Pharmacovigilance Update - national

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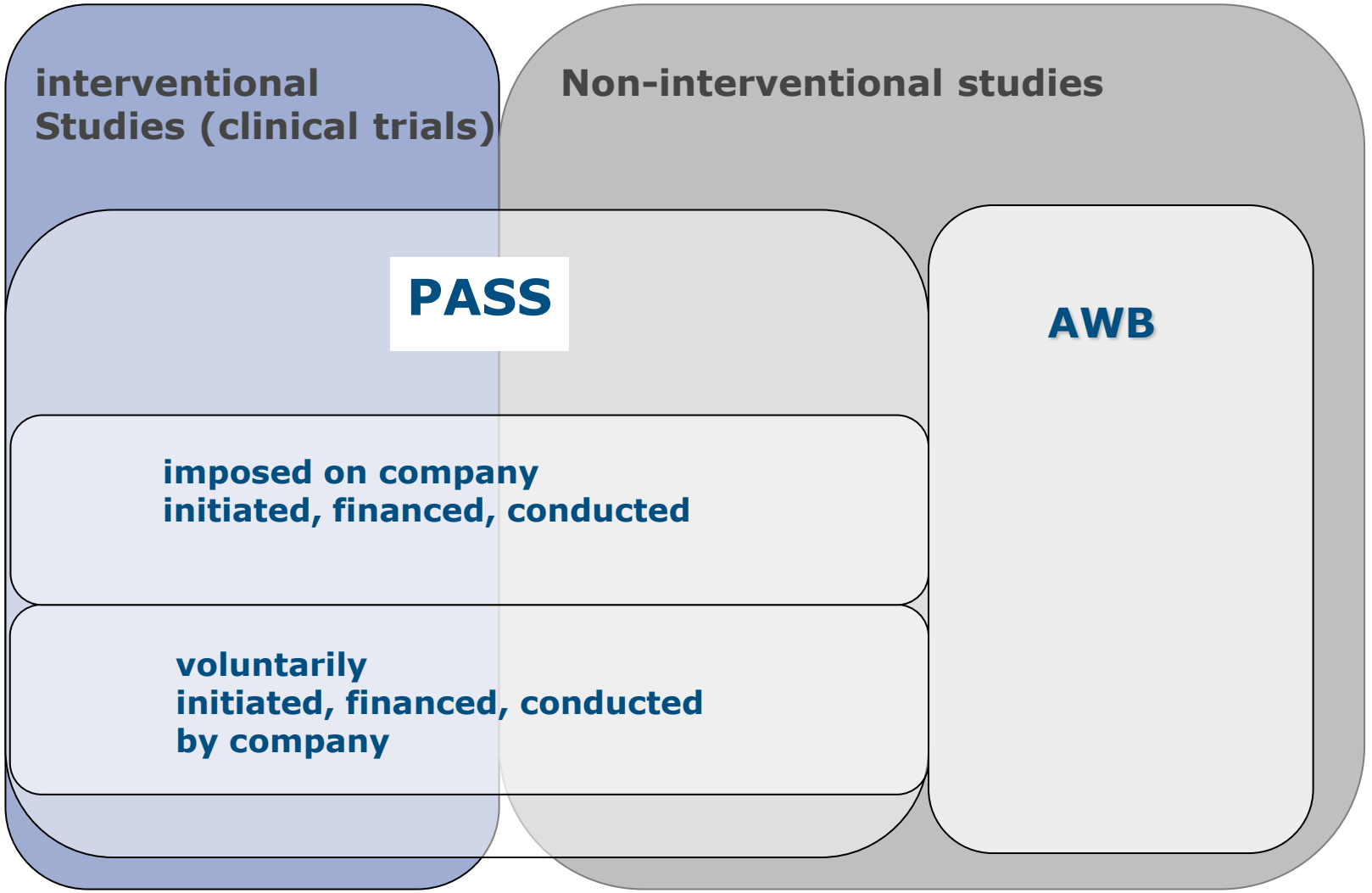
Bonn, May 2015

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



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"

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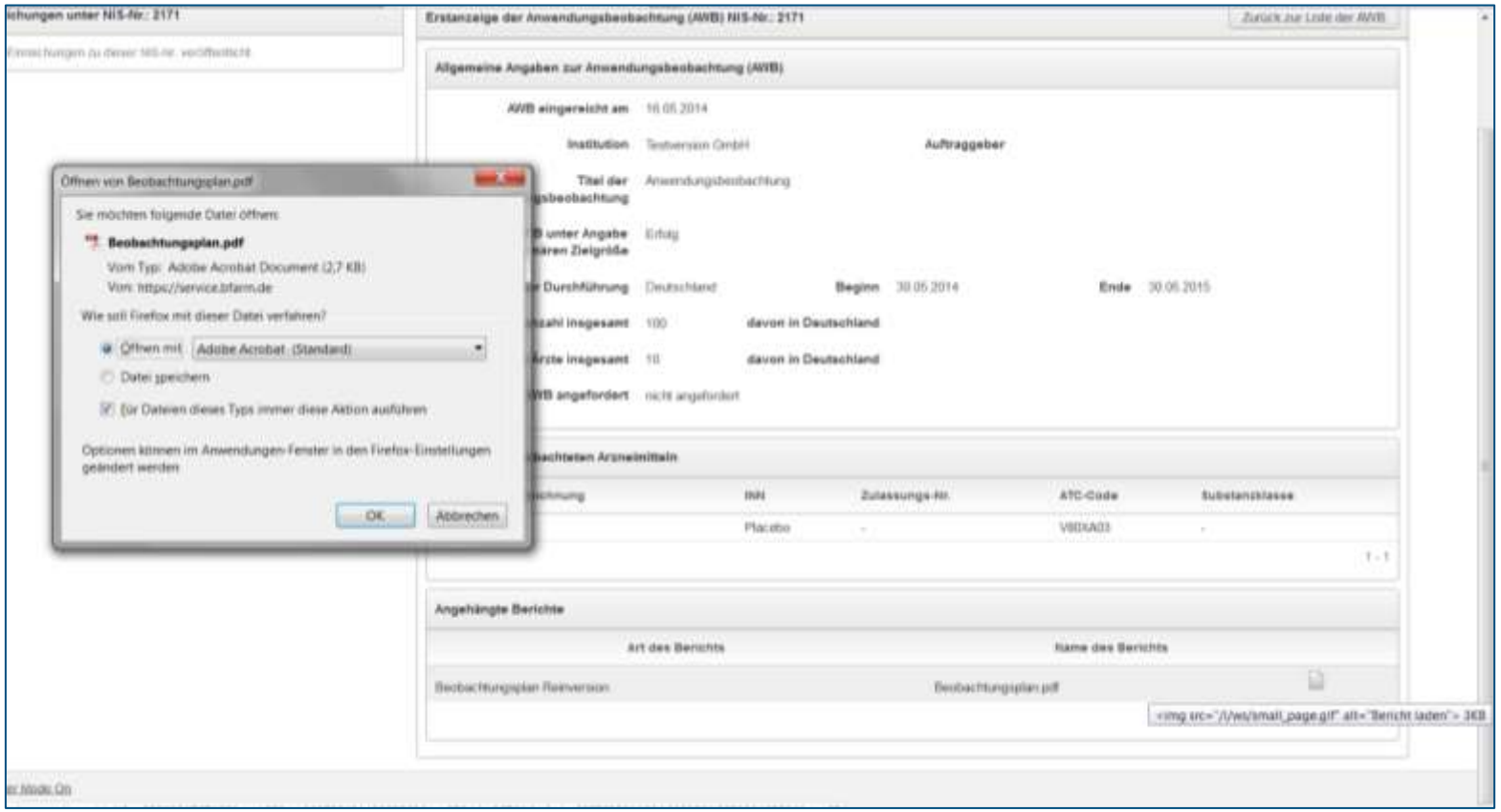
	eingereicht am	Art der Anzeige	Institution	Auftraggeber	Titel der AWB	NIS-Nr.
	23.03.2015	Erstanzeige	Institut Dr. Schauerte	-	NEMO:Nicht-interventionelle Studie zur Erfassung der Neurotoxizität unter adjuvanter oder palliativer Therapie mit Oxaliplatin Omnicare® bei Patienten mit kolorektalem Karzinom	6501
	20.03.2015	Änderungsanzeige	medac GmbH	-	Untersuchung des Einflusses von Komorbiditäten, Alter sowie weiteren Faktoren auf die Intensität, Wirksamkeit und Sicherheit einer Taxceus-Behandlung	1908
	12.03.2015	Erstanzeige	NeuroTransData GmbH	-	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.	6494
	09.03.2015	Änderungsanzeige	RIEMSER Pharma GmbH	-	Beobachtung der Anwendung von Vagantin® bei der Behandlung der Hyperhidrosis peri- und postmenopausaler Frauen	1681
	25.02.2015	Abschlussbericht	UCB Biosciences GmbH	-	A naturalistic, multisite, observational study of rotigotine transdermal patch and other currently prescribed therapies in patients with idiopathic parkinson´s diesease	159

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**

PASS notifications submitted to BfArM from 2/2014 – 1/2015	
Overall Number	34
Number of notified studies registered in ENCePP-registry	22 (65%)
Number of notified studies with protocol published via ENCePP-registry	10 (29%)
Number of PASS not included in the PV-plan of the RMP	3 (9%)

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

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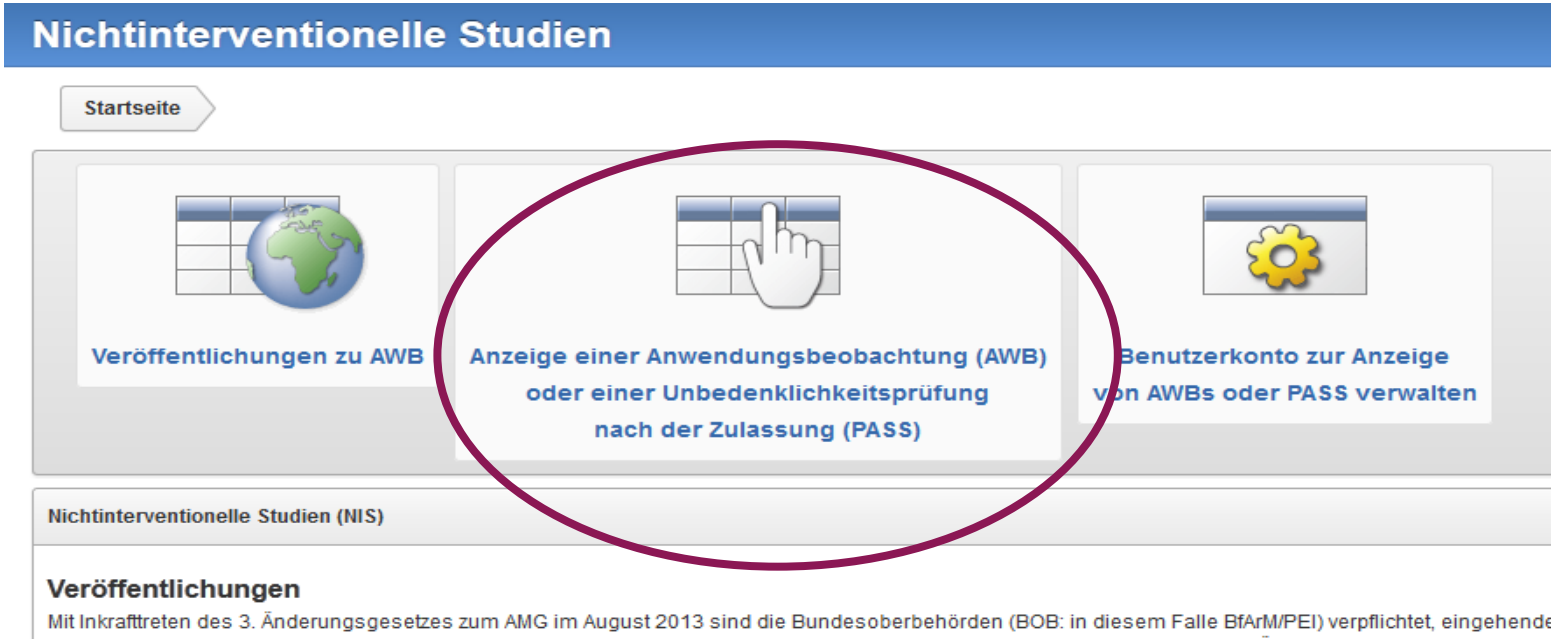


- **Interface will allow**
  - to create user accounts
  - structured data input
  - upload of documents
  - Test phase planned but not yet started

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 developped 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
  - physicicans as well as pharmacists
  - Transparency

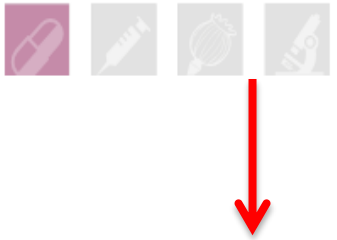
Central Access for Imposed Educational Material

- **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
  - particulalry educational material für patients
- **No replacement of current distribution**

Information Currently Available plus Additional Column for Weblinks

BfArM

BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

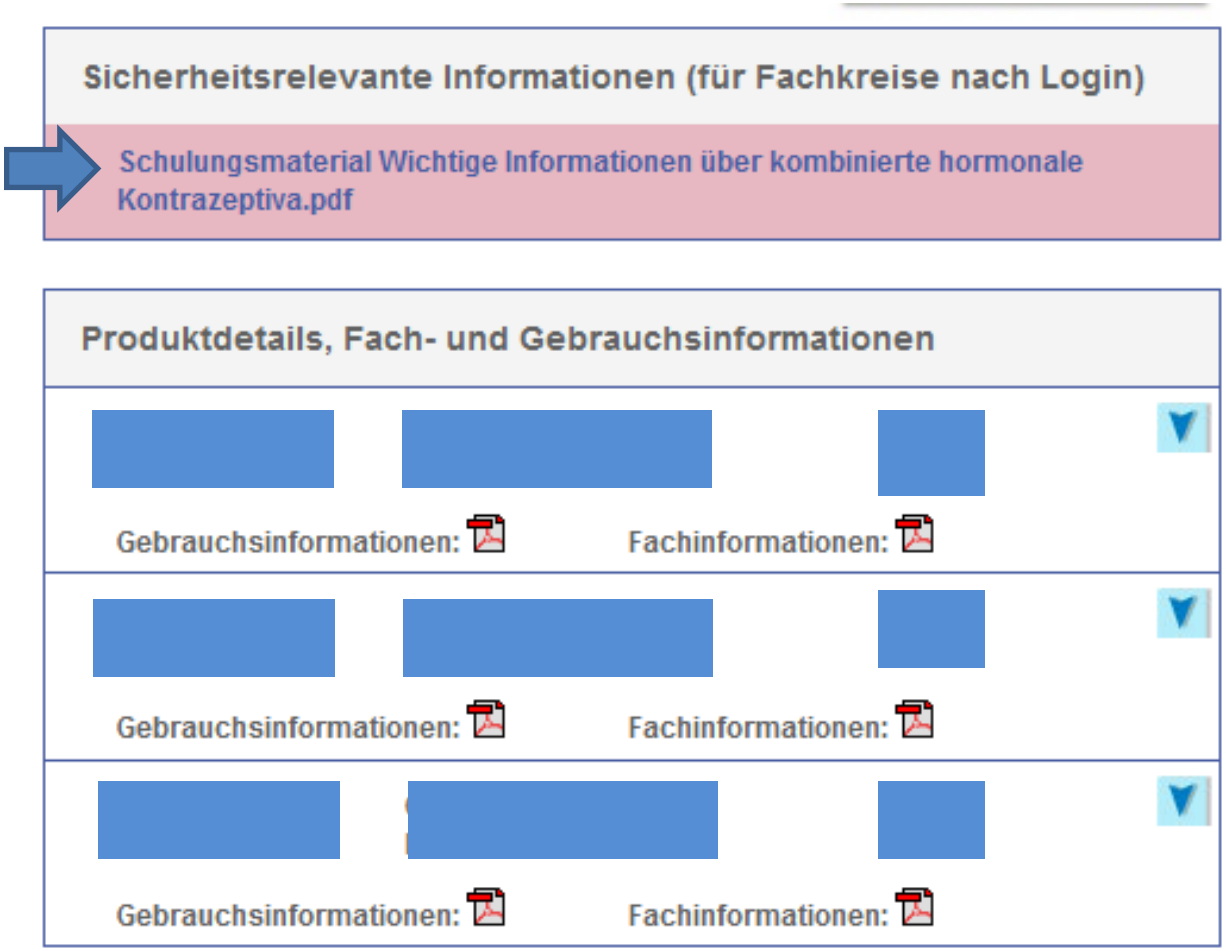


Wirkstoffe und Warenzeichen, für die Schulungsmaterial beauflagt ist

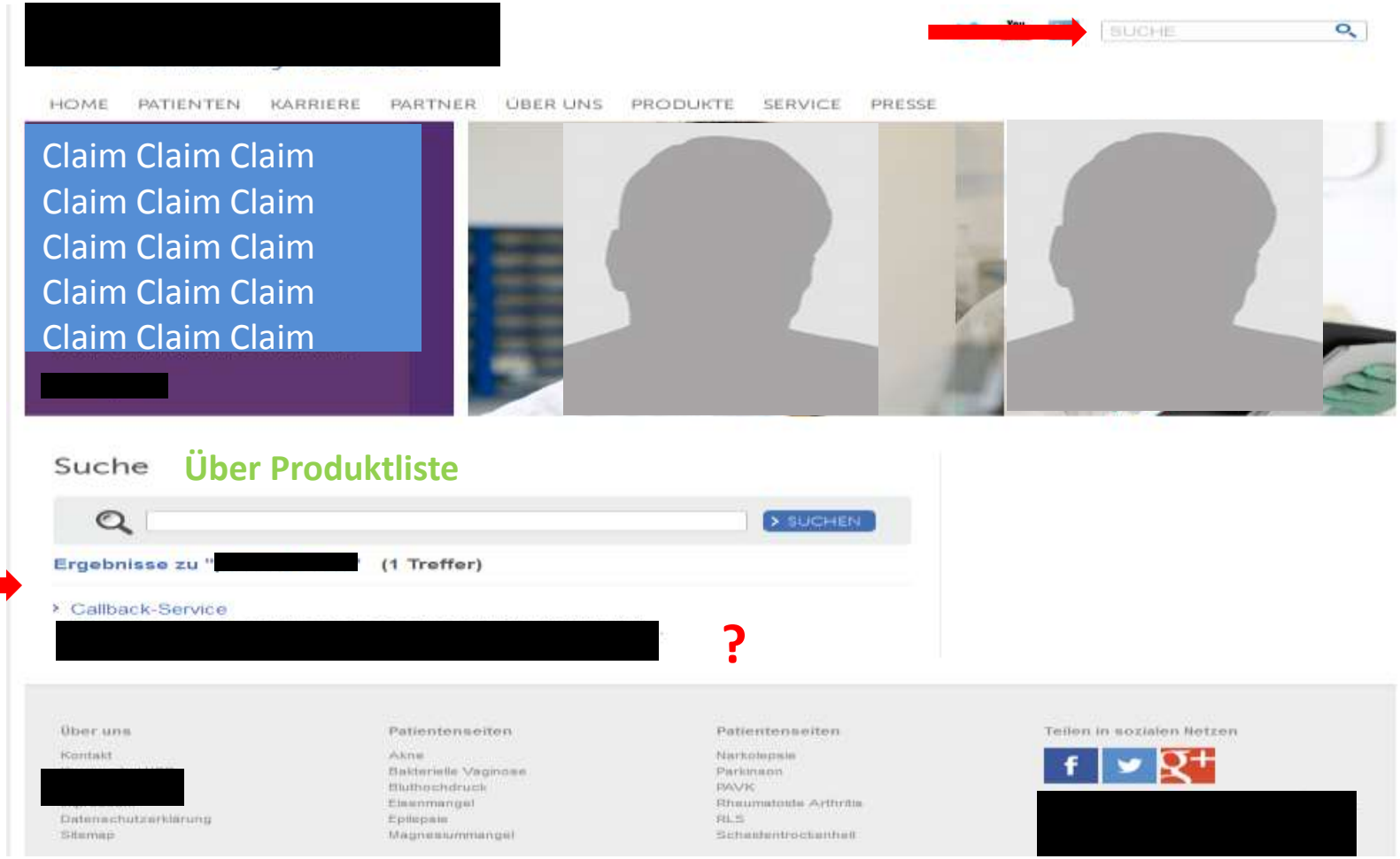
Stand: 22.07.2014

Warenzeichen u.a.	*EU-Verfahrensnummer*	Wirkstoff	In Kombination mit	Siehe Fußnote	ATC-Code	Status der Zulassung	Zulassungsdatum	Schulungsmaterial - Weblink
Oslif Breezhaler	*EMEA/H/C/001210*	Indacaterolmaleat			R03AC18	zugelassen	30.11.2009	
Tresiba	*EMEA/H/C/002498*	Insulin degludec			A10AE06	zugelassen	21.01.2013	
Aknefug, Aknenormin, Isoderm und weitere	*national/MRP/DCP*	Isotretinoin			D10BA01	zugelassen	26.06.2002	
Peyona	*EMEA/H/C/001014*	Koffeincitrat			N06BC01	zugelassen	02.07.2009	
Arava	*EMEA/H/C/000235*	Leflunomid			L04AA13	zugelassen	02.09.1999	
Leflunomide medac	*EMEA/H/C/001227*	Leflunomid			L04AA13	zugelassen	27.07.2010	
Leflunomide ratiopharm	*EMEA/H/C/002035*	Leflunomid			L04AA13	zugelassen	29.11.2010	
Leflunomide Teva	*EMEA/H/C/002356*	Leflunomid			L04AA13	zugelassen	10.03.2011	
Leflunomide Winthrop	*EMEA/H/C/001129*	Leflunomid			L04AA13	zugelassen	08.01.2010	
Repso	*EMEA/H/C/001222*	Leflunomid			L04AA13	zugelassen	14.03.2011	
Revlimid	*EMEA/H/C/000717*	Lenalidomid			L04AX04	zugelassen	14.06.2007	
Jaydess	*SE/H/1186/001/DC*	Levonorgestrel			G02BA03	zugelassen	02.04.2013	
Elvanse	*national/MRP/DCP*	Lisdexamfetamindimesilat			N06BA12	zugelassen	18.03.2013	
Lojuxta	*EMEA/H/C/002578*	Lomitapid			C10AX12	zugelassen	31.07.2013	
Adasuve	*EMEA/H/C/002400*	Loxapin			N05AH01	zugelassen	20.02.2013	
Opsumit	*EMEA/H/C/002697*	Macitentan			C02KX04	zugelassen	20,12.2013	
Bronchitol	*EMEA/H/C/001252*	Mannitol			R05CB16	zugelassen	13.04.2012	
Increlex	*EMEA/H/C/000704*	Mecasermin		2)	H01AC03	zugelassen	03.08.2007	
Lariam	*National*	Mefloquin			P01BC02	zugelassen	15.09.1987	www.lariam.de
Procysbi	*EMEA/H/C/002465*	Mercaptaminbitartrat			A16AA04	zugelassen	06.09.2013	
Ritalin, Medikinet und weitere	*National, DE/H/2222/001-003/DC*	Methylphenidat			N06BA04	zugelassen	15.01.1997	
Mycamine	*EMEA/H/C/000734*	Micafungin			J02AX05	zugelassen	25.04.2008	
MisoOne	*NL/H/2355/001/DC*	Misoprostol			G02AD	zugelassen	26.03.2013	
Xyrem	*EMEA/H/C/0593*	Natriumoxabat			N07XX04	Zugelassen	31.10.2005	
Eziclen	*FR/H/511/01/DC*	Natriumsulfat, Kaliumsulfat			A06AD10	zugelassen	08.08.2013	
Tasigna	*EMEA/H/C/000798*	Nilotinib			L01XE08	zugelassen	19.11.2007	
Zoely	*EMEA/H/C/1213*	Nomegestrol	Estradiol		G03AA14	zugelassen	27.07.2011	
IOA	*EMEA/H/C/2068*	Nomegestrol	Estradiol		G03AA14	zugelassen	16.11.2011	

Presentation on Websites: Good Example



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)

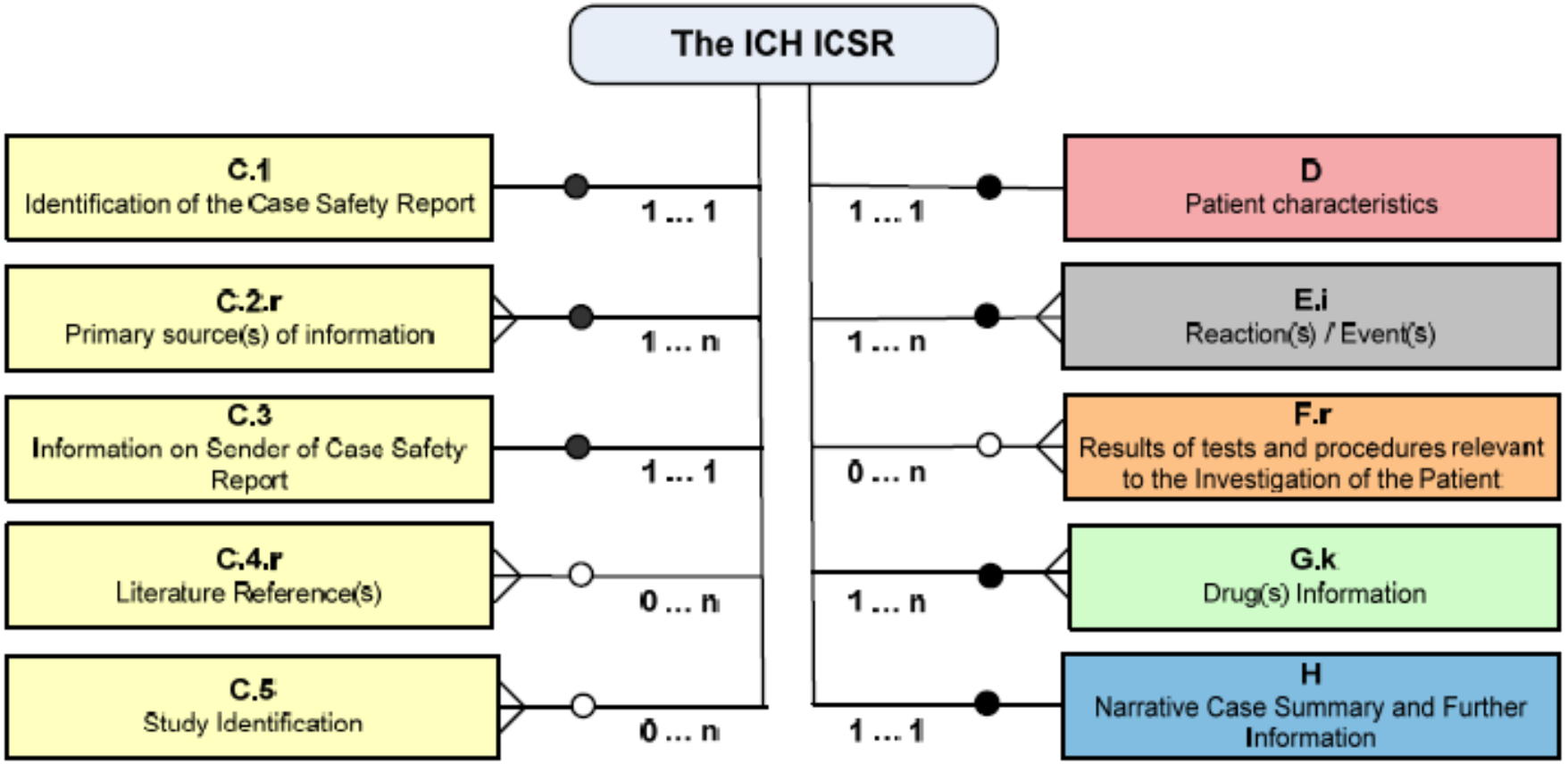
- **DRAFT detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency**
  - Art 27 of Reg.726/2004, Implementing Regulation 520/12
  - Monitoring of selected literature
  - Publication of a list 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-Webseite
  - „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 annoncement 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



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) ←→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 othe 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 fieds
      - Marked with ‚r'
- **Implementation of „Access Policy" in Eudravigilance**


Thank you for your attention!