

Pharmacovigilance Update - national

Norbert Paeschke
Bonn, May 2015

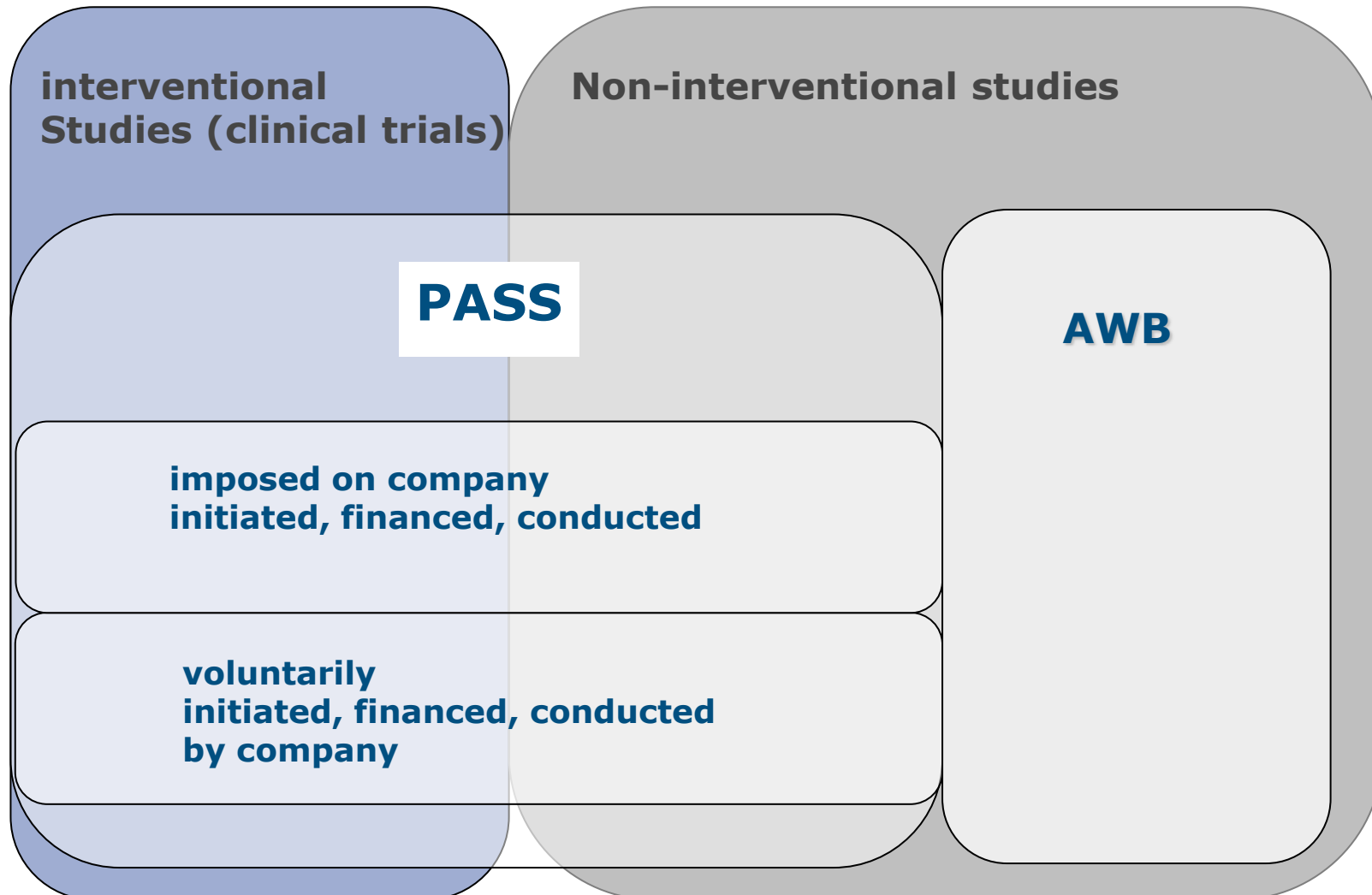


Overview

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



AWB versus PASS



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"



Startseite



Veröffentlichungen zu AWB

Nichtinterventionelle Studien (NIS)

Veröffentlichungen

Mit Inkrafttreten des Dritten Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften im August 2013 sind die Bundesoberbehörden verpflichtet, alle Anzeigen zu Anwendungsbeobachtungen, die nicht bis zum 31.12.2013 beendet wurden und Anzeigen zu Anwendungsbeobachtungen, die auch alle seit dem 1.1.2014 eingehenden Anzeigen zu AWB, die nicht bis zum 31.12.2013 beendet wurden.

Das BfArM veröffentlicht dabei lediglich die ihm angezeigten Angaben zu den Anwendungsbeobachtungen und ist nicht für die Bundesoberbehörden genehmigungspflichtig sind. Das BfArM führt daher keine detaillierten Prüfungen zu inhaltlichen oder formalen Durchführenden. Eingehende Anzeigen werden vom BfArM auf formelle Anforderungen hin überprüft und aufgrund dessen veröffentlicht.



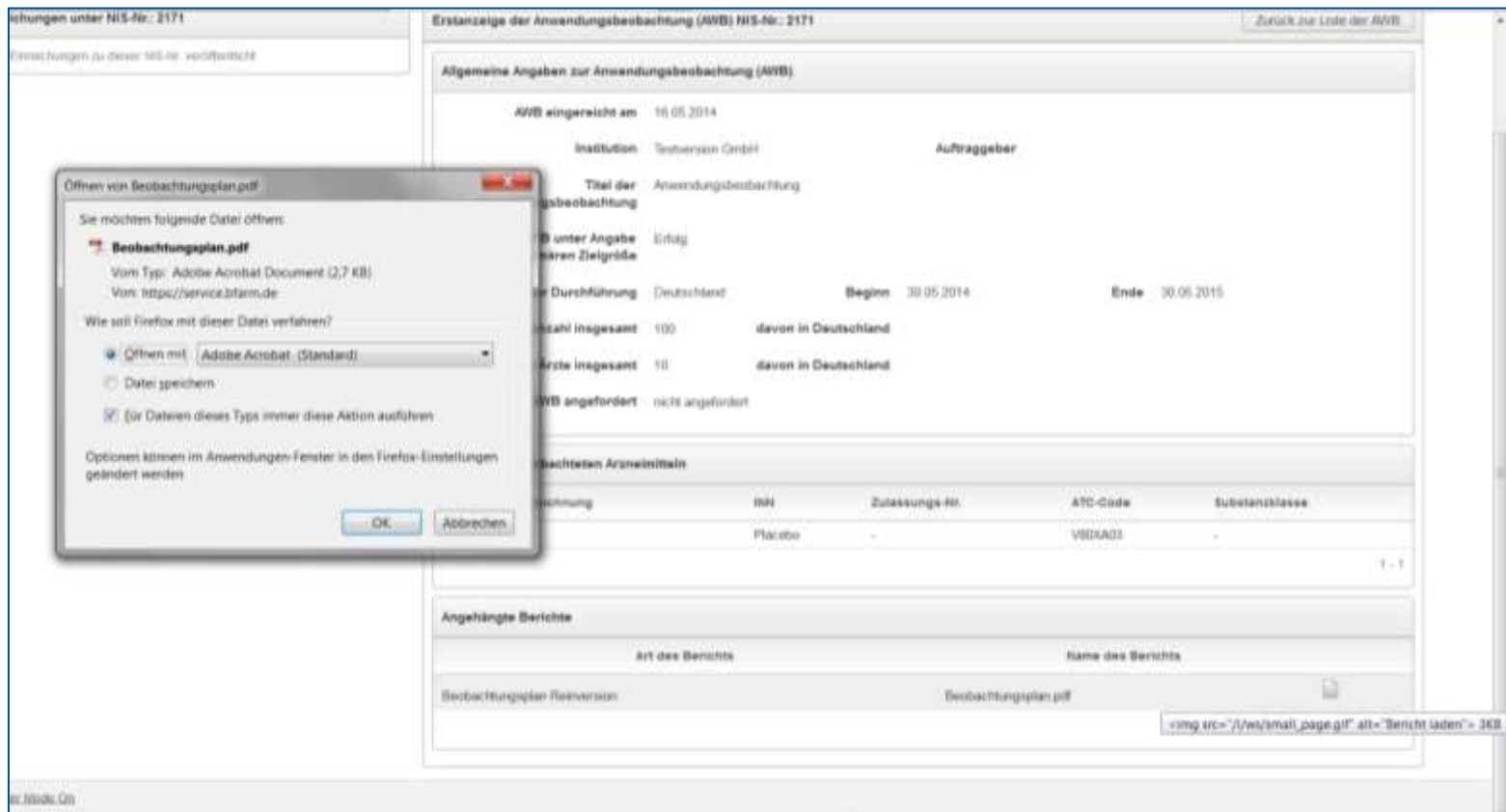
Publication of AWB - BfArM's database on "AWB"

	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 disease	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.)



Erstanzzeige der Anwendungsbeobachtung (AWB) NIS-Nr.: 2171

AWB eingereicht am: 16.05.2014

Institution: Testversan GmbH Auftraggeber: [unbekannt]

Teil der Anwendungsbeobachtung: [unbekannt]

Ergebnis unter Angabe der zu ermittelnden Zielgröße: Erfolgreich

Durchführung: Deutschland Beginn: 30.05.2014 Ende: 30.06.2015

Anzahl insgesamt: 100 davon in Deutschland: [unbekannt]

Arzte insgesamt: 10 davon in Deutschland: [unbekannt]

AWB angefordert: nicht angefordert

Beobachtete Arzneimittel	INN	Zulassungs-Nr.	ATC-Code	Substanzklasse
[unbekannt]	Placebo	-	V08DA03	-

Angehängte Berichte

Art des Berichts	Name des Berichts
Beobachtungsplan Reinsversion	Beobachtungsplan.pdf

Öffnen von Beobachtungsplan.pdf

Sie möchten folgende Datei öffnen:

Beobachtungsplan.pdf

Vom Typ: Adobe Acrobat Document (2,7 KB)

Von: <http://service.bfarm.de>

Wie soll Firefox mit dieser Datei verfahren?

Öffnen mit: Adobe Acrobat (Standard)

Datei speichern

[Für Dateien dieses Typs immer diese Aktion ausführen]

Optionen können im Anwendungen-Fenster in den Firefox-Einstellungen geändert werden

OK Abbrechen



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



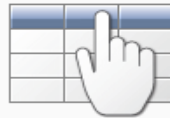
AWB – Electronic Submission

Nichtinterventionelle Studien

Startseite



Veröffentlichungen zu AWB



Anzeige einer Anwendungsbeobachtung (AWB)
oder einer Unbedenklichkeitsprüfung
nach der Zulassung (PASS)



Benutzerkonto zur Anzeige
von AWBs oder PASS verwalten

Nichtinterventionelle Studien (NIS)

Veröffentlichungen

Mit Inkrafttreten des 3. Änderungsgesetzes zum AMG im August 2013 sind die Bundesoberbehörden (BOB: in diesem Falle BfArM/PEI) verpflichtet, eingehende

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



Information Currently Available plus Additional Column for Weblinks



Wirkstoffe und Warenzeichen, für die Schulungsmaterial beauftragt 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	EMA/H/C/001210	Indacaterolmaleat			R03AC18	zugelassen	30.11.2009	
Tresiba	EMA/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	EMA/H/C/001014	Koffeincitrat			N06BC01	zugelassen	02.07.2009	
Arava	EMA/H/C/000235	Leflunomid			L04AA13	zugelassen	02.09.1999	
Leflunomide medac	EMA/H/C/001227	Leflunomid			L04AA13	zugelassen	27.07.2010	
Leflunomide ratiopharm	EMA/H/C/002035	Leflunomid			L04AA13	zugelassen	29.11.2010	
Leflunomide Teva	EMA/H/C/002356	Leflunomid			L04AA13	zugelassen	10.03.2011	
Leflunomide Winthrop	EMA/H/C/001129	Leflunomid			L04AA13	zugelassen	08.01.2010	
Repsol	EMA/H/C/001222	Leflunomid			L04AA13	zugelassen	14.03.2011	
Revlimid	EMA/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	
Loiuxta	EMA/H/C/002578	Lomitapid			C10AX12	zugelassen	31.07.2013	
Adasuve	EMA/H/C/002400	Loxapin			N05AH01	zugelassen	20.02.2013	
Opsumit	EMA/H/C/002697	Macitentan			C02KX04	zugelassen	20.12.2013	
Bronchitol	EMA/H/C/001252	Mannitol			R05CB16	zugelassen	13.04.2012	
Increlex	EMA/H/C/000704	Mecasermin		2)	H01AC03	zugelassen	03.08.2007	
Lariam	National	Mefloquin			P01BC02	zugelassen	15.09.1987	www.lariam.de
Procysbi	EMA/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	EMA/H/C/000734	Micafungin			J02AX05	zugelassen	25.04.2008	
MisoOne	NL/H/2355/001/DC	Misoprostol			G02AD	zugelassen	26.03.2013	
Xyrem	EMA/H/C/0593	Natriumoxabat			N07XX04	Zugelassen	31.10.2005	
Eziclen	FR/H/511/01/DC	Natriumsulfat, Kaliumsulfat			A06AD10	zugelassen	08.08.2013	
Tasigna	EMA/H/C/000798	Nilotinib			L01XE08	zugelassen	19.11.2007	
Zoely	EMA/H/C/1213	Norgestrel	Estradiol		G03AA14	zugelassen	27.07.2011	
IOA	EMA/H/C/2068	Norgestrel	Estradiol		G03AA14	zugelassen	16.11.2011	

Presentation on Websites: **Good** Example

Sicherheitsrelevante Informationen (für Fachkreise nach Login)

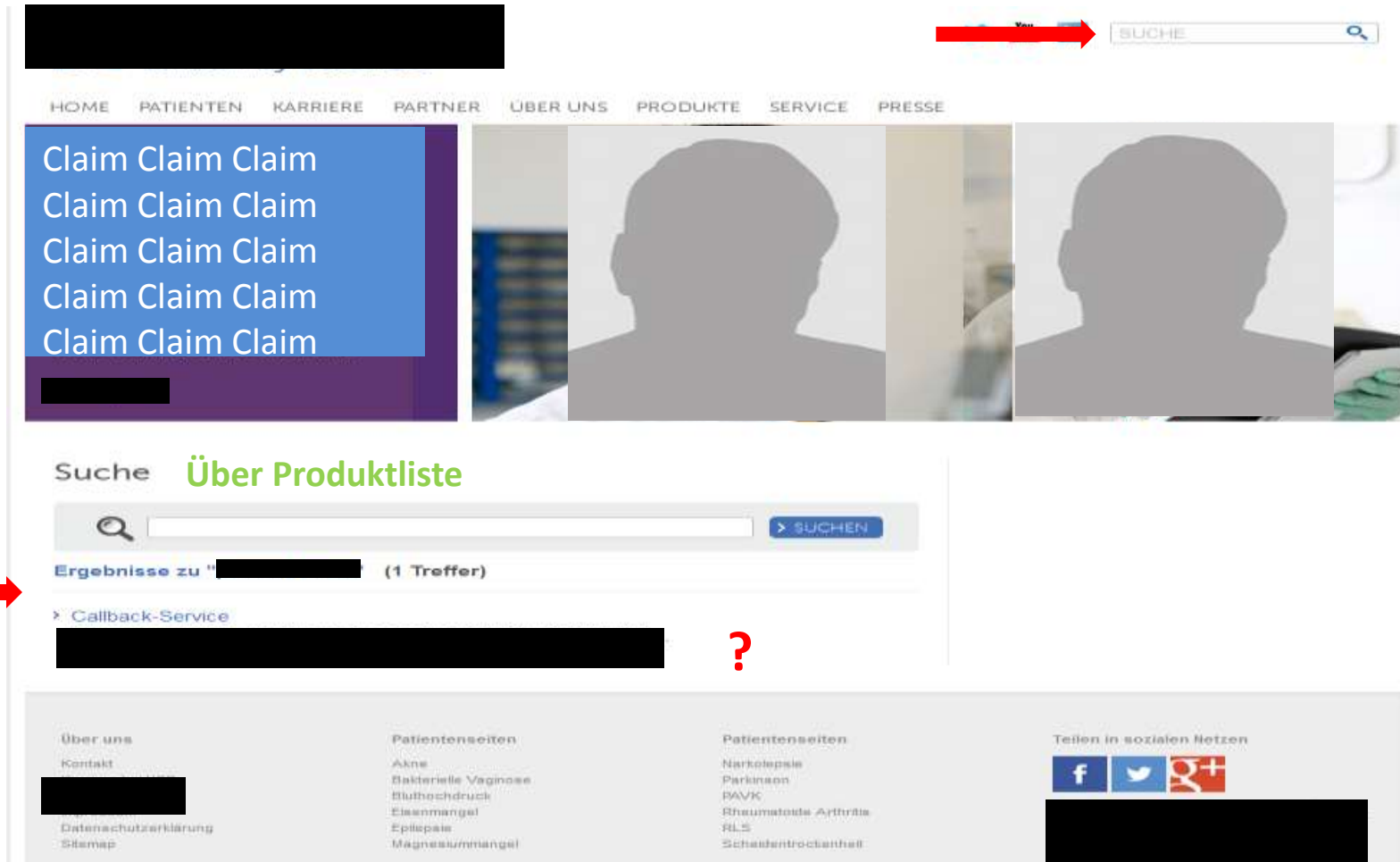
 Schulungsmaterial Wichtige Informationen über kombinierte hormonale Kontrazeptiva.pdf

Produktdetails, Fach- und Gebrauchsinformationen

			
Gebrauchsinformationen: 	Fachinformationen: 		
			
Gebrauchsinformationen: 	Fachinformationen: 		
			
Gebrauchsinformationen: 	Fachinformationen: 		



Presentation on Websites: Example **not** fulfilling the intended purpose



The screenshot shows a website header with a navigation menu: HOME, PATIENTEN, KARRIERE, PARTNER, ÜBER UNS, PRODUKTE, SERVICE, PRESSE. A search bar at the top right contains the text "SUCHE" and a magnifying glass icon, with a red arrow pointing to it from the left. Below the navigation is a blue banner with the text "Claim Claim Claim" repeated five times. To the right of the banner are two grey silhouettes of people. Below the banner is a search section titled "Suche Über Produktliste". It features a search input field with a magnifying glass icon and a blue button labeled "SUCHEN". Below the search bar, it says "Ergebnisse zu "[REDACTED]" (1 Treffer)". A red arrow points to this search result. Below the result is a link "> Callback-Service" followed by a large red question mark. At the bottom of the page, there are four columns of links: "Über uns" (with a redacted link), "Patientenseiten" (with links for Akne, Bakterielle Vaginose, Bluthochdruck, Eisenmangel, Epilepsie, Magnesiummangel), "Patientenseiten" (with links for Narkolepsie, Parkinson, PAVK, Rheumatoide Arthritis, RLS, Schenckentrieb), and "Teilen in sozialen Netzen" (with icons for Facebook, Twitter, and Google+).

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?

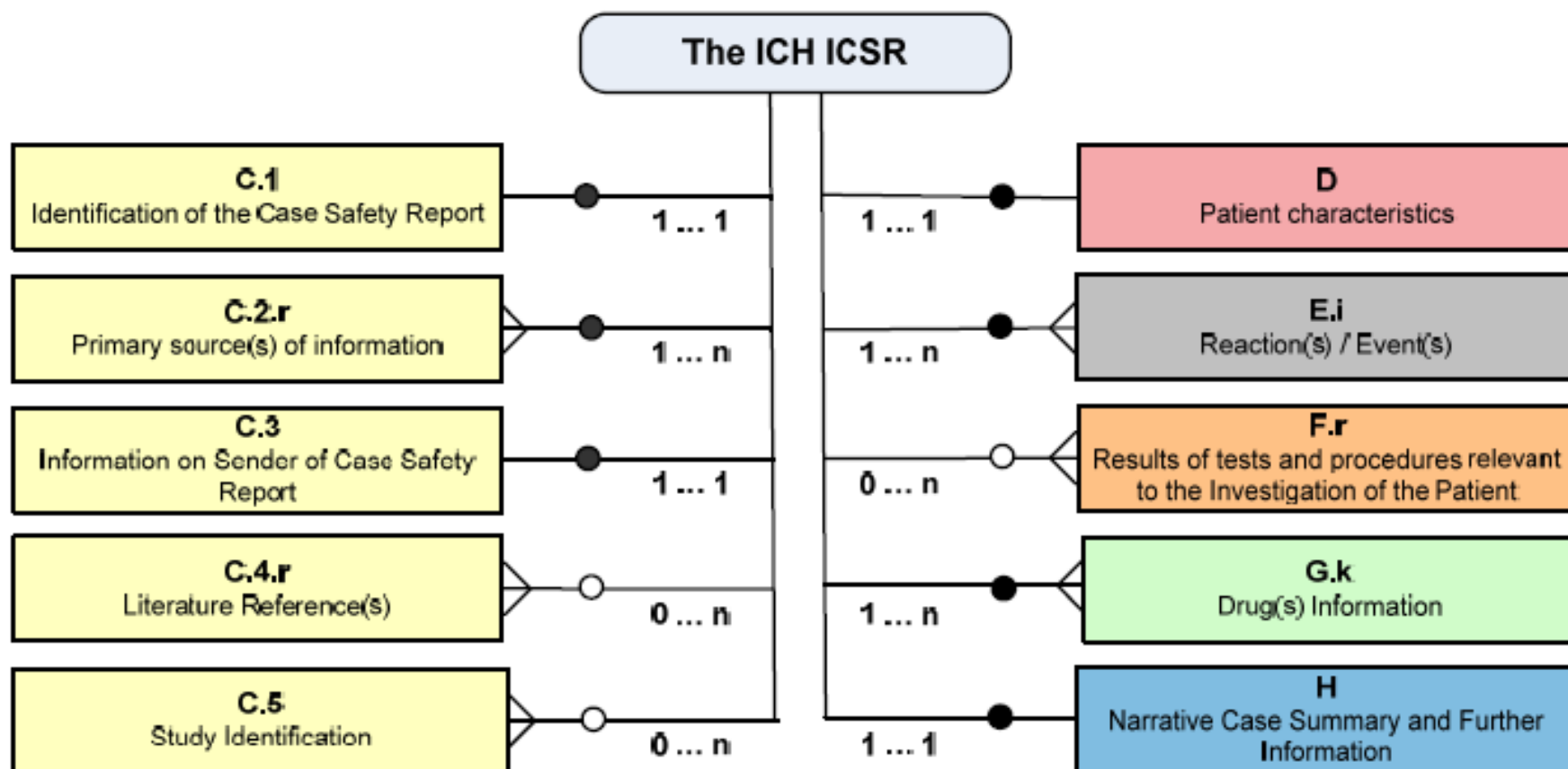
- **MLM-Service outsourced**
 - Test phase
 - „go live“ planned for August 2015
- **Current reporting obligations**
 - all cases from scientific literature
- **Future Reporting obligations**
 - **Once EV-functionalities established** no reporting requirements for literature cases covered by MLM-Service
 - What about the **interim phase** between MLM's „go live“ and 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



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!

