South African Regulatory Pharmacovigilance
SAHPRA

Ms. Busisiwe Mosane
22 November 2019
Contents

• SAHPRA Background
• Vigilance Legal Basis
• Applicant PV obligations
• Role PV officer
• Collection and management of case reports
• Reporting lines
• VigiFlow® system
• Electronic submission of ADRs
• Challenges
• Conclusion

South African Regulatory Pharmacovigilance
SAHPRA
SAHPRA Background

• SAHPRA – South African Health Products Regulatory Authority
• Established in February 2018 as an organ of state within the public administration but outside the public service as Schedule 3A Public Entity
• Replaces the Medicines Control Council (MCC) as well as the Directorate of Radiation Control (DRC)
• Accountable to and reports to the Minister of Health & acts through the Board
Vision
• To strive towards excellence in health product regulation with the aim of promoting and protecting human and animal health in South Africa (SA), being recognised and respected both nationally and globally as a leading and exemplary health product regulator.

Mission
• To safeguard health & wellbeing of all who live in SA and to support human and animal health through scientific and ethical regulation of medicines, medical devices, radiation emitting devices and radioactive nucleides.
The legislative mandates of SAHPRA are derived from:

- The Constitution; Chapter 9
- The National Health Act, 2003 (Act No. 61 of 2003)
- The Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), as amended (referred to as “the Medicines Act”) and other relevant legislation and policies.
In terms of the Medicines Act, the objects of the Authority are to provide for:

- the monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, scheduled substances, medical devices, radiation control, clinical trials and related matters in the public interest.

The Authority must, among others, in order to achieve its objects:

- Ensure that evidence of existing and new adverse events and reactions, interactions, and signals emerging from post-marketing surveillance and vigilance activities are investigated, monitored, analysed and acted upon; and this is achieved through vigilance

- ‘Vigilance’ in relation to a medicine, medical device or IVD, means the continuous monitoring and evaluation of its safety, efficacy and performance profile and management of any risk throughout its life cycle.
According to Regulation 40 of Medicines Related Substances Act, 1965 (Act 101 of 1965) as amended,

(1) A Holder of Certificate of Registration (HCR)/applicant and licence holder must inform the Authority of any:

(a) new or existing quality, safety or effectiveness concerns related to any medicine, including but not limited to adverse drug reactions; and

(b) risk management activities associated with paragraph (a).

(2) A Holder of Certificate of Registration (HCR)/applicant and licence holder, must maintain or have access to records of the reports and case reports referred to in subregulation (1).

(3) A health care provider, veterinarian or any other person should inform the Authority, in the manner as determined by the Authority, of any:

(a) suspected adverse drug reactions; or

(b) new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance.
Pharmacovigilance Obligations of the applicant

3.1 The Role and Responsibilities of the Holder of a Certificate of Registration/ Applicant

(i) The holder or applicant should ensure that it has in place an appropriate system for pharmacovigilance that will provide for the proper management of safety data for its medicines and to ensure that appropriate action can be taken when necessary. It is a requirement that the applicant has available, in South Africa, a full-time qualified person responsible for pharmacovigilance and post-marketing surveillance i.e. pharmacovigilance officer. This person should have experience and training in all aspects of pharmacovigilance and, if not a healthcare professional/ provider, should have access to a medically qualified person.

(ii) The Responsible Pharmacist must nominate a specific individual, i.e. pharmacovigilance officer responsible for pharmacovigilance activities. The Authority must be informed in writing the name of the person who will assume responsibility for all matters pertaining to pharmacovigilance, including the person’s contact details (postal and e-mail addresses and telephone and fax numbers).

(iii) The holder or applicant should ensure that there is full documentation covering all procedures and activities of the pharmacovigilance officer and that mechanisms are in place to ensure that the pharmacovigilance officer may receive or seek all relevant information.
3.2 The Role and Responsibilities of the Holder of a Certificate of Registration’s/ Applicant’s Pharmacovigilance Officer

Responsibilities of the holder’s or applicant’s pharmacovigilance officer should include:

(i) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions, which are reported to the holder or applicant, including to medical representatives and clinical research associates, is collected and collated so that it is accessible at a single point;

(ii) serving as a contact person for the Authority and NADEMCo for all matters relating to pharmacovigilance;

(iii) the preparation of the following, either directly or by delegation/supervision, for submission to the Authority:
- adverse drug reaction reports;
- summary report for both serious and non-serious ADRs occurring in South Africa;
- Periodic Safety Update Reports (PSURs) or Periodic Benefit-Risk Evaluation Reports (PBRER), when necessary;
- company-sponsored post-registration study reports, when required; and
- ongoing pharmacovigilance evaluation during the post-registration period; and

(iv) ensuring that any request from the Authority for additional information deemed necessary for the evaluation of the risk-benefit ratio of a medicine, is provided to the Authority promptly and in accordance with all requirements,
Collection and management of case reports

What to report?

• Minimum reportable information for an ADR Report
  • identifiable patient
  • identifiable reporter (including contact details)
  • suspect medicine (ideally trade name)
  • adverse effect

• All the relevant information available (causality)
  • treatment start date & reaction onset date – temporal relation
  • dose and dosing regimen
  • indication
  • concomitant medicines & comorbidities
  • age and gender
  • action taken – dechallenge/rechallenge & outcome

• Other information that may be relevant

• Discharge summaries, Post-mortem reports & Relevant laboratory data
Collection and management of case reports

Important information to note!

• The original words/description (verbatim) of the reaction as used by the initial reporter
• The medicine name as reported by the initial reporter, preferably the proprietary name.
• Email address/telephone number & qualification of the initial reporter
• Additional information - follow-up reports
  ▪ must be cross-referenced to the MFR #
  ▪ must be clearly marked that it is a follow up
Collection and management of case reports

• Where to report?
  - NADEMC (Cape Town) or
  - Pharmacovigilance Unit (Pretoria)

• How to report?
  - Fax – 021 4486181 (NADEMC)
  - Email (adr@sahpra.org.za/ e2b@sahpra.org.za)
  - Use adverse reaction report form
    (https://www.sahpra.org.za/documents/12e54dcaADRForms.pdf) or CIOMS
  - Mobile Application-EML Clinical Guide – HCPs
07 November 2019

SUBMISSION OF PHARMACOVIGILANCE CORRESPONDENCES

To all stakeholders

The Pharmacovigilance Unit hereby issue the following communication for all stakeholders to note.

The submission of all correspondences to the Pharmacovigilance Unit should be done as follows:

All adverse drug reactions/CIOMs forms in paper format must be sent to adre@sahealth.gov.za or faxed to (+27) 21 445 6181. Please note that forms should only be submitted to either of the two but not both.

All adverse drug reaction reports submitted in edc format should be sent to phvs@sahealth.gov.za

All safety notifications and pharmacovigilance related queries should be sent to pvqueries@sahealth.gov.za

All hard copy correspondences should be sent to:

South African Health Products Regulatory Authority
Pharmacovigilance Unit
Cape Town, building 35
Meyling Radial Road,
Brummett,
PRETORIA, 0001

Tel: (+27) 12 842 7689/10

CPh

National Adverse Drug Event Monitoring Centre (NADEMC)

via Department of Pharmacy

University of Cape Town

Groote Schuur Hospital

Old Main Building

KAE-78

Tel: (+27) 21-428 5158

Fax: (+27) 21-428 5151

Please note that this is with immediate effect and should continue until further notice.
# Reporting Timelines

<table>
<thead>
<tr>
<th>Type of ADR</th>
<th>Timeframe for reporting</th>
<th>Format</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SA Reports (spontaneous/published /study):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious (expected and unexpected)</td>
<td>• 15 calendar days</td>
<td>• ADR form # /e2b format</td>
</tr>
<tr>
<td>• Non-serious (expected and unexpected)</td>
<td>• Annually</td>
<td>• SES/Summary report</td>
</tr>
<tr>
<td>• Subject to change</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Foreign Reports (spontaneous/published / study):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious</td>
<td>• On request or relating to specific safety issue</td>
<td>• As appropriate</td>
</tr>
<tr>
<td><strong>Notification of Change in Nature, Severity or Frequency or Risk factors</strong></td>
<td>3 calendar days</td>
<td>Detailed report (including publications)</td>
</tr>
<tr>
<td><strong>New information impacting on benefit-risk profile of medicine including decisions by national medicines regulatory authorities other than SAHPRA</strong></td>
<td>3 calendar days</td>
<td>Detailed report (including publications)</td>
</tr>
</tbody>
</table>
VigiFlow® System

- Web-based Individual Case Safety Report (ICSR) management system
- Developed by Uppsala Monitoring Centre (UMC)
- Compatible with the ICH-E2B standard for electronic transmission of ICSRs
- Available via an encrypted (https) connection & different access rights and password control
- Authorised users only, different access levels, usernames & passwords
- Traceability of changes in data, audit trails (also for historical/deleted data)

- Used for:
  - Data entry & import
  - Assessment
  - Storage
  - Retrieval (e.g. follow-ups)
  - Admin statistics
  - Data exchange – Electronic ICSR import & export

- Common standards for sharing data
  - Reporting format – ICH-E2B
  - Terminologies – MedDRA
  - Dictionary: WHODrug

South African Regulatory Pharmacovigilance
SAHPRA
VigiFlow® System – E2B

• Standard for sharing of drug safety information
• Developed by ICH
• Primarily used for reporting of suspected ADRs in the post-marketing phase and also in clinical trials
• Defines the transmission of Individual ADR reports bundled in batches i.e. it is not a standard for transfer of summary data
• Only correct E2B files xml format can be imported
• The report Id(s) are generated reports Id(s) during import. The generated report Id(s) will then be included in the acknowledgement file
• For follow-up reports, report ID of the already existing report will be included
VigiFlow® system

VigiFlow® can be simple or advanced depending on the needs of the country

Regional Centre (NWP) 1
Region Centre (LP) 2
Region Centre (WCP) 3

Healthcare Professionals/Consumers
ICSR

eReporting

SAHPRA

ICSR (PDF)
ICSR (E2B xml)

WHO global ICSR database (VigiBase®)

Pharmaceutical Industry

ICSR (PDF)
ICSR (E2B xml)

Healthcare Professionals/Consumers

South African Regulatory Pharmacovigilance
SAHPRA
VigiFlow® system eReporting

Reporters -> eReporting -> VigiFlow National ICSR Database -> VigiBase WHO global ICSR database

Confirmation email
South African Regulatory Pharmacovigilance
SAHPRA
Electronic submission of ADRs

Pilot - 2017

1. Participation - 7 Applicants
2. Implementation - 1st November 2017

In order to join, applicants need the following technical information regarding e2b:

2. The preferred encoding is ISO-8859-1 but UTF8 is also acceptable
3. Each xml file can contain up to 100 ICSRs.
4. Organisation identifier – SAHPRA

Important points to note:

1. No testing of cases is required anymore
2. No simultaneous reporting via e2b and paper formats is allowed
3. “no reply” email addresses should be avoided
4. All applicants are encouraged to join the e2b reporting since this will be a requirement in the near future
5. e2b@sahpra.org.za
ELECTRONIC SUBMISSION OF ADVERSE DRUG REACTION (ADR) REPORTS - E2B REPORTING

TO ALL APPLICANTS

For over a decade, ADR reports have been submitted to the National Adverse Drug Events Monitoring Centre (NADEMC) via fax. These reports were previously captured on the ADRI database. The ADRI database restricted electronic reporting by both applicants and healthcare professionals, and direct uploading of information onto the international database of the WHO Uppsala Monitoring Centre’s VigiBase®. This feature forms part of the VigiFlow® software used to record ADR reports received.

SAHPRA obtained the VigiFlow® license and has since initiated capturing of ADR reports onto this database since 2016. During 2017, a pilot for electronic submission of ADR reports (E2B) by interested applicants was conducted. The outcome of the pilot was positive and confirmation to submit ADR reports via e2b format from the 01 of November 2017 were issued to all applicants who participated in the pilot.

To date, 10 applicants are approved to submit reports via the e2b format. All applicants are encouraged to join the e2b reporting since this method of reporting will be a requirement in the near future, more details will be provided. In order to join, applicants need the following technical information regarding e2b:

1. Technical specifications - ICH guidelines downloadable from http://eudr.ch.org/e2br22/index.htm
2. The preferred encoding is ISO-8859-1 but UTF8 is also acceptable
3. Each xml file can contain up to 100 ICSRs.
4. Organisation identifier – SAHPRA

Important information to note:
- Testing of cases is no longer required.
- Reports can be uploaded in either E2B R2 or E2B R3 formats.

Applicants joining the e2b reporting portal are advised to refrain from sending ADR reports in both paper and e2b formats simultaneously, as this results in duplication of reports on the system. That is, once an applicant has started sending reports in e2b format, they must immediately stop sending ADRs in paper formats. Applicants are not required to inform the Authority before they begin with e2b submissions. A response message will be forwarded to the email address used together with acknowledgement letter/s, therefore “no reply” email addresses should not be used. All ADR reports in E2b format must be send to e2b@sahealth.org.za
Challenges

1. Duplication of reports
   - One report scanned twice on the same PDF
   - Initial, Follow-ups on one email

2. Literature reports
   - Literature source (articles) should be included
   - ADR reports from old literature sources
   - Different standards of reporting

3. Lack of sufficient information on the CIOMS forms
   - Patient details
   - Suspect drug information (dosage, strength, ROA)
   - Outcomes of the reaction

4. Reporting of hospitalisation as a reaction

5. Tautology

6. Death – outcome not reaction

7. Use of incorrect email addresses e2b reports to adr@sahpra.org.za

8. “no-reply” emails

9. Company partnership – reports from unknown companies
## Challenges

### South African Regulatory Pharmacovigilance

**SAHPRA**

### 1. REACTION INFORMATION

<table>
<thead>
<tr>
<th>1. PATIENT INITIALS</th>
<th>1a. COUNTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIVACY</td>
<td>SOUTH AFRICA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. DATE OF BIRTH</th>
<th>2a. AGE</th>
<th>3a. SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Month</td>
<td>Year</td>
</tr>
<tr>
<td>Privy</td>
<td>Unk</td>
<td>Female</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3a. WEIGHT</th>
<th>4-6 REACTION ONSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unk</td>
<td>Day</td>
</tr>
</tbody>
</table>

7 + 13 DESCRIBE REACTION(S) (including relevant test/lab data)
- Event Version [LOWER LEVEL TERM] (Related symptoms if any separated by commas)
- Other Serious Criteria: Medically Significant, Medically Significant
  used during pregnancy [Maternal exposure during pregnancy]

Case Description: Initial report was received on 06-JUN-2019.
This is a Literature report received from a Physician concerning a Female patient. Age/age group are not reported.

Literature:
- Journal - South African Medical Journal
- Author - M Conradie, B D Henderson, C van Wyk.

(Continued on Additional Information Page)

---

### 2. REACTION INFORMATION

<table>
<thead>
<tr>
<th>1. PATIENT INITIALS (cont. last)</th>
<th>1a. COUNTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unk</td>
<td>SOUTH AFRICA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. DATE OF BIRTH</th>
<th>2a. AGE</th>
<th>3a. SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Month</td>
<td>Year</td>
</tr>
<tr>
<td>Privy</td>
<td>Unk</td>
<td>Female</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3a. WEIGHT</th>
<th>4-6 REACTION ONSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unk</td>
<td>Day</td>
</tr>
</tbody>
</table>

7 + 13 DESCRIBE REACTIONS (including relevant test/lab data)
- Event Version [PREFERRED TERM] (Related symptoms if any separated by commas)
- Other Serious Criteria: Medically Significant
- Low birth weight [Low birth weight baby]

Patient's mother received [Foetal exposure during pregnancy]

Case Description: Baby case: Case number PPHY2019ZA177144, is an initial literature case report received on 29 Jul 2019 from an article titled 'Non-nucleoside reverse transcriptase inhibitor levels among HIV-exposed uninfected infants at the time of HIV PCR testing-findings from a tertiary healthcare facility in Pretoria, South Africa'.

(Continued on Additional Information Page)
Challenges

South African Regulatory Pharmacovigilance
SAHPRA
Conclusion

Poor quality data leads to risk of drawing wrong or delayed conclusions about safety signal & this could lead to patients being harmed unnecessarily.
South African Regulatory Pharmacovigilance
SAHPRA
Questions?