Pharmacovigilance in Germany

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Federal Institute for Drugs and Medical Devices (BfArM)

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Authorised Medicinal Products for Human Use in Germany (excl. Blood Products and Vaccines)

Total = 53,882 Medicinal Products

Of these authorised through community procedures:

1. Mutual Recognition = 2,856 Med Prod
   with Germany as Reference Member State (RMS) = 409 Med Prod
   e.g. Aggrastat®(Tirofiban-hcl), Codiovan® (Valsartan+Hydrochlorothiaz.) , Euthyrox® (Levothyroxin), Propofol® (Narcofol), Xusal® (Levocetirizin-hcl)
2. And authorised via the Centralised (EMEA-) Procedure

with a German Rapporteur = 193 Med Prod*

or Co-rapporteur = 301 Med Prod*

z.B. Aranesp®(Darbepoetin alfa), Neorecormon®(Epoetin beta), Xeloda®(Capecitabin) and e.g. Ovitrelle® (Choriogonadotropin alfa), Pegintron® (Peginterferon alfa2b), Micardis®(Telmisartan) resp.

* with central authorisations each individual package size is counted as one Med Prod
The House of Pharmacovigilance
(PhVWP 10/99, “Brainstorming Group III“)
Observe! 
Measure! 
Explain!

Galileo Galilei

“This telescope has the advantage of discovering the ships of the enemy two hours before they can be seen with the natural vision.”
Sources of Information on ADRs, General

Single Case Reports:
Quality + Causality

Body of Evidence

Epidem. Studies:
Frequency + Causality

Pharmacol. Studies:
Mechanism + Causality
Sources of Information on Drug-related Risks, Specific (1)

I  ADR-Cases, absolute
   - Spontaneously reported ADR cases
     • Single cases
     • Case series in “Line Listings“
     - “Solicited“ ADR cases
       • from Intensive Observation Projects
       • from systematic complete surveillance (e.g. skin reactions)

II  Sales Figures
Sources of Information on Drug-Related Risks, Specific (2)

- III Studies investigating the relation ADR-Cases / Exposition
  - Controlled Clinical Studies with intervention
  - Observational (epidemiological) studies without intervention
    - Cohort studies (prospective, starting with actually treated women)
      -- comparative, i.e. two- oder more arms
      -- non-compartive, i.e. one arm only
Routes of Information

Physician, Pharmacist, Patient

Companies

Drug Commissions of Medical Professions

§29 Drug Law

WHO

BfArM

EMEA
BfArM’s ADR-Reporting Requirements
German Drug Law (AMG) §29, 5th amendment

The Marketing Authorisation Holder has to

- report without delay any change in the scientific background relevant to approval of a drug
- report within 15 days any suspected case of serious ADR or serious interaction or serious misuse
- record and report after first approval of a drug all non-serious cases of ADR or interaction, which have to be reported every six months for two years, yearly for next three years, then every five years together with the five yearly reports the application for renewal of authorisation
- provide a scientific assessment
- continue to report even when the drug is no longer on the market
Number of Reports per Year
(1978 - 2003, ICSRs incl. follow-ups and Reports in PSURs)

Drug Law:
2nd amendm.  4th amendm.  5th amendm.

until 2003
Number of ADR-Reports
(1996 - 2003, ICSRs incl. follow-ups)

Number of ADR-Reports (1996 - 2003, ICSRs incl. follow-ups)


*until 30.6.2003
Number of ICSRs (Domestic)
Distinguishable Cases since 1995 (n=81,200)

<table>
<thead>
<tr>
<th>Year</th>
<th>Fatalities</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003*</td>
<td>386</td>
<td>6682</td>
</tr>
<tr>
<td>2001</td>
<td>756</td>
<td>10245</td>
</tr>
<tr>
<td>1999</td>
<td>675</td>
<td>8642</td>
</tr>
<tr>
<td>1997</td>
<td>679</td>
<td>8644</td>
</tr>
<tr>
<td>1995</td>
<td>494</td>
<td>7204</td>
</tr>
</tbody>
</table>

*until 30.6.2003
Management and Documentation of ICSRs

administrative part

- assignment of BfArM case report number
duplicate check

- letter exchange: e.g. confirmation of receipt,
information of concerned companies about ICSRs received directly
from physicians in accordance with data privacy legislation

- image scans

- electronic transmission of ICSRs
  (Drug Commission of German Medical Profession,
  WHO, EMEA[Line-Listing])

medical documentation and coding

- drugs
  WHO-Drug Dictionary and ATC

- ADRS
  Adverse Reaction Terminology der WHO
  (MedDRA to be implemented mid 2004)

- indications
  ICD9
  (MedDRA to be implemented mid 2004)

- WHO-Guide to Participating Countries
  ICH E2B to be implemented mid 2004
Degrees of Assumed Causality and their Meanings in Terms of Probability of Causal Relation in the Assessment of Adverse Events / Drug Reactions

Assumed causality

- unlikely
- possible (narrow sense)
- probable (narrow sense)
- possible (wide sense)
- probable (wide sense)
- certain

Assumed % probability of causal relation

0 5 50 95 100
Number of Reported Cases, Causality and Seriousness of an ADR as Components for a "Signal" or the Motivation to Take Actions in Terms of Informing about the Risk.

- Causality:
  - Certain
  - Probable
  - Possible

- Seriousness:
  - Volume = harm = Motivation for further investigation (Signal) or already an information in the SPC

- AUC = Evidence for the AE cases to represent a true ADR

- Number of ADR Cases

- Graph showing the relationship between the number of reported cases, causality, and seriousness.
Under-Reporting from the Viewpoint of the Chairman of the Pharmacovigilance Working Party of the CPMP
(Sue Wood Symposium)

Myths about Under-Reporting

- Level is fixed at 90%
  i.e. 10% of reactions are reported
- Level of reporting has a linear relationship with the effectiveness of a scheme
- Under-reporting undermines the concept of ADR reporting
What can ADRs Inform about?

1. Quality of ADRs
2. Interactions
3. Additional determinants of the risk
4. Possible mechanisms (hypothesis generation)
5. Habits an trends in prescription and use of a drug
6. Profils of reporting and (to a limited degree) occurrence of ADRs
7. Significantly excessive numbers of reports of certain ADRs of certain drugs in the whole data base (creating a signal)
8. (Possibly) relative differences in the frequency of a specific ADR of two or more drugs
9. Minimum occurrence of an ADR in an exposed population (if population exposure can be estimated)
### ADR-Database Analysis

by Calculation of “Proportional Reporting Ratios“

<table>
<thead>
<tr>
<th>Drug under consideration</th>
<th>All other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR under Consideration</td>
<td>a</td>
</tr>
<tr>
<td>All other ADRs</td>
<td>c</td>
</tr>
</tbody>
</table>

1. Calculation of $\text{PRR} = \frac{a}{a+c} \cdot \frac{b}{b+d}$

2. Calculation of $\chi^2$
   as a measure of the reliability of the assumption that the PRR indicates a true peculiarity of the reporting frequency for the drug/ADR under consideration
"Evidence-Weighted" Risk of a Certain ADR = Weight/Importance of the Aspect of this ADR in Making Pharmacovigilance Decisions

Seriousness of the ADR

Evidence of Risk from this ADR

Frequency of the ADR
"Evidence-Weighted" Benefit = Weight/Importance of the Benefit Argument (for one Indication)
Weighing Positive Benefit - versus Negative Risk-Arguments in the Assessment of a Drug

\[ \text{Sum of all evidence-weighted risks} \]

\[ \text{Benefit} \]

\[ + \alpha \]

\[ - \alpha \]

\[ \text{Argument} \]

\[ \text{Argument} \]
Comparing the Benefit / Risik-Balance between Therapies

(Risik associated with several ADRs are combined in single cubes)
"Hey, I thought we were working with the same data..."
# Pharmacovigilance Working Party and Germany’s Role

<table>
<thead>
<tr>
<th></th>
<th>Drugs on behalf of CPMP</th>
<th>Drugs with only national competence</th>
<th>Organisational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of issues per CPMP meeting</td>
<td>15</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>No. with Germany’s contribution</td>
<td>5</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Contribution of Germany [%]</td>
<td>34</td>
<td>29</td>
<td>10</td>
</tr>
</tbody>
</table>
§ 5 German Drug Law: Prohibition in respect of unsafe drugs

(1) The placing on the market of unsafe drugs shall be prohibited.

(2) Drugs shall be considered unsafe if, according to the current level of scientific knowledge, there is reason to suspect that, when used in accordance with their intended purpose, they have harmful effects which exceed the limits considered tolerable in the light of current medical knowledge.
### Severity of Suspicion Concerning a Risk, Actions of BfArM

<table>
<thead>
<tr>
<th>Severity of Suspicion</th>
<th>Actions of BfArM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No suspicion</td>
<td>Collection of information „wait and watch“, screening of literature</td>
</tr>
<tr>
<td>Significant ADR reports, first concern</td>
<td>Signal procedure, Urgent Drug Information („ASI“)</td>
</tr>
<tr>
<td>First suspicion of a specific risk</td>
<td>Graduated Step Plan, Step I, Open minded discussion with MAH</td>
</tr>
<tr>
<td>Well-founded suspicion concerning unacceptable risks, but proviso of error</td>
<td>Graduated Step Plan, Step II, BfArM announces to take actions, (written) hearing of MAH</td>
</tr>
<tr>
<td>Well-founded suspicion not refuted</td>
<td>BfArM decides on actions (appeal and court case possible thereafter)</td>
</tr>
</tbody>
</table>

- 0 %
- 100 %
Graduated Step Plan

Initiation:
ADR Cases, PSURs, Studies, ARs

Step I

Possible Hazard

MAH Response

Step II

Well-founded Suspicion of Health Risk

MAH Hearing

written oral

Suspicions refuted ordered self-responsible Actions

Court Case
Number of Drugs during the Years 1990 - 2003
affected by Measures of a Graduated Step Plan

Revocation of authorisation: 15 substances in ca. 175 drugs

Suspension of authorisation: 5 substances in ca. 100 drugs

Changes of authorisation: several hundred substances in several thousand drugs
Information about Risks, Co-ordination of Assessment and - if necessary - measures in the EU

National Graduated Step Plan, Step I

Rapid Alert, Infofax to MS

Discussion at Pharmacovigilance Working Party and CPMP, usually with MAH

Art. 31/36 Referral

Preparation of Opinion and Binding Decision

Preparation of non-binding Position Statement; national comp. authority decides

Prosecution of Measures via Graduated Step Plan, Step II
Arbitration Procedure

Community Interest

Discussion of the CPMP: Rapporteur / LoQ

Clock Stop (max. 60 days)

Response of MAH

(Co-) Rapporteur’s Assessment Report (AR)

Comments to AR

Final AR

Oral Hearing of MAH

Opinion of CPMP

Submission of the Opinion to MS and MAH(s)

MAH(s)

Day

1

2

3

-45

-60

-90

90

-120
### Appeal Procedure

1. **Opinion of the CPMP**
2. **Deadline for Appeal**
3. **Reason for Appeal**
4. **Decision of the CPMP: Change of Opinion**
   - **New Rapporteur**
5. **Assessment Report**
6. **Hearing of MAH(s)**
   - **Discussion in the CPMP: Opinion**
7. **European Commission: Binding decision**

**Day**
- 1
- -15
- -60
- 60
- -90
- -120
## Procedures to Minimise the Risk

<table>
<thead>
<tr>
<th></th>
<th>National</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure</strong></td>
<td>Graduated Step Plan</td>
<td>Referral under Art. 31, 36 or 18</td>
</tr>
<tr>
<td><strong>Initiator</strong></td>
<td>Higher federal authority (BfArM or PEI)</td>
<td>MS, EU, MAH</td>
</tr>
<tr>
<td><strong>Criteria for start of procedure</strong></td>
<td>1. hint for risks 2. reasonable suspicion concerning unacceptable risks</td>
<td>Community interest (severe risk, actions, some concerned MS)</td>
</tr>
<tr>
<td><strong>Conduct of procedure</strong></td>
<td>Higher federal authority with own or with external experts if necessary</td>
<td>EMEA with Rapporteur/Co-Rapporteur in discussion with all MS</td>
</tr>
<tr>
<td><strong>Decision</strong></td>
<td>Higher federal authority</td>
<td>Commission on the basis of CPMP Opinion</td>
</tr>
</tbody>
</table>
## Important Recent Pharmacovigilance Activities of the BfArM (I)

<table>
<thead>
<tr>
<th>Medicinal product</th>
<th>Procedure</th>
<th>Risk</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorectics</td>
<td>EU</td>
<td>Cardiovascular ADRs</td>
<td>Revocation (court case)</td>
</tr>
<tr>
<td>Medicinal products made of human materials</td>
<td>National</td>
<td>Transmission of vCJD</td>
<td>Measures to select donators</td>
</tr>
<tr>
<td>Medicinal products made of bovine materials</td>
<td>National/EU</td>
<td>Transmission of BSE</td>
<td>Varification of safety</td>
</tr>
<tr>
<td>Bupropion</td>
<td>EU</td>
<td>Cardiovascular ADRs</td>
<td>Changes of SPC</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>National/EU</td>
<td>Rabdomyolysis</td>
<td>Market withdrawal</td>
</tr>
<tr>
<td>COX 2 inhibitors</td>
<td>EU</td>
<td>Cardiovascular and gastro-intestinal ADRs</td>
<td>Changes of SPC (procedure ongoing)</td>
</tr>
</tbody>
</table>
## Important Recent Pharmacovigilance Activities of the BfArM (II)

<table>
<thead>
<tr>
<th>Medicinal product</th>
<th>Procedure</th>
<th>Risk</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone replacement therapy (HRT)</td>
<td>National/EU</td>
<td>Breast cancer, thrombembolism</td>
<td>Procedure ongoing</td>
</tr>
<tr>
<td>Ionic contrast media</td>
<td>National</td>
<td>Hypersensitivity reactions</td>
<td>Revocation</td>
</tr>
<tr>
<td>Kava kava</td>
<td>National</td>
<td>Liver toxicity</td>
<td>Revocation</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>National/EU</td>
<td>Venous thrombembolism</td>
<td>Changes in SPC</td>
</tr>
<tr>
<td>Plant laxantins</td>
<td>National</td>
<td>Dependancy</td>
<td>Restriction of use</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>EU</td>
<td>Arrhythmia</td>
<td>Changes of SPC</td>
</tr>
</tbody>
</table>
Thank you for your Attention!