Pharmacovigilance Update - national

Norbert Paeschke
Bonn, May 2015
Overview

- Anwendungsbeobachtungen (AWB)
- DHPC
- Impact of Selected new EU Guidance Documents
  - Educational Material - Module XVI Addendum I
  - Literature Monitoring
  - ICSR-Implementation Guide
AWB versus PASS

Interventional Studies (clinical trials)

PASS

- imposed on company
  initiated, financed, conducted

Non-interventional studies

AWB

- voluntarily
  initiated, financed, conducted
  by company
What is an “AWB”?  

• Clear definition in German Medicines Act lacking  
  • [...] examinations which serve the purpose of gathering knowledge resulting from the use of authorised or registered medicinal products [...]  
• What is included under this definition?  
  • More specific interpretation of “AWB-concept” included in BfArM’s and PEI’s new (draft) announcement for AWB  
  • Cancer registries? no  
  • Analyses of health care databases (e.g. Arzneiverordnungsreport)? no  
  • Studies on pharmacoeconomics?  
  • Retrospective Chart Reviews? no  
  • Studies conducted by independent researchers?  
• PASS excluded from notification requirements of section 67 par. 6 since 2012 (introduction of PASS-definition into German Medicines Act), PAES not excluded  
  • PASS and PAES are part of the RMP and aim to gather knowledge on efficacy and safety in the post-authorisation phase
Notification of “Anwendungsbeobachtungen” (AWB)

Recent changes of section 67 par. 6 of German Medicines Act

- **2012:**
  - *Any person* who conducts tests which serve the purpose of gathering knowledge resulting from the use of authorised or registered medicinal products shall immediately inform the competent higher federal authority, the […]

- **2013:**
  - The information pursuant to this sub-section is to be transmitted electronically
  - a *final report* shall be transmitted to the competent higher federal authority *within one year following completion* of the data collection process […]
  - […] the competent higher federal authority is to make the *notifications* received and the *final reports available* to the public through an *internet portal.*
Transitional Arrangements § 146 AMG

§ 146 AMG Abs. 8 AMG
(legal implementation of PASS, newly introduced art.. § 63f und 63g)

Art. §§ 63f und 63g are applicable for studies started after
October 26th, 2012.

- PASS, started until 26. Oktober 2012 are considered AWB, i.e. transparency rules according to § 67 Abs. 6 AMG apply
Transitional Arrangements: § 147 AMG

§ 147 AMG

For non-interventional studies falling under § 63f and examinations according to art. § 67 par. 6, started before August 13th, 2013, art. § 63f par. 4 and art. § 67 par. 6 as being valid until August 12th, 2013 are applicable until December 31st, 2013, i.e.

Transparency rules apply for all AWB, that

• started after August 13th, 2013,
• started before August 13th, 2013 and have not been finalized until December 31st, 2013

➢ Consequences:

➢ Publication of all initial AWB-submissions since August 13th, 2013
➢ submissions concerning ongoing and new AWB since January 1st, 2014
Publication of AWB - BfArM’s database on “AWB”

Veröffentlichungen zu AWB

Nichtinterventionelle Studien (NIS)

Veröffentlichungen


Das BfArM veröffentlicht dabei lediglich die ihm angezeigten Angaben zu den Anwendungsbeobachtungen und ist nicht für die Bearbeitung der Anzeige und die Durchführung der Beendigung der Anzeige verantwortlich. Das BfArM führt daher keine detaillierten Prüfungen zu inhaltlichen oder Durchführenden. Eingehende Anzeigen werden vom BfArM auf formelle Anforderungen hin überprüft und aufgrund dessen erledigt.
# Publication of AWB - BfArM’s database on “AWB”

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<th>eingereicht am</th>
<th>Art der Anzeige</th>
<th>Institution</th>
<th>Auftraggeber</th>
<th>Titel der AWB</th>
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<td>23.03.2015</td>
<td>Erstanzeige</td>
<td>Institut Dr. Schauerte</td>
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<td>NEMO:Nicht-Interventionelle Studie zur Erfassung der Neurotoxisität unter adjuvanter oder palliativer Therapie mit Oxaliplatin Omnicare® bei Patienten mit kolorektalem Karzinom</td>
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<td>Eine multizentrische, prospektive, nicht-interventionelle Register-Studie zur Dokumentation von Adhärenz, Sicherheitsprofil und pharmakoökonomischen Aspekten bei Patienten mit schubförmiger Multipler Sklerose, die mit Tecfidera® behandelt werden.</td>
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<td>A naturalistic, multisite, observational study of rotigotine transdermal patch and other currently prescribed therapies in patients with idiopathic parkinson’s disease</td>
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BfArM’s database on “AWB”

- Full publication of submitted study protocols and reports
- Publication of meta-data submitted with announcement (title, number of patients, etc.)
Transparency on “PASS” equivalent to “AWB”?

PASS excluded from “AWB”-Transparency requirements, however, they should be registered in the ENCePP Registry as per GVP Module VIII and should be included in the RMP as per GVP-Module V

<table>
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<th>PASS notifications submitted to BfArM from 2/2014 – 1/2015</th>
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<td>Overall Number</td>
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<td>Number of notified studies registered in ENCePP-registry</td>
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<tr>
<td>Number of notified studies with protocol published via ENCePP-registry</td>
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<tr>
<td>Number of PASS not included in the PV-plan of the RMP</td>
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One of the ENCePP guiding principles is transparency to the general public about ongoing research relating to medicines used in clinical practice. The Declaration of Helsinki, last amended in October 2013, requires that every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
AWB – Electronic Submission

WORKS IN PROGRESS
SORRY FOR THE INCONVENIENCE
**Interface will allow**

- to create user accounts
- structured data input
- upload of documents
- Test phase planned but not yet started
Dear Health Professional Communication
Rote Hand Brief
Current Way of Distribution Best Way Forward?

• Increase in number of DHCPs
• Current way of direct postal mailing distribution cost intensive
• Initiative by company associations to use regular publications to HCPs, particularly „Deutsches Ärzteblatt“
  • Co-ordination with EU communication timelines might be difficult
  • Time needed for internal review
  • Could be quicker
  • Traditional way in exceptional circumstances
• BfArM and PEI could agree, no final agreement by Federal Ministry of Health yet
  • However, study to show that the new of dissemination is similarly effective than the traditional way is needed
Educational Materials – Improving Access
Module XVI Addendum I – Educational materials (Draft)

- Add I.1. Introduction
- Add I.2. Principles for educational materials
- Add I.3. Submission of educational materials
- Add I.4. Format of educational materials
- Add I.5. Content of educational materials
- Add I.6. Assessment of educational materials at the level of Member States
- Add I.7. Publication of educational materials by marketing authorisation holders on specific websites
How to make Educational materials available to users

- **Imposed and voluntarily developed materials**
- **Currently available on company websites**
  - in addition to initial distribution
  - sometimes difficult to find
  - For HCPs as well as Consumers
- **Imposed materials**
  - Central access useful as seen by HCP-organisations
  - physicians as well as pharmacists
  - Transparency
Central Access for Imposed Educational Material

• **Solutions:**
  - Publication of educational materials on NCA website
  - Linking to company websites (favoured solution by BfArM for legal reasons)

• **BfArM has requested weblinks from a number of companies**

• **Implementation started**
  - Pitfalls still present
  - Good and bad examples
  - Sometimes links provided don’t work

• **Password protection?**
  - free access as much as possible
  - particularly educational material für patients

• **No replacement of current distribution**
Information Currently Available plus Additional Column for Weblinks

Stand: 22.07.2014

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Presentation on Websites: Good Example

Sicherheitsrelevante Informationen (für Fachkreise nach Login)

Schulungsmaterial Wichtige Informationen über kombinierte hormonale Kontrazeptiva.pdf

Produktdetails, Fach- und Gebrauchsinformationen

Gebrauchsinformationen: Fachinformationen:
Presentation on Websites: Example not fulfilling the intended purpose
Additional Challenge

- clear distinction between educational and advertising material
- BfArM has received information that HCPs
  - Do not recognize educational material as such
  - Assuming advertisements
  - Dump it due to this misunderstanding
- Company associations have been approached for creation of a logo to be used when imposed educational material is distributed
  - Discussion not yet finalized
Educational Material Q&A

- **Q&A document requested by companies**
  - Method and format of submission
  - Data requested
  - Type of variation
  - Contact points
  - Obligations of parallel distributors and importers
  - Development of Educational Material for drugs with same active ingredients
    - Co-ordination of development
    - Harmonisation of layout
  - Questions concerning dissemination
    - Target groups, relation to other materials such as DHCP
Medical Literature Monitoring
(EMA’s MLM Service)
Medical Literature Monitoring (MLM Service) (EMA/161530/2014)

- **DRAFT** detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency
  - Art 27 of Reg.726/2004, Implementing Regulation 520/12
  - Monitoring of selected literature
  - Publication of a list of substances
    - Chemically defined, herbals
    - Based on data in Art. 57 database
    - High number of MAHs concerned
  - Publication of literature sources used
  - Data entry in Eudravigilance
  - Download of ICSRs from EMA-Website
  - „detailed Guide“ in preparation
- **Handling of ICSRs** in accordance with Art. 107/107a of Dir. 2001/83 and GVP Modul VI
Consequences for current reporting obligations?

- **MLM-Service outsourced**
  - Test phase
  - „go live“ planned for August 2015

- **Current reporting obligations**
  - all cases from scientific literature

- **Future Reporting obligations**
  - Once EV-functionalities established no reporting requirements for literature cases covered by MLM-Service
  - What about the interim phase between MLM‘s „go live“ and announcement of EV-functionalities being established?

- **Challenge: Duplicate handling**
  - More duplicates than now (?) when current reporting obligation remain valid and MLM Service is established
Submission of ICSRs
(ICSR-Implementation Guide)
ICSR-Structure

**C.1**
Identification of the Case Safety Report

**C.2.r**
Primary source(s) of information

**C.3**
Information on Sender of Case Safety Report

**C.4.r**
Literature Reference(s)

**C.5**
Study Identification

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**D**
Patient characteristics

**E.i**
Reaction(s) / Event(s)

**F.r**
Results of tests and procedures relevant to the Investigation of the Patient

**G.k**
Drug(s) Information

**H**
Narrative Case Summary and Further Information
Overview about Changes

- Implementation of ISO-Standards (substances, drugs, pharmaceutical forms, routes of administration)
- EU-Implementation Guide (Umsetzung geplant in 2015/2016)
  - differences in ICH-regions
  - Mapping E2B (R2) \(\leftrightarrow\) E2B (R3)
  - Flow of Information to NCAs
    - Original reports, recoded reports, combined (Master-) cases
    - Changes in EMA-business rules for data fields
      - deleted (e.g. format specifiers in date fields CCYYMMDD)
      - newly introduced fields
      - changes (length, allowed field values)
      - Identical but move to other parts in the ICSR-structure
    - Codes for datafield identification
      - E.g. Arzneimittel: old: E2B(R2): B.4. ...
        new: E2B(R3): G.k.2......
      - new repeatable fields
        - Marked with 'r'
- Implementation of „Access Policy“ in Eudravigilance
Thank you for your attention!