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Full Length Original Research Paper

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

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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 [2].

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:[3]

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

	Changes requiring control		Not Requiring Control
	Major Changes	Minor Change	
Significance of change	Influences product quality or process reliability	Influences a unit requiring control	No relevance to GMP or authorization
Possible measures (selection)	➢ Official license ➢ New approval ➢ Revalidation	➢ Amendment ➢ Review ➢ Documentation	➢ No relevance to GMP or authorization
Examples	➢ Change of manufacturer: other synthesis route of a starting material (other impurities) ➢ Removal of processes to another site ➢ Change in the product composition ➢ Change to the process parameters	➢ Replacement of apparatus part of the same design ➢ Change of cleansing agent for floors ➢ Change of laundry for work clothing (nonsterile or antibiotics area) ➢ Introduction of co-sales right	➢ Change to working times ➢ Renovations in administration area ➢ Installation of air conditioner in staff room ➢ Introduction of electronically readable plant ID cards

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:

Covered in Scopus & Embase, Elsevier Int. J. Drug Dev. & Res., January-March 2015, 7 (1): 10-22

Table 2: List of Guidance Documents

S. No	Country	Guidance Documents
1.	US	Guidance for Industry, Changes to an Approved NDA or ANDA, U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), April 2004, CMC, Revision 1[4]
2.	EU	Questions and answers on post approval change management protocols, European Medical Agency, Committee for Medicinal Products for Human Use (CHMP), EMA/CHMP/CVMP/QWP/586330/2010, 30 March 2012[5]
3.	India	Guidance for Industry, Post approval changes in Biological Products: Quality Safety and Efficacy Documents, Document No. - PAC/1108, Version – 1.1[6]
4.	Saudi Arabia	Regulatory Framework for Drug Approvals, Saudi Food and Drug Authority, Version 5.0, March 2014[7]
5.	Singapore	Guidance On Medicinal Product Registration In Singapore, Health Sciences Authority, Regulatory Guidance, 1 April 2011[8]

DISCUSSION:

Post Approval Changes – European Union[5]:

Types of Variation:

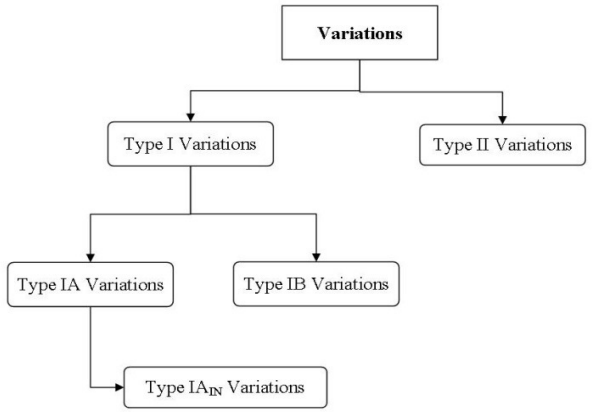

Figure 1: Classification of Variation

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

	Type of Application	Days
Timelines : (Working Days)	Type IA$_{IN}$	30
	Type IB	30
	Type II	30,60,90
	Type II Extension	210

Flow Chart for Type IA Variation Approval Process

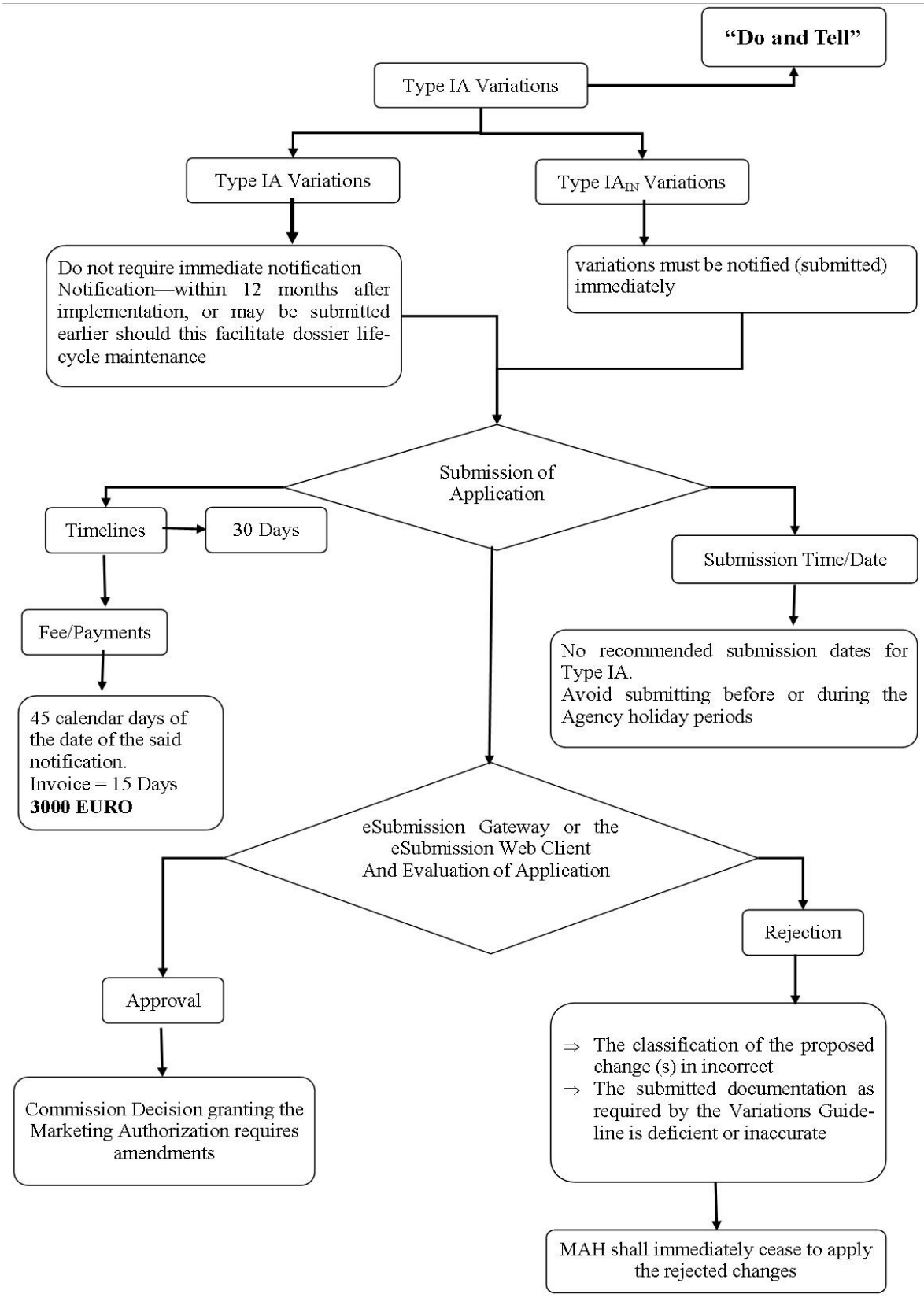

Figure 2: Process of Approval of Type IA Variation

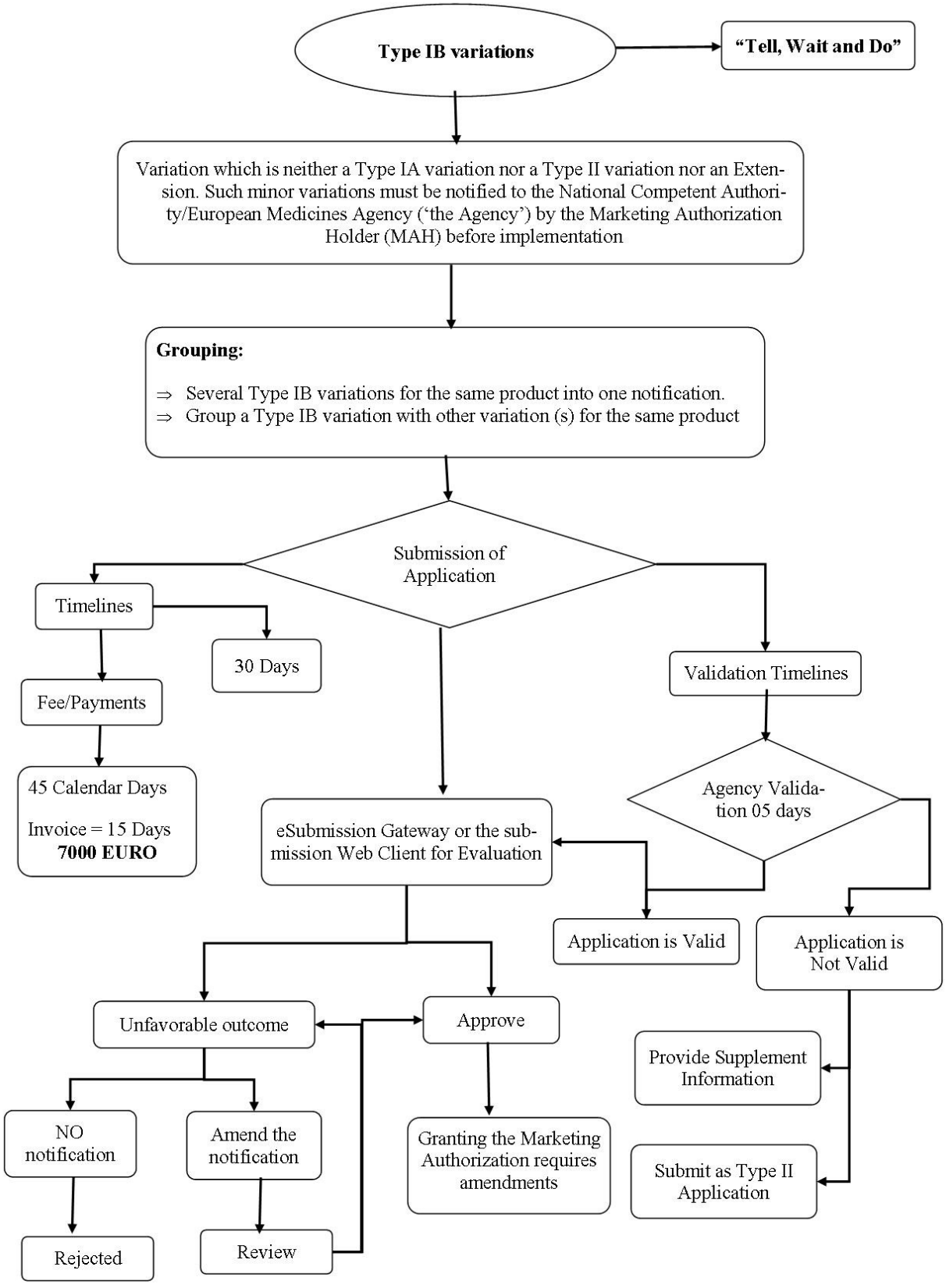

Figure 3: Process of Approval of Type IB Variations

Flow Chart for Type II Variation Approval Procedures

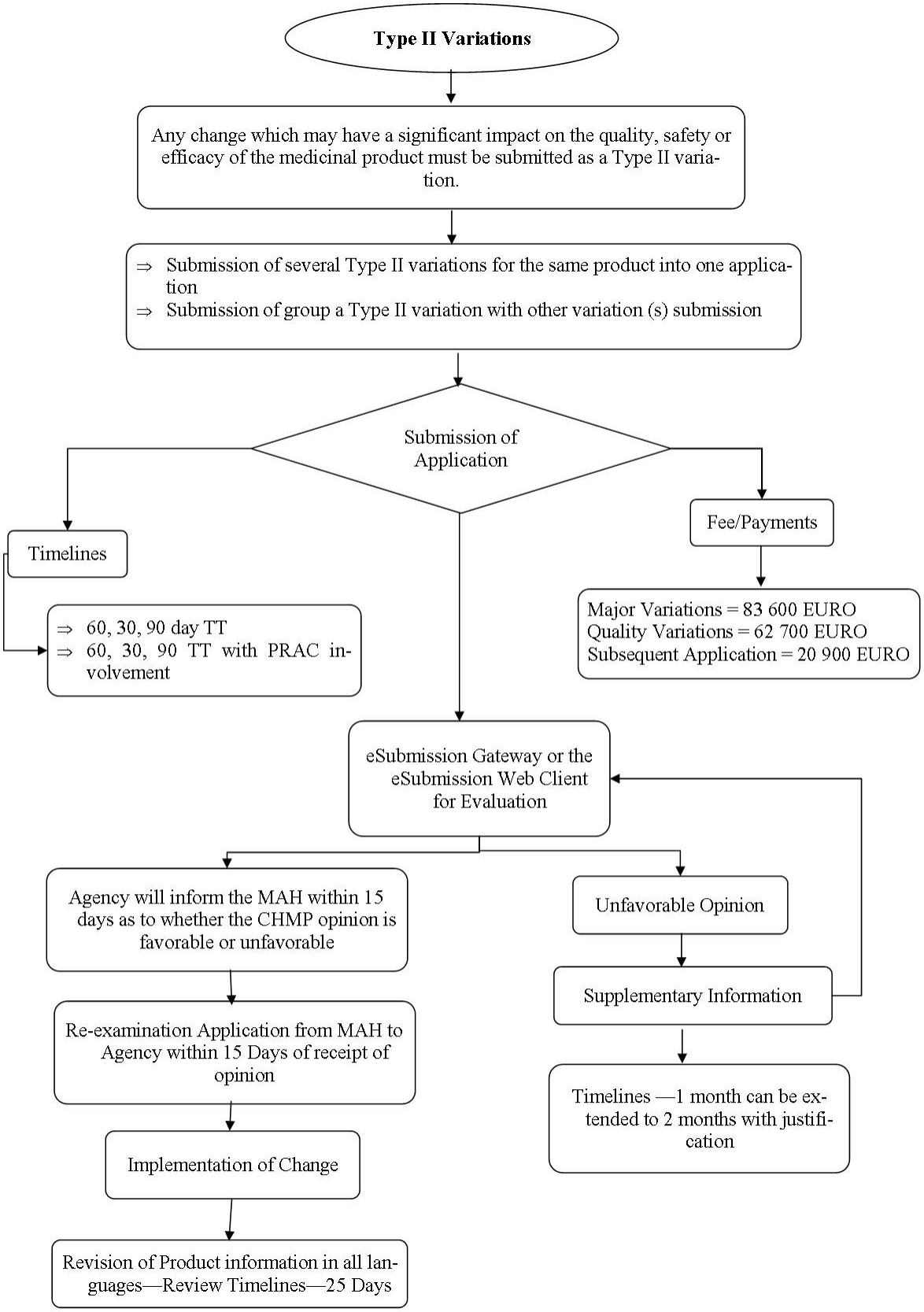

Figure 4: Process of Approval of Type II Variations

Post Approval Changes – US[4]

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 3: Classification of Post Approval Changes

Type of Changes	Rules	Type of application
Major Change	21 CFR 314.70(b)	Prior Approval Supplement
Moderate Change	21 CFR 314.70(c)(5)	Changes Being Effected in 30 days
	21 CFR 314.70(c)(6)	Changes Being Effected
Minor Change	21 CFR 314.70(d)	Annual Report / Notification

Flow Chart for Application Submission and Approval

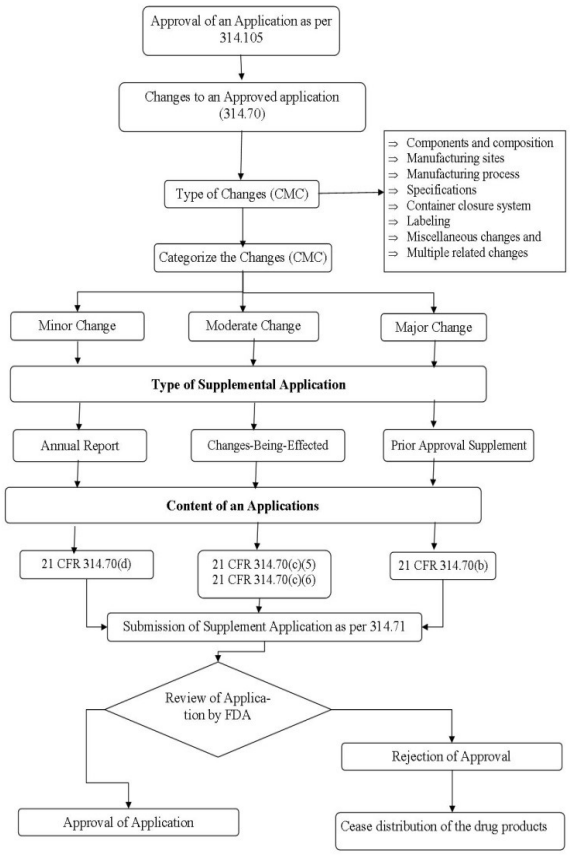

Figure 5: Process of Approval

Post Approval Changes – Saudi Arabia [7]

Type of Variations:

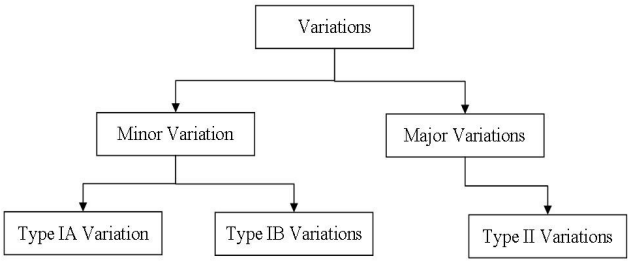

Figure 6: Classification of Variations

Minor Variations:

Type IA: Minor Changes that does not require prior approval before implementation but require notification submitted by the MAH within 60days 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

Steps	Type IA	Type IB	Type II
Validation	10 Days	10 Days	10 Days
Product Licensing (May be)	10 Days	10 Days	10 Days
Assessment	45 Days	105 Days	120 Days
Inspection (May be – Parallel Process)	45 Days	105 Days	120 Days
Pricing (May be – Parallel Process)	20 Days	20 Days	20 Days
Variation Approval	5 Days	5 Days	15 Days
Total Timeline	**60 Days**	**120 Days**	**145 Days**

Flowchart for Variation Application Process:

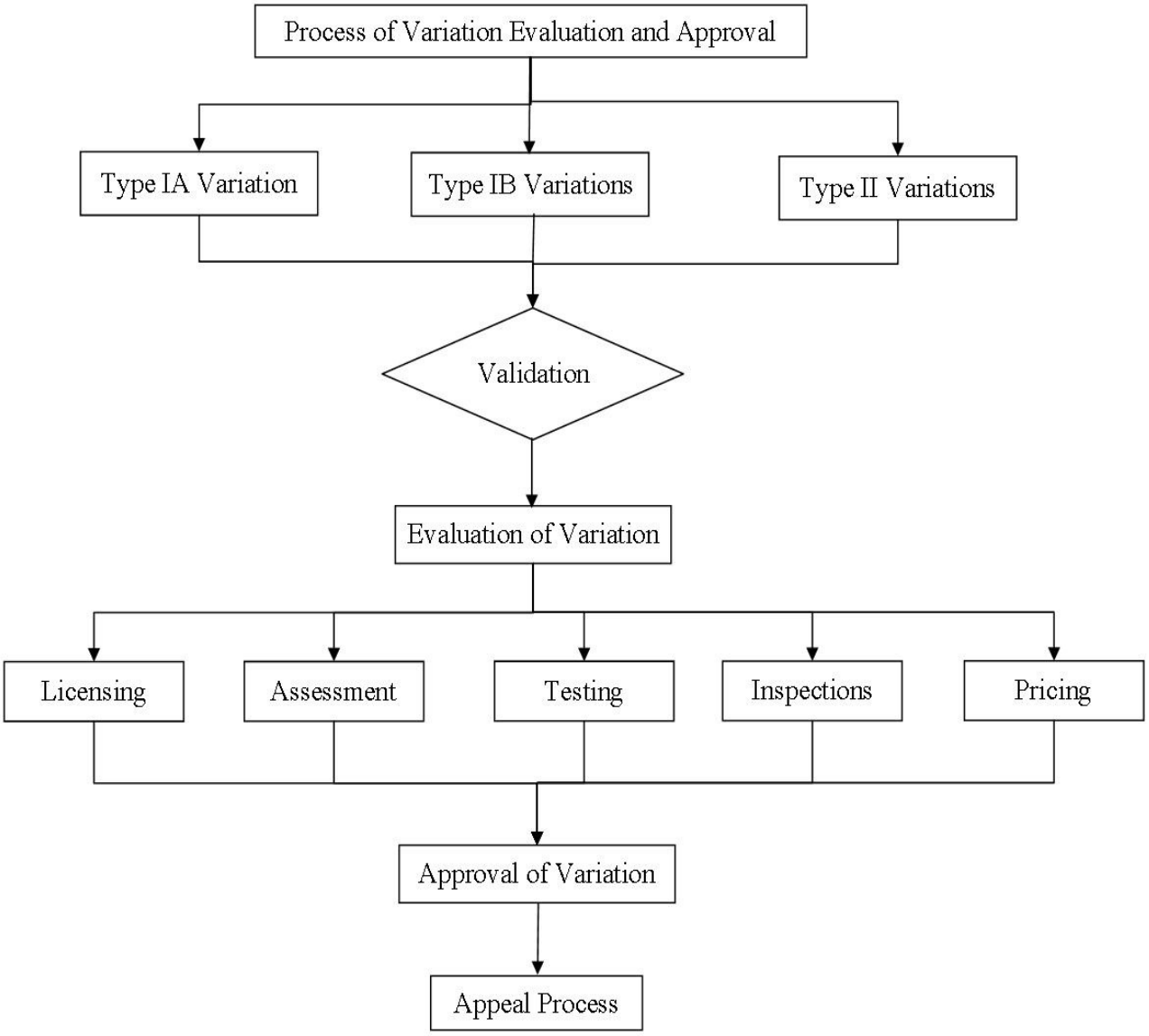

Figure 7: Variation application approval process

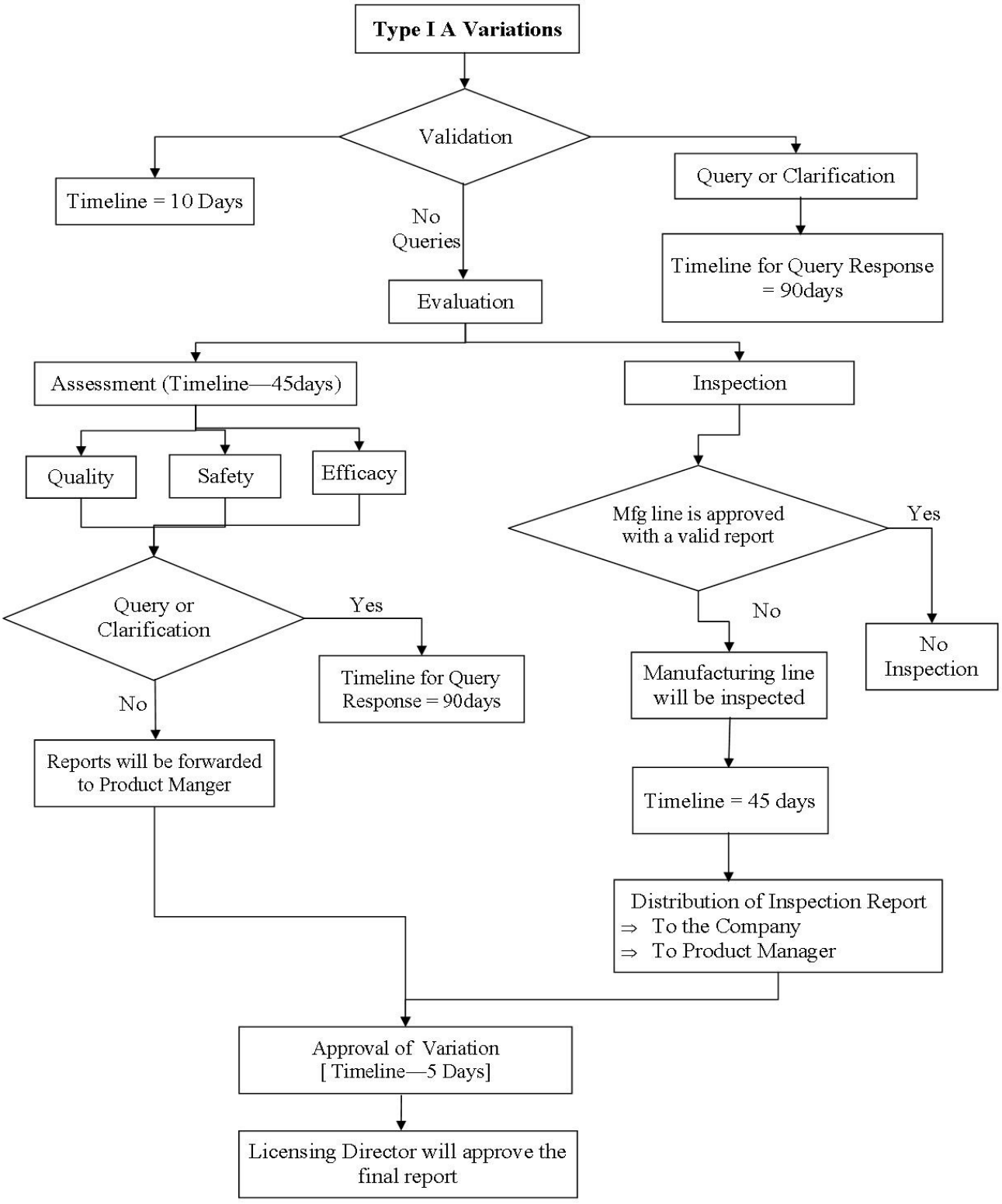

Figure 8: Process of approval of type IA variations

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Flow Chart for "Process of Approval of Type IBVariation"

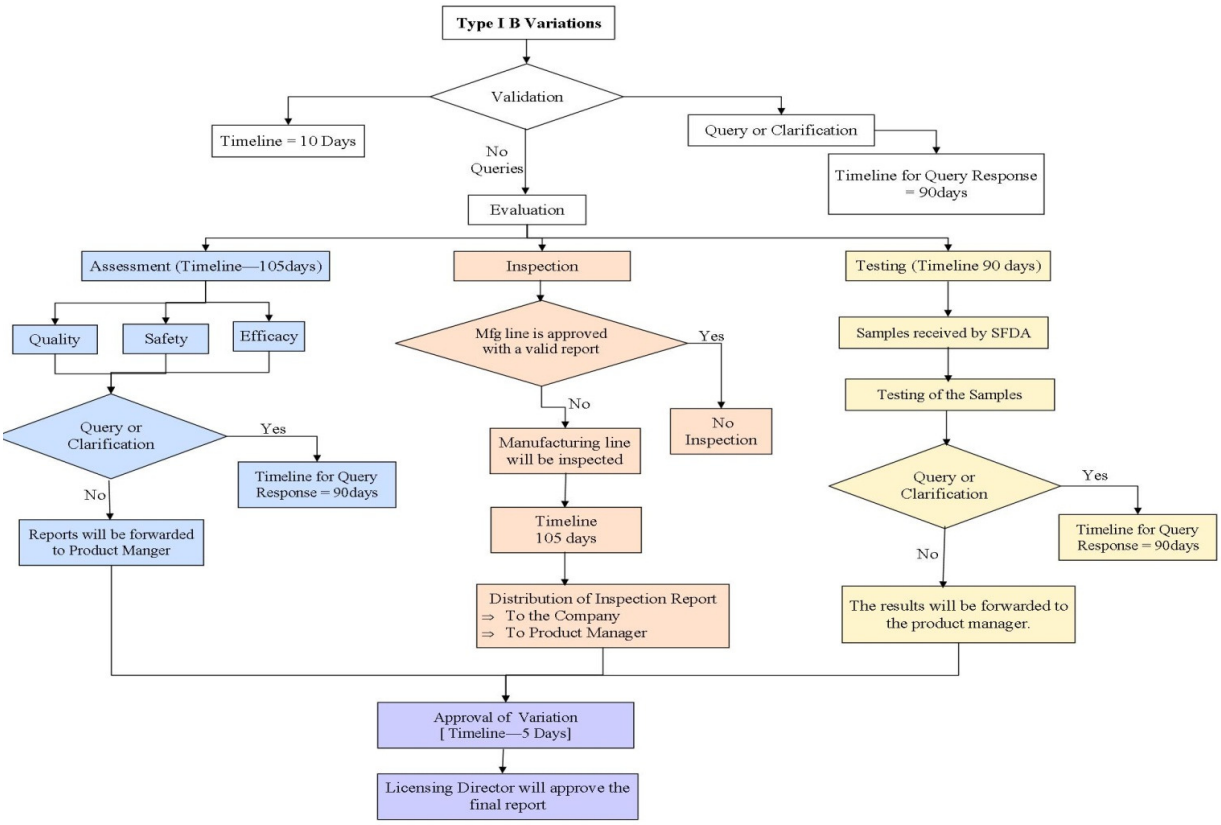

Figure 9: Approval of type IB variations

Flow Chart for Process of Approval of Type IIVariation

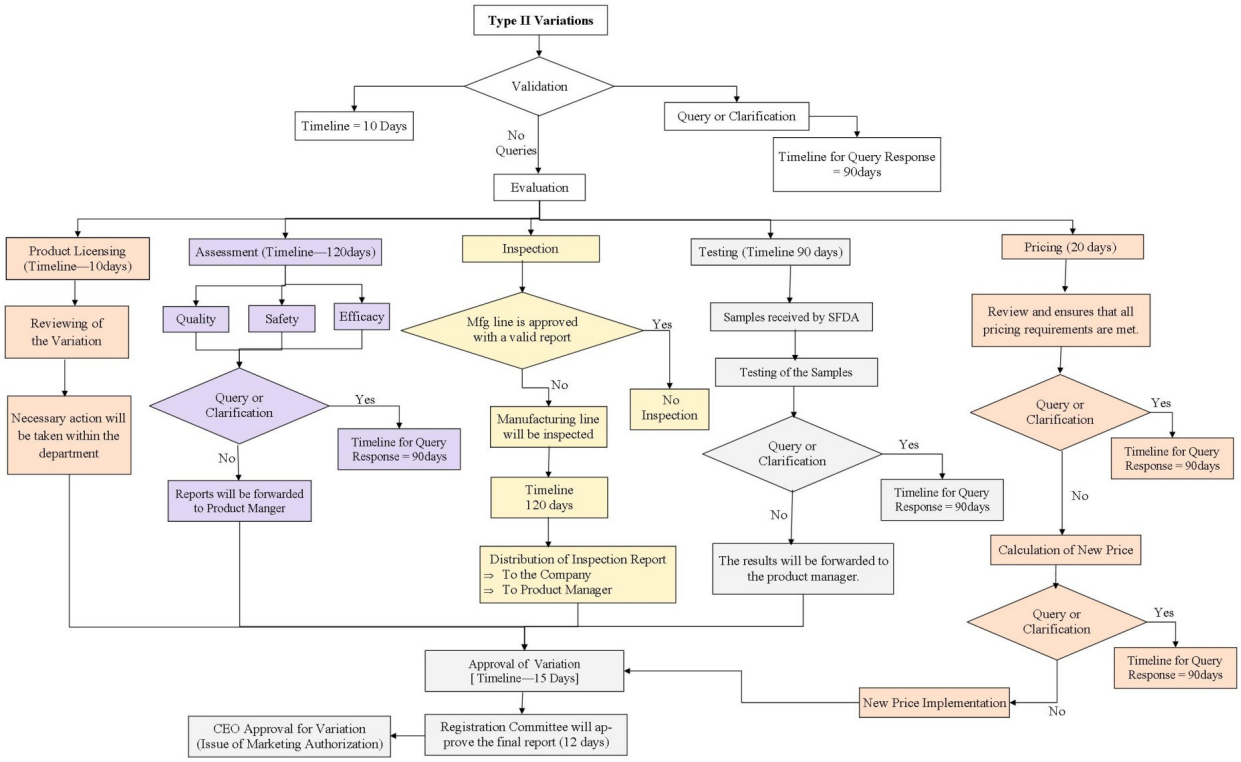

Figure 10: Approval of type IB variations

Post Approval Changes – Singapore [8]

Types of Variations:

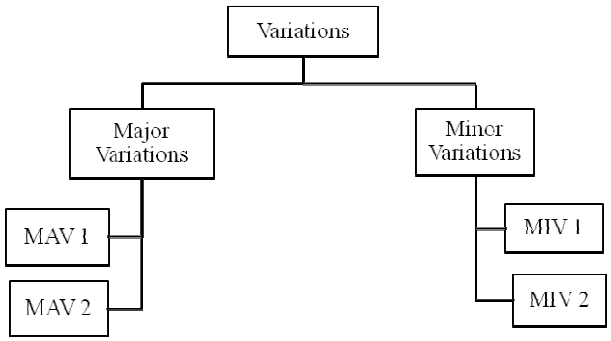

Figure 11: Classification of variation

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

Prescreening Timeline	25 Days		
Dossier Type	Timeline in Days		
	MAV 1	MAV 2	MIV 1
Full	270	---	---
Abridged	180	180	120
Verification	60	---	---
MIV 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		

% of Fee Payable at each stage for MAV I applications:

Stage	% Fee
Acceptance for Evaluation	: 30%
Active Evaluation	: 40%
Midway Evaluation	: 20%
Evaluation Completed	: 10%

Flowchart for Variation Application Process

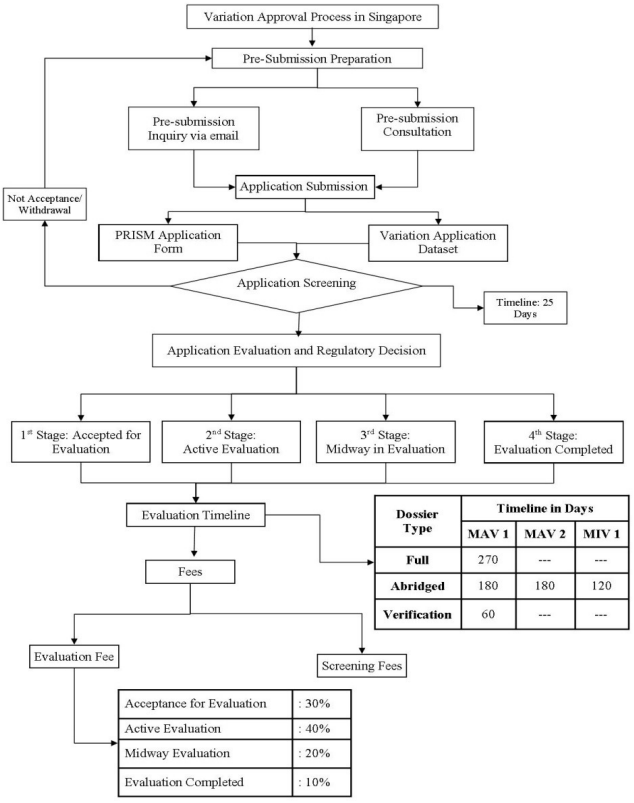

Figure 12: Process of approval of variation application

Post Approval Changes: India[6]

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

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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

Summary of Post Approval Changes in EU, US, Saudi, Singapore & Saudi					
Country	**EU**	**US**	**Saudi Arabia**	**Singapore**	**India**
Regulatory Agency	European Medicines Agency	U.S. Food and Drug Administration	Saudi Food and Drug Authority	Health Sciences Authority	Central Drug Standard Control Organization
Designation	Variations	Scale Up and Post Approval Changes	Variations	Variations	Post Approval Changes
Classification	Type I – Type IA (IA_{IN}), IB Type II – Type II (Extension)	Level I - Minor Level II - Moderate Level III - Major	Type I – Type IA, IB Type II	Major Variation: MAV 1 & MAV 2 Minor Variations: MIV1 & MIV 2	Level I - Major Level II - Moderate Level III- Minor
Reporting Category	Type I: Annual Report Type IA_{IN}: Immediate Notification Type IB: 30 days before distributing the product Type II: Prior Approval Supplement	Level I: Annual report Level II: CBE-30 Days, CBE Level III: Prior Approval Supplement	Type IA: Notification (Within 60days) Type IB: Prior Approval (Optional) Type II: Prior Approval Supplement	MAV 1: Prior Approval Supplement MAV 2: Prior Approval Supplement MIV 1: Prior Approval MIV 2: Notification	Level I: Supplement Level II: Notifiable Level III: Annual Report
Notification Type	Type IA (IA_{IN})	Level I	Type IA	MIV 2	Level III
Application Format	EU CTD	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	ICH CTD, ACTD	No specific format, DMF and supporting justifications &/or undertakings as applicable.
Application Submission	eSubmission Gateway or the eSubmission Web Client	Electronic Submissions, Gateway FDA eSubmitter		PRISM or Variation Application Datasheet	Paper submission.
Timelines (Working Days)	Type IA_{IN}: 30 Type IB: 30 Type II: 30,60,90 Type II Extension: 210	Level II: CBE 30 days	Type IA:60 Type IB:120 Type II: 145	MAV 1: 180,270,60 MAV 2: 180 MIV1: 120	Level I: 180 Level II: 90
Dosage Forms Covered	OSDs, Biologics & Medical Devices	OSDs, Biologics & Medical Devices (Labeling)	OSDs Medical Devices, Biologics	OSDs and Medical Devices	Biologics

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:

1) Comment DFOR. WHO General Guidance On Variations To Multisource Pharmaceutical Products Development of draft based on WHO Expert Committee. 2014;(April):1–24. Available from: http://www.who.int/medicines/areas/quality_safety/quality_assurance/VariationsMultisourcePharmaceuticalProducts_QAS14-575_24022014.pdf accessed on 12th December 2014
2) Wharf C, Kingdom U. Questions and answers on post approval change management protocols Use of Post Approval Change Management Protocols. 2012;44(October):1–6. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125400.pdf accessed on 14th December 2014
3) Implementation C. Pharma Change Control. Available from: http://www.fdanews.com/ext/resources/files/The_Food_And_Drug_Letter/2013/Pharma-Change-Control-Peither-ExecSeries.pdf accessed on 12th December 2014
4) Services H. Guidance for Industry Changes to an Approved NDA or ANDA Guidance for Industry Changes to an Approved. 2004;(April). Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf accessed on 13th December 2014
5) Protection PH. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. 2014;2(June). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003981.pdf accessed on 20th December 2014
6) Safety E, Documents E. Guidance for Industry Submission of Clinical Trial. Available from: http://www.cdsco.nic.in/writereaddata/CDSCO-GuidanceForIndustry.pdf accessed on 21st December 2014
7) Regulatory Framework for Drug Approvals. 2014; Available from: http://www.sfda.gov.sa/en/drug/drug_reg/Regulations/Regulatory_Framework_for_Drug_Approvals_v_5 0.pdf accessed on 12th December 2014
8) GUIDANCE ON MEDICINAL PRODUCT. 2011;(April). Available from: http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/western_medicines/files_guidelines.Par.22361.File.dat/Guidance on Medicinal Product Registration in Singapore 2011 (COMPLETE).pdf accessed on 18th December 2014

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