

'Off – label' use

Consideraciones sobre uso off-label e errores de la medicación



XIV Encuentro Internacional de
Farmacovigilancia de las Americas

Ulrich Hagemann
22- 25 Agosto 2017
Bogotá-Colombia

Conflict of interests and disclaimer

I have no conflicts of interests to declare.

I was member of the ISoP Executive Committee
from 2009 to 2016 and ISoP Secretary General
from 2012 to 2016.

The views expressed in this presentation reflect the
personal views of the author.

Ulrich Hagemann



In this talk

- ❑ Definitions and overlapping terms
- ❑ A collection of statements
- ❑ 'Off - label' use or prescription: a bad thing?
- ❑ Frequency in 'off - label' prescription
- ❑ Types of 'off - label' use and examples
- ❑ Consequences following 'off - label' use
- ❑ 'Off-label' use and adverse drug reactions
- ❑ Classification of 'off-label' use



Current definition

- ❑ 'Off-label' **prescribing** is the practice of prescribing pharmaceuticals for an unapproved indication or in an unapproved age group, unapproved dose or unapproved form of administration.' *
- ❑ Does verbally not address 'off -label' **use**
- ❑ The only common characteristic is: **intentional!**

* R S Stafford, NEJM 2008: 358, 1427-29

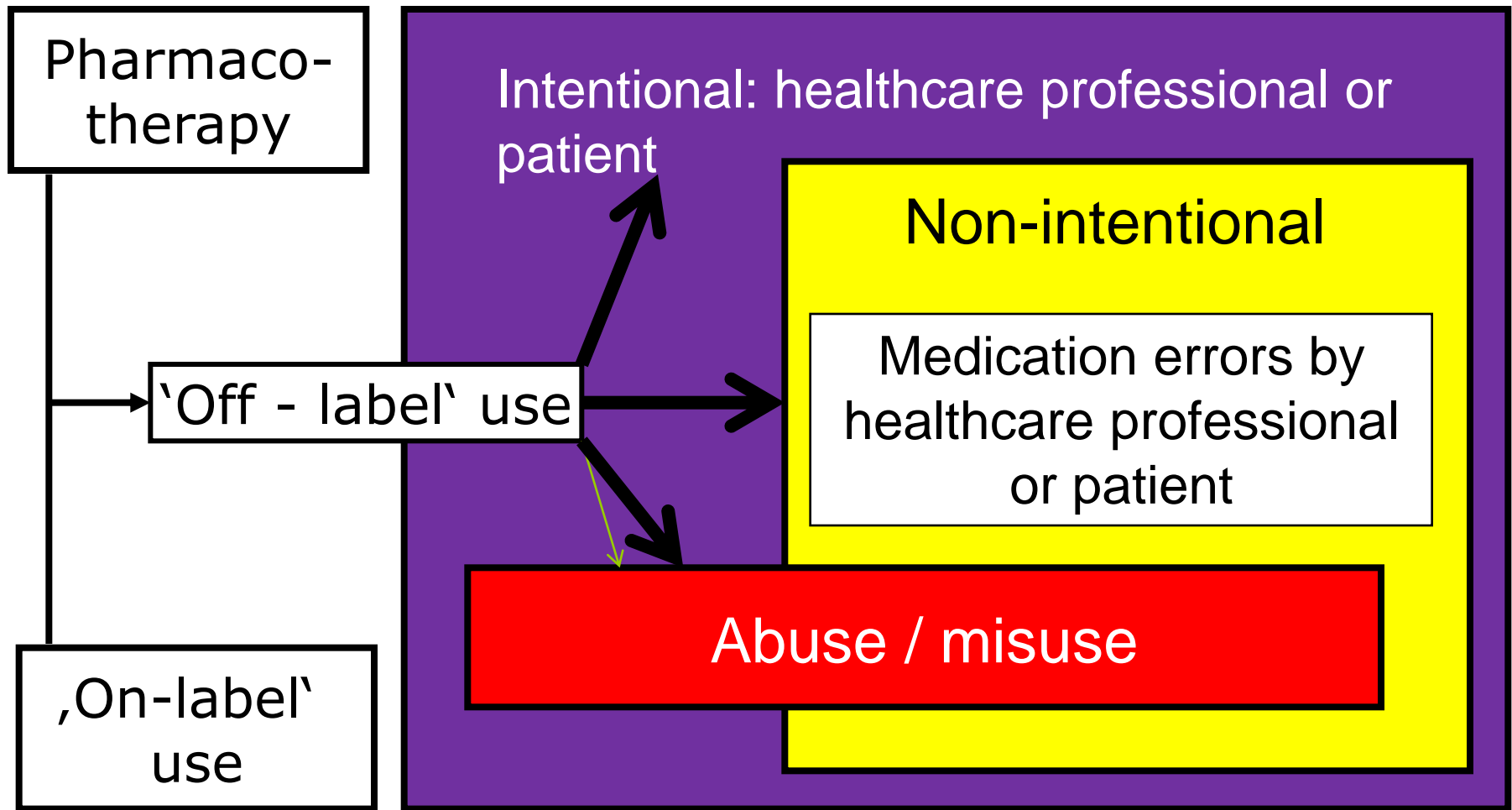


Definitions and overlapping terms

- To be distinguished from
 - Medication error → treatment process related, **not intentional**
 - Misuse, abuse → may be **intentional or non-intentional**, 'off – label' use or medication error
 - Compassionate use (?) → unauthorised drug, **intentional**
 - Orphan disease treatment → **intentional**



The relation between 'off-label' use and medication error



A collection of statements

- ❑ ‚Off - label` is an **operational term**:
 - comprises information and specific language of the approved product information,
 - implicitly excludes drug related information which is not mentioned in the product information

- ❑ **An unsatisfactory term:** many aspects of a drug or treatment are not declared or explained



A collection of statements, ctd.

- ❑ ‚Off-label‘ prescription or use **is legal!**
- ❑ In compassionate use programmes:
 - legal and officially supported
- ❑ ‚Off – label‘ use or prescription may be
 - guideline - recommended (!)
 - first line therapy or
 - last resort / ‚third line‘ therapy



A collection of statements, ctd.

- ❑ In case of safety concerns
 - uncertainty is greater compared to use in approved indications or conditions
- ❑ 'Off – label' determinants are a moving target:
 - drug licences may be extended, or restricted, shifting 'off-label' use to 'on-label' use or vice versa.



A collection of statements, ctd.

- ❑ 'Off – label' term must be seen in the context of affecting
 - complex biological systems, e.g. subgroups of genetic variations in oncology, and
 - administration of specific dosage forms.



'Off - label' use or prescription: a bad thing?

- ❑ 'Off - label' prescription and use may be of benefit for a specific patient.
- ❑ Outcome of 'off - label' use (outside of formal clinical trials) are of interest including for pharmacovigilance.

'Off - label' use or prescription: a bad thing?

- Permits innovation in clinical practice (?)
*
- Offers early access to potentially valuable medication *
- Treatment in ,orphan' conditions *

* R S Stafford, NEJM (2008) 358: 1427-29



Frequency in 'off – label' prescription or use *

- ❑ Frequency in 'off – label' **prescription** varies substantially across therapeutic classes
- ❑ In general, more frequent when scientific support is limited or lacking compared to evidenced therapies

* D C Radley, Arch Intern Med (2006) 166: 1021-26
(data from 'Office-based' physicians)



Frequency in 'off – label' prescription or use *

- ❑ Likelihood for 'off – label' **prescription** is increased (compared to analgesics or diabetes medications) in
 - epilepsy, asthma, allergy, peptic ulcer and dyspepsia, cardiac medications or psychiatric drugs
- ❑ Frequency unknown in 'off – label' **use**

* D C Radley, Arch Intern Med (2006) 166: 1021-26
(data from 'Office-based' physicians)

Types of 'off - label' - use

- ❑ Medically conditioned:
 - Outside of licensed indications, e.g. milder forms, related forms
 - Disregard of contraindications
 - Disregard of warnings and precautions
 - Omission of pre-treatment testing
 - Dosage not recommended or licensed



Types of 'off - label' – use, ctd.

- ❑ Technically conditioned:
 - Intentionally or (unintentional) medication error
 - Dosage form misused/used incorrectly
- ❑ Inadequate lab values monitoring or therapy
- ❑ Non-compliance



Possible consequences following 'off - label' use

- ✓ Lack of effectiveness / efficacy
- ✓ Adverse drug reactions and harm
- ✓ Effective treatment of a specific clinical condition!
- ✓ Legal: liability of HCPs and industry
- ✓ No consequences!



'Off - label' use and ADRs

- Cave: new legal definition (EU):
 - ,a response to a medicinal product which is noxious and unintended' *

Means: suspected ADR **following any use**, not only after use according to the package leaflet or SmPC

* EU, Directive 2001/83/EC as amended, December 2010



'Off-label' use and reporting ADRs

- ❑ Reporting ADRs:
 - Doctors, companies
- ❑ Patient reporting!
- ❑ Could indicate
 - Rare ADRs
 - Serious ADRs
 - Misuse or abuse and sequelae
 - Administration problems (medical devices, intake, application etc.)



Regulatory and legal aspects, ctd.

- ❑ Companies should anticipate and describe possible 'off – label' prescription or use within the application for licensing
- ❑ Agencies should request robust data for 'off – label' conditions and 'legalize' when appropriate.



Proposal for a classification for 'off - label' use

'Off - label' use

Class A
High impact:
positive or negative

Class B
Medium impact,
not determinable

Class C
Low impact

continuum

continuum

Indication
Contraindication
Warning and precautions
Abuse
Incorrect administration

Lower dose, higher dose,
Incorrect administration
Warnings and precautions
Drug holidays
Unapproved subpopulation

Lower dose, higher dose
Incorrect administration
Warnings and precautions
Drug holidays

Summary and conclusions

- ❑ 'Off – label' is an unsatisfactory operational term overlapping with other terms
- ❑ Magnitude of 'off – label' prescription varies substantially, magnitude of use is unknown
- ❑ 'Off – label' prescription and use is not preventable
- ❑ Multiple consequences of different types
- ❑ Medical, legal and economic consequences



Teaching Pharmacovigilance

- ❑ Teaching Pharmacovigilance: the WHO-ISoP Core Elements of a Comprehensive Modular Curriculum
 - Beckmann, J. Hagemann, U. et al., Drug Safety, October 2014, Volume 37, [Issue 10](#), pp 743–759
 - <https://link.springer.com/article/10.1007/s40264-014-0216-1> (open access)
- ❑ Developing a crowdsourcing approach and tool for Pharmacovigilance education material delivery
 - Bate, A, Beckmann J et al., Drug Safety, March 2017, Volume 40, [Issue 3](#), pp 191–199
 - <https://link.springer.com/article/10.1007/s40264-016-0495-9> (open access)



Uppsala
Monitoring
Centre

ISoP-UMC training course



4th ISoP-UMC Training
Panama city, Panama
4-6 September 2017

Pharmacovigilance concepts
and tools in Latin America



isoponline.org/training/isop-umc-training-courses