Development of a Guideline on the Off-Label-Use of Drugs

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Structure

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Motivation

Off-Label-Use:

...is widely practiced and recommended throughout the medical society

...is a legal cross-section → concerns drug law, liability law, health insurance law and professional rights

...has no legal concept in Germany

Motivation

- **>20%** of physicians are not familiar with the term „off-label-use“[1]
- **73%** of all off-label-uses have little to no scientific support[2]
- **>80%** of pediatricians feel that the information about the risks and benefits of an off-label-use is inadequate[3]

1) Ekins-Daukes S, Helms PJ, Taylor MW, McLay JS. Off-label prescribing to children: attitudes and experience of general practitioners. Br. J. Clin. Pharmacol. 2005;60(2):145–9

2) Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch. Intern. Med. 2006 166(9):1021–6

3) Saullo F, Saullo E, Caloiero M. A questionnaire-based study in Calabria on the knowledge of off-label drugs in pediatrics. J. Pharmacol. Pharmacother. 2013

Off-Label-Use in Pediatrics

- „Children are not just small adults“
- **20%** of the European population is aged under 16 [4]
- **50-90%** of all medicines are not tested on children[5]
- Prevalence of off-label-use in children is **13%-90%**[6-7]
- High risk of adverse drug reactions

4) European Commission. Better Medicines for Children From Concept to Reality. 2013
5) Conroy S, Choonara I, Impicciatore P. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ. 2000;320:79–82
6) Buecheler R, Schwoerer P, Gleiter CH. Off-Label-Verordnungen in der Paediatrie. Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz. 2003 ; 46(6):467–76
7) O'Donnell CPF, Stone RJ, Morley CJ. Unlicensed and Off-Label Drug Use in an Australian Neonatal Intensive Care Unit. Pediatrics. 2002

Reasons for the Lack of Pediatric Studies

- Studies with children are much more expensive and time consuming
- Few experts in pediatric pharmacology
- Need for special formulations
- Low market potential and low profitability

Pediatric Regulation (EC) 1901/2006

- Pediatric Investigation Plan (PIP)
  - Waiver or deferral possible
- Pediatric Committee (PDCO)
- Pediatric Use Marketing Authorization (PUMA)
- Creation of financial incentives

Definitions of Off-Label-Use

No legal term for „off-label-use“ in Germany:

→ Can lead to uncertainties concerning liability and patient safety

→ Great need for a **single, uniform legal definition** for both patients and medical staff

Definitions

 vs. 

Off-label-use is:

The use for an indication, dosage form, dose regimen, population or other use parameter **not mentioned in the approved labeling**. (FDA Modernization Act)

The use of a drug which has a marketing authorization but is used for a condition, at a dose, via a route or for an age that is **not listed in the Summary of Product Characteristics** for that drug. (British NHS Guideline)

Definitions in the Scientific Literature

Off-label-use is the use of an approved drug for medical treatment that is not described or intended in the drug labeling and that would require a corresponding **adjustment or amendment of the drug approval or a new drug approval**. (Plate et al.)[8]

Considering the drug approval an off-label-use will not come about after a violation of §22 para. 3 AMG, but rather the off-label-use only exists, when the drug is used in a way that causes an **amendment of the drug approval according to §29 para. 2a AMG or a new drug approval according to §29 para. 3 AMG.** (Schroeder-Printzen & Tadayon)[9]

8) Plate, V. et al. Wohin treibt der Off-Label-Use?. A&R, 2008, H. 6, 261-269

9) Schroeder-Printzen, J. and Tadayon, A. Die Zulässigkeit des Off-Label Use nach der Entscheidung des BSG vom 19.3.2002. SGB 12 (2002): 664.

Off-Label-Use in Germany
Expert Group „Off-Label“

Assigned by the Federal Ministry of Health (BMG) in 2002

→ Reviews on the scientific knowledge on the off-label-use of certain medicinal products

→Submits learned information to BMG and Federal Joint Committee (G-BA)

→G-BA decides whether off-label-use is covered by health insurance

Verdict of the Federal Social Court B1 KR 37/00 R

Coverage of off-label-drugs by health insurance if:

1. Serious disease
2. Lack of treatment alternative
3. Reasonable prospect for a successful treatment with the drug in question according to the state of scientific knowledge

→ Affirmed by Federal Constitutional Court in 2005

Liability in Germany

§84 para. 1 German Medicine Act:

Legal responsibility lies with the producer only if a medicinal product is used in the designated way.

→ Is off-label-use a designated use?

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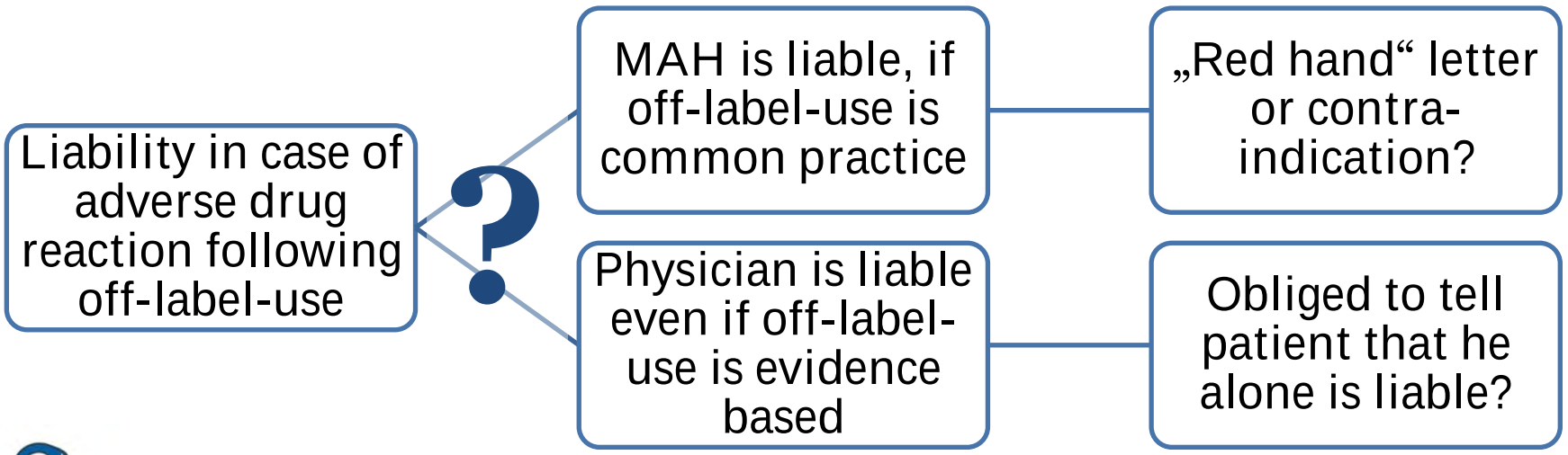

Health Care in the UK

- Department of Health supervises the National Health Service (NHS)
- Publicly funded
- Individual regulations in England, Wales, Scotland and Northern Ireland:
  - National Health Service (England)
  - Health and Social Care in Northern Ireland (HSCNI)
  - NHS Scotland
  - NHS Wales

National Institute for Health and Clinical Excellence (NICE)

- Establishes guidelines for:
  - Use of health technologies within the NHS
  - Clinical practice
  - Guidance for public sector workers on health promotion and ill-health avoidance

- NHS must cover all NICE-recommended treatments

Off-Label-Use in the UK

- NHS Guideline for Unlicensed and Off-Label-Use Medicines:
  - Definition of off-label-use
  - Checklist for practitioners
  - Register of unlicensed and off-label-use of medicines
- NICE Evidence Summaries: Unlicensed/Off-Label Medicines (ESUOM)

Liability in the UK

Marketing Authorization Holder (MAH) are generally not liable for harm as a result of unapproved use, but:

→ NHS Trust accepts liability, provided the NHS Guideline has been followed

→ Patient has to be informed about unlicensed drug use

Health Care in France

- „Close to best overall health care in the world“[10]
- Government has responsibility for the financial and operational management
- Insurers are non-profit agencies
- 70% of most health care costs are refunded, 100% of costly or long-term ailments

10) http://www.who.int/whr/2000/media_centre/press_release/en

Off-Label-Use in France

Temporary Recommendations for Use (TRU):

- Granted for a maximum of three years by ANSM
- Aims to assess risks and benefits and collect scientific information on designated off-label-use
- Reimbursment for designated indication
- If there appears to be a risk to public health, ANSM can suspend or modify the TRU

Questionnaire
Main Topics

- Definition of off-label-use
- Main problems of off-label-use for physicians
- Reimbursement and liability
- Off-label marketing

Questionnaire
Definitions of Off-Label-Use

Perfect agreement on the following definition:

„Off-label-use means the use of a licensed medicinal product outside the terms of the marketing authorization issued by the national or European competent authorities.“

Questionnaire
Reimbursement

- Agreed main problems of off-label-use for physicians are **liability and recourse claims**

- Many doctors are afraid of prescribing off-label, even if it is in the best interest of the patient, because of possible recourse claims

- Most physicians argued that it would be in the best interest of the patient, if the reimbursement of off-label-drugs was regulated similar to the NHS-system

Questionnaire
Liability

No agreement on liability:

→ Some questionees stated that MAH should be liable in case of common off-label-uses

→ Others argued that there should be a system based on the British NHS Guideline or an independant fund

Questionnaire
Marketing

All agreed, that there is a great need for more information for physicians, but:

→ most argued, that information should not be provided freely by MAHs

→ but by independent experts or as part of planned expanded approvals and only available to the medical society

Summary

- Legal term for off-label use is highly needed and should be implemented
- Recourse claims and liability issues are a great problem for both physicians and patients

→ A combination of the French TRU decree and the British NHS Guideline should be applied to German law

→ Need for information on off-label-drugs could be adressed similar to the ESUOM

List of references

1) Ekins-Daukes S, Helms PJ, Taylor MW, McLay JS. Off-label prescribing to children: attitudes and experience of general practitioners. Br. J. Clin. Pharmacol. 2005;60(2):145–9
2) Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch. Intern. Med. 2006 166(9):1021–6
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7) O'Donnell CPF, Stone RJ, Morley CJ. Unlicensed and Off-Label Drug Use in an Australian Neonatal Intensive Care Unit. Pediatrics. 2002
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10) http://www.who.int/whr/2000/media_centre/press_release/en