An Industry Perspective: The Complexity of Post-approval CMC Changes and Proposed Regulatory Strategies

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1. BioPhorum Operations Group (BPOG) and the Post-approvals Strategy (PAS) Workstream

2. Post-approval Changes

3. Complexity and Impact

4. Health Authority Constraints

5. Mitigation Strategies

6. The Ideal State

7. References and Acknowledgements
BPOG and the PAS Workstream

BioPhorum Operations Group (BPOG) is an industry-wide collaboration for process improvement in biopharm drug substance (DS) operations. BPOG consists of 26 member companies with over 600 participating representatives, primarily experts in biopharm DS in the USA and Europe. Telecon and meet regularly on workstreams to establish best practice on critical quality, engineering, and organizational topics.
BPOG and the PAS Workstream

Post-approval Strategies:

- The approaches companies take to meet the needs of regulators around the world, when improving manufacturing processes, increasing capacity and responding to changes in regulations, after a product has been approved initially and launched in the marketplace.

The PAS Workstream was established to:

- Understand the problems associated with biological products CMC post-approval changes;
- Understand what might be regarded as best practice in CMC PAS;
- Take steps to influence industry and Health Authority improvements

This Presentation illustrates the complexities and impact of the current post approval change management situation, health authority constraints, current mitigation strategies and transformational recommendations for driving improvement.
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6. The Ideal State

7. Conclusion
Post-approval Changes are Inevitable and Essential

- 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.
The International Conference on Harmonization (ICH) has recently implemented reforms targeting wider inclusion of all key regulatory authorities and industry stakeholders to participate in global pharmaceutical harmonization.

Following publication of guidelines promoting enhanced product and process understanding, quality risk management and robust quality systems in ICH Q8 to Q11, ICH Q12 is being drafted to facilitate management of post approval CMC changes to promote innovation and continual improvement.

Now is the time for patients, industry representatives and health authorities to work together with ICH to develop what is needed to enable efficient and effective reviews of post approval changes so we can use our global resources wisely and enable fast patient access to high quality products that save or improve their lives.
Contents

1. BioPhorum Operations Group (BPOG) and the Post-approvals Strategy (PAS) Workstream
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4. Health Authority Constraints
5. Mitigation Strategies
6. The Ideal State
7. Conclusion
Submission of Post Approval Change to Health Agency Approval...... A Journey

- Same Core data/ information submitted to ~140 countries
- Multiple reviews of same core information
- Multiple rounds of responses to health authority queries

**Industry**

- Higher costs/ complex supply chain
- Sophisticated systems to maintain regulatory compliance
- Multiple versions of submissions, potentially resulting in issues with errors/compliance/resources
- Product supply to patients could be interrupted due to lagging approval timelines

**Health Agencies**

- Diverse regulatory requirements, eg
  Extensive real time stability data, ancillary documents, GMP Certs, (inclusive of signed and original documentation) and legalization
- Variability in review and approval times for the same change across markets (1 month to 4 yrs)
- Multiple rounds of health agencies' questions
Regulatory and Supply Challenges- Increased Cost and Risk of Product Supply Shortage or Interruptions

**Regulatory**
- Understand and stay abreast with evolving 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 individual country requirements
- Maintenance of several processes for manufacturing or testing the same product to ensure availability of product globally
- Numerous PAI inspections
- Legislation favoring in-country manufacture and/or testing

**Supply**
- 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
- Delay implementation of innovative technologies that could increase process robustness or improve analytical method due to long review times
- Need to build sufficient inventory to ensure continuous product supply in markets that are slow to approve changes and have no clear approval dates to target
- Discard of product manufactured if estimate of approval times are incorrect
- Delays due to in-country QC testing
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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4. Health Authority Constraints

5. Mitigation Strategies

6. Suggestions

7. Conclusion
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 constrains;
- 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.
Contents

1. BioPhorum Operations Group (BPOG) and the Post-approvals Strategy (PAS) Workstream
2. Post-approval Changes
3. Complexity and Impact
4. Health Authority Constraints
5. Mitigation Strategies
6. The Ideal State
7. Conclusion
Mitigation Strategies by Industry

- Follow international guidance documents (ICH, WHO)

- Establish a database of high level expectations
  - To include country specific guidance and historical experience;

- Create templates for CMC information
  - To clearly define detailed expectations;
  - Based on guidance, historical experience and agency feedback;

- Create region or country specific dossiers to accommodate market specific requirements and/or facilitate the submission process

- Bundle several changes into a single submission
  - To reduce the number of submissions to be reviewed and approved;

- Consultation with Health Authorities
  - To gain concurrence on strategy prior to implementation.

- Request a prioritized review to avoid interruption in product supply
Mitigation Strategies by Health Authorities

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

- Collaborate with other Health Authorities to harmonize requirements

- Implementation of post approval change principles such as those established by the World Health Organization in Guidelines on procedures and data requirements for changes to approved vaccines

- 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)
The strategies used by MAHs are effective in meeting country-specific expectations, but they are not efficient.

- Significant time, effort and expertise are needed to customize CMC information for health authorities in each country.

- Once health authorities receive the information, significant time, effort and expertise are needed to review it.

When considering the balance between:

- The importance of the review of CMC information to ensure safety, efficacy and quality;

- And the total resources required on a global scale to approve CMC changes in each market,

- Alternate strategies to those listed emerge.
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3. Complexity and Impact

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5. Mitigation Strategies

6. The Ideal State

7. Conclusion
Ideal State

- Health Authority model of mutual recognition for GMP inspections (Follow the Pharmaceutical Inspection Cooperation Scheme (PIC/S))

- Create a Global Master File for review of CMC information in a centralized location for all countries
  - Reviews could be performed collaboratively during the same time period. (Protection of intellectual property would need to be considered.)

- Health Authorities form consortia to follow a Centralized Authorization Procedure (similar to EU)

- Use comparability or post approval change protocols in the markets that permit them

- Health Authorities establish or enhance expedited review mechanisms
The Ideal State

- 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:
  - Facilitates management of post approval CMC changes to promote innovation and continual improvement
  - Work on ICH Q12 is in progress and offers potential for harmonization and likely reduction of number of changes requiring approval (such as the use of established conditions)

- It would be ideal to submit a single CMC package:
  - 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 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. (with set review timelines)
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4. Health Authority Constraints

5. Mitigation Strategies

6. The Ideal State

7. Conclusion
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 patients, 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.

- 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.

- Intermediate actions can be taken now to improve patient access and reduce resources spent by Health Authorities and industry by working with industry to fashion laws or guidances that could pave the way for this ideal state in the future.
Conclusion - Roadmap toward One Global Approval

1. Only File Changes to Established Conditions
2. Global Harmonized Requirements
3. Create New Guidance
4. Mutual Recognition

- Global Comparability or Change Protocols
- Update Existing Guidance
- Global Master File
- Consortia for Centralized Authorization

-One Global Approval

< 6 months
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Questions/ Thoughts?