The Ever-increasing Complexity of Biotech Changes
- A Pledge for Global Convergence

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Presentation Outline

• Summarize complexity and current challenges of global life-cycle management including case study

• Reflect on pragmatic solutions to drive harmonization and global convergence of post-approval change regulations
Many pharmaceutical companies manufacturing biotherapeutics are operating globally and have global manufacturing sites

- Global registration with Health Authorities
- Global supply chain
- Multiple sourcing strategy
Life Cycle Complexity and Challenges

Complexity – Case study

Reflect on pragmatic solutions
The content differences at original submission are the first main cause for life-cycle complexity

- Approximately 192 recognized states
  - Activities in ~140 countries
- Two categories of CMC packages
  - ICH-like requirements in 20 countries
  - Countries accepting less detailed information
- Trend towards introduction of country-specific or regional data
  - Degree of detail
  - Declarations
  - Raw data
  - Submission of GMP documents - “paper inspections”
Approved details differ from country to country after Q&A compared to the submitted dossier.
One global submission can lead to multiple locally registered contents

For Example: Each pin reflects a dossier with separate regulatory commitments for one product application. ...24 separate registrations for one product

Adapted from: Colgan; ISPE annual meeting Nov.-2013
Introducing changes to the manufacturing process or the control system is an essential part of a product's life-cycle.

- Ensure market access and **continuous supply of live-saving drugs to patients** by reacting to supply demands.

- Support **continuous improvement** and optimization of manufacturing process and quality of the medicinal products.

- Remain **state-of-the-art** with manufacturing methods and analytical techniques.

- Fulfill regulatory **agency requirements**.
Approved details differ from country to country after Q&A compared to the submitted dossier.
Post approval change requirements and need for sequential submission complicate further.

- Change classifications different or not available
- Country-specific requirements (e.g., stability, raw data)
- Long/unpredictable approval timelines
  Backlog due to high review demand at Health Authorities
- Complex supply planning/ high bridging stocks
- Drug shortage
- Hinder innovation and continual improvement of process and product
- Quality and safety

*CPP= Certificate of Pharmaceutical Product
Any change is a multiple year endeavor when it is executed on a global scale.

Wave 1: “ICH dossier” countries*
- Review 0-10 m
- Review 6-20 m

Wave 2: Non-CPP
- Review 6-24 m

Wave 3: CPP countries
- Review 6-24 m

* Predictable timelines in EMA and FDA
Life cycle complexity is resource intensive for authorities and industry

Complexity – Case study

Reflect on pragmatic solutions
Case Study:
an “apparently” minor change in an in-process analytical method

• Change description
  
  – Modification of a Virus IPC test method of cell culture fluids
Case Study:
Product A is registered in 127 countries at the time of the minor change.
Case Study:
The dispatch to all concerned countries was done mid May-2011
Case Study: The last approval took 20 months from submission and closure was after 26 months.

- Within 30 days
- More than 12 months
- Submission not required
- Within 6 months
- Within 12 months
Life cycle complexity is resource intensive for authorities and industry

A global change requires multiple years until complete implementation

Reflect on pragmatic solutions
Harmonization of key principles will accelerate implementation of changes globally

- Change Classification concept
- Procedural guidance incl. timelines
- Documentation and data requirements
Global Model for Pharmaceutical Regulatory Cooperation

Hub/Network for Regulatory Cooperation
And Convergence
at Technical/Operational level

Regulators Forum*
Spectrum of activities depending on:
• Need
• Maturity of topic
• Existing initiatives/organizations
  • Coordinated, operational focus
  • Undertake or refer activities
  • Optimize effort and resources

Partner or Affiliate Organizations

ICH
Harmonization venue
Common regulatory Standards/Tools

APEC
Training/
Capacity Building
Promote Convergence
and Best Practices

PIC/S
NRA Assessment
Training
Information-sharing

Special Role of WHO

*Now the International Pharmaceutical Regulators Forum - IPRF
WHO could coordinate convergence of regulation

- **Change classification** driven by potential to impact patient safety and efficacy
  - **Risk based categorization**
  - Post-approval change management plans / comparability protocols

- Development of global classification and **procedural guidance**
  - Drive progress: Fast track changes that improve quality

- Definition of **documentation and data requirements** for each change type
  - Remove GMP elements
Driving global regulatory convergence

Efforts under discussion - Expand the scope of WHO draft guideline for changes to a vaccine to biotherapeutic products

World Health Organization

Guidelines for Procedures and Data Requirements for Changes to Approved Vaccines and Biotherapeutic Products

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the Guidelines for Procedures and Data Requirements for Changes to Approved Vaccines to a broad audience and to improve transparency of the consultation process.

These Guidelines were developed based on the outcomes and consensus of the WHO consultation convened in 2013 with participants from national regulatory authorities, national control laboratories, vaccine manufacturers and academia researchers.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee on Biological Standardization. Written comments proposing modifications to this text MUST be submitted by 31 March 2014 in the Comment Form.
5.

REPORTING CATEGORIES FOR QUALITY CHANGES

Based on the potential effect of the quality change (e.g., manufacturing change) on the quality attributes (i.e., identity, strength, quality controls, purity, potency) of the vaccine and on their potential impact on the quality, safety or efficacy of the vaccine, changes are categorized into major, moderate and minor and are identified as:

- **Major** Quality Changes,
- **Moderate** Quality Changes, or
- **Minor** Quality Changes.

Quality changes listed in Appendices 2 and 3 should be reported in one of the reporting categories described in this section. If a quality change may have a potential impact on the quality, safety and efficacy of the vaccine and is considered to be major, moderate or minor, but is not included in Appendix 2 or 3, then the NRA should be consulted for proper classification.

» Classification concept is applying risk-based approach

» Clear procedural guidance and review timelines are suggested
Key elements for biotherapeutics have to be included:

- Describe relevant changes
- Identify the conditions
- Define supporting data for given change, e.g. batch analysis data, stability standards (e.g. accelerated stability studies + NMT 6 months real time data to maintain shelf-life...)

<table>
<thead>
<tr>
<th>Manufacture</th>
<th>Description of Change</th>
<th>Conditions to be Fulfilled</th>
<th>Supporting Data</th>
<th>Reporting Category</th>
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<tbody>
<tr>
<td>2. Change to an antigen manufacturing facility:</td>
<td></td>
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<tr>
<td>a. replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen</td>
<td>None</td>
<td>1-4, 6-8</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>b. deletion of a manufacturing facility or manufacturer for an antigen intermediate, or antigen bulk</td>
<td>5, 6</td>
<td>None</td>
<td>Minor</td>
<td></td>
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</table>

| Conditions | | | | |
|-------------|----------------|----------------|----------------|
| 1. The new manufacturing facility(suite) is an approved antigen manufacturing site. | | | |
| 2. Any changes to the manufacturing process and/or controls are considered either moderate or minor. | | | |
| 3. The new facility(suite) is under the same QA/QC oversight. | | | |
| 4. The proposed change does not involve additional containment requirements. | | | |
| 5. There should at least remain one site manufacturer, as previously authorized, performing the same function as the one(s) concerned by the deletion. | | | |
| 6. The deletion should not be due to critical deficiencies concerning manufacturing (e.g., recurrent | | | |
Feedback from WHO meeting (May, Seoul 2014)

Post-approval changes for biotherapeutics becomes high priority for WHO.
New ICH topic – Q12
Life Cycle Management

Problem statement

• Implementation of ICH Q8/Q11, Q9 and Q10 provides opportunities for a more science and risk based approach to assessing changes across the life cycle*
  
  • Main emphasis is during the Development stage

• Opportunities and benefits have not been fully realized (or enabled), and the envisioned ‘operational flexibility’ has not been achieved

• Need to focus on the Commercial Manufacturing phase of the lifecycle

Desired state

➡ A system that facilitates managing quality and continual improvement throughout the product lifecycle i.e. emphasis on post-approval

*Product and Process LifeCycle:
Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation
APEC Regulatory Harmonization Efforts

Contribute to the international community by supporting the regulatory officials from APEC travel-eligible economies to participate in the AHC workshops, which provides further opportunities for regional training and education.

- 54 delegates from Asia region (2009-2011)
- 24 delegates from Central/ South America region (2009-2011)
Global convergence of post-approval change regulations offers a «Win-Win» outcome for regulators, industry & patients

Harmonized post-approval regulations
⇒ Change classification, procedures, dossier requirements

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<th>Regulators</th>
<th>Industry</th>
<th>Patients</th>
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<tr>
<td>- Prioritize based on criticality of change</td>
<td>- Allow better planning and execution of changes</td>
<td>- Improved drug quality rapidly accessible to the market</td>
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<tr>
<td>- Facilitate assessment of changes</td>
<td>- Enable more efficient use of resources</td>
<td>- High quality standard maintained globally</td>
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<td>- Enhance collaboration/knowledge sharing with other agencies</td>
<td>- Reduce risk of non-compliance</td>
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<td>- Reduce complexity in supply chain</td>
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<tr>
<td>Continuous and reliable supply of high quality drugs to all patients GLOBALLY</td>
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<td>Mutal recognition of regulatory decisions</td>
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<td>Transparency</td>
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Life cycle complexity is resource intensive for authorities and industry.

A global change requires multiple years until complete implementation.

Convergence of requirements and mutual recognition can reduce the complexity of life cycle changes, efforts are on the way...
Acknowledgements

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Doing now what patients need next