Comparative Study of Process of Post Approval Change Application Submission and Approval for Marketing Authorization Variations in EU, US, India, Saudi Arabia and Singapore

Lokesh M.S.
N. Vishal Gupta*
Bhushan Dinesh Belagoankar

Pharmaceutical Quality Assurance Group, Department of Pharmaceutics
JSS College of Pharmacy, JSS University, Sri Shivaratreeeshwara Nagara, Mysuru - 570015, Karnataka, India

Corresponding Authors:
N. Vishal Gupta
Asst. Professor
Department of Pharmaceutics, JSS College of Pharmacy, sri Shivaratreeeshwara Nagara, Mysuru - 570 015, Karnataka, India.
E-mail: vkguptajss@gmail.com

Abstract:
The present research endeavors to shed light onto the role that post approval change management in overcoming non-compliance. The present study has focused on identifying the existing policies and procedure in this area and understanding the underlying concepts for post approval compliance for licenses pertaining to marketing authorization. The study compared and contrasted policies and procedures of regulatory authorities in India, US, EU, Saudi Arabia and Singapore. The major finding of the study indicates that though change management plays a crucial role in the lifecycle of a pharmaceutical. However, lack of defined framework coupled with lack of comprehension of the same has increased the cost of compliance resulting step-motherly treatment being mitigated towards compliance and license maintenance. The initiatives by the ICH with drafting of ICH Q12 guidelines is a welcome step forward and may help the pharmaceutical industry to comply with the regulations.

Keywords: Post Approval Changes, Non-Compliance, ICH

INTRODUCTION:
Change is defined as “A change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labeling and product information”. [1]

Changes to approved products should be evaluated to assess their impact on product quality, safety and efficacy/effectiveness. These changes should be documented properly. Depending on the degree of impact, some changes may simply need the company to document the change being evaluated. Different mechanisms exist in different jurisdictions for reporting these changes and these can vary from an annual report to an amendment/variation application to a new license application. Manufacturers should consult the guidance documents specific to the jurisdiction in order to follow the proper compliance procedures.

The various post approval changes are observed in:

- Components and composition
- Manufacturing sites
- Manufacturing process
- Specifications
- Container closure system
- Labelling
- Miscellaneous changes and
- Multiple related changes

Post Approval Change Management:
A post-approval change management describes specific changes that a company would like to implement during the lifecycle of the product and...
how these would be prepared and verified. Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the Marketing Authorization Holder will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.

In US, EU, Saudi Arabia, Singapore and India Post approval changes are designated as:

- **US**: Scale Up and Post Approval Changes
- **EU**: Variations
- **Saudi Arabia**: Variations
- **Singapore**: Variations
- **India**: Post Approval Changes

### Grading the Changes

According to the area of consideration (e.g. approval conformity or validation status), it may be necessary to use different change procedures as a base. This is the way many companies deal with changes to printed packaging material (information for use, folding cartons, and labels) in accordance with a special change control procedure, because these changes occur relatively frequently in practice and the process sequences can be standardized easily. In these cases, the sequences and the criteria used are not independent, but are carefully matched to suit and coordinate with each other.

#### Table 1: Grading the Change

<table>
<thead>
<tr>
<th>Changes requiring control</th>
<th></th>
<th>Not Requiring Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Change</td>
<td>Minor Change</td>
<td>No relevance to GMP or authorization</td>
</tr>
<tr>
<td>Significance of change</td>
<td>Influences product quality or process reliability</td>
<td>Amendment</td>
</tr>
<tr>
<td>Possible measures (selection)</td>
<td>New approval</td>
<td>Review</td>
</tr>
<tr>
<td></td>
<td>Revalidation</td>
<td>Documentation</td>
</tr>
<tr>
<td>Examples</td>
<td>Change of manufacturer: other synthesis route of a starting material (other impurities)</td>
<td>Replacement of apparatus part of the same design</td>
</tr>
<tr>
<td></td>
<td>Removal of processes to another site</td>
<td>Change of cleansing agent for floors</td>
</tr>
<tr>
<td></td>
<td>Change in the product composition</td>
<td>Change of laundry for work clothing (nonsterile or antibiotics area)</td>
</tr>
<tr>
<td></td>
<td>Change to the process parameters</td>
<td>Introduction of co-sales right</td>
</tr>
</tbody>
</table>

### Material and Methods:

Regulatory guidelines are the backbone of the present study; the complete study is based on the guidelines and/or regulations which are published by Regulatory Agencies of each country.

Pharmaceutical Regulatory Agencies: Regulatory authority and organizations are responsible in operational drug regulation essential to ensure the safety, efficacy and quality of drug products and/or substances. Regulatory bodies provide strategic and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world.

Guidance documents for Post Approval Changes in US, EU, India, Saudi Arabia and Saudi:
Table 2: List of Guidance Documents

<table>
<thead>
<tr>
<th>S. No</th>
<th>Country</th>
<th>Guidance Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Singapore</td>
<td>Guidance On Medicinal Product Registration In Singapore, Health Sciences Authority, Regulatory Guidance, 1 April 2011[8]</td>
</tr>
</tbody>
</table>

DISCUSSION:

Post Approval Changes – European Union[5]:

Types of Variation:

<table>
<thead>
<tr>
<th>Variations</th>
<th>Type IA IN Variations</th>
<th>Type IA Variations</th>
<th>Type IB Variations</th>
<th>Type II Variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IA Variations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IB Variations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IA IN Variations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Classification of Variation

Type IA Variations:

Do not require immediate notification. May be submitted by the marketing authorization holder (MAH) within 12 months after implementation, or may be submitted earlier should this facilitate dossier life-cycle maintenance. The 12 months deadline to notify minor variations of Type IA allows for an ‘annual reporting’ for these variations.

Type IA IN Variations: Type IA IN variations must be notified (submitted) immediately to the National Competent Authorities/European Medicines Agency (‘the Agency’) following implementation.

Type IB Variations: Variation which is neither a Type IA variation nor a Type II variation nor an Extension; such minor variations must be notified to the National Competent Authority/European Medicines Agency (‘the Agency’) by the Marketing Authorization Holder (MAH) before implementation. MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the National Competent Authority/the Agency before implementing the change.

Type II Variations: Any change which may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation.

Type II Extension: Change which may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation.

Changes requiring an extension application:

- Changes to the active substance(s)
- Changes to strength, pharmaceutical form and route of administration

Timelines:

<table>
<thead>
<tr>
<th>Type of Application</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IA IN</td>
<td>30</td>
</tr>
<tr>
<td>Type IB</td>
<td>30</td>
</tr>
<tr>
<td>Type II</td>
<td>30, 60, 90</td>
</tr>
<tr>
<td>Type II Extension</td>
<td>210</td>
</tr>
</tbody>
</table>
Flow Chart for Type IA Variation Approval Process

Type IA Variations

Do not require immediate notification. Notification—within 12 months after implementation, or may be submitted earlier should this facilitate dossier life-cycle maintenance.

Type IA\textsubscript{INT} Variations

Variations must be notified (submitted) immediately.

Submission of Application

Timelines
30 Days

Fee/Payments

- 45 calendar days of the date of the said notification.
- Invoice = 15 Days
- \textbf{3000 EURO}

eSubmission Gateway or the eSubmission Web Client And Evaluation of Application

Approval

- Commission Decision granting the Marketing Authorization requires amendments

Rejection

- The classification of the proposed change(s) in incorrect
- The submitted documentation as required by the Variations Guideline is deficient or inaccurate

MAH shall immediately cease to apply the rejected changes

“Do and Tell”

Figure 2: Process of Approval of Type IA Variation
Flow Chart for Type IB Variation Approval Process

Type IB variations

“Tell, Wait and Do”

Variation which is neither a Type IA variation nor a Type II variation nor an Extension. Such minor variations must be notified to the National Competent Authority/European Medicines Agency (“the Agency”) by the Marketing Authorization Holder (MAH) before implementation.

Grouping:
⇒ Several Type IB variations for the same product into one notification.
⇒ Group a Type IB variation with other variation(s) for the same product

Submission of Application

- Timelines
  - 30 Days
  - 45 Calendar Days
  - Invoice = 15 Days
  - 7000 EURO

- eSubmission Gateway or the submission Web Client for Evaluation

- Validation Timelines
  - Agency Validation 05 days

- Application is Valid
- Application is Not Valid

Unfavorable outcome

⇒ NO notification
⇒ Amend the notification
⇒ Granting the Marketing Authorization requires amendments
⇒ Submit as Type II Application

⇒ Approved
⇒ Review
⇒ Provide Supplement Information

Figure 3: Process of Approval of Type IB Variations
Flow Chart for Type II Variation Approval Procedures

**Type II Variations**

Any change which may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation.

- Submission of several Type II variations for the same product into one application
- Submission of group a Type II variation with other variation(s) submission

**Submission of Application**

- **Timelines**
  - 60, 30, 90 day TT
  - 60, 30, 90 TT with PRAC involvement

- **Fee/Payments**
  - Major Variations = 83 600 EURO
  - Quality Variations = 62 700 EURO
  - Subsequent Application = 20 900 EURO

- **eSubmission Gateway or the eSubmission Web Client for Evaluation**

- **Agency will inform the MAH within 15 days as to whether the CHMP opinion is favorable or unfavorable**

- **Unfavorable Opinion**

  - **Supplementary Information**

    - Timelines — 1 month can be extended to 2 months with justification

- **Implementation of Change**

- **Revision of Product information in all languages—Review Timelines—25 Days**

**Figure 4:** Process of Approval of Type II Variations
Post Approval Changes – US

In US post approval changes are designated as Scale Up and Post Approval Changes, the changes are categorized into three level:

- **Level I**: Major Changes
- **Level II**: Moderate Changes
- **Level III**: Minor Changes

Type of Application to be submitted:

<table>
<thead>
<tr>
<th>Type of Changes</th>
<th>Rules</th>
<th>Type of application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Change</td>
<td>21 CFR 314.70(b)</td>
<td>Prior Approval Supplement</td>
</tr>
<tr>
<td>Moderate Change</td>
<td>21 CFR 314.70(c)(5)</td>
<td>Changes Being Effected in 30 days</td>
</tr>
<tr>
<td>Minor Change</td>
<td>21 CFR 314.70(d)</td>
<td>Annual Report / Notification</td>
</tr>
</tbody>
</table>

**Table 3: Classification of Post Approval Changes**

Flow Chart for Application Submission and Approval

**Figure 5: Process of Approval**

Post Approval Changes – Saudi Arabia

**Type of Variations:**

- **Minor Variations:**
  - **Type IA**: Minor Changes that does not require prior approval before implementation but require notification submitted by the MAH within 60 days after implementation.
  - **Type IB**: Minor variations that must be notified to the SFDA by the MAH before implementation, but do not require formal approval; however MAH must wait for period of 120 days to ensure that the application is denied acceptable by the SFDA before implementing the change.

- **Major Variations:**
  - **Type II**: Major variations in which there might be a significant impact on the Quality, Safety or Efficacy of a medicinal product and require prior approval before implementation;

**Variation Review Process:**

1. Validation
2. Product Licensing
3. Assessment
4. Testing
5. Inspection
6. Pricing
7. Variation Approval
8. Appeal Process

Timelines for Approval of Variation Application As per SFDA guidelines:
Table 4: Timelines for Approval of application

<table>
<thead>
<tr>
<th>Steps</th>
<th>Type IA</th>
<th>Type IB</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>10 Days</td>
<td>10 Days</td>
<td>10 Days</td>
</tr>
<tr>
<td>Product Licensing (May be)</td>
<td>10 Days</td>
<td>10 Days</td>
<td>10 Days</td>
</tr>
<tr>
<td>Assessment</td>
<td>45 Days</td>
<td>105 Days</td>
<td>120 Days</td>
</tr>
<tr>
<td>Inspection (May be – Parallel Process)</td>
<td>45 Days</td>
<td>105 Days</td>
<td>120 Days</td>
</tr>
<tr>
<td>Pricing (May be – Parallel Process)</td>
<td>20 Days</td>
<td>20 Days</td>
<td>20 Days</td>
</tr>
<tr>
<td>Variation Approval</td>
<td>5 Days</td>
<td>5 Days</td>
<td>15 Days</td>
</tr>
<tr>
<td><strong>Total Timeline</strong></td>
<td><strong>60 Days</strong></td>
<td><strong>120 Days</strong></td>
<td><strong>145 Days</strong></td>
</tr>
</tbody>
</table>

Flowchart for Variation Application Process:

Figure 7: Variation application approval process
**Flow Chart for “Process of Approval of Type IA Variation”**

**Figure 8:** Process of approval of type IA variations
Flow Chart for “Process of Approval of Type IB Variation”

Figure 9: Approval of type IB variations

Flow Chart for Process of Approval of Type IIVariation

Figure 10: Approval of type IB variations

N. Vishal Gupta et al; Comparative Study of Process of Post Approval Change Application Submission and Approval for Marketing Authorization Variations in EU, US, India, Saudi Arabia and Singapore

Covered in Scopus & Embase, Elsevier


© 2015 N. Vishal Gupta et al, publisher and licensee IYPF. This is an Open Access article which permits unrestricted noncommercial use, provided the original work is properly cited.
Post Approval Changes – Singapore

Types of Variations:

**Major Variations (MAV):**
- MAV – 1: Any variation to the approved indication(s), dosing regimen(s), patient group(s), and/or inclusion of clinical information extending the usage of the product (e.g., clinical trial information related to an unapproved indication, dosing regimen and/or patient population; recommendation for concomitant administration of vaccines; additional bacterial strains to expand the indication(s) for antimicrobial products).
- MAV – 2: A change in current approved forensic classification, also known as reclassification

**Minor Variations (MIV):**
- MIV-1: A minor variation, which requires regulatory approval.
- MIV-2: A minor variation or an administrative change.

**Timelines:**

**Table 5:** Timeline for approval of application

<table>
<thead>
<tr>
<th>Prescreening Timeline</th>
<th>25 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dossier Type</strong></td>
<td><strong>Timeline in Days</strong></td>
</tr>
<tr>
<td>Full</td>
<td>270</td>
</tr>
<tr>
<td>Abridged</td>
<td>180</td>
</tr>
<tr>
<td>Verification</td>
<td>60</td>
</tr>
</tbody>
</table>

**MAV 2**
- The applicant can implement the proposed change(s) if HSA does not raise any objection within 40 working days from the date of submission

**Flowchart for Variation Application Process**

**Post Approval Changes: India**

**Classification of Changes:**

- Level I: Changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a biological product as these factors may relate to the safety or effectiveness of the product.
- Level II: Changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product.
biological product as these factors may relate to the safety or effectiveness of the product.

Level III: Changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product;

**Timelines:**

- **Major Changes:** 180 working days
- **Moderate Change:** 90 Working Days

**Conclusion:**

Table 6: Summary of the study

<table>
<thead>
<tr>
<th>Country</th>
<th>EU Regulatory Agency</th>
<th>US Food and Drug Administration</th>
<th>Saudi Food and Drug Authority</th>
<th>Health Sciences Authority</th>
<th>Central Drug Standard Control Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Designation</strong></td>
<td>Variations</td>
<td>Scale Up and Post Approval Changes</td>
<td>Variations</td>
<td>Major Variation: MAV 1 &amp; MAV 2</td>
<td>Level I - Major</td>
</tr>
<tr>
<td><strong>Classification</strong></td>
<td>Type I – Type IA (IA1), IB</td>
<td>Level I - Minor</td>
<td>Type I – Type IA, IB Type II</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type II – Type II (Extension)</td>
<td>Level II - Moderate</td>
<td>Type II</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Level III - Major</td>
<td></td>
<td>Major Variations: MAV1 &amp; MAV2</td>
<td>Level I - Major</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level I: Supplement</td>
</tr>
<tr>
<td><strong>Notification Type</strong></td>
<td>Type IA (IA1)</td>
<td>Level I</td>
<td>Type IA</td>
<td>MIV 2</td>
<td>Level III</td>
</tr>
<tr>
<td><strong>Application Format</strong></td>
<td>EU CTD</td>
<td>No Specific format, the application should be compliance with 21 CFR 314.70(b), 314.70(c), 314.70(d) Retrieved from the original application in SDR</td>
<td>ICH CTD, ACTD</td>
<td>No specific format, DMF and supporting justifications &amp;/or undertakings as applicable.</td>
<td></td>
</tr>
<tr>
<td><strong>Application Submission</strong></td>
<td>eSubmission Gateway or the eSubmission Web Client</td>
<td>Electronic Submissions, Gateway FDA eSubmitter</td>
<td>PRISM or Variation Application Datasheet</td>
<td>Paper submission.</td>
<td></td>
</tr>
<tr>
<td><strong>Timelines (Working Days)</strong></td>
<td>Type IA: 30 Type IB: 30 Type II: 30, 60, 90 Type II Extension: 210</td>
<td>Level II: CBE 30 days</td>
<td>Type IA: 60 Type IB: 120 Type II: 145</td>
<td>MAV 1: 180, 270, 60 MAV 2: 180 MAV 1: 120</td>
<td>Level I: 180</td>
</tr>
<tr>
<td><strong>Dosage Forms Covered</strong></td>
<td>OSDs, Biologics &amp; Medical Devices</td>
<td>OSDs, Biologics &amp; Medical Devices (Labeling)</td>
<td>OSDs Medical Devices, Biologics</td>
<td>OSDs and Medical Devices</td>
<td>Biologics</td>
</tr>
</tbody>
</table>

With an ever evolving industry such as the pharmaceutical industry, we can hope that advances will always be made, technology improved but this process will also probably result in an ever changing set of marketing authorization applications and legal guidelines. The present study provides a detailed analysis of the current EU, US, India, Saudi Arabia and Singapore regulations and/or guidelines for post approval application submission and approval process in both GMP.

European Medical Agency provides detailed guidance for submission of application including established timelines where as in US FDA has limited guidance for the process of submission and related aspects. Saudi Arabia classification of variation is quite similar to EU but there minor changes in terms of classification and timelines.
for approval of application, Saudi Arabia have various levels of parallel evaluation procedures which include pricing, Inspection, Assessment, Testing and Product Licensing. HSA process of submission of all type of variation is relatively similar, only modifications in the format of the application and evaluation timelines. Indian guidelines are not much established, it’s restricted only to biologics, only timelines have been clearly published and process is not clearly defined.

References:


Article History: ------------------------
Date of Submission: 20-12-2014
Date of Acceptance: 19-01-2015
Conflict of Interest: NIL
Source of Support: NONE