Coding of Off Label Use and Differentiation to other Concepts with practical Coding Examples

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Definition of Off Label Use

Guideline on good pharmacovigilance practices (GVP) - Annex I (Rev 2)
EMA/876333/2011 Rev 2

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. Off-label use includes use in non-authorised paediatric age categories. Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU.

MedDRA Introductory Guide Version 17.0

Off Label Use is the intentional use of a product for a medical purpose not in accordance with the authorised product information.
The Need for Coding

Guideline on good pharmacovigilance practices (GVP) - Volume VI (ICSRs)

VI.B.6.3. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

[...]

Reports of overdose, abuse, **off-label use**, misuse, medication error or occupational exposure with no associated adverse reaction **should not be reported as ICSRs**. They should be considered in periodic safety update reports as applicable.

Accordingly:

**Off Label Use is a Drug Risk** that does not need to be reported as ICSR but may need to be addressed in a PSUR (and needs to be subject to Risk Management)
Available Coding Guidance

3.27.1 Off label use when reported as an indication
If a medical condition is reported as an indication along with “off label use”, the preferred option is to select terms for the medical condition and LLT Off label use or other appropriate LLTs linked to PT Off label use. Alternatively, select a term for the medical condition/indication alone. Select LLT Off label use alone only if it is the only information available.

Example

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Preferred Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension; this is off label use</td>
<td>Off label use Hypertension</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

MedDRA Term Selection: Points to Consider (17.0, see section 3.27 for complete guidance)
3.27.2 Off label use when reported with an AR/AE
If an AR/AE occurs as a result of off label use, the preferred option is to select LLT Off label use, or other appropriate LLTs linked to PT Off label use, and a term for the medical condition in addition to a term for the AR/AE. Alternatively, select a term for the medical condition and a term for the AR/AE.

Example

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Preferred Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient was administered a drug off label for pulmonary hypertension and suffered a stroke</td>
<td>Off label use Stroke Pulmonary hypertension</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Stroke Pulmonary hypertension</td>
<td></td>
</tr>
</tbody>
</table>

MedDRA Term Selection: Points to Consider (17.0, see section 3.27 for complete guidance)
Available Codes

[Image showing MedDRA Browser - SOC View: MedDRA 17.0 - English with codes for off-label use and related terms]
No Challenges?

- Physician prescribed the medication to a 12 year old, this was off-label as the medication is for adults only.

- Physician prescribed a lymphoma medication for an eye-condition, this was off-label.

- ...

When the reported verbatim states „off-label use“ respective guidance is available.
Challenges?

- Physician prescribed the medication to a 12 year old (medication is not licenced for children)

- Physician prescribed strong analgesic for back-pain (medication is only licenced for cancer pain in the respective country of origin)

What is your policy if the use reported is off-label but not named as such (i.e. “implied”)?
Differentiation

<table>
<thead>
<tr>
<th>Concept</th>
<th>Intentional?</th>
<th>By Whom?</th>
<th>Therapeutic Use?</th>
<th>Additional Sections in this Document</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misuse</td>
<td>Yes</td>
<td>Patient/consumer</td>
<td>Yes</td>
<td>3.16.1</td>
</tr>
<tr>
<td>Abuse</td>
<td>Yes</td>
<td>Patient/consumer</td>
<td>No</td>
<td>3.16.2</td>
</tr>
<tr>
<td>Addiction</td>
<td>Yes</td>
<td>Patient/consumer</td>
<td>No</td>
<td>3.16.3</td>
</tr>
<tr>
<td>Medication error</td>
<td>No</td>
<td>Patient/consumer or healthcare provider</td>
<td>Yes</td>
<td>3.15</td>
</tr>
<tr>
<td>Off label use</td>
<td>Yes</td>
<td>Healthcare provider</td>
<td>Yes</td>
<td>3.27</td>
</tr>
</tbody>
</table>

From MedDRA Term Selection: Points to Consider (3.16)
Medication Error vs Off Label Use

The essential difference between a Medication Error and Off Label Use is the **intention** of the prescribing / administering physician or other health care professional.

But the intention may not be reported!

(Do you have a policy?)
Example of a Medication error

- Physician asked if it is possible that Drug A and Drug B interacted and caused his patient, who was suffering from seizures (controlled by Drug B), to experience additional epileptic fits.

  “Drug interaction”, “Epileptic fit” are directly in verbatim

BUT: Medication has warning in label that patients with epilepsy treated with this medication require special monitoring as it is known for lowering the convulsive threshold.

  “Labelled drug-disease interaction medication error” may also apply due of the reporting context:

  Physician would not have asked question if aware of the warning!
Another Medication error

- Patient took twice daily medication thrice daily as this was helping more.

Off label use is for actions of health care professionals* (see MedDRA Term Selection: Points to Consider: 3.16)

Patient actions rather will be considered “Medication errors” or “Misuse”
Deadly Challenges?
(Imagine Drug A is “yours”)

- Patient used Drug A and B for self-euthanasia

- State of X used Drug A and B as a new method to execute a delinquent who raped and killed six victims

What do you think?
A Recipe?

- If reported:
  - Code (in addition to AEs, i.e. preferred option)
- If “implied”:
  - Only code when sole reported event
    (to make a data-set in PV data-base),
    else capture in other data-elements
    or
  - Code as if reported

Make sure you can analyse Off label use of your products for Risk Management!
Summary

- Off label use is considered a drug risk requiring documentation (for Risk Management and PSUR)
- A policy for coding “implied off-label use” is advisable
- Recognition of “implied off-label use” is challenging to the involved personnel (detailed knowledge of label (SmPC) is required
- Differentiation with Medication errors may be difficult