Regulatory Requirements of Eu Post Approval Procedures of Austrila

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***Abstract*—The main goal of the work is to illustrate the present situation of generic product approval in various nations throughout the world. The ASEAN nations and regulatory framework, which give a summary of important laws and protocols that must be adhered to in each nation. Information about post-approval submission in the EU and its implications across several categories of variation method is included, along with examples of industrial practices involving post-approval management procedure and post-approval submission in the USA. In order to compare bridging approaches between Australia, Canada, Europe, Russia, and ASEAN countries using pertinent case studies from the industry level, the regulatory submissions required for Australia are combined with general requirements that apply here. This allows for the development of appropriate strategies that will enable common development to be achieved at cost-effective rates. A significant advancement in contemporary medicine is the creation of a generic medication that can be sold anywhere in the world. Countries and regulatory agencies must work together during this process to make sure that each nation's laws are considered when creating the product. To ensure that products are launched on time and in compliance with current rules, a thorough regulatory strategy must also be created to direct this process. With new rules being put into place in the US and the EU, the pharmaceutical business is going through a time of tremendous transformation and change. Companies will have more freedom going ahead if they are aware of the criteria in other nations. This will enable them to reach broader markets, which may eventually result in higher earnings. As a result, reading these four articles together can provide a wealth of information about the current trends in the pharmaceutical sector. Understanding the various needs for each nation's regulatory system and how these systems interact with one another is one of the challenges in creating a global pharma product.**

***Index Terms*—ASEAN Nations, post-approval submission in the EU, post-approval submission in the USA**

I. INTRODUCTION

If pharmaceutical businesses hold European Medicines Agency (EMA) licenses for their medicines, they can ask the agency for scientific and regulatory guidance. It is referred to as the product lifecycle's post-authorization stage. The most recent amendment standardized the variation method throughout the EU and made implementation mandatory at the national level.
A guideline offers a standardized list of anticipated variations together with categorization codes, in addition to the European legislation that defines the categories of variations.Since the adoption of the Mutual Recognition Procedure (MRP) in 1998, a standardized list of modifications for European MAs has been in place.
However, at the time, a number of EU member states had not completely embraced the national standards controlling European variation processes. The European Medicines Agency (EMA) may need to be contacted by holders of marketing authorizations in a number of post-authorization scenarios.
Throughout post-authorization review processes, the medical product's Product Lead serves as the primary point of contact; however, in certain situations, EMA can be contacted via other channels.
It may be necessary to get in touch with EMA outside of the parameters of a specific review procedure for questions pertaining to specific post-authorization procedure types, and the EMA offers a pre-submission

inquiries service.Your product's EMA Product Lead is the primary point of contact for the marketing authorization holder (MAH). The Product Lead should be contacted if you have any questions concerning the evaluation procedure. If necessary, additional product team members may be included in the review, depending on the type, extent, and complexity of the application. To address certain aspects of the review, they are encouraged to get in touch with the MAH directly. For specific procedures (post-authorization safety studies (PASS) and periodic safety update single assessments (PSUSA) for nationally approved products (NAPs), the MAH should get in touch with the Risk Management Specialist, who collaborates closely with the Product Lead.Any correspondence between the candidate and other EMA product team members should always be copied to the Product Lead. For some procedures (type IA and IB modifications, marketing authorization transfers, and Article 61(3) notices), the European Medicines Agency (EMA) keeps a dedicated pre-submission inquiries service. The service aims to provide prompt pre-submission support to aid in the validation of these post-authorization applications.

Before submitting an application, MAHs can consult with an EMA procedure manager about any pre-submission questions and receive comprehensive regulatory assistance on prospective applications. Please include the product name and as much other pertinent information as you can. If you are not sure what kind of submission you intend to submit, use the option that is most likely related to your procedure. If the question is about more than one procedure (for example, both a type IA and a type IB variation), please only submit one query.

Contacting EMA outside of a post-authorization procedure: The Product Lead can also talk about a variety of other product-related issues during the post-authorization phase that aren't connected to a particular evaluation method (i.e., not related to a variation, extension, renewal, annual-reassessment, PSUR, referral, postauthorization measure, or an administrative procedure).

For instance, limitations on the supply of future pharmaceutical products; details on new safety concerns; the release of important late-breaking information that could affect the product's profile or marketing authorization; and the revocation of marketing authorization. Communication via the Product Lead complements, not replaces, formal reporting requirements and established reporting channels, such as for pharmacovigilance reporting. A Product Lead is assigned by EMA to handle any pre-submission inquiries during the eligibility phase of an initial marketing authorization application.

Submitting a post-authorisation application: The electronic Common Technical Document (eCTD) has been the only accepted electronic format for all applications and submission types in the centralised system from January 1, 2010. This applies to all new and current applications to the European Medicines Agency, as well as all forms of submissions (EMA).

- New applications, extra information, variations, renewals, follow-up measures (FUMs), periodic safety update reports (PSURs) for centrally approved goods, Notifications, and other items fall under this category.
- Any Word document required for Module 1 (e.g. product information Annexes) and Module 2 should be located in the same e Submission Gateway and e Submission Web Client package within a folder called "xxxx- working documents," where the number
- (xxxx) equals the sequence number, when submitting an application in eCTD**.**

II. RESEARCH METHODOLOGY

EU Post Approval

EU Agency Initiation

1. There is no concept of Annual Report in Europe, Australia and Canada market.
2. EU aim with the ultimate target of reducing the number of issues raised during validation.

Continuously monitoring and improving our procedures, guidance and interaction with stakeholders

What is Variation?

1. Changes to the contents of the approved dossier for medicinal products called variations in Europe.
2. The changes must be notified to or approved by the relevant regulatory authorities.
3. Alongside the European legislation that defines variation types, a guideline lays out a harmonised list of anticipated variations with classification codes.1 A defined list of variations for European

MAs has existed since implementationof the Mutual Recognition Procedure (MRP) in 1998. However, the legislation governing European variation procedures was not fully adopted at the national level by many EU member states at that time. Legislation has periodically been updated and in the most recent update, in August 2013, implementation was made mandatory at the national level and the variation process has been completely harmonised across the EU. The classification codes are as follows:

Minor Variation:

Type-IA/IAIN

Type-IA - ("Do and Tell") These variations do not require any prior approval, but MAH should notify within 12 months.

Type-IA_{IN} ("Do and Tell")

It requires immediate notification after implementation ("Do and Tell").

Changes that fall under this category are commonly referred to as "do and tell" variations because the applicant is required to implement the change and then notify the agency of the details. This level of variation is reserved for administrative changes that are anticipated to have no impact on the safety or efficacy of a product. Variations that can be submitted as Type IA must be implemented and then the required submission made within one year of the implementation date. For changes that are categorised as Type IAIN the applicant must notify the agency within 14 days of implementation. Multiples of these variations for a single product can be made at the same time, as long as all of them fall within the required submission deadline. According to Commission Regulation (EC) No 1234/2008, Type IA/IAIN procedures are minor variations which have only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned. These are clearly classified in the Guidelines on the details of the various categories of variations and in the CMD. Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008.These are clearly classified in the Guidelines on the details of the various categories of variations and in the CMD Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008. Type IA variations do not require assessment. These are simple, administrative procedures.

Major Variation:

Type-II ("Tell and do")

• This requires regulatory approval before implementation.

• Timeline: Usually 60 day review; range 30-90 days

• Significant impact on the Quality, Safety or Efficacy of the medicinal product E.g.- o New API DMF source o Change in batch size for MR product o Change outside the approved FP specification limits.

Extension applications: e.g., additional strengths, pharmaceutical form and route of administration (up to 210- day review)

• This classification is reserved for major variations which are expected to affect the safety and efficacy of a product and require careful assessment before the applicant can implement the change.

• They require considerable supporting documentation and must be assessed and signed off by an appropriately qualified expert in their respected field before being submitted.

• Line Extensions-Certain changes which affect the fundamentals of the terms of the authorisation cannot be granted via a variation and are submitted as an "extension application": changes to the active substance(s); changes to strength, pharmaceutical form and route of administration. The invented name will remain the same for the "extension".

Guideline Structure:

ADMINISTRATIVE CHANGES

B. QUALITY CHANGES

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

D. PMF / VAMF

I. Active Substance

a) Manufacture
b) Control of active substance
c) Container closure system
d) Stability
e) Design Space and post approval change management protocol

II. Finished Product

a) Description and composition
b) Manufacture
c) Control of excipients
d) Control of finished product
e) Container closure system

f) Stability
g) Design Space and post approval change management protocol
h) Adventitious Agents Safety III. CEP/TSE/monographs
IV. Medical Devices
V. Changes to a marketing authorisation resulting from other regulatory procedures
a) PMF/VAMF
b) Referral
c) Other changes to the quality dossier requested by the competent authority
C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES
I. Human and Veterinary medicinal products
II. Veterinary medicinal product – specific changes
D. PMF / VAMF
Case Study
Case study: Type- IA Variation
Type- IA Variation
- Minor change in analytical procedure of dissolution (Removal of SS filters) B.II.d.2
a) Change in test procedure for the finished product
- Minor changes to an approved test procedure
Minor change in analytical procedure of dissolution.
Types of Applications submitted to the TGA for Registration of medicines
Category 1 applications
- Category 1 applications are provided for under sub regulations 16C (3) (b) and 16D (3)
- (b). An application for a new medicine or a change to a medicine constitutes a Category 1 application if it does not meet the specific requirements for Category 2 or 3. For example, an application for a medicine containing a new active substance normally belongs to Category 1 or 2.
- These are applications submitted for new medicine, new dosage forms, new strengths, and new generics. Extensions to indications and changes to product information (PI) also constitute category 1 application

Category 2 applications

Category 2 application provisions can only be utilised when an application has been previously approved in two acceptable countries. For a Category 2 application, two independent evaluation reports from acceptable countries, where the product is already approved, are required to be provided at the time of application. Product proposed to be registered in Australia should be identical to that registered in the acceptable countries, with respect to formulation, directions for use and indications.
Please note that if the data submitted in Australia are different to that submitted overseas, questions may be raised leading to a delay in approval, Acceptable countries: Canada, Sweden, the Netherlands, the United Kingdom and the United States of America.
Category 3 applications

Category 3 applications involve changes to the quality data of medicines already included on the ARTG, which may or may not render the medicines separate and distinct (and therefore subject to separate registration), and which, in the opinion of the Secretary, do not need to be supported by clinical, non-clinical or bioequivalence data.
The quality changes subject to category 3 application may include:

1. The specifications for the active ingredient, finished products
2. The method of manufacture of active ingredient
3. The manufacturing procedure for finished product
4. The site of manufacture of active ingredient or finished product
5. Shelf life
6. Storage
7. Labelling

The regulatory process for evaluation of prescription medicines consists of eight phases. Each phase has a milestone that must be completed before commencement of the following phase. This approach allows effective and transparent management of resources and timelines for all applications.The legislated TGA commitment of 255 working days between acceptances for evaluation through to the delegate's decision will also remain but will not be used for planning or for target times. The registration process is designed to take, on average, 330 calendar days (11 months), including the time for applicant activities.

1. Before the Pre-submission (Pilot-ANDA) Phase

Pre-submission (pre-ANDA) meetings: A pre-submission meeting between TGA Delegates and sponsors who intend to submit an application to the DSEB is strongly recommended in certain cases. Such cases include:

Complex applications. A face-to-face meeting with TGA staff is appropriate for complex applications, especially if there is a need for either party to provide clarity on a particular issue or there is some uncertainty as to whether the registration dossier to be submitted will meet all Australian regulatory requirements.

A pre-submission meeting is also available to sponsors for other applications. Guidelines for meetings with the TGA are provided at Appendix 5 (Conduct of meetings between TGA and sponsors).

If sponsor wishes to discuss scientific or procedural issues, and for complex submissions. Selection of overseas reference product for Bio-study can be discussed A pre-submission ID is assigned by the TGA for submission purpose.

Considerable points:

1. Date of Submission
2. Nomination Time for S.31 – (30 days or 60 Days)
3. Draft PI
4. Selection of Reference Product
5. GMP Clearance Tracking Number (Valid Up to 6 M)
6. Risk Management Plan
7. Draft Summary of Module – 2 (Quality/Non Clinical/Clinical)

The pre-submission phase applies to category 1 and category 2 applications, excluding requests for additional trade names.The pre-submission phase begins with the lodgement of the Pre-submission planning form (PPF). The PPF provides the TGA with the necessary information on the scope and scale of an application to arrange appropriate resourcing for the processing and evaluation of the application. Once a PPF has been considered complete and acceptable, the TGA begins the process of securing appropriate evaluators for the dossier.A complete PPF identifies the proposed application type, and contains general information about the quality, nonclinical, and clinical evidence to be included in the dossier. The information provided in the PPF allows the TGA to commit to timeframes for the evaluation of the application.

III. RESULTS AND DISCUSSIONS

The exact content of the application dossier will vary according to the:

1. Application category
2. Nature of the medicine
3. Application type

A dossier documents matrix is provided in CTD Module 1: Administrative information and prescribing information for Australia which provides a high-level overview of the application dossier CTD section requirements for different application types.

CTD Module 1: Administrative information and prescribing information for Australia establishes the Module 1 content for different application types.

CTD Module 2 is a summary module which provides an overview of the information/data provided in the quality (Module 3), nonclinical (Module 4), and clinical (Module 5) modules of the dossier. Information on the content of Module 2 is provided at the beginning of CTD Modules 3, 4, and 5.The organisation of Modules 3, 4, and 5 is specified by the CTD Modules 3, 4, and 5. These modules contain headings and sub-sections under which applicants must insert technical data.The application dossier must provide appropriate documentation (in the correct format and locations, as determined by the CTD modules), including outcomes of trials and studies, to allow the Delegate of the Secretary to assess quality, safety, and efficacy claims. The technical data requirements that establish the documentation to be provided in the dossier are:Australia-specific requirements are identified in CTD Module 1: Administrative information and prescribing information for Australia and TGA guidelines.EU guidelines adopted in Australia - guidelines prepared by the European Committee for Medicinal Products for Human Use (CHMP) and/or those prepared within the ICH process that have been adopted by the TGA.The use of EU guidelines adopted in Australia and other Australia-specific guidelines is not mandated in the legislation. However, section 25(1)(d) of the Act requires that when making a decision on whether to approve a medicine for registration, the delegate determines: “whether the quality, safety and efficacy of the goods for the purposes for which they [the goods] are to be used have been satisfactorily established;”Where a dossier does not address the applicable requirements/guidelines, or fails to

adequately justify why an applicable requirement/guideline has not been addressed in the application, we may be unable to establish satisfactorily the quality, safety or efficacy of the proposed good.

Post approval Changes Change in Sponsor

Documentation:1. Name and address of new sponsor

2. List of affected products

3.Timeline: One week

Change in Drug Product Manufacturing Site

Documentation:

Process validation of 3 batches at new sites

GMP certificate

Batch analysis: 3 batches at new site vs. 3 batches at old site

Dissolution profile 3 batches at new sites vs. old site

Comparison of mfg. processes at the new vs. old site

Validation of finished product test methods at the site of quality control testing

Stability protocol and data (if available) or assurance

Timeline (Prior Approval Change): 2-3 months

IV. SUMMARY & CONCLUSION

The combination of legal, administrative, and technical measures that governments take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information, can be defined as pharmaceutical regulation. The goals of all national pharmaceutical laws across the globe are the same: to protect and promote public health. However, the execution of procedures and systems to achieve these similar goals has been quite variable, with national rules and technological requirements varying dramatically, at times.The formation of distinct institutional pharmaceutical systems has been influenced by a variety of histories, cultures, and political experiences, as well as country economic characteristics. The evolution of pharmaceutical systems and laws, as well as the availability of drugs, varies greatly around the globe. International cooperation mainly focuses on establishment of bilateral and multilateral efforts to leverage human, scientific, and financial resources, as well as the knowledge and experience of other key regulatory authorities, in order to avoid duplication of efforts and focus limited resources on higher-risk areas of concern.The process of integrating national standards with international standards in a way that is generally acceptable to participating nations in order to allow efficient global drug development and local registration has been termed as pharmaceutical regulatory harmonisation. This process must be distinguished from regulatory convergence, which is a method by which regulatory requirements in different countries/regions gradually become more similar or aligned as a result of the gradual adoption of internationally recognised technical guidance documents, standards, and best practises. Harmonization of pharmaceutical rules necessitates close collaboration not just among regulators throughout the world, but also among other stakeholders. Cooperation and harmonisation are, in fact, inextricably linked. Harmonization of standards and languages is required for collaboration, because harmonisation implies cooperation. As a result, this book examines both aspects: pharmaceutical regulation harmonisation and international collaboration. Cooperation and standardisation in the pharmaceutical industry are already a reality, and have grown in importance over the last few decades, thanks to a high level of commitment from all players.From the regulatory point of view, the FDA's primary concern is to protect the American public on drug products that are not interchangeable due to bioequivalence, clinical equivalence or other concerns that would not require a drug product to be therapeutically equivalent to another drug product. Upon the implementation of the changes which are approved by the regulatory authority which helps to increases the product safety for the patients as well as meets the organization’s requirements. Generally, the drug approval process to be composed mainly in the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug.Regardless of a product’s route or country of registration, one constant across the pharmaceutical industry is the requirement to keep dossiers updated and current. A change to an approved application must be reported to FDA in accordance with all statutory and regulatory requirements, including section 506A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. Making and reporting manufacturing modifications to an authorised application, as well as distributing a drug product created with such changes, are all covered under

Section 506A of the FD&C Act.Pharmaceutical companies can request scientific and regulatory guidance from the European Medicines Agency if their medicinal products have been licensed in Europe (EMA). A consistent list of variations for European MAs has existed since the Mutual Recognition Procedure (MRP) was adopted in 1998. 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. Regardless of a product's route or country of registration, one constant across the pharmaceutical industry is the requirement to keep dossiers updated and current.Pharmaceutical companies can request scientific and regulatory guidance from the European Medicines Agency if their medicinal products have been licensed in Europe (EMA). A consistent list of variations for European MAs has existed since the Mutual Recognition Procedure (MRP) was adopted in 1998. 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.The European Commission is a key player in the regulation of drugs in the European Union. The European Medicines Agency (EMA) gives, denies, alters, or suspends marketing authorisations for medicines submitted through the centralised method based on scientific findings.The Heads of Medicines Agencies forum brings together the national competent authorities (NCAs) in charge of regulating human and veterinary medicines in the EU (HMA).The heads of the NCAs collaborate closely with the European Pharmaceuticals Agency (EMA) and the European Commission to maximise collaboration and ensure that the European medicines regulation network runs smoothly.The HMA meets four times a year to discuss critical network strategic topics such as information exchange, IT advances, and best practise sharing, as well as to simplify mutual recognition and decentralised procedures.The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which brings together medicines regulatory authorities and the pharmaceutical industry from around the world, is one of the main forums for multilateral international cooperation for the EU.The International Conference on Harmonization (ICH) is committed to harmonisation in terms of safety, quality, and effectiveness as the primary criterion for licencing and authorising new pharmaceuticals. For veterinary medications, the Veterinary International Conference on Harmonisation (VICH) is the similar venue.Overall, this conducted work describes the basics of pharmaceutical regulatory framework along with comparison study between various pharmaceutical regulation or approaches followed among ASEAN countries. We can say that, manufacturing of good quality medicines is the basic core behind every pharmaceutical regulatory approaches. The conducted work also gives idea about therapeutic goods and pharmaceutical regulatory procedure in European Union. It also describes Post Approval management scenario of United States and European Union.

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