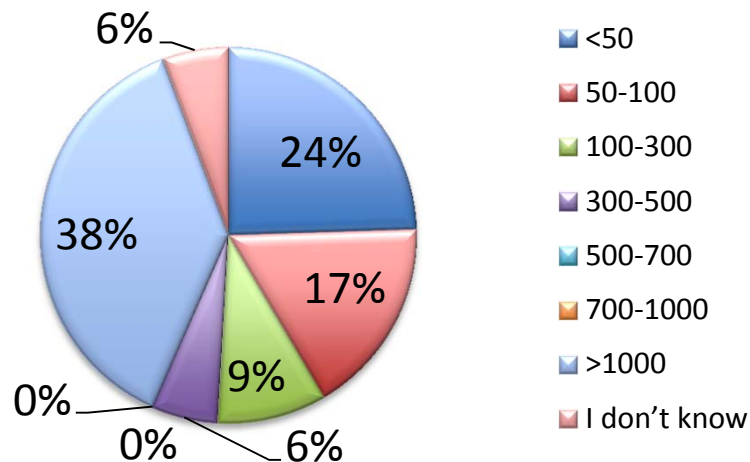
26. How many different item versions/product variants for a typical drug product or drug substance (API) do you handle in a given year?



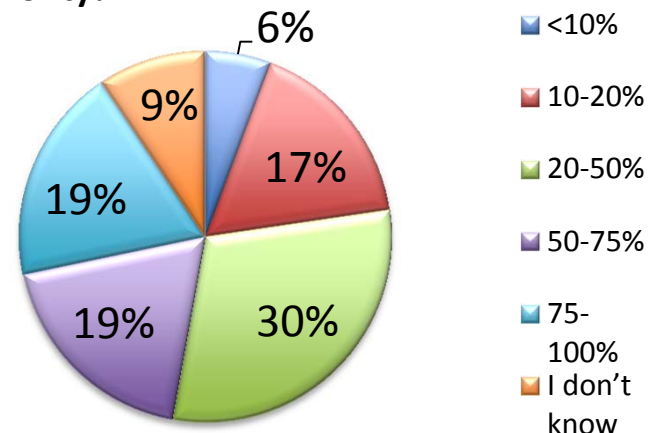
Postapproval Change Activities



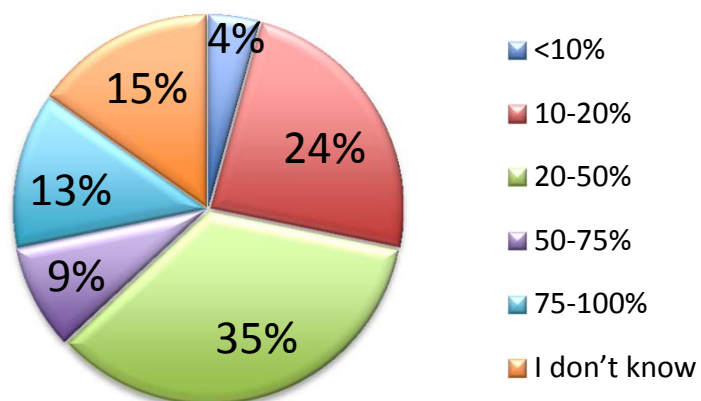
5. How many post-approval changes (PAC), not including submissions, does your company typically process in a given year?



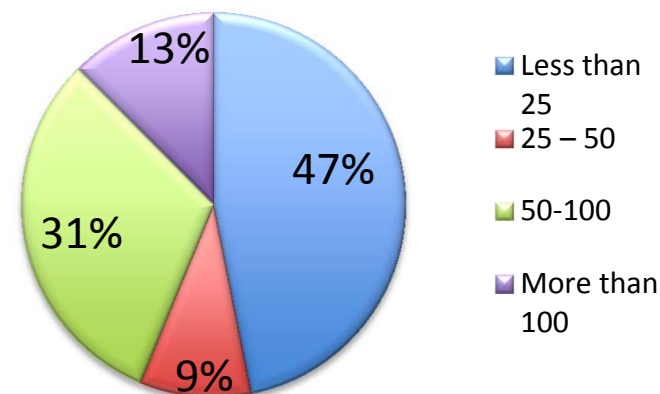
6. How many PACs require submission to a health authority?



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



17. In how many different countries do you typically file changes?



9. Why does your company make Post-Approval Changes? (check all that apply)



| Answer Options | Response Percent | Response Count |
|---|------------------|----------------|
| Process improvement | 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 |

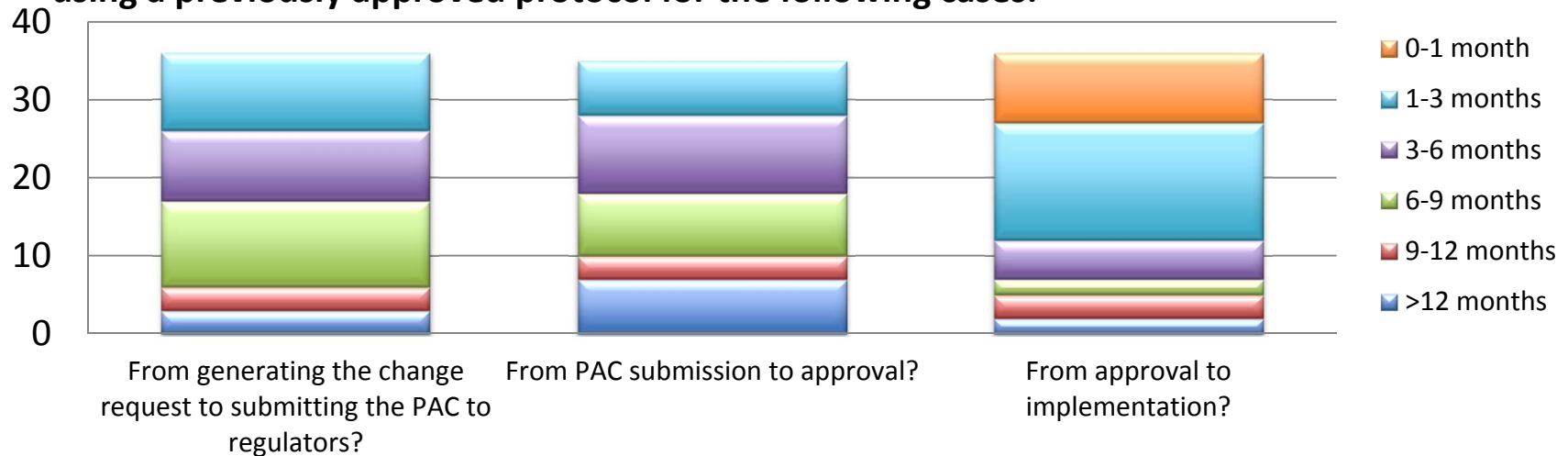
Others Specified:

- Analytical methods upgrades
- Change in QC reference standards

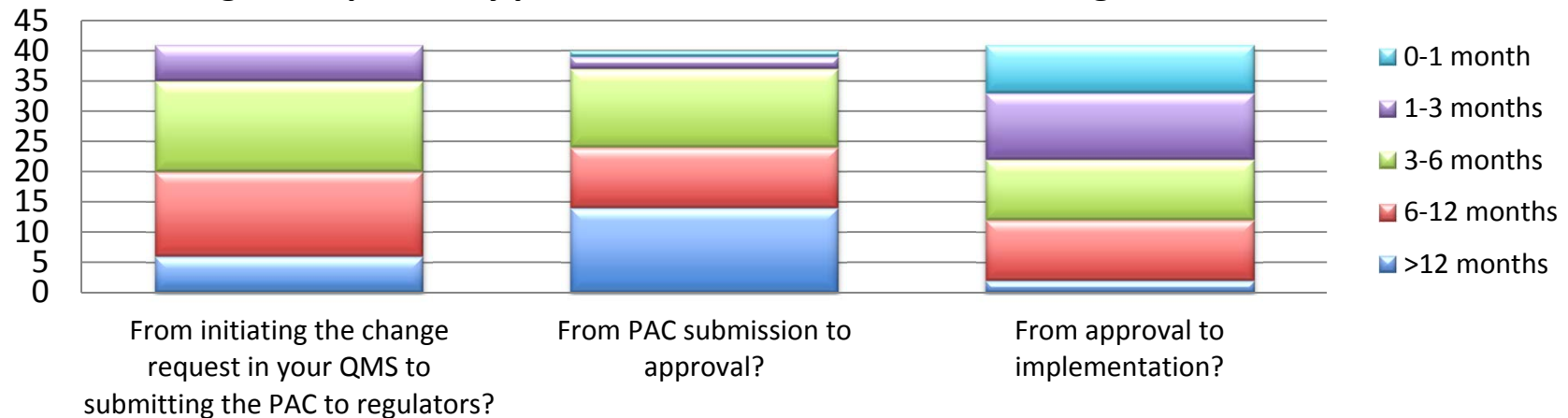
Time Required for Post Approval Changes



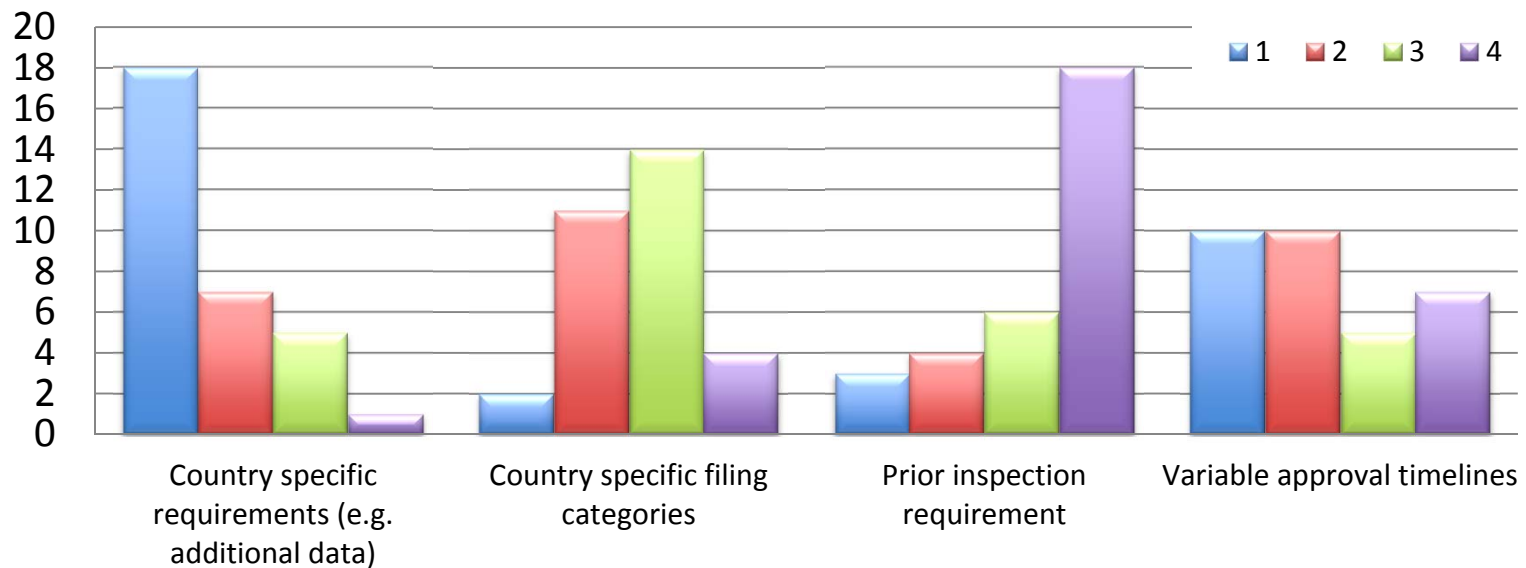
12. How much time does it generally take to process Moderate PAC (type 1b, CBE30) without using a previously approved protocol for the following cases:



10. How much time does it generally take to process a Major PAC (i.e. EU Type 2, FDA PAS) without using a comparability protocol or PACMP for the following cases:



18. Please rank each of the following contributing factors to the current worldwide PAC regulatory complexity for globally marketed products? (1 is the most important and 4 is the least important)



MS8

Slide 21

MS8

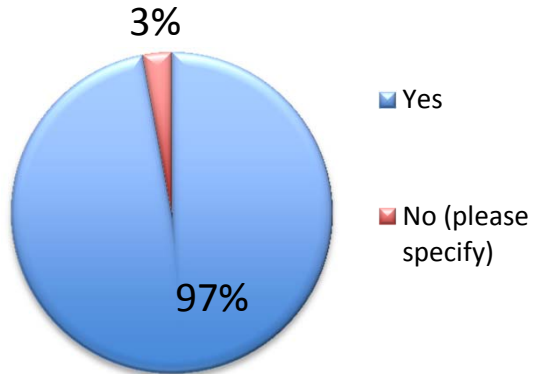
I think this data could be relevant, but I'm not sure how the question was asked - we should figure out how to show in an easier way

Melissa Seymour, 3/8/2017

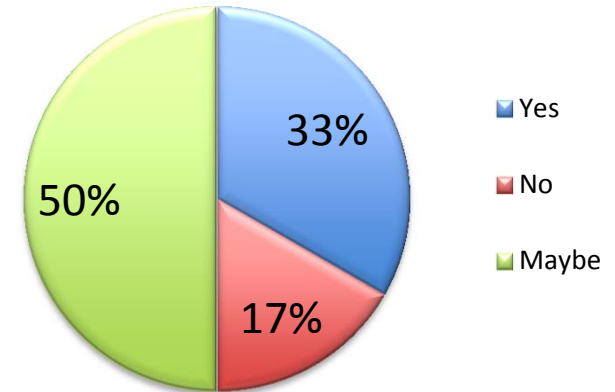
Impact on Compliance, Drug Shortage and Innovation



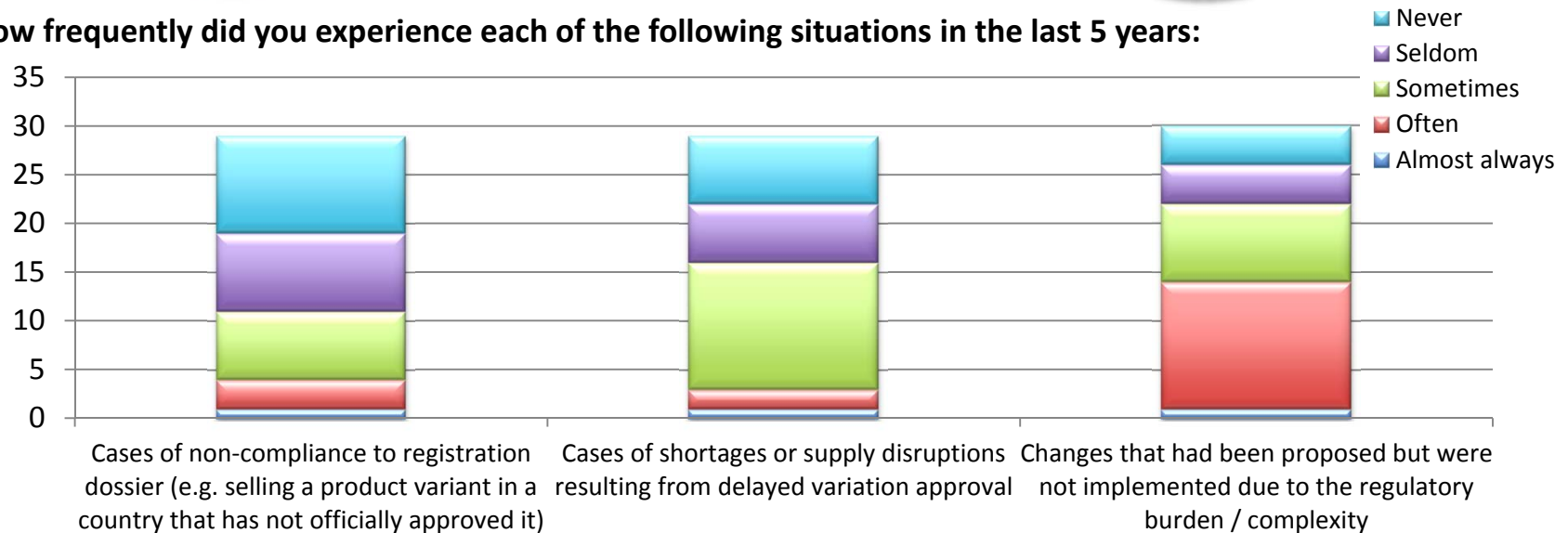
30. Do you think the current post approval change process hinders technology progress?



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



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

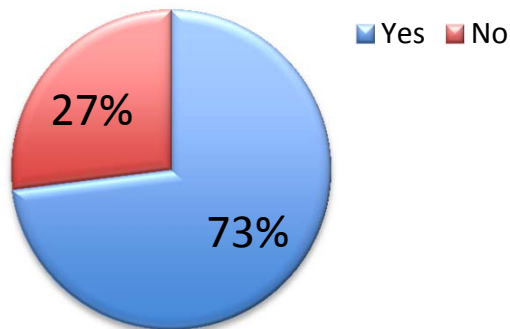


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Post Approval Change Management Protocols (PACMPs)



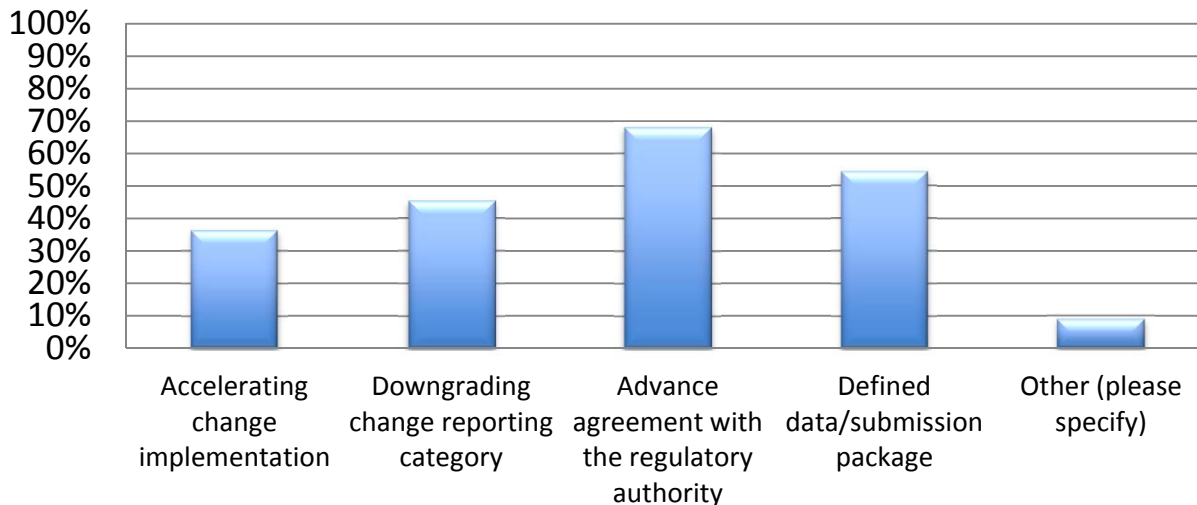
21. Do you currently use Post-Approval Change Management Protocols (PACMPs) or comparability protocols?



22. If yes, for what kind of changes do you use comparability protocols and/or PACMPs? (Select all that apply)

| Answer Options | Response Percent |
|---|------------------|
| Process | 78% |
| Process improvement | 61% |
| Analytical | 52% |
| Site Transfers | 52% |
| Technology transfer | 48% |
| Manufacturing site changes | 48% |
| Expansion/reduction of manufacturing capacity | 44% |
| Introduction of innovative technologies | 35% |
| Upgrade or replacement of obsolete equipment | 35% |
| Raw material replacement | 30% |
| Raw Materials | 26% |
| Specification/testing change | 22% |
| Regulatory commitment | 17% |
| Compliance to new regulations | 13% |
| Product-related change (e.g., combination product, new formulation) | 13% |
| Compliance | 4% |
| Other (please specify) | 0% |

23. What kind of benefit did you gain from using comparability protocols and/or PACMPs? (select all that apply)



- **Anders Vinther, Sanofi Pasteur (co-lead)**
- **Emma Ramnarine, Roche/Genentech (co-lead)**
- Ursula Busse, Novartis
- Marcello Colao, GSK Vaccines
- Julia Edwards, Allergan
- Kara Follman, Pfizer
- Karolyn Gale, Emergent BioSolutions
- Cassidy Good, Mylan Laboratories
- Suzanne Kiani, Mylan
- Maik Jornitz, G-CON LLC
- Morten Munk, NNE Pharmplan
- Kevin O'Donnell, HPRA
- Melissa Seymour, Biogen
- Mihaela Simianu, Pharmatech Associates
- Lisa Skeens, Pfizer
- Denyse Baker, PDA
- Rich Levy, PDA

- **Additional contact information**
 - Denyse Baker, baker@pda.org

- **Website for PAC iAMsm pda.org/PAC**

Questions???