COMPARATIVE ANALYSIS OF PHARMACOVIGILANCE REGULATION IN EUROPE AND MALAYSIA

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ABSTRACT
Pharmacovigilance is science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems. Regulatory requirements for Pharmacovigilance in different countries are varying from each other so it is challenging for companies to develop and making pharmacovigilance requirement and comply with the requirement of different countries. The objective of this work to compared the regulatory requirement of pharmacovigilance in Europe and Malaysia. It also helps to understand the regulatory requirement in relation to pharmacovigilance in regulated (Europe) and semi regulated country (Malaysia). This article mainly focuses on pharmacovigilance guideline related to adverse drug reaction (ADR), Periodic Safety Update Report (PSUR); and Risk Management system in Europe and Malaysia.

Key Words: Pharmacovigilance, ADR, PSUR, Risk Management Plan (RMP)

INTRODUCTION OF PHARMACOVIGILANCE
WHO defines Pharmacovigilance is the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems. Pharmacovigilance (PV), also known as Drug Safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. The word "pharmacovigilance" means: Pharmakon (Greek for drug) and Vigilare (Latin for to keep watch).
PHARMACOVIGILANCE OF EUROPE

Europe is a regulated country and the Pharmacovigilance documents filing rules is mainly divided into three types. 1) Centralized procedure 2) Decentralized and mutual recognize procedure and 3) National authorise procedure. All medicinal products in the EU are subject to a strict testing and assessment of their quality, efficacy, and safety before being authorized.

The European Medicines Agency (EMA) has released good pharmacovigilance practice guidelines (GVP) in order to facilitate the performance of pharmacovigilance activities. These GVP modules replace Volume 9A of "The rules governing medicinal products in the European Union - Pharmacovigilance."

GVP Module I Pharmacovigilance systems and their quality systems

It includes a system used by an organization to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance.

The quality system is part of the pharmacovigilance system and consists of its own structures and processes.

GVP Module II Pharmacovigilance System Master File (PSMF)

The definition of Pharmacovigilance System Master File is "A detailed description of the Pharmacovigilance (PV) system used by the marketing authorization holder (MAH) with respect to one or more authorized medicinal products."

Information to be contained in the pharmacovigilance system master file

1. PSMF section on qualified person responsible for pharmacovigilance
2. PSMF section on the organisational structure of the marketing authorisation holder
3. PSMF section on the sources of safety data
4. PSMF section on computerised systems and databases
5. PSMF section on pharmacovigilance processes
6. PSMF section on pharmacovigilance system performance
7. PSMF section on quality system.

GVP Module III Pharmacovigilance inspections

Pharmacovigilance is also concerned with the inspection system. It is responsibility of marketed authorise to comply with requirement specify by authority and inspect it as per guideline.
It contains different Inspection types such as
1. System and product-related inspections
2. Routine and “for cause” pharmacovigilance inspections
3. Pre-authorisation inspections
4. Post-authorisation inspections
5. Announced and unannounced inspections
6. Re-inspections
7. Remote inspections.

GVP Module IV Pharmacovigilance audits
The principles in this Module are aligned with internationally accepted auditing standards, issued by relevant international auditing standardisation organisations and support a risk-based approach to pharmacovigilance audits.

GVP Module V Risk Management Plan (RMP)
Marketed authorize holder (MAH) must be necessary to follow and submit RMP as per GVP module 5.
The RMP consists of seven parts. Part II is divided in to eight modules.
1. Part I “Product overview”
2. Part II “Safety (S) specification”
   2.1 Module SI Epidemiology of the indication(s) and target population(s):
   2.2 Module SII Non-clinical part of the safety specification
   2.3 Module SIII Clinical trial exposures
   2.4 Module SIV Populations not studied in clinical trials
   2.5 Module SV Post-authorization experience
   2.6 Module SVI Additional EU requirements for the safety specification
   2.7 Module SVII Identified and potential risks
   2.8 Module SVIII Summary of the safety concerns
3. Part III “Pharmacovigilance plan”
4. Part IV Plans for post-authorization efficacy studies
5. Part V “Risk minimization measures”
6. Part VI Summary of activities in the risk management plan by medicinal product
7. Part VII Annexes to the risk management
RMP submission requirements in specific situations is given in table.1
Table 1. Requirements in specific situations

<table>
<thead>
<tr>
<th>Type of new application</th>
<th>Part-I</th>
<th>Part-II Module SI</th>
<th>Part-II Module SII</th>
<th>Part-II Module SIII</th>
<th>Part-II Module SV</th>
<th>Part-II Module SVI</th>
<th>Part-II Module SVII</th>
<th>Part-II Module SVIII</th>
<th>Part-III</th>
<th>Part-IV</th>
<th>Part-V</th>
<th>Part-VI</th>
<th>Part-VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>New active substance</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Similar Biological</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Informed consent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Generic medicine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
</tr>
<tr>
<td>Hybrid medicinal products</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fixed combination</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Same active substance</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

GVP Module VI Adverse drug reaction reporting

Adverse drug reaction reporting system is given in GVP module 6 and time period of reporting is given in Table 2

Table 2. Reporting requirements applicable to MAH to final arrangement

<table>
<thead>
<tr>
<th>Marketing authorisation procedure</th>
<th>Origin</th>
<th>Adverse reaction type</th>
<th>Destination</th>
<th>Time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Centralised</td>
<td>EU</td>
<td>All serious</td>
<td>EudraVigilance</td>
<td>15 days</td>
</tr>
<tr>
<td>• Mutual recognition or decentralised</td>
<td></td>
<td></td>
<td>database</td>
<td></td>
</tr>
<tr>
<td>• Purely national</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All serious</td>
<td>EU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonserious</td>
<td>EU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non EU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GVP module VII Periodic Safety Update Reports (PSUR)

PSUR is a systematic review of the global safety data which become available to the manufacturer of a marketed drug during a specific time period in an internationally agreed format.

Marketing authorisation holders for products authorised before 02 July 2012 (centrally authorised products) and 21 July 2012 (nationally authorised products) and for which the frequency and dates of submission of PSURs are not laid down as a condition to the marketing authorisation or determined otherwise in the list of European Union reference dates shall submit PSURs according to the following submission schedule.
• At 6 months intervals once the product is authorised, even if it is not marketed;
• Once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.

Marketing authorisation holders should submit PSURs to the Agency according to the following timelines:
• Within 70 calendar days of the data lock point for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
• Within 90 calendar days of the data lock point for PSURs covering intervals in excess of 12 months;
• The timeline for the submission of ad hoc PSURs requested by competent authorities will normally be specified in the request, otherwise the PSURs should be submitted within 90 calendar days of the data lock point.

They follow format and content for PSUR is given in GVP module VI

Part I: Title page including signature
Part II: Executive Summary
Part III: Table of Contents includes: Introduction, Worldwide marketing authorisation status, Actions taken in the reporting interval for safety reasons, Changes to reference safety information, Estimated exposure and use patterns, Data in summary tabulations, Summaries of significant findings from clinical trials during the reporting interval, Findings from non-interventional studies, Information from other clinical trials and sources, Non-clinical Data, Literature, Other periodic reports, Lack of efficacy in controlled clinical trials, Late-breaking information, Overview of signals: new, ongoing or closed, Signal and risk evaluation, Benefit evaluation, Integrated benefit-risk analysis for authorised indications, Conclusions and actions, Appendices to the PSUR.

GVP Module VIII Post-authorisation safety study
It is a study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk-management measures.

This Module contain format of Protocols, abstracts and final study reports for post-authorisation safety studies.
Format of the final study report contains: Title, Abstract, Marketing authorisation holder, Investigators, Milestones, Rationale and background, Research question and objectives, Amendments and updates to the protocol, Research methods, Results, Discussion, References.

GVP Module IX Signal management
It is as the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed.

The signal management process covers all steps from detecting signals to recommending action(s) as follows:

- Signal detection;
- Signal validation;
- Signal analysis and prioritisation;
- Signal assessment;
- Recommendation for action
- Exchange of information.

GVP Module X Additional monitoring
The list of medicines under additional monitoring includes medicines authorised in the European Union (EU) that are being monitored particularly closely by regulatory authorities. The list includes centrally and nationally authorised medicines in the following categories:

- Medicines that contain a new active substance that was not contained in any authorised medicine in the EU on 1 January 2011
- Biological medicines authorised after 1 January 2011 - this applies to all biological medicines including biosimilars
- Medicines for which the marketing-authorisation holder is required to carry out a post-authorisation safety study (PASS)
- Medicines given conditional approval or authorised under exceptional circumstances and medicines authorised with specific obligations on the recording or monitoring of suspected adverse drug reactions

Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and summary of product characteristics, together with a short sentence explaining what the triangle means.
GVP Module XV Safety communication
This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency on how to communicate and coordinate safety information in the EU.

Safety communication is a broad term covering different types of information on medicines, including statutory information as contained in the product information (i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging) and public assessment reports.

Different communication tools and channels
- Direct healthcare professional communication (DHPC)
- Documents in lay language
- Press communication
- Website
- Bulletins and newsletters
- Responding to enquiries from the public

GVP Module XVI Risk minimisation measures: selection of tools and effectiveness indicators
The risk minimisation plan is an integral part of the RMP.
Risk minimisation measures may consist:
- Routine risk minimisation
- Additional risk minimisation measures

PHARMACOVIGILANCE OF MALAYSIA
The National Pharmaceutical Control Bureau (NPCB) is regulatory authority of Malaysia. Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) was established under Drug Control Authority (DCA) to perform the function of pharmacovigilance for drugs registered for use in Malaysia.

Malaysia was 30th member of the World Health Organisation (WHO) Programme for International Drug Monitoring in 1990.
Adverse drug reaction reporting

ADR reporting system in Malaysia is given in “Malaysian Guidelines for the Reporting & Monitoring”

Summary of reporting requirement is given in Table.3

Table.3 Summary of reporting requirements

<table>
<thead>
<tr>
<th>Types of ADR</th>
<th>Time frame for reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening or Fatal</td>
<td>As soon as possible but No later than 7 calendar days after first knowledge by the register holder, followed by as complete a report as possible within 8 additional calendar days.</td>
</tr>
<tr>
<td>Serious, expected</td>
<td>As soon as possible but no later than 15 calendar days after first knowledge by the register holder.</td>
</tr>
<tr>
<td>Serious, unexpected</td>
<td>As soon as possible but no later than 15 calendar days after first knowledge by the register holder.</td>
</tr>
<tr>
<td>Non Serious, unexpected</td>
<td>Within 15 calendar days</td>
</tr>
<tr>
<td>Non Serious, expected</td>
<td>Within 15 calendar days</td>
</tr>
<tr>
<td>Foreign reports</td>
<td>Not require on routine bases</td>
</tr>
<tr>
<td>Local and foreign report</td>
<td>Notification of change in nature severity, frequency or risk factors</td>
</tr>
<tr>
<td>New information on risk-benefit profile of product including international regulatory decisions</td>
<td>3 days</td>
</tr>
<tr>
<td>Withdrawal of registration in any country</td>
<td>24 hours after first knowledge by the register holder.</td>
</tr>
</tbody>
</table>

Periodic Safety Update Reports (PSUR)

Registration holders who have registered a product containing a new chemical entity after 1 January 2002 must routinely submit PSURs on that product 6 monthly for the first 2 years after approval in Malaysia and annually for the subsequent 3 years.

This time frame may be varied in order to harmonize periodic safety updates internationally. However, the periodic safety update should be submitted no later than 6 months after the date of approval.

The registration holders should inform the DCA of any steps which are to be taken with regards to safety concerns raised in the PSUR.
A copy of the most updated relevant package insert/s should be submitted together with the PSUR.

The registration holder should submit any significant variations (e.g. package insert changes) simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort.

Registration holders may, in addition, be requested to submit PSURs in the following circumstance –

- New indications
- Dosage form
  
  Route of administration or use in populations beyond the registration for the active ingredient.

Malaysia is follow format and content for PSUR submission as per ICH E2C (R1) which contains:

- Introduction
- Worldwide market authorization status
- Update of regulatory authority or market authorization holder (MAH) actions taken for Safety reasons
- Changes to reference safety information
- Patient exposure
- Presentation of individual case histories
- Studies
- Other information
- Overall safety evaluation
- Concluding statement

**Risk Benefit Evaluation**

The registration holder should aim to achieve as high as possible "benefit to risk balance" for an individual product and to ensure that the adverse consequences of a product do not exceed the benefits within the population treated.

The benefit-risk profile of a product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The "benefit to risk" ratio can be improved either by increasing the benefits or by minimising risk factors. When proposing measures to improve the benefit to risk of a product (e.g., restricting use to a patients group most likely to benefit or where there is no alternative) their feasibility in normal conditions of use should be taken into account.

The following types of action may be necessary and can be undertaken voluntarily by registration holders or compulsorily by the DCA:
• Making changes to the indications, dosage recommendations, contraindications, special precautions
• Warnings or adverse effects and in consequence
• Amendments to the products dossier and the product information material
• Modification of advertising material
• Direct provision of important safety information to health-care professionals (e.g., through letters and/or bulletins).

When any significant alteration to the safety information is made, the appropriate health-care professionals must be informed promptly and provided with the new product information materials. The product inserts should also be updated and means found to draw the prescribers and patients' attention to important warnings.

COMPARISON OF PHARMACOVIGILANCE REGULATION

Comparison of pharmacovigilance regulation in Europe and Malaysia is given in table 4

Table.4 Comparison of pharmacovigilance regulation

<table>
<thead>
<tr>
<th></th>
<th>Europe</th>
<th>Malaysia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory authority</td>
<td>European medicinal agency</td>
<td>National Pharmaceutical Control Bureau</td>
</tr>
<tr>
<td>Pharmacovigilance responsible authority</td>
<td>Eudravigilance</td>
<td>Malaysian Adverse Drug Reactions Advisory Committee</td>
</tr>
<tr>
<td>Guidelines</td>
<td>Good Pharmacovigilance practice</td>
<td>Malaysian Guidelines for the Reporting &amp; Monitoring is guideline for pharmacovigilance related activity in Malaysia</td>
</tr>
<tr>
<td>Process for Pharmacovigilance filing</td>
<td>Centralize process, Decentralize/Mutual recognize process, National authorization process</td>
<td>National authorization process</td>
</tr>
<tr>
<td>Pharmacovigilance systems and their quality systems</td>
<td>GVP Module I</td>
<td>No specific module is available</td>
</tr>
<tr>
<td>Pharmacovigilance System Master File (PSMF)</td>
<td>MAH have require to submit as per format given in GVP Module II</td>
<td>Not require</td>
</tr>
<tr>
<td>Pharmacovigilance inspections</td>
<td>This system is given in GVP Module III</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Pharmacovigilance audits</td>
<td>GVP Module IV is specific guideline given for Pharmacovigilance audits</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Risk management system</td>
<td>As per GVP Module V Risk Management Plan</td>
<td>They are requiring The Benefit To Risk Balance check.</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>This system is given in GVP</td>
<td>“Malaysian Guidelines for the</td>
</tr>
<tr>
<td>All serious ADR reporting time period</td>
<td>Module VI Management and reporting of adverse reactions to medicinal products</td>
<td>Reporting &amp; Monitoring’ This guideline give information related to Malaysia</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>15 days</td>
<td>Within 7 calendar days if it is Fatal Otherwise 15 days</td>
<td></td>
</tr>
<tr>
<td>Non serious ADR reporting time</td>
<td>90 days</td>
<td>Within 15 calendar days</td>
</tr>
<tr>
<td>Periodic Safety Update Report guideline and Time periods</td>
<td>It is given in GVP Module VII • 6 months intervals once the product is authorised, even if it is not marketed Once a product is marketed, • 6 monthly for 2 years • Yearly basis for subsequent 2 years • Thereafter every 3 year</td>
<td>• 6 monthly for 2 years • Yearly basis for subsequent 3 years • Thereafter when require by authority</td>
</tr>
<tr>
<td>Signal management</td>
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<td>No specific module is available</td>
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<tr>
<td>Additional monitoring</td>
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<tr>
<td>Safety communication</td>
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<td>Risk minimisation measures</td>
<td>It is given in GVP Module XVI</td>
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</table>

CONCLUSION
Now a days in market each and every day new drug is comes each drug has adverse reaction. In Europe and Malaysia has pharmacovigilance system. In Europespecific guideline related to signal management process, Pharmacovigilance inspection system and pharmacovigilance audit system and they are not use additional monitoring system. Malaysia is also not requiring Pharmacovigilance System Master File (PSMF). In relation to PSUR Europe is require continue for every 3 yearly after completing of 7 year time period while in after completing time period 5 years not require continue submission.so we can conclude that European regulation is better and strict compare to Malaysia.

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