An Industry Perspective: Reducing the Complexity and Impact of Regulatory Changes in Latin America

SPEAKERS:
Janett Mugaburu-Richards, M.S. – Pfizer Inc.
Kavita Ramalingam Iyer, Ph.D – Merck & Co., Inc.
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 Desired State

7. References and Acknowledgements
BioPhorum Operations Group (BPOG)

Consortium of Biopharmaceutical Companies

A powerful collaboration

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

DECEMBER 15, 2014
BIOBURDEN CONTROL

DECEMBER 2, 2014
MULTI-PRODUCT FACILITY

DECEMBER 7, 2014
METHODOLOGY FOR ASSESSING PRODUCT INACTIVATION DURING CLEAN...
BPOG’s mission is to accelerate the advancement of biologics manufacturing in terms of product and process quality.

Currently 33 participating Companies

- 1800 active participants
- 40 current working groups
- 25 F2F mtgs/yr
- 30 papers published since 2012
- 60 Conference presentations since 2012
- 25 Facilitators
6 Phorums covering all aspects of operations and accelerating biopharma industry’s journey to maturity

- **Technology Roadmapping**
  - Revolutionise the way the industry develops longer term transformational manufacturing and technology capabilities

- **Supply Partner Phorum**
  - Transform the inbound supply chain to
    - Deliver a step reduction in risk, non value adding waste and lead-times
    - Deliver a step increase in reliability and quality compliance

- **BPOG DS, BPOG Fill Finish, Development Group, and BPIT**
  - Accelerate the way the industry delivers near term results making best practice development and implementation faster, cheaper and smarter

- **Regulatory Interaction**
  - Engage and align with Health Agencies in the design and adoption of advances in manufacturing
PAS is one of the 12 work streams within BioPhorum Operations Group DS

PAS work stream was established to work towards a state of ‘One Global Submission’ for CMC changes:

- 360 degree view and understanding of challenges with CMC post-approval changes
- Benchmark and develop best practices for filing CMC changes
- Collaborate with industry and Health Authorities to improve processes

PAS ongoing efforts – described in the following slides:

- Complexities and impact of current post approval change management systems,
- Health authority challenges
- Mitigation strategies
- Transformational recommendations for driving improvement
Post-Approval Changes Are Inevitable And Essential

- Speed to launch products as soon as possible after clinical efficacy – changes are made **often after approval**
- Changes like increased batch sizes and new manufacturing facilities are needed to **expand patient access**
- **Improve product quality or process robustness** as companies gain experience in commercial manufacture
- To **comply** with new regulatory expectations

**Regulatory Review of CMC changes is critical**

**Global Regulatory Approval can take a long time**
Submission of Post Approval Change to Health Agency Approval……. A Journey

- Same Core data/ information submitted to ~140 countries, ~20 in Latin America (LA)
- Guidelines exist only in few LA countries which leads to different agency expectations
- Multiple reviews of same core information and multiple rounds of responses concurrently to health agency questions

Health Agencies

- Diverse regulatory requirements, eg. Extensive real time stability data, ancillary documents, (inclusive of signed and original documentation) and legalization
- Variability in review and approval times for the same change across markets- LA region approval can range between 5 - 36 months
- Multiple rounds of health agencies' questions

Industry

- Higher costs/ complex supply chain
- Sophisticated systems to maintain regulatory compliance
- Multiple versions, resulting in issues with errors/compliance/resources
- Product supply to patients interrupted
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
Complexity and Impact

Estimated Global Approval Times for Major Changes in Latin America
E.g. New drug product manufacturing site:

- Great majority of countries in the region with approval times longer than 6 months

Country Approval Times for Major Variations

Belize, Fr. Guiana, Guyana, and Suriname not included
Regulatory and Supply Challenges - Increased Cost and Risk of Product Supply Shortage or Interruptions

**Regulatory**
- Understand evolving requirements in each country
- Constant demand for resources to meet emerging regulatory expectations
- Development and maintenance of customized 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

**Supply**
- Designing a supply strategy to cope with diverse review timelines and country specific processes
- Delayed implementation of innovative technologies that could increase process robustness or improve analytical method due to long review times
- Build sufficient inventory for continuous product supply in markets with slow approvals or without approval targets
- Delays due to import testing
- Legislation favoring in-country manufacture and/or testing
Health Authority Constraints - An Industry Perspective

Health authorities strive to ensure medicines that will save or improve lives are available to the patients but are faced with challenges such as:

- Limited resources considering the number and complexity of products;
- Regulating industry with diverse levels of product development expertise;
- Mandatory templates or checklists, resulting in limited review options;
- Updates to guidelines or legislations
  - Not fully developed across the region (limited capacity in certain cases)
  - Will allow the use of harmonized approaches where possible, address complex products and risk-based review considering the significance of the change
- Regional and country specific priorities/governmental environment highly variable.
Health Authority Mitigation Strategies

- Collaborate with other Health Authorities to harmonize requirements and/or leveraging principles established by other organization like WHO/ICH

- Expedited reviews:
  - On-site regulatory audits
  - Priority review (by use of a formal process or case by case agreements)
  - Implementation of a fee for service

- Implementation of risk-based reviews, where possible

- Limited reliance on approval of reference country or well established Agencies (e.g. United States FDA, European EMA)

- Participation at industry workshops to keep current with critical elements of product development, manufacturing processing and/or analytical testing;
MAH Mitigation Strategies

- Follow international guidance documents (ICH, WHO)
- Establish a database including country specific guidance and historical experience;
- Templates created for CMC information
- Bundle changes, where feasible, into a single submission to reduce the number of submissions to be reviewed and approved;
- Create region or country specific dossiers to accommodate market specific requirements and/or facilitate the submission process;
- Consultations, as allowed by the HA, to gain concurrence on strategy prior to implementation.
- Request a prioritized review to avoid interruption in product supply
MAH Mitigation Strategies

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

- Customization - Significant time, effort and expertise required
- HA review - Significant time, effort and expertise are needed to review it
- Long Approval timelines - Supply constraints and delays to the population

When considering the balance between:

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

Alternate strategies to those listed are needed

And the total resources required on a global scale to approve CMC changes in each market
Desired State
Harmonized Filing Requirements towards One Global Submission

Opportunities For Consideration

- Ability and willingness to harmonize requirements across the region
- HA use of mutual recognition for GMP inspections, such as PIC/S model
  - Allow use of uniform principles for facility inspection and leverage other HA's inspections
- MAH creates single dossier for review of CMC information
  - Allow simultaneous collaborative review by health authorities in a single time period
- HAs use a “Centralized Authorization Procedure” model similar to European Union
  - Single approval by a committee of representatives from participating countries/regions
- MAH and HA use comparability/post approval change protocols
  - Allow approval of the testing strategy prior to implementation of a change
- HAs establish or enhance existing expedited review mechanisms
  - Leverage and/or expand existing processes for a more consistent approval process
Desired State
Harmonized Filing Requirements towards One Global Submission

ICH Efforts Underway Enable the Desired State

- 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)

Benefits of Desired State

- Promote efficiency for MAH and health agencies
- Enhance level of patient access to medicines that will save or improve lives
Roadmap Toward One Global Approval
Conclusion

- Considering the growing complexity for approval of CMC changes globally and the best interests of patients, it will be essential to:

  - Recognize that health authorities limitations need to be considered in efforts towards a global approval process

  - Continue to seek innovative alternatives to improve patient access and maximize resources

  - Increase partnership and transparency between HAs and MAHs
Acknowledgements

Members of the BPOG PAS ‘Complexity and Impact’ Sub-team:

- Cathy Hoath            Merck
- Heather Smith          Alexion
- Janett Mugaburu-Richards  Pfizer
- Joe Kutza              AZ Bio
- Kavita Ramalingam Iyer  Merck
- Lucy Chang             Sanofi
- Mic McGoldrick         Merck
- Suzanne Murray         Biogen
- Tim Wagner             BMS

For direct contributions to the content of this presentation.

All others in the BPOG PAS team representing:

Abbvie, Baxalta, Bayer, Eli Lilly, EMD Serono, GSK, Novartis, Pfizer, Regeneron, Shire and UCB.

For reviewing and commenting on the content.
Questions/ Thoughts?