Basics of Pharmacovigilance Writing

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AMWA
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Outline

• What is pharmacovigilance?
• Similarities and differences with writing for clinical development
• Pharmacovigilance documents
• Case study
• Where do I start?
• Q & A
Outline

• What is pharmacovigilance?
Where does pharmacovigilance fit in?

• Throughout the product lifecycle

https://www.quanticate.com/blog/the-history-of-pharmacovigilance
Pharmacovigilance - what's that?

Pharmacovigilance
dictionary.com, urbandictionary.com, merriam-webster.com,
dictionary.cambridge.org

Search suggestions for pharmacovigilance

We have these words with similar spellings or pronunciations:
- pharmacologic
- pharmacological
- pharmaceutical
- pharmaceuticals
- pharmacetics
- pharmacologist
- pharmacologists
- pharmacology
- recognisance
- recognizance

Did you mean?

More suggestions:

\_\_(ツ)\_/\n
There aren't any definitions for pharmacovigilance yet.

Can you define it?

Aren't you smart – you've found a word that is only available in the Merriam-Webster Unabridged Dictionary. To view the full definition of pharmacovigilance, activate your free trial today.
Pharmacovigilance - getting closer

Pharmacovigilance

/nəˈmækəˌvɪdʒələns/

noun

noun: pharmacovigilance; noun: pharmaco-vigilance

the practice of monitoring the effects of medical drugs after they have been licensed for use, especially in order to identify and evaluate previously unreported adverse reactions.

"the partnership hopes to develop diagnostic tools to improve pharmacovigilance"
Pharmacovigilance (PV): definition

- A set of activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem
Signal - we got this!
Signal: PV definition

- Information arising
  - from 1 or multiple sources,
  - including observations and experiments,
  - which suggests a new potentially causal association,
  - or a new aspect of a known association
  - between an intervention and an event
  - or set of related events,
  - either adverse or beneficial,
  - that is judged to be of sufficient likelihood to justify verificatory action
Adverse what?

- Adverse event
- Treatment emergent adverse event
- Adverse reaction
Causality
Causality: PV definition

- For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction.

- All spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.
What is a “safety concern”?

• Important identified risk

• Important potential risk

• Missing information
What are risks?

• **Identified risk:**
  – An untoward occurrence for which there is adequate evidence of an association with the medicinal product
    – e.g. adverse reactions adequately demonstrated in studies and where the causality is strongly supported

• **Potential risk:**
  – An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product but where this association has not been confirmed
What is “important”?  

**Important risk:**
- An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health

**From EMA:**
Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important

❖ For team discussion - not a medical writer’s decision❖
What is a missing information?

• Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be **clinically significant**

• Examples of potential missing information:
PV - Other key abbreviations and terms

- DIBD - development international birth date
- IBD - international birth date
- DLP - data lock point
- MAH - marketing authorization holder
- QPPV - qualified person for pharmacovigilance
- Spontaneous report
- Solicited report
- Social media report
PV activities

- Case processing
- Safety database
- Expedited reporting to health authorities
- Literature screening
- Signal detection and assessment
- Periodic (aggregate) reporting
- Risk management planning
- Benefit-risk assessment
- Labeling
Adverse effects or any other drug-related problem

• Adverse reactions
• Medication errors - actual and potential
• Drug interactions
• Off-label use
• Misuse, abuse
• Overdose, underdose
• Lack of effect
• Special populations
• Exposure in pregnancy
• Product administration issues
Outline

• Similarities and differences with writing for clinical development
Pre-approval (development)
Approval
Postmarketing
Pre- and post-approval PV
Pre-approval development data
Postmarketing data
Regulatory authority feedback

• No defined pre-meetings with regulator to discuss content/strategy

• In EU, Pharmacovigilance Risk Assessment Committee (PRAC) evaluates each submitted document
  • Provides feedback
  • Queries need resolution in a specified timeline
  • Approves the document
  • Provides feedback for subsequent submission

• In other regions, feedback mechanism not as well established as in EU
Timelines

- Reporting period start date - nothing before this date applies
- Reporting period end date (ie. data lock point) - nothing after this date applies
  - LATE BREAKING section
- For DSUR, PBRER, and ACO there is a definite, unnegotiable submission due date set by regulatory authorities
Definitions

• Ongoing clinical trial - CTA has been authorized anywhere in the world

• Completed clinical trial - CSR is available
“Harmonized” documents

- Single (core) document for global use
  - Additional appendices may be generated for individual local country/region requirements
    - EU, US, Canada, Brazil, Mexico, Colombia, Japan
- Regardless of the size of the program, each document must have the same sections and contain the same information
- Document content/format is specified by guidance document, including numbering and headings of sections and appendices
Integrated evaluation

• Single document for same active substance
  – All authorized indications
  – All routes of administration
  – All dosage forms and dosing requirements
• Only separate when clinically relevant
  – Different formulations for entirely different indications
  – Agreement from regulatory authorities needed
• Writing about clinical studies
  o It is known exactly how many people make up the denominator
  o % calculations can be made based on this

• Postmarketing PV
  o There is no accurate count of how many people actually received the product
  o Patient counts cannot be used as denominators
  o Calculation from sales volume...that gets estimated to be a certain number of patient/years exposure
Data completeness

- If any required data for report sections is missing, it must be stated that it is missing, preferably with a reason why it’s missing
- Missing patient data is missing and unlikely to be available
- Actual dosing information is usually very limited
## Data analysis - subgroups

<table>
<thead>
<tr>
<th>Writing about clinical studies</th>
<th>PV writing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• clinical team defines subgroups</td>
<td>• writer analyzes the data</td>
</tr>
<tr>
<td>• biostats creates TFLs</td>
<td>• writer filters datasets, determines if subgroups need to be evaluated</td>
</tr>
<tr>
<td>• writer analyzes and summarizes the data</td>
<td>• writer analyzes and summarizes the data</td>
</tr>
</tbody>
</table>
## Data sources

<table>
<thead>
<tr>
<th>Writing about clinical studies</th>
<th>PV writing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Predefined TFLs</td>
<td>• Limited predefined tables/listings</td>
</tr>
<tr>
<td>• Everything attached to final document</td>
<td>• A few mandatory appendix inclusions</td>
</tr>
<tr>
<td>• In-text table direct reference/copy to appendix source</td>
<td>• Nothing else attached to report</td>
</tr>
<tr>
<td></td>
<td>• No duplication of appendix to in-text data</td>
</tr>
</tbody>
</table>
Data analysis - efficacy/effectiveness

• Efficacy has been demonstrated in CTD submission(s)
• Benefit evaluation is continuation of efficacy evaluation
  – In real life use
  – Publications of real life use
  – Treatment guidelines
  – New studies data supporting new approvals
Data analysis - safety

• Safety in limited population has been demonstrated in CTD submission(s)

• Look for most frequently reported events/groups of events

• Use of MedDRA SMQs highly encouraged

• Differentiation for “known” population vs “new” exposures
Data “QC”

• Limited ‘number for number’ quality checks
• Logic checks for data parameters
• Consistency across sections and documents
• Consistency against regulation/guidance document
• Frequently a peer review instead of dedicated QC team
  • Contributing groups expected to provide QCd data
  • Contribution source documents not necessarily available to writer
Data searches to be evaluated
Outline

• PV documents
  • Where they “live”
  • Who sees them
  • What are the most frequent ones
  • Scope of each of the frequent documents
Where do PV documents live in the CTD?

Mostly in Module 5.3.5.3
PV documents: external audiences
PV documents: internal audiences

- PV group
- Medical affairs
- Clinical development
- Development/marketing partners
- Outcomes research
- Upper management
- Board of Directors
Four documents - one story

**Pre-approval**
- DSUR
  - Important risks

**Approval**
- • subRMP
  - RMP update
  - Important risks + missing information

**Post-marketing**
- • (DSUR)
  - (RMP+update)
  - PBRER
  - ACO
  - Important risks + missing information
  - Benefits
  - Interval vs cumulative

SAFETY PROFILE / RISK MANAGEMENT

Risk-benefit monitoring

Safety reference information up-to-date

RISK-BENEFIT ANALYSIS
PV documents: periodic reports (external)

- **DSUR = development safety update report**
  - Summarizes the safety of the product in studies
  - Answers the question: Is the product safe enough to continue giving to people in clinical trials?

- **RMP = risk management plan**
  - A detailed description of the risk management system
  - Answers the question: How is the sponsor limiting the risks to people taking the product?

- **PBRER = periodic benefit risk evaluation report**
  - Summarizes the benefit-risk profile, signal evaluation and updates to product information in marketed setting
  - Answers the question: Is the product safe enough to continue giving to people in the real world?

- **ACO = addendum to clinical overview**
  - Summarizes all *cumulated effectiveness and safety data* related to the product since *MA or its last renewal*, in order to obtain a *new renewal* for the product
  - Answers the question: Is the product safe enough to keep on the market?
Scope of the DSUR

Annual requirement, triggered by first approval of a clinical study by a health authority anywhere in the world (DIBD)

– Determines if reporting period safety information is in accordance with prior product safety knowledge
– Takes cumulative knowledge into account but focus is on new data
– Provides clinical development program update
– Includes safety data from studies in unapproved indications or populations
Generally required with first CTD submission, with each subsequent CTD submission, and if any new clinically significant risk information becomes available

- Describes the safety profile of the product (known and unknown)
- Describes measures to prevent or minimize the risks associated with the product
- Describes post-authorization obligations (as a condition of the marketing authorization)
- Summarizes whether efficacy shown in clinical trial populations is seen in everyday medical practice
- In some countries, now required for renewal of really old products, eg. isosorbide mononitrate
Scope of the PBRER

Periodic requirement generally tied to how long the product has been approved. Triggered by the first approval of the product anywhere in the world (IBD).

- Use all data you ‘can reasonably be expected to have access to’ - not just the company’s product e.g. journal articles
- Take cumulative knowledge into account, but focus on new data
- New information may require a new integrated benefit-risk evaluation
- Real-life experience data
Scope of the ACO

Required for renewal of marketing authorization in EU, as well as a few other countries

– Critical evaluation addressing the current benefit-risk of the product
– Similar in content to PBRER
– Plus need to provide PV inspection history
– Need to provide Module 1.4.3 clinical expert statement
### DSUR/RMP/PBRER/ACO common sections

<table>
<thead>
<tr>
<th>Section</th>
<th>DSUR</th>
<th>RMP</th>
<th>PBRER</th>
<th>ACO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug introduction</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Marketing status</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Regulatory actions</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Clinical trial and post marketing exposure</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Summary of clinical trials</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Summary of non-clinical study findings</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Summary of signals</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Summary of benefits</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Summary of risks</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Summary of new information on risks and benefits</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Summary of adverse events</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
The Accountant’s Prayer:
Lord, help me be more relaxed about insignificant details, starting tomorrow at 10:53:16 am, Eastern Daylight Saving Time.
PV documents: cumulative (mostly internal)

- **Signal assessment report**
  - Summarizes the safety of a single event or related group of events after a trigger
  - Answers the question: Is this event a new risk or safety concern with this product?

- **Safety analysis document/report**
  - Summarizes the safety of a single event or related group of events without a trigger
  - Answers the question: Is this event a new risk or safety concern with this product?

- **Company Core Data Sheet (CCDS)**
  - Summarizes the company position on the product
  - Answers the question: What are the key messages to share globally about this product?

- **Benefit-Risk Analysis**
  - Summarizes the benefits and key identified risks of the product
  - Answers the question: Does the benefit for the patient outweigh the potential risks for this product?
Documented output of the process of further evaluating a validated signal

- Provides analysis of cumulative data
- May include safety data from nonclinical and clinical studies, literature, epidemiology, and postmarketing setting
- Determine whether there are new risks causally associated with the active substance or whether known risks have changed
- Executive summary of signal assessment report can be utilized in PBRER
A document prepared by the marketing authorization holder containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product

• Contains core safety information

• All relevant safety information contained in the CCDS prepared by the marketing authorization holder and which the marketing authorization holder requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification

• Regulatory authority has no input into content

❖ No regulation/guidance for content requirement❖
Scope of benefit-risk analysis

Documents evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients’ health or public health

- Takes cumulative knowledge into account but focus is on new data
- Takes actual use data into account
- Summary of may be utilized in periodic reports

-No regulation/guidance requirement-
Documents analysis of data that has not reached the level of a signal, could be analysis of known risks

- Provides analysis of cumulative data or new period of data compared to cumulative knowledge
- May include safety data from nonclinical and clinical studies, literature, epidemiology, and postmarketing setting
- Determine whether there are new risks causally associated with the active substance or whether known risks have changed
- Summary may be utilized in periodic reports

❖ No regulation/guidance requirement ❖
They are all connected

IB + summary of changes

CSR summary/synthesis

Clinical Summary of Efficacy

Clinical Summary of Safety

Clinical Overview

RMP

Benefit Risk Assessment

Regulatory responses

DSUR

PBRER

CCDS

Signal Assessment

Addendum to Clinical Overview
They are all connected

- IB - summary of changes and effective IB(s) in DSUR
- CCDS - summary of changes and latest version in PBRER
- CSR - summary or CSR synopsis in DSUR, PBRER, RMP
- What are the most frequent adverse experiences
- CTD 2.5.6 continued in PBRER
- CTD 2.7.4 analysis evaluated in PV
Outline

• Case study
Hyper/hypoglycemia with product X - cumulative analysis

- Search criteria including expanded MedDRA PTs
- Request for clinical trial data for same MedDRA PTs
- Request for nonclinical data
- Request signal detection by disproportionality analysis
- Request literature search for product X and MedDRA PTs and synonyms
- Analysis steps for AE dataset
  - Review the patient population in dataset
    - Overview of dataset
    - Medically confirmed report: yes/no
    - Med hist of diabetes or other glucose condition, or concomitant medication indicative of glucose issues: yes/no
    - Stated “no glucose issues” in med hist: yes
    - Other risk factors in med hist: yes/no
    - Unknown med hist
# Hyper/hypoglycemia with product X - cumulative analysis (Analysis groups)

<table>
<thead>
<tr>
<th>Patients with diabetes in MH or con med indicative of diabetes/glucose control issues: YES</th>
<th>Other risk factors in med hist (e.g., morbid obesity, sedentary, conmeds known to affect blood glucose): YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the diabetes controlled?</td>
<td>Was this undiagnosed diabetes?</td>
</tr>
<tr>
<td>Did they have a worsening of condition?</td>
<td>Was another product causing the events?</td>
</tr>
<tr>
<td>Was there a dose effect?</td>
<td>Was there a dose effect?</td>
</tr>
<tr>
<td>Was this normal fluctuation?</td>
<td>Are glucose values reported?</td>
</tr>
<tr>
<td>Was this unexpected fluctuation?</td>
<td>Medically confirmed yes/no</td>
</tr>
<tr>
<td>Are glucose values reported?</td>
<td>Temporal relationship from start of treatment to event.</td>
</tr>
<tr>
<td>Medically confirmed yes/no</td>
<td>Is the product “triggering” blood glucose control issues in patients with risk factors?</td>
</tr>
<tr>
<td>Temporal relationship from start of treatment to event.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with stated “No blood glucose issues in the past”: YES</th>
<th>Patients with diabetes in MH or con med indicative of diabetes/glucose control issues: NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other risk factors in med hist: NO</td>
<td>Unknown med hist: YES</td>
</tr>
<tr>
<td>Are glucose values reported?</td>
<td>Are glucose values reported?</td>
</tr>
<tr>
<td>Was there a dose effect?</td>
<td>Was there a dose effect?</td>
</tr>
<tr>
<td>Any other risk factors for glucose issues?</td>
<td>Medically confirmed yes/no</td>
</tr>
<tr>
<td>Medically confirmed yes/no</td>
<td>Temporal relationship from start of treatment to event.</td>
</tr>
<tr>
<td>Temporal relationship from start of treatment to event.</td>
<td>Absence of any other indicators, could the product be causing this as a new event?</td>
</tr>
<tr>
<td>Absence of any other indicators, could the product be causing this as a new event?</td>
<td>Absence of any other indicators, could the product be causing this as a new event?</td>
</tr>
</tbody>
</table>
Hyper/hypoglycemia with product X - cumulative analysis - Summary

• A search of the clinical trial databases for product X revealed X reports of PT1, 2, 3, 4, etc. out a total population of X.

• A review of nonclinical data for product X showed no indication of glucose control issues in mice, rats, monkeys, etc.

• A disproportionality analysis from FDA WAERS database showed...

• A search of literature found X articles describing events indicative of hyper/hypoglycemia or potential other events indicative of lack of glucose control.

• A total of X cases involving MedDRA PTs of PT1, 2, 3, 4, etc. have been cumulatively received. X cases were medically confirmed. X cases of pre-existing condition, of which X involved aggravation, worsening, loss of control. X cases with no previous glucose control issues, of which X involved patients with risk factors, X involved patients with no known risk factors... Temporal association was noted in X cases. In x cases, no dose or duration of treatment was provided by the reporter, precluding meaningful analysis. In x cases, no confounding factors were identified in the data provided.

• Conclusion statement...
Outline

• Where do I start?
PV documents: role of the medical writer

• Writing skills
  – Clear data presentation
  – Consistency across modules
  – Consistent wording, style, abbreviations, etc
  – Timeliness
  – Document quality
  – Management of a high number of files within a team (modules and versions; not consolidated reviewed files)

• Project management

• Understand focus and aims of the documents

• Know PV guidance and be aware of changes
  • Make contributors aware of requirements
  • Provide guidance on format and content
PV documents: who contributes

Nonclinical

Regulatory affairs

Biostats

Clinical

Medical affairs

Epidemiology

Patient safety

QPPV

Sales

Writer
Practical approaches - To begin

• Familiarize yourself with the current guidance(s):
  – ICH
  – EMA
  – US FDA
  – PMDA
  – Multiple country guidances
  – Significant guidance updates in the last 6 years

• Many guidances provide templates or at least required headings and expected content
Sampling of PV guidances

• ICH E2A through E2F  

• EMA Good Pharmacovigilance Practices (GVP)  

• US FDA Drug Safety Guidances  
  https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

• Japan information for Industry (for Business)  

• Brazil Good Pharmacovigilance Practices and Inspection for MAHs  
Sampling of device vigilance guidances

- GCP (ICH E6) + ISO 14155
- EU Regulatory Framework
- US FDA Device Regulation Overview
  https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm
- WHO
  http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf
- UK
- International Medical Device Regulators Forum
  http://www.imdrf.org/
Practical approaches - Getting Started

• Several Q&A documents clarify what to include and what NOT to include in the documents

• Learn the product

• Learn the disease

• Learn the event(s)
Practical approaches - Tips

• Consistency is key
  • Keep alignment within sections of the same document
  • Keep alignment across the PV documents
  • Keep alignment across other regulatory submission documents

• Planning meetings
  • Timelines
  • Who provides the data
  • What is the source of the data
  • Document/message strategy
Role titles that may involve PV writing

• PV Scientist/Analyst/Author/Writer/Manager/Specialist
• Safety Scientist/Specialist/Writer
• Periodic Report Scientist/Analyst/Manager/Officer
• Associate/Manager/Director PV

❖ The term “Medical Writer” is not generally utilized in PV ❖
Summary

• PV writing is a related capability to regulatory medical writing

• Many of the same principles apply

• To succeed in PV writing

  • Be able to adhere to tight timelines

  • Be able to accept missing data

  • Be able to analyze and provide opinions to team

  • Know what is the expected content in each document