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Mr. Silvey joined Baxalta (formerly Baxter Healthcare) in 1996 in the Thousand Oaks California facility as a Quality Operations Supervisor, and since then has worked in increasing Quality and Compliance operations roles in Baxalta manufacturing facilities and at the Corporate level in the US. His current role encompasses leadership of the Regulatory Affairs CMC organization providing service to Baxalta's global manufacturing operations producing plasma protein therapies, recombinant analogs, vaccines, and medical devices.

This includes extensive experience in FDA, EMA, and other regulatory authority engagements in areas of Quality/cGMP compliance and Regulatory licensing/Post-Approval Changes of products/facilities. Prior to Baxter, Mr. Silvey was with Bristol-Myers Squibb for 14 years in QA/QC staff and management roles.

Mr. Silvey holds a Bachelor's degree in Chemistry from Colorado State University.

An Industry Perspective: The Complexity of Post-approval CMC Changes and ICH Q12

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AGENDA

Post-approval Changes and ICH Q12: An Industry Perspective

- Introduction – Post Approval Changes (PAC)
- Complexity and Impact
- Health Authority Constraints
- Mitigation Strategies – Industry and Health Authority Practices
- ICH Q12 and Established Conditions
- Conclusion
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Introduction - Post Approval Changes (PAC)

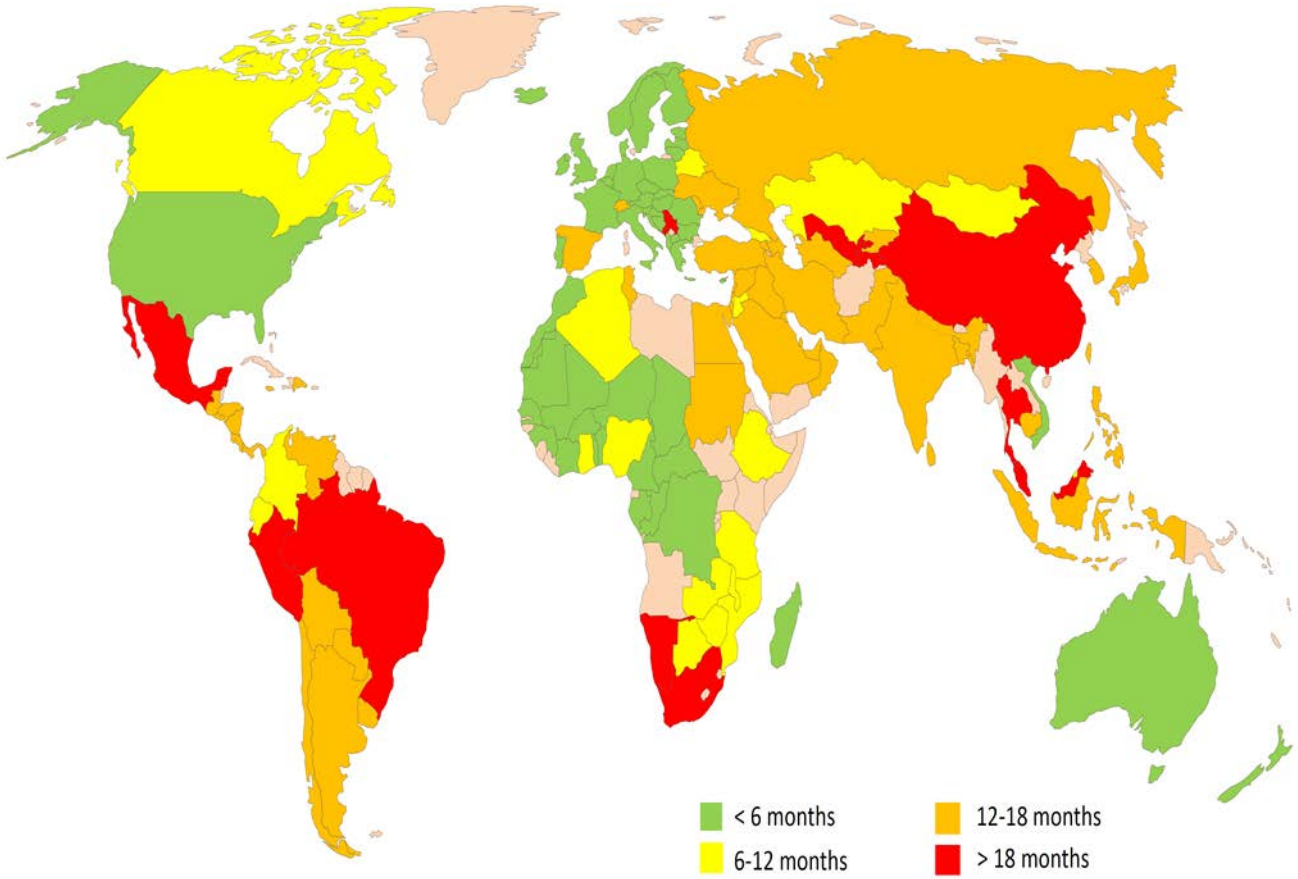
- Pharmaceutical products save or improve the lives of millions of people each year;
- Regulatory review of Chemistry, Manufacturing and Controls (CMC) information is critical to ensure the safety, quality and efficacy of the product;
- Companies launch products to patients as soon as possible after clinical efficacy is demonstrated;
- Changes such as increased batch sizes and new manufacturing facilities are needed to expand patient access;
- Additional changes are made to improve product quality or process robustness as companies gain experience in commercial manufacture.
- Regulatory approval is needed for many of these changes and it can take a long time to obtain global approval.

Complexity and Impact

- Tremendous variability in review and approval times for the same change across markets;
- Some markets approve in 1 month, others take more than 4 years;
- One country may only approve a single change, another country may approve several changes at once;
- The same core data and information may be reviewed by approximately 140 individual regulatory bodies.
  - Guidelines exist in many of those countries to outline what is needed to support CMC changes. While many of the core scientific requirements are aligned, many countries have ancillary requirements for documentation needed at the time of submission, such as CPPs, GMP certificates, extensive real time stability data, legalized copies of documents or other country approval letters that cause delays in submitting changes.

Complexity and Impact

Estimated Global Approval Times for Major Changes
(e.g., new drug product manufacturing site)



< 6 months

6-12 months

12-18 months

>18 months

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Complexity and Impact

Regulatory:

- Understanding and staying abreast of ever-changing requirements in each country;
- Constant demand for additional resources to support emerging regulatory expectations;
- Development and maintenance of country-specific versions of similar information to address country requirements;
- Maintenance of several processes for manufacturing the same product to ensure availability of product;
- Numerous PAI inspections
- Legislation favoring in-country manufacture and/or testing.

Complexity and Impact

Supply:

- Tracking of approvals of changes in each country and designing a supply strategy to cope with varying review timelines and the many different processes approved in each country as a result of those timelines

- Delaying implementation of improvements to enable greater patient access, enhance product quality or increase process robustness due to long review times

- Building up sufficient inventory to ensure continuous supply of product in markets that are slow to approve changes with no clearly defined approval dates to target

- Discard of product manufactured to cover the change review and approval period if estimates of approval times are incorrect

Health Authority Constraints

Health authorities strive to ensure medicines that will save or improve lives are available to the patients.

However, they are faced with challenges of their own, when reviewing changes to approved products:

- Lack of resources needed to hire and train enough reviewers considering the growing number of products introduced to the market and the increasing complexity of those products;
- Mandatory use of templates or checklists;
- Legacy guidance or legislation that does not contain provisions for a risk-based review based on the significance of the change being proposed;
- Limited capacity to update guidance or legislation;
- Having to address the needs and challenges of regulating manufacturers with diverse levels of product development experience;
- Changes in leadership and priorities resulting from government elections, periodic restructuring, differences in budget allocations.

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Mitigation Strategies - Industry

- Create region or country specific dossiers:
  - To address differences in expectations;
  - Reducing the amount of detail in countries;
    - That do not require detailed information;
    - Or for intellectual property protection;

- Use comparability or post approval change protocols in the markets that permit them:
  - To obtain approval of the testing strategy prior to implementation of a change;
  - And seek quicker approval once data are available;

- Request a prioritized review of changes to avoid interruption in product supply.

Mitigation Strategies - Health Authorities

Health authorities may use strategies of their own to address challenges in the review of CMC information, such as:

- Implementation of risk-based reviews:
  - Where regulators spend more available time reviewing submissions of higher
    risk while reviewing and approving submissions of lower risk more quickly;
- Attendance at industry workshops:
  - To understand the critical elements of product development, manufacturing processing, analytical testing;
  - And comparability, technology transfer, scale-up, and post-approval changes.
- Implementation of a fee for service:
  - Through which health authorities pay for employment of reviewers by charging fees for timely review of CMC changes;
- Relying on approval of reference country or well established Agencies (e.g. United States FDA, European EMA)

ICH Q12

- It would be ideal to have harmonized requirements for approval of CMC changes worldwide.
- ICH Q12 is being drafted for just that reason and with recent ICH reforms promoting greater inclusion of the global health authorities, the time for transformational change for the good of the patients, health authorities and MAHs is now.
- Establishment of this guideline could enable the following improvements:
  - MAH use of the principles being proposed in ICH Q12, whereby "**established conditions**" are used as the basis for reduction of the number of changes which require health authority approval. Implementation of changes would be based on the applicants' quality management systems and demonstrated understanding of their products and which parameters would be likely to have the potential to adversely impact product quality if changed.
  - Use of global comparability or **post approval change management protocols (PACMP)** for commonly submitted routine major changes, such as addition of a new drug substance or drug product manufacturing site to facilitate quick implementation once data is obtained. This would only be helpful if health authorities would review the protocols within 6 months and the subsequent data within 30 days.

ICH Q12 and Established Conditions

Current Draft Definition with ICH Q12

- ‘Established Conditions for Manufacture and Control (EC) are certain binding information or elements concerning the manufacture and control of a pharmaceutical product, including description of the product, elements of the manufacturing process, facilities and certain equipment, specifications [i.e., test, method and criteria] and other elements of the associated control strategy (e.g. storage conditions or shelf-life), found in a submission, that assure process performance and desired quality of an approved/licensed product.’

- ICH Q12 will provide guidance and multiple examples on how to identify and present the ECs in the dossier.

- Location: part of CTD Module 2 and/or 3 (tbd, e.g. QOS or 3.2.A), as all ICH regions should apply the same rules. This is critical for Industry to have as much as possible one single set of EC and in all ICH regions.

ICH Q12 and Established Conditions

An Element of EC, and within ICH Q12 -

- A PACMP describes specific changes that the MAH would like to implement during the lifecycle of the product and how these would be prepared and verified (detailed description)
- Procedure (**tool**) for a faster and predictable implementation of a change.
- Not to confuse with GMP change management!
- Types Protocols for specific changes
  (e.g., Analytical method)
  - Manufacturing site
  - Broader protocols will enhance utility e.g. More changes across multiple products or sites

Conclusion

- Considering the growing complexity, time and resources needed for getting CMC changes for pharmaceutical products approved globally, it would be in the best interests of both health authorities and MAHs to work together to ensure the greatest possible level of patient access to the medicines that will save or improve their lives.

- ICH Q12 is being drafted for just that reason and with recent ICH reforms promoting greater inclusion of the global health authorities, the time for transformational change for the good of the patients, health authorities and MAHs is now.

- Although a single, global approval process would provide the quickest solution and require the least global resources with minimal adverse impact on product quality, it is recognized that there are limitations within health authorities that would slow or prevent implementation of such a process now.

- Near term efforts as those outlined in the current draft ICH Q12, can be utilized now to improve patient access and reduce resources spent by Health Authorities and industry.

Acknowledgement

BioPhorum. A Professional Collaboration Group

BPOG's mission is to accelerate the advancement of biologics manufacturing in terms of product and process quality

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