Federal Institute
for Drugs
and Medical Devices

Risk mitigation when switching – Germany's experience within the wider European perspective

Martin Huber | 20 October 2017

Risk mitigation when switching – topics

Interface between substance, product and practice

Ø **Diversity in Europe – regulatory framework in Germany**

What role for pharmacist education and additional controls in access to reclassified/switched products?

Ø **Example: emergency contraceptives**

How to regulate longstanding OTC medicines that may lack efficacy evidence?

Ø **Recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC)**

Are OTC medicines special?

Before approval

Proof of:
- Ø **Quality**
- Ø **Efficacy**
- Ø **Safety**

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After approval

Pharmacovigilance

Ø Monitoring of drug safety after approval

Ø **Same requirements for both prescription-only and OTC medicines**

Who decides on legal status?

Centralised procedure

Ø European Medicines Agency (CHMP)

Ø European Commission

=> Applicable to **all European Member States**

Decentralised and national procedures

Ø Reference Member State + Concerned Member States

Ø National agency

Ø Responsible ministry in Member State, as applicable

=> Depending on **national situation**

Marketing authorisations for OTC medicines

Harmonised marketing authorisation (DCP – Decentralised Procedure):

- Ø Product authorised in Reference Member State + Concerned Member States
- Ø **Product information harmonised** (except some national aspects)

Legal status determined on **national level** (not part of DCP):

- Ø Impact of different practices in European Member States

- Ø Operational and procedural challenges both for industry and regulators
- Ø Consistent risk mitigation?

Establishment of European platform for OTC products

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

MANDATE, OBJECTIVES AND RULES OF PROCEDURE OF THE NON-PRESCRIPTION MEDICINAL PRODUCTS TASK FORCE

Doc. Ref.: CMDh/350/2016/Rev0
December 2016

1. Background information

The Non-prescription medicinal products Task Force is established to explore new ways to improve convergence on evaluation and facilitate the access to the EU patients to safe and effective OTC products.

http://www.hma.eu

Mandate and objectives

Non-prescription medicinal products Task Force

Ø Established to provide recommendations to the CMDh and HMA on matters relating to OTC products

Tasks of the group include the following aspects:

Ø Explore **best practices** at both NCA and industry level

Ø If appropriate, revise the Best Practice Guide on DCP for non-prescription medicines

Ø **Engage with relevant trade associations** to discuss OTC status at European level

Duration of activity:

Ø Task Force is constituted for the period of **time needed to complete tasks** committed by the CMDh

Regulatory framework in Germany

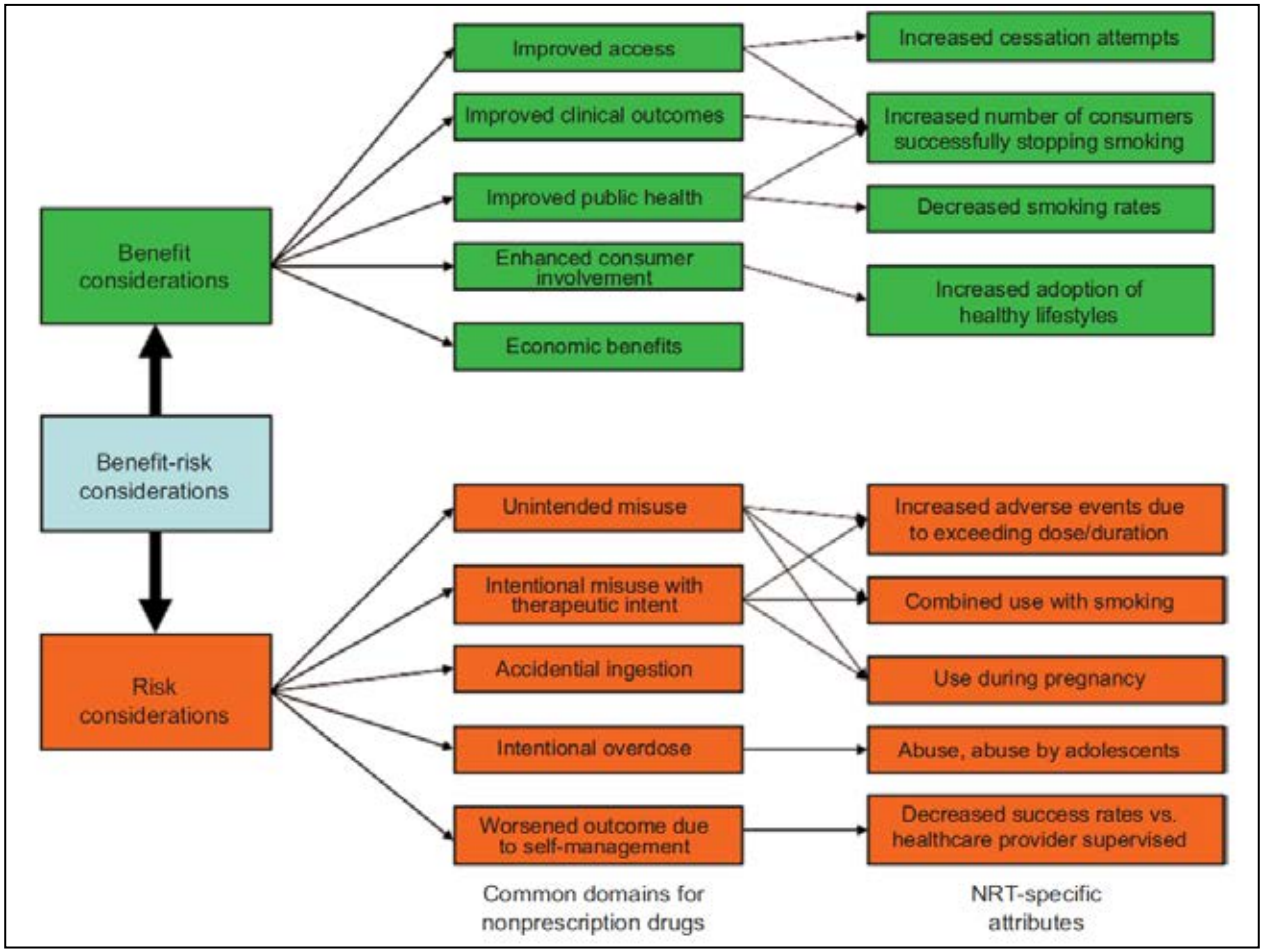
Who makes the classification decision?

- Decision is taken by the **Ministry of Health** in a legal act
- Except in cases where a substance not generally known in medical science is affected (such a substance is automatically subject to medical prescription), prior consultation of an **Expert Advisory Committee** is warranted
- Committee is composed of stakeholders and experts in the field (academia, **clinical practice**, **pharmacists** etc.)
- **BfArM** acts as the secretary and contact point for this committee (unit within division of pharmacovigilance)
- BfArM hosts the meetings, and BfArM staff is involved in meetings

How to determine the legal status

- **Substance-based approach**
- **Criteria** are laid down in the German Medicines Act
- Subject to medical prescription are:
  - substances not generally known in medical science
  - substances able to directly or indirectly **harm** patients when given without medical supervision
  - substances with a high potential for **abuse/misuse/off-label** use when this is associated with harm
- Once a substance has been identified based on these criteria it will be put on a **list of substances subject to medical prescription** (annex to a **legal regulation**)

Other approaches – BRASS model



Brass et al. Clin Pharmacol Ther 2011; 90(6): 791-803.

Different approaches for assessing OTC switches

AESGP Self-Care Agenda 2020

"A balanced and proportionate approach to future submissions to change legal status should be put in place. The so-called **Brass** et al. **benefit-risk model** and methodology should become the established standard for evaluating and deciding on switch applications in Europe."

BRASS

Ø Approach considering both **benefits** and **risks** when reviewing OTC switch

Germany

Ø **Risk**-based approach as outlined in national legislation (and „Switch Guideline")

Ø **„Safety first"**

Emergency contraceptives – ulipristal

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2014
EMA/710568/2014
Press Office

Press release

EMA recommends availability of ellaOne emergency contraceptive without prescription

Change in status to facilitate access for women in the European Union

http://www.ema.europa.eu

Levonorgestrel

March 2015

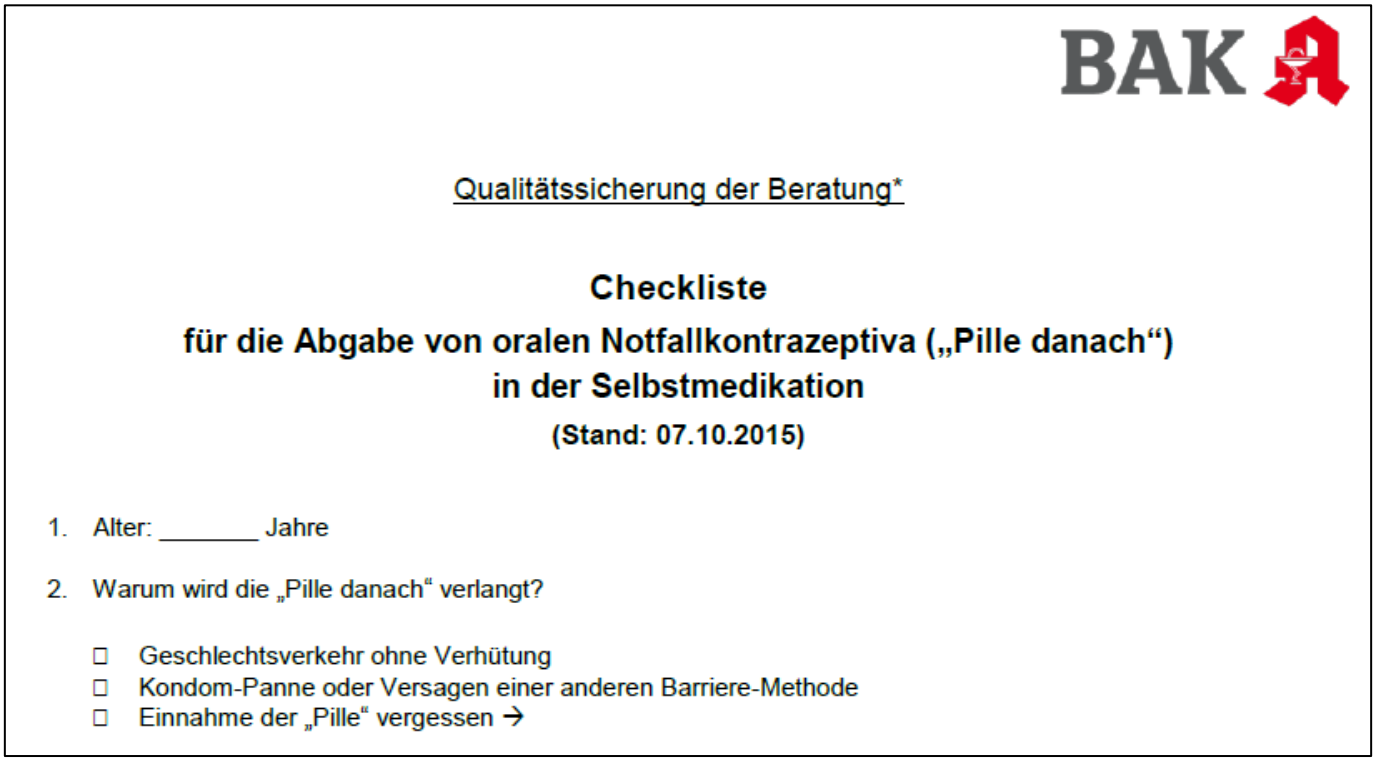
- **National switch** of levonorgestrel for emergency contraception to **OTC**
- Decision follows recommendation from **Expert Advisory Committee**
- Switch restricted to **pack size** containing one single dose (1,5 mg)

At the same time **amendment of pharmacy regulation**:

- Ulipristal and levonorgestrel are excluded from **sale via internet**
- Additional control in access

Pharmacist education

Ø German Federal Chamber of Pharmacists developed detailed **training materials** (including **checklist for consultation in pharmacies**)



BAK

Qualitätssicherung der Beratung*

Checkliste

für die Abgabe von oralen Notfallkontrazeptiva („Pille danach“)
in der Selbstmedikation

(Stand: 07.10.2015)

1. Alter: _____ Jahre

2. Warum wird die „Pille danach“ verlangt?

   ☐ Geschlechtsverkehr ohne Verhütung
   ☐ Kondom-Panne oder Versagen einer anderen Barriere-Methode
   ☐ Einnahme der „Pille“ vergessen →

https://www.abda.de

Challenges regarding safety and efficacy

AESGP Self-Care Agenda 2020

"**Non-prescription medicines** are in most cases well-established medicines with **recognised efficacy** and an **acceptable level of safety** which have been on the market for 10 years or more. Their **safety profile is well-known** due to their **long-term experience and widespread use**, which should make them of less interest to the Pharmacovigilance Risk Assessment Committee (PRAC).

Since the PRAC became operational in July 2012, a **number of referrals** on well known substances were made. AESGP believes that, due to its limited resources, the **PRAC should focus on new/innovative substances** and that there are better ways to deal with safety issues of well-known substances (e.g. increase of Periodic Safety Update Report (PSUR) frequency)."

How to deal with safety and efficacy issues of OTC medicines?

- Public health importance of safety issues independent of legal status
- OTC status does not necessarily exclude the potential for new safety issues
- Same medicines have different legal status in European Member States
- Lack of (evidence for) **efficacy** of longstanding OTC medicines

Recent examples from PRAC

- Ambroxol and bromhexine
- Fusafungine

Ambroxol and bromhexine

Ø European review started in April 2014 (trigger: **safety concerns**)

Ambroxol and bromhexine expectorants: safety information to be updated

Risk of allergy and skin reactions to be included in the product information

The CMDh[1] has endorsed by majority vote recommendations to update the product information for ambroxol- and bromhexine-containing medicines with information about the small risk of severe allergic reactions and severe cutaneous adverse reactions (SCARs). The medicines are widely available in the EU for use as expectorants (to help clear mucus from the airways).

The recommendations were originally made by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which confirmed the previously known risk of allergic reactions and also identified a small risk of SCARs, a group of skin conditions which include erythema multiforme and Stevens-Johnson syndrome.

http://www.ema.europa.eu

Evidence source for efficacy

Clinical studies

- Studies performed during development of bromhexine and ambroxol (1950 to 1980) were considerably less standardised than would be necessary today
- These studies would not completely fulfil contemporary requirements with regard to validated endpoints, statistical confirmation or Good Clinical Practice
- Majority of available evidence (in particular in indications that were first authorised e.g. secretolytic indication) comes however from these studies

Therapeutic setting

- Endpoints are poorly defined
- Lack of scientific consensus as to the most appropriate clinical trial methodologies

Conclusion on efficacy

- Ø Limitations and uncertainties attached to the dataset hinder ability to draw robust conclusions on efficacy
- Ø Studies conducted after initial marketing authorisation do not provide new significant scientific data on efficacy of the products
- Ø Clinical evidence from studies in children is weak due to their heterogeneity and to the lower number of children enrolled

Nevertheless, overall **modest positive results** as regards **efficacy** were reported for ambroxol and bromhexine

Fusafungine

September 2015

Fusafungine containing medicinal products for oromucosal and nasal use

Summary | Key facts | All documents

CMDh endorses revocation of authorisations for fusafungine sprays used to treat airway infections

Medicines to be withdrawn due to serious allergic reactions and limited evidence of benefit

The CMDh[1] has endorsed by consensus the revocation of marketing authorisations for fusafungine sprays in the EU. This follows a review by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) which concluded that the benefits of fusafungine do not outweigh its risks, particularly the risk of serious allergic reactions.

Fusafungine is an antibiotic and anti-inflammatory nose and mouth spray used to treat upper airway infections such as rhinopharyngitis (common cold).

March 2016

http://www.ema.europa.eu

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Critical assessment

Safety

- Ø **Serious allergic reactions** (involving bronchospasm) have occurred soon after use of fusafungin sprays
- Ø These reactions are rare, but they can be **life-threatening**
- Ø **No measures** have been identified to sufficiently reduce or manage this risk

Efficacy

- Ø **Evidence** for beneficial effects is **weak**
- Ø Taking into account **the mild and self-limiting nature** of upper airway infections such as rhinopharyngitis, the benefits of fusafungine were not considered to outweigh the risks

Contact details

Dr Martin Huber MPH

Federal Institute for Drugs and Medical Devices
Division of Pharmacovigilance
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

martin.huber@bfarm.de
www.bfarm.de

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