Medical Writing Techniques in Pharmacovigilance

Mari Welke
Trilogy Writing & Consulting

AMWA
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Outline

• What is pharmacovigilance?
• Reference documents
• Search strategies and data breakdowns
• Analysis topics
• Q & A
Audience survey

- Who has worked directly with patients in the healthcare field?
- Who has ever reported an adverse event?
  - To the doctor
  - To the manufacturer
- Who has worked on Pharmacovigilance documents?

Pharmacovigilance (PV): definition

- A set of activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem
Where does pharmacovigilance fit in?

• Throughout the product lifecycle

https://www.quanticate.com/blog/the-history-of-pharmacovigilance

Pre-approval development data
Postmarketing data

Pharmacovigilance (PV) Writing

- DSUR
- CCDS
- DLP
- RMP
- PSUR
- IBD
- BRA
- ACO
- SUSAR
- DIBD
- SSAR
- PBRER
PV activities

- Case processing/Safety database
- Literature screening
- Expedited reporting to health authorities
- Signal detection and assessment
- Periodic (aggregate) reporting
- Risk management planning
- Benefit-risk assessment
- Labeling

causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions
The basics of PV Medical Writing

• Getting ready
  • Know the product
  • Know the disease
  • Know the event

• Analyze what you have in the dataset
  • Overview of dataset
  • Review of data

• Plan a conclusion based on your analysis
• Write event conclusion
• Confirm actions, if any, with product team

Outline

• Reference documents
## Reference Safety Documents

- **Investigator’s Brochure (IB)**
  - Preapproval and ongoing studies post-approval
  - Expected adverse events
  - Used to determine reportability of adverse events (AEs)
- **Company Core Data Sheet (CCDS)**
  - Postapproval
  - Minimum safety specifications (AEs)
  - Indications the company believes are valid for the product
- **Local labels (eg, SmPC, US PI)**
  - What the local authority has agreed for AEs and indications
  - May be different than CCDS
  - Used to determine local reportability of AEs

## Product Use

- **Therapeutic Indications** - what the product should be used for
  - Relevant for off-label use analysis
  - Relevant for therapeutic efficacy analysis
- **Posology** - what is the appropriate dosing
  - Relevant for off-label use analysis
  - Relevant for overdose, drug abuse, misuse analysis
  - Relevant for drug withdrawal symptoms analysis
  - Relevant for special populations analysis
  - Relevant for therapeutic efficacy analysis
  - Relevant for long-term use analysis
  - Use of product in Contraindicated ways could indicate current label/Risk Management is not working
- **Overdose** - what is known of overdose with the product
Adverse effects and cautions

- **Contraindications** - when the product should not be used
  - Has the event occurred under a contraindicated use?
  - Relevant for drug abuse, misuse analysis
  - Relevant for special populations analysis
  - Relevant for therapeutic efficacy analysis

- **Special warnings and precautions for use**
  - Particular concerns known or suspected with the product

- **Interactions with other medicinal products and other forms of interaction** - known/suspected interactions or confirmation of no known interactions
  - Relevant for interactions analysis
  - Relevant for abuse, misuse analysis
  - Relevant for therapeutic efficacy analysis

- **Undesirable effects** - listed adverse events

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Special populations

- **Fertility, pregnancy and lactation** - special considerations and any known data on effects of drug
  - Relevant for pregnancy/lactation analysis
  - Relevant for pediatric analysis

- **Pharmacological properties** - PD and PK properties
  - Relevant for interactions analysis
  - Relevant of overdose, abuse, misuse analysis
  - Relevant for special populations analysis
  - Relevant for AE analysis
Indication and events

• What is the disease indication
  • Review the disease to understand disease course
  • “Normal” progression
  • Known potential complications

• What is the event of concern
  • Review the disease to understand disease course
  • “Normal” progression
  • Known potential complications

• What is the population under treatment
  • Known characteristics of the population
  • Pediatrics, elderly, pregnancy, immunocompromised patients, etc

Outline

• Search strategies and data breakdowns
Data searches to be evaluated

Data analysis - safety

- Use of MedDRA SMQs highly encouraged
  - Broad and Narrow categories
  - SMQs can create noise
  - Companies create customized MedDRA Queries
- Create customized searches for identified or potential risks
- Create customized searches for specific event groupings/terms
Integrated evaluation

- Generally single analysis for same active substance
  - All authorized indications
  - All routes of administration
  - All dosage forms and dosing requirements
  - All trade names the company owns
- Are there differences in events due to indication/route/dosage form/population?
  - If the overall summary indicates any trends, need to evaluate for subgroups

Events over time

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>All periods</th>
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<tr>
<td></td>
<td>N=450</td>
<td>N=484</td>
<td>N=536</td>
<td>N=692</td>
<td>N=2162</td>
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<td>21 (4.7)</td>
<td>32 (6.6)</td>
<td>41 (7.6)</td>
<td>64 (9.2)</td>
<td>158 (7.3)</td>
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<tr>
<td>PT 2</td>
<td>7 (1.6)</td>
<td>12 (2.5)</td>
<td>17 (3.2)</td>
<td>60 (8.7)</td>
<td>96 (4.4)</td>
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<tr>
<td>PT 3</td>
<td>1 (0.2)</td>
<td>8 (1.7)</td>
<td>8 (1.5)</td>
<td>9 (1.3)</td>
<td>33 (1.5)</td>
</tr>
<tr>
<td>PT 4</td>
<td>7 (1.6)</td>
<td>10 (2.1)</td>
<td>12 (2.2)</td>
<td>0</td>
<td>19 (0.9)</td>
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<tr>
<td>PT 5</td>
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<td>0</td>
<td>0</td>
<td>13 (1.9)</td>
<td>13 (0.6)</td>
</tr>
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</table>

N is the number of total cases in the period
Period is the sequential reporting interval (monthly, 3 monthly, 6 monthly, annual, etc)
All periods total is cumulative number of events/occurrences

% is calculated by n/N*100

- Look for most frequently reported events/groups of event
New compared to known

<table>
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<th>Preferred Term</th>
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<th>Periods 1-3 (N=1470)</th>
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<td>n (%)</td>
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<tr>
<td>PT 5</td>
<td>13 (1.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Differentiation for “known” population vs “new” exposures
- For aggregate/periodic reporting, need to analyse for data during the period compared to baseline - Did anything change?

Outline

- Analysis topics
  - Overview
  - Specific topics
“Harmonized” documents

- Single (core) document for global use
  - Additional appendices may be generated for individual local country/region requirements for documents that are to be submitted to regulators
    - EU, US, Canada, Brazil, Mexico, Colombia, Japan, Egypt
- Generate internal company alignment on safety profile (regulators may disagree)

Overview analysis of the dataset - Demographics

- Gender
  - Is there a disproportionate reporting of one gender or another
  - Is the current dataset different from previous or cumulative
  - Is the gender reporting proportion consistent with treatment/disease population
- Age
  - Is there a disproportionate reporting of one age group
  - Is the current dataset different from previous or cumulative
  - Is the age consistent with treatment/disease population
- Race/ethnicity
- Any unexpected patterns?
### Overview analysis of the dataset - Case origin/type

- **Country**
  - Is the proportion of cases received by country in line with previous reports
  - Is there a correlation with a new approval in a country
  - Was there any activity in a country that may have provoked increased reporting

- **Source**
  - Most postmarketing product cases would be expected to be spontaneously received, is this in line with dataset
  - Are there any “spikes” in source type

- **Type of case**
  - Most cases would be expected to be “initial”. Are there a significant number of follow-up reports?
  - Is there a change in the serious/non-serious proportion from previous reporting period or cumulative data

### Overview analysis of the dataset - Dosing

- **Dose at event onset**
  - Is there any pattern to reported dose
  - Increased dose => increased AE reports?
  - Any change from previous period or cumulative data

- **Duration of treatment**
  - Is there any pattern to reported duration
  - Increased duration => increased AE reports?
  - Was steady state reached
  - Any change from previous period or cumulative data

- **Route of administration/Formulation**
  - Is there any pattern
  - Any change from previous period or cumulative data
Overview analysis of the dataset - Concomitants

- Co-Suspect products
  - Are there many cases with co-suspect products
  - Are there new co-suspect products compared to previous or cumulative data

- Concomitant medications
  - Are there any
  - Is there a change from the types of concomitant medications compared to previous or cumulative data

- Medical history
  - Is medical history provided
  - Is there any change from the types of medical history provided in this dataset compared to previous or cumulative data

Overview analysis of the dataset - Adverse events

- Is there a change from previous reporting period or cumulative knowledge
  - What are the most frequently reported SOCs?
  - What are the most frequently reported events?
  - What are the listed events or listed-compatible (synonyms)?
  - What are the unlisted events?

- Are there any unusual events?
  - Eg. Single instance of a rare event
Medication error - actual and potential

- Can be very similar to misuse or overdose. Were these medication error and misuse cases as well? Coding conventions are critical.
  - Is there a misuse due to product instructions?
  - Is the packaging confusing?
  - Is the label or product name easily confused for another product?
  - Is there a pharmacy misinterpretation of a physician intent?
  - Accidental overdose - wrong prescription, child took grandparents meds, unable to tell the difference in various medications
  - Prescribed overdose - physician intentionally provides patient higher dose
- Medication error with or without adverse events

Overdose - or is it?

- Is the overdose reported for the product in question
- Is the dose an overdose according to the reference safety document (ie CCDS for PSUR, USPI for PADER, IB for DSUR)
  - An overdose according to USPI or SmPC may not be an overdose by CCDS due to local restrictions, though overdose will be coded in the case
- Is the patient taking an overdose because of lack of efficacy at maximal dosing?
**Overdose - event assessment**

- What are the events reported as associated to the overdose
- Are these events listed in the reference safety document
- At what level of overdose do more significant events appear
- What kind of an overdose is it
  - Intentional - look for suicide intent, misuse, abuse
  - Accidental - wrong prescription, child took grandparents meds, unable to tell the difference in various medication
  - Prescribed - physician intentionally provides patient high dose
- Did the overdose require treatment and was treatment successful
- Is there anything different about the reported AE when compared to the rest of the dataset?

**Abuse, Misuse**

- SMQ pulls in many more cases than present actual abuse or misuse
  - Is it a true abuse or misuse case or ‘overdose’?
  - Is the abuse or misuse reported for the product in question
- Does the patient have a history of abuse?
  - Does the case describe illegal drug use/abuse?
- Is there abuse potential for the class or products?
- Is there abuse potential for the treatment indication?
  - Pain treatment
- Is there a misuse due to product instructions?
- Is the packaging confusing?
- Is the label or product name easily confused for another product?
- Is there a pharmacy misinterpretation of a physician intent?
- As a result, are there any AE that are seen in this population when compared to the rest of the dataset.
- Any withdrawal symptom issues?
Off-label use

- Is if off-label use according to the reference safety document?
- Is off-label use for product in question?
- Can be overlapping with overdose, misuse/abuse, medication error
- Look for possible pattern with overdose, misuse/abuse, medication error cases, especially with coding and data entry conventions
- What is the type of off-label use?
  - Indication
    - Prescribed? Intentional by patient?
    - Is there lack of efficacy for off-label indication?
  - Population
    - Is there an intentional misuse/med error by prescriber?
- As a result, are there any AE that are seen associated to the off-label use when compared to the rest of the dataset?

Drug withdrawal symptoms

- Are drug withdrawal symptoms expected for the product?
  - Does the CCDS/IB address discontinuation of product?
  - Were the guidances followed?
- Are the events consistent with CCDS/IB?
- Is there anything new noted in the AE that are reported associated to drug withdrawal?
- Are there any patient demographic patterns noted in the dataset for withdrawal events
Drug interaction

- Analysis is required to determine if an interaction is plausible
  - Is the reported interaction between the product of interest and another product/food
  - Is it listed in the CCDS/IB
  - Is the combination contraindicated in the CCDS/IB
  - Is it noted for the class
  - Is it a known interaction (e.g., paracetamol/alcohol)
  - Is it reasonable based on pharmacodynamics of products involved
- What are the events associated with the interaction
  - Are they listed events for either product individually
- Was any treatment required to resolve the event
- Is there anything different about the reported AE when compared to the rest of the dataset (i.e., non-interaction dataset)?
- Is the patient population any different for the subset when compared to the rest of the dataset?
- Were any AE associated directly to the reported interaction?

Long term treatment

- Generally 6 months or year of treatment, depending on product
- Usually not that many cases as duration is not frequently reported
- Are there different AE showing up in this patient population when compared to the rest of the dataset?
- Are there any patterns with the patient population when compared the rest of the dataset?
Lack of efficacy/effect

- Evaluate the indication
  - Was the product used for an approved indication?
- Evaluate the dose
  - Was the correct dose initiated?
  - Was the correct titration completed?
  - Was the maximal dose reached?
  - Has enough time been allowed for the dose to take effect?
- Was a drug interaction involved?
- Were there any contraindications?
- Were there any AE as a result of the LOE? (eg. Contraceptive failure resulting in pregnancy)

Fatal cases

- Was the product possibly the cause of the event leading to patient death?
- Initial per case assessment already done and reported to regulatory authorities, need to look at the aggregate
  - How many deaths during the period and is there any change?
  - Is this number expected/unexpected for the treatment population?
  - Is this number expected/unexpected for the population as a whole?
  - Is there a pattern in the causes of death?
  - Is there a pattern in the AE reported in these cases?
Pregnancy and Lactation

- Generally limited info about pregnancy/lactation in the CCDS/IB. If clearly contraindicated, could be worth mentioning.
- How many actual pregnancies occurred?
  - Match parent/baby cases to describe unique count of pregnancy occurrences
  - Not always a complete match
- What was the outcome of the pregnancy occurrences, not necessarily count of case outcomes
- What were the unfavorable outcomes?
- Baby cases will also show up in the pediatric search, concentrate analysis here on pregnancy or lactation related events, not any events that may be experienced by a baby treated with the product.
- Fetus cases should be considered in Pregnancy analysis, not pediatric.

Pediatric populations

- Is this an approved treatment population?
- Is there anything specific in the CCDS/IB about pediatric treatment, AE?
- Are there different dosing guidelines for pediatrics?
- Is there any dose effect?
- Are there events showing up more frequently in the pediatric dataset versus the non-pediatric dataset?
  - Are the events typical of pediatric population?
  - Is there a proportionate difference in the SOC and PT for pediatric vs non-pediatric AE?
- For pregnancy and lactation cases, including fetus cases, concentrate analysis in P&L if exposure was in the parent.
Elderly populations

- Similar to pediatric
- Is this an approved treatment population?
- Is there anything specific in the CCDS/IB about elderly treatment, AE?
- Are there different dosing guidelines for elderly?
- Is there any dose effect?
- Are there events showing up more frequently in the elderly dataset versus the non-elderly dataset?
  - Are the events typical of elderly population?
  - Is there a proportionate difference in the SOC and PT for elderly vs non-elderly AE?
- Frequently many conmeds, what other comorbidities might there be?

Pre-existing conditions

- Is this an approved treatment population?
- Is there anything specific in the CCDS/IB about treatment, AE in this special population?
- Are there different dosing guidelines for hepatic/renal/etc impaired?
- Is there any dose effect?
- Are there events showing up more frequently in this dataset versus the non-impaired dataset?
  - Are the events typical of the population?
  - Is there a proportionate difference in AE in the SOC and PT for impaired vs rest of the dataset?
- Frequently this is may also be the elderly population, are the events typical of the elderly?
- If clearance has been noted an issue, is the dose an overdose/underdose for the patient? Are the events similar to that seen in overdose?
Other co-morbidities

- Is there anything specific in the CCDS/IB about treatment, AE in any special population?
  - If yes, were these conditions adhered to in dosing, etc?
- Are there different dosing guidelines for any co-morbid conditions?
- Is there any dose effect?
- Are there events showing up more frequently in this dataset versus the rest of the dataset?
  - Are the events typical of the population?
  - Is there a proportionate difference in AE in the SOC and PT for patients with relevant co-morbid conditions versus rest of the dataset?

Populations with specific racial and/or ethnic origins

- Is there anything specific in the CCDS/IB about treatment, AE in this population?
- Is there any dose effect?
- Are there events showing up more frequently in this dataset versus the rest of the dataset?
  - Are the events typical of the population?
  - Is there a proportionate difference in AE in the SOC and PT for patients with any racial or ethnic origins versus rest of the dataset?
Disease severity different from that studied in clinical trials

- Is there anything specific in the CCDS/IB about treatment already, AE in this population from the post-marketing experience?
- Could this be considered medication error?
- Is there any dose effect? Higher prescribed dosing?
- Is lack of efficacy seen for more severe disease population?
- Are there events showing up more frequently in this dataset versus the rest of the dataset?
  - Are the events typical of the population?
  - Is there a proportionate difference in AE in the SOC and PT for patients with more severe underlying illness versus rest of the dataset?

Summary

- Answering the questions:
  - Is there anything new
  - Are there any trends or patterns
  - Is there anything unexpected in the data
- Having standardized output for analysis is key
- Be able to analyze the data and provide opinions to team