Post-approval Change and Knowledge Management – Where are We?

Results from the PAC iAM Task Force Survey

Emma Ramnarine
Sr. Director, Head, Global Biologics Quality Control
Genentech/Roche

Effectiveness of Post-approval Change (PAC) Management

ICH Q10 Annex 1 provides the basis for more effective post approval change management

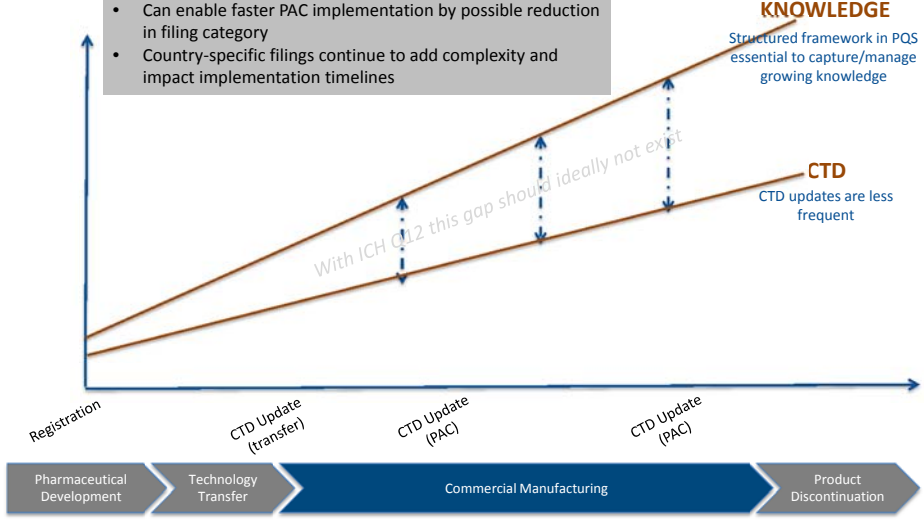
When companies can demonstrate an effective PQS and product and process understanding, including the use of QRM they "gain the opportunity to optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement"

Current ICH Q12 Thinking

- Firms that have implemented an effective PQS per Q10 and regional GMPs, provide confidence to the regulatory authority that changes are supported by data obtained through application of patient-centric, risk-based principles. As a result, regulatory authorities can allow more post-approval changes to be managed under the PQS, without requiring prior review and approval by the regulatory authority.
- Building an effective PQS is the responsibility of a firm and it is not the intent to require by default a specific inspection assessing the state of the PQS before the firm can use the post-approval change benefits described in the guideline.
- If the PQS is found not to be effective, it may result in restrictions on the ability to make changes with downgraded notification to regulatory authorities.

Knowledge Management, Lifecycle Management and PAC Management

- ↑knowledge leads to ↑ product and process understanding
- enables lifecycle management, risk reduction, continual improvement
- Can enable faster PAC implementation by possible reduction in filing category
- Country-specific filings continue to add complexity and impact implementation timelines



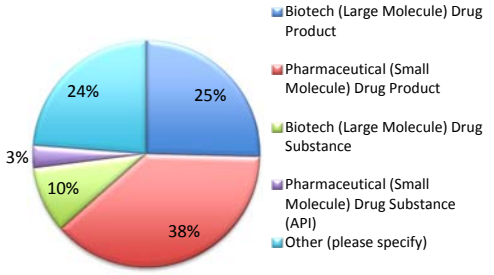
PDA PAC iAM Survey

- Blinded survey on industry experience with post-approval changes in the current global regulatory environment
  - number of PACs, reasons, time commitments/cycle time, impact of regional differences on change implementation, current use of tools (e.g. PACMPs), impact on supply chain complexity (e.g. inventory, variants to manage, non-compliance to filings, drug shortages), and manufacturing innovation and resources needed
- 85 respondents – Quality, Regulatory, Manufacturing, Technical Operations, Development

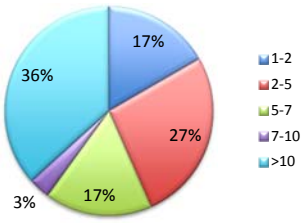
- Data supports ongoing efforts to ease post-approval regulatory complexity, accelerate innovation, and ensure sustainable supply of quality medicines to patients

Survey Demographics

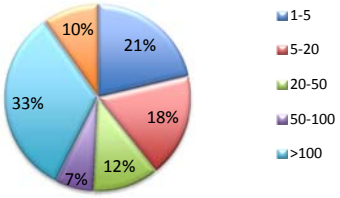
Primary product type you are responsible for



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

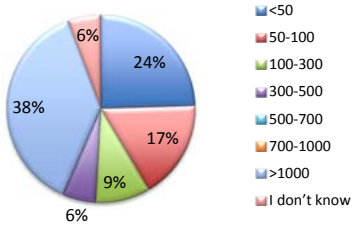


How many different products approved by global regulators are distributed by your company?

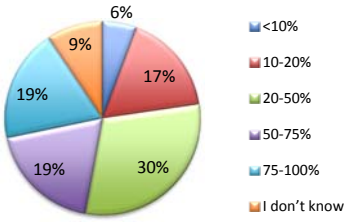


Post-approval Change (PAC) Activities

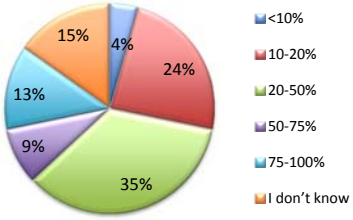
How many PACs, not including submissions, does your company typically process in a given year?



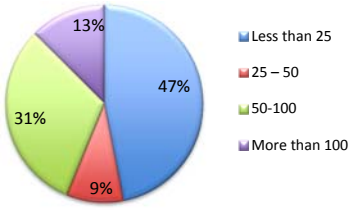
How many PACs require submission to a health authority?



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?



Why does your company make PACs? (check all that apply)

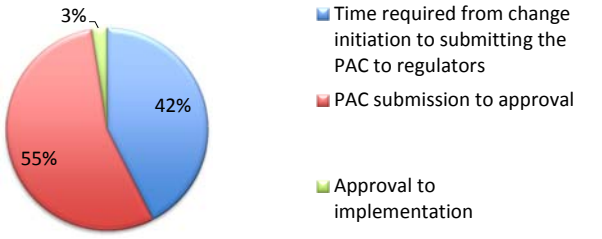
Answer Options	Response Percent	Response Count
Process improvements	89%	40
Expansion/reduction of manufacturing capacity	76%	34
Manufacturing site changes	73%	33
Upgrade or replacement of obsolete equipment	71%	32
Tech transfer	69%	31
Specification/testing change	69%	31
Raw material replacement	64%	29
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
answered question		**45**
skipped question		**40**

Others Specified:

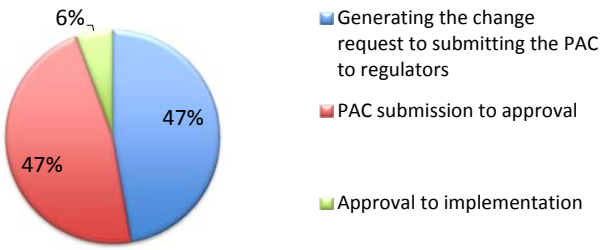
- Analytical methods upgrades
- Change in QC reference standards

Time required for PACs

Which step is the most unpredictable for your Major changes?

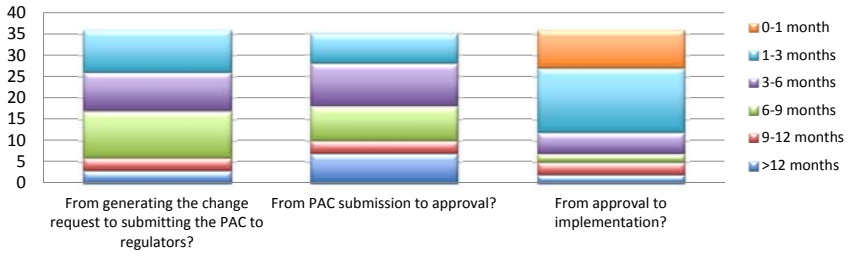


Which step is the most unpredictable for your Moderate changes?

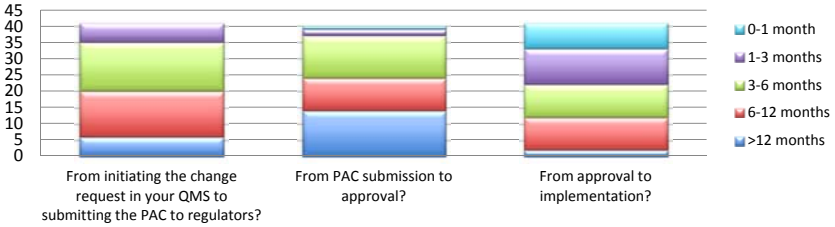


Time required for PACs

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

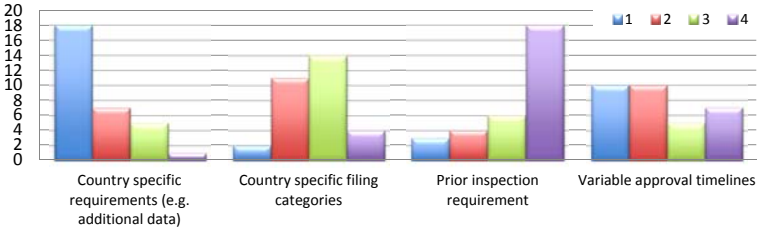


How much time does is generally take to process a Major PAC (i.e. EU Type 2, FDA PAS) without using a comparability protocol or PACMP for the following cases:



Global complexity

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)

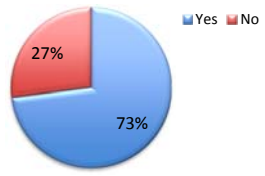


Rate the following countries/regions with regards to the current PAC regulatory complexity?

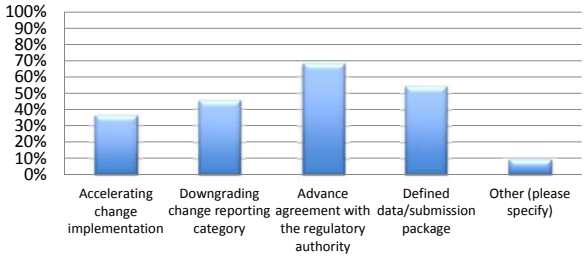
Answer Options	1	2	3	4	5	6	7	8	9	10	Response Count
European Union (EU)	4	6	1	2	1	0	2	2	0	2	**20**
Brazil	2	1	2	3	1	2	2	0	2	3	**18**
United States of America (USA)	6	1	3	1	2	0	0	1	2	1	**17**
Japan	1	0	2	3	1	3	4	0	2	1	**17**
China	4	3	0	0	0	1	0	1	3	2	**14**
Canada	0	1	4	1	1	0	3	2	2	0	**14**
Australia	0	2	3	2	1	2	0	2	1	1	**14**
Russia	0	2	2	0	4	2	0	0	0	2	**12**
South-Korea	0	0	0	0	3	1	1	3	1	2	**11**
Singapore	1	0	1	0	0	2	3	1	0	1	**9**
South-East Asia	0	0	1	2	0	1	1	2	2	0	**9**
Turkey	0	1	0	1	1	2	2	1	0	0	**8**
Middle-East	0	0	0	0	1	2	2	1	0	0	**6**
Switzerland	0	0	0	1	2	0	2	1	0	0	**6**
India	0	0	1	2	0	0	0	1	2	0	**6**
Sub-Saharan Africa	0	0	0	1	0	0	0	1	1	2	**5**

Post-approval Change Management Protocols (PACMPs)

Do you currently use PACMPs or comparability protocols?



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

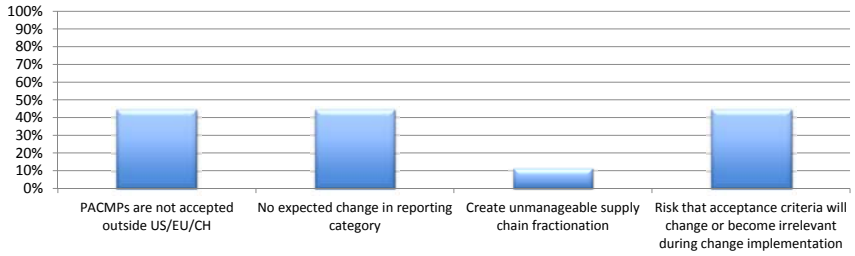


If yes, for what kind of changes do you use comparability protocols and/or PACMPs?

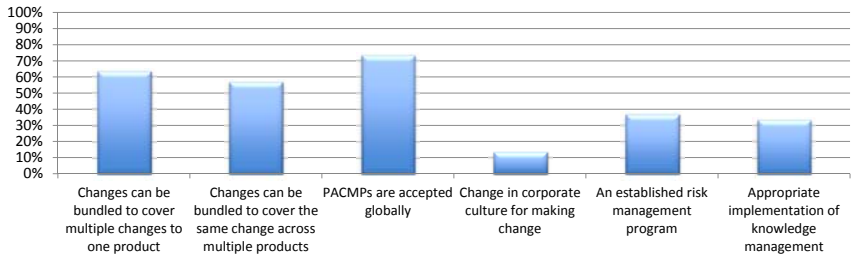
Answer Options	Response Percent
Process	78%
Process improvement	61%
Analytical	52%
Site Transfers	52%
Technology transfer	48%
Manufacturing site changes	48%
Expansion/reduction of manufacturing capacity	44%
Introduction of innovative technologies	35%
Upgrade or replacement of obsolete equipment	35%
Raw 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%

Post-approval Change Management Protocols (PACMPs)

If no, why are you not using PACMPs or comparability protocols?

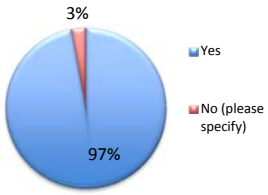


Which of the factors below would encourage you to use PACMPs or comparability protocols?

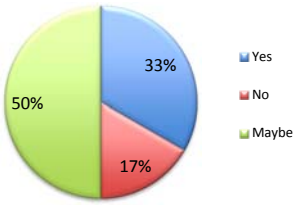


Impact on Compliance, Drug Shortage and Innovation

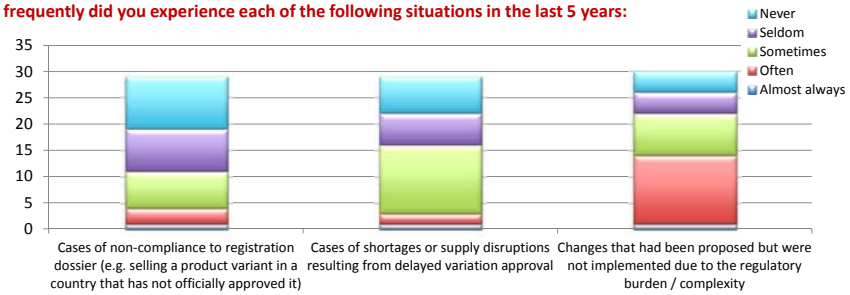
Do you think the current PAC process hinders technology progress?



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:



How do you think hindrance to effective PAC management can be remediated?

Global agency approvals takes ~5 years. This causes the manufacturer to either delay implementation or carry different version of inventory to maintain supply. This complexity drives increased costs, so the manufacturer may just abandon the change in the first place.

- Agreement that if requirements of major regional regulatory bodies are met then individual countries will accept change without further delay
- Global acceptance of other regulatory agencies approvals
- Convergence towards harmonization of PAC process across the many countries in the world. Referring mainly to non EU, non US, non SRA countries
- Consensus among regulatory authorities on the common procedure for PAC
- Clear and harmonized regulations throughout the world. Same definitions and terms. Common classification of changes across all the regions and defined review process and timelines for approvals.
- Further global acceptance of protocols/PACMPs
- Worldwide deployment of concepts described in draft ICH Q12
- Relying more on Company's QMS to evaluate and manage changes will decrease the number of changes to be reviewed at Authorities level; will reduce the amount of submission awaiting approvals thus resulting in less products blocked due to their evaluation

Acknowledgements

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