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EXPERIENCES WITH A REFERRAL PROCEDURE ART 31 ON AN OTC-PRODUCT: A COMPANY PERSPECTIVE

DGRA Annual Congress
7 and 8 May, 2015 , Bonn
Clinical Trial Regulation, Pharmacovigilance

Dr. Petra Kammann

Disclaimer and Special thanks

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- The views expressed in this presentation are purely personal views from individuals and do not represent any official view of a company or any department thereof

- Special thanks for the great support in the preparation of this presentation go to Martina Nittel, global CHC Regulatory Affairs

My goal today

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Share my personal experience

Focus on process rather than on contents

Explain the particular challenges

Point out most important lessons learned

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Bromhexine and Ambroxol

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- Registered in the EU Member States for decades:
  - Bromhexine since 1963
  - Ambroxol since 1978
- The majority of marketing authorizations are purely national
- Bromhexine (Bisolvon®) developed for secretolytic treatment
- Ambroxol (Mucosolvan®) also investigated for effects on surfactant production and in blocking afferent nerves, leading to a local anaesthetic activity (Mucoangin®)

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Bromhexine and Ambroxol

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The cumulative patient exposure until March 31st 2014 worldwide for the mono-products:

- Mucosolvan: 31 881 769 patient-years
- Mucoangin: 364 223 patient-years
- Bisolvon: 20 737 760 patient-years

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WHAT WAS THE TRIGGER?

PSUR Worksharing procedure for Ambroxol with BE as P-RMS:

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Submitted in Oct. 2011
Started in Jan. 2012

P-RMS FINAL ASSESSMENT REPORT

famhp
federal agency for medicines and health products

An in depth reevaluation of the benefit-risk balance of ambroxol hydrochloride in all its currently approved indications seems to be necessary. As this conclusion results from a pharmacovigilance assessment (signal detection and PSUR) conducted by the lead Member State and the P-RMS of ambroxol and involves the interests of the Union, a safety driven referral may be initiated. As the urgency criteria outlined in the *article 107i(1)* are not met, the re-examination of the benefit-risk balance of ambroxol hydrochloride containing products under the *article 31* of the Directive 2001/83/EC should be considered.

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famhp
federal agency for medicines and health products

04.04.14

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- Identification **of immediate and delayed-type hypersensitivity issues**
  → significant impact on safety profile
- Negative outcome of the re-evaluation of the B/R balance of ambroxol in the indication in all paediactric populations below 6 years of age

↳ Conclusion from BE: B/R balance of Ambroxol (AX) is questionable in all its currently approved indications and thorough re-evaluation of B/R balance of AX containing products is necessary

Scope of referral was extended to Bromhexine (BX) containing products as AX is a metabolite of BX

NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EC made by Belgium-FAMHP

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	All ambroxol hydrochloride- and bromhexine hydrochloride-containing products and strengths
Active Substance(s)/Therapeutic class	R05CB06 and R05CB02
Marketing Authorisation Holder(s)	Various

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Main topics under discussion:

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- → SCAR causally related to intake of AX/BX products?
- → Limitation of age groups
- → Limitation of indications
- → Benefit/Risk profile (positive or negative?)

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HOW TO ORGANISE A RESPONSE WITHIN THE GIVEN TIMELINES ?

Which thoughts would have come to YOUR mind?

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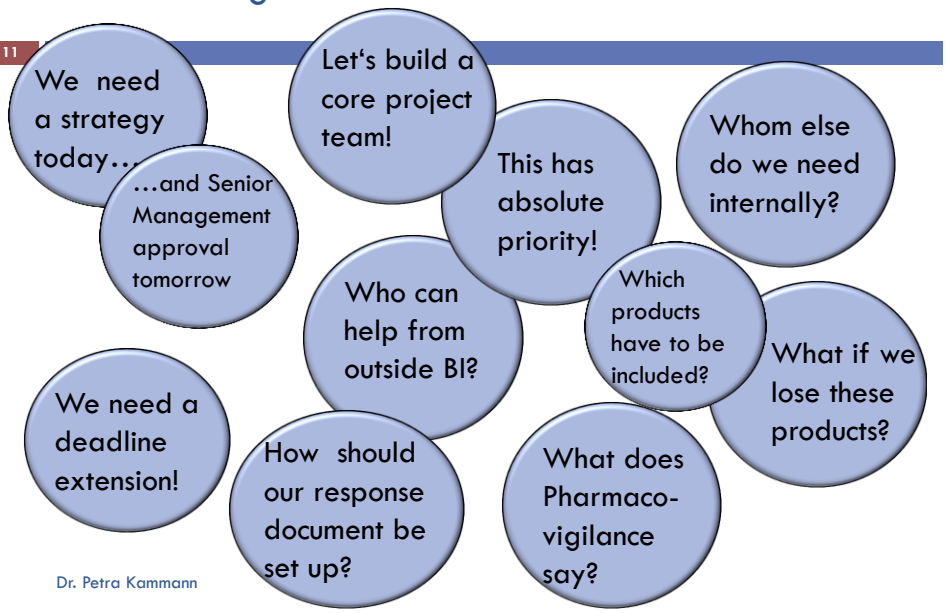

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Let's build a core project team!

Representatives:

- Global Pharmacovigilance
- Medicine
- Regulatory Affairs
- Corporate Communication
- Legal
- Marketing
- Business Development
- Commercial Management

For CHC and RX functions!

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We need a strategy today…

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- Basic Core Team proposal prepared within days
- Projects Timelines considered review cycles for Management Review
- Final approval of response at the level of Board of Managing Directors

…and Senior Management approval tomorrow

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Which products have to be included?

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- 3 main brands:
  - Mucosolvan
  - Mucoangin
  - Bisolvon
- 2 combination products
  - Spasmo-Mucosolvan
  - Bisolvomycin

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Which products have to be included?

EU country	Bromhexine		Ambroxol		
	Mono products	Combi-nation products	Mono products (secretolytic + other indications)	Mono products (sore throat)	Combi-nation products
Austria (AT)	X		X	X	X
Belgium (BE)	X		X	X	
Bulgaria (BG)			X	X	
Croatia (HR)	X		X		
Cyprus (CY)			X	X	
Czech Republic (CZ)			X		
Denmark (DK)	X			X	
Estonia (EE)			X		
Finland (FI)	X				
France (FR)	X	X	X	X	
Germany (DE)	X		X	X	X
Greece (EL)	X		X	X	
Hungary (HU)				X	
Ireland (IE)	X			X	
Italy (IT)	X		X	X	
Latvia (LV)			X		
Lithuania (LT)			X		
Luxembourg (LU)	X		X	X	
Malta (MT)	X		X		
Netherlands (NL)	X			X	
Poland (PL)			X	X	
Portugal (PT)	X		X		X
Romania (RO)			X		
Slovakia (SK)			X		
Slovenia (SI)	X				
Spain (ES)	X		X	X	
Sweden (SE)	X			X	
United Kingdom (UK)					
Iceland (IS)	X				
Norway (NO)	X				
Number of MAs in the EU (+ NO and IS)	**77**	**1**	**113**	**51**	**6**

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Whom else do we need internally?

- Colleagues in the local affiliates
- PV Writing
- Archiving
- Administrative support

Several Sub-Teams + ad hoc Working Teams

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Who can help from outside BI ?

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- Legal Experts
- Regulatory Affairs Experts
- Scientific and medical support for PV questions
- Support in ICSR evaluation
- Key Opinion Leaders in the local affiliates

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We need a deadline extension!

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Procedural step	Date	Comments
Start of procedure/notification	04.04.2014	
List of questions (LoIs)	10.04.2014	
Submission of response to LoIs	23.06.2014	No deadline extension accepted, less than 3 months to reply

Clarification of several aspects of the Questions needed to be addressed with the PRAC

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How should our response document be set up?

- Create a shareroom for the 5 modules of the response document
- A summary response to cover the main aspects in a short version
- Format needed to be archivable

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What does Pharmaco-vigilance say?

- Ad-hoc preliminary assessment on the topics to be prepared within days
- Comprehensive Data Analysis plan needed
- Workload not managable in house:
  - Contact with external experts on immunology to be set up
  - CRO for the causality assessment of ISCRs on severe allergic reactions needed

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What if we lose these products?

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- AX/BX product portfolio one of the most important Brands for BI CHC
- Contingency plan to be set up
- Operational aspects to be worked-out in case immediate label-changes would be required

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WHAT WERE THE CHALLENGES OF THE LIST OF QUESTION?

A flavour of complexity

Example: Question 1b

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In question 1b of the PRAC List of Questions the MAH is requested to provide sales figures and estimated patient exposure for ***ambroxol and/or bromhexine and combination products****, if possible stratified by age, by member state and by indication*

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What does that mean for Ambroxol?

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- Approved in 18 EU countries
- For 4 indications

Member states x indications = subsets of exposure

18 x 4 = 72

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Mucosolvan formulations

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- Ampoule 15mg/2ml
- Ampoule 30mg/4ml
- Infusion sol. 1000mg/50ml
- Contr. Rel. capsule
- Drops 15mg/ml
- Effervesc. tab. 60mg
- Filmcoated tab. 60mg
- Inhalat. Liquid 7.5mg/ml
- Lozenge 15mg
- Syrup 15mg/5ml
- Syrup 30mg/5ml
- Tablet 30mg
- Sachet powder 15mg
- Sachet powder 30mg
- Sachet powder 60mg
- Adult Supp. 60mg
- Paed. Supp. 15mg
- Paed. Supp. 30mg

Mucosolvan exposure datasets

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72 subsets of exposure data x 18 formulations

= 1296 total exposure subsets

….not yet considering the different age groups

Mucosolvan exposure tables

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Table 2 Exposure to Mucosolvan (Ambroxol) by formulation/strength and country

	2004		2005		2006		2007		2008	
	Bulk Units	Patient Years	Bulk Units	Patient Years	Bulk Units	Patient Years	Bulk Units	Patient Years	Bulk Units	Patient Years
000 - Germany	**737.278.840**	**148.557**	**864.801.220**	**171.302**	**761.523.940**	**163.651**	**618.592.330**	**148.253**	**532.475.930**	**128.901**
ampoule 15mg/2ml	3.200.000	1.460	2.759.420	1.259	2.293.180	1.046	1.792.620	818	1.059.000	483
contr. rel. capsule 75mg	7.008.620	19.189	5.791.820	15.857	10.472.570	28.672	13.294.070	36.397	12.400.650	33.951
drops 15mg/ml	35.113.700	12.017	34.045.250	11.651	28.411.900	9.723	23.417.650	8.014	18.947.400	6.484
effervesc. tab. 60mg	2.660.120	4.855	3.563.120	6.504	2.832.420	5.170	2.488.000	4.541	2.177.020	3.974
filmcoated tab. 60mg	2.655.740	3.636	2.456.620	3.363	1.849.190	2.531	1.501.260	2.055	1.459.670	1.998
infusion sol. 1000mg/50ml	9.213.000	504	8.576.000	470	7.772.500	426	6.518.000	357	5.975.000	327
inhalat. liquid 7.5mg/ml	21.300.500	9.720	23.694.900	10.812	19.256.800	8.787	20.364.400	9.292	17.247.300	7.870
lozenge 15mg	19.575.720	8.933	29.399.600	13.415	29.244.440	13.344	26.298.400	12.000	25.679.120	11.718
syrup 15mg/5ml	77.180.100	7.044								
syrup 30mg/5ml	553.407.800	75.757	748.476.450	102.461	654.641.200	89.615	518.800.400	71.020	446.457.950	61.117
tablet 30 mg	5.963.540	5.442	6.038.040	5.510	4.749.740	4.335	4.117.530	3.758	1.072.820	979
313 - Malta	**2.819.480**	**448**								
contr. rel. capsule 75mg	50.880	139								
syrup 15mg/5ml	2.700.000	246								
tablet 30 mg	68.600	63								
321 - Belgium	**3.653.770**	**1.467**	**3.978.550**	**1.517**	**3.364.090**	**1.303**	**3.421.780**	**1.290**	**3.325.380**	**1.234**
filmcoated tab. 60mg	747.610	1.023	754.930	1.033	656.820	899	642.100	879	632.380	866
sachet powder 60mg	141.660	65	132.120	60	103.020	47	96.180	44		
syrup 30mg/5ml	2.764.500	378	3.091.500	423	2.604.250	357	2.683.500	367	2.693.000	369
323 - France	**278.914.878**	**67.051**	**252.958.242**	**62.402**	**112.877.420**	**31.212**	**105.717.304**	**26.375**	**66.971.328**	**13.758**
ampoule 15mg/2ml	5.383.608	2.457	6.031.608	2.752	4.568.112	2.084	8.908.944	4.065	626.520	286
ampoule 30mg/4ml	16.278.480	7.428	17.779.824	8.113	13.452.288	6.138	5.720.640	2.610	-672	0
sachet powder 30mg	-60	0					-60	0		
sachet powder 60mg	17.037.060	7.774	17.093.400	7.800	7.285.260	3.324	-7.140	-3	-4.680	-2
syrup 30mg/5ml	218.934.600	29.971	193.093.350	26.433	77.675.600	10.633	81.771.550	11.194	60.688.800	8.308
tablet 30 mg	21.281.190	19.422	18.960.060	17.303	9.896.160	9.031	9.323.370	8.509	5.661.360	5.167

Example Question 3

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. …For this purpose, all the MedDRA Preferred Terms (PTs) within the SMQ Hypersensitivity (broad), reported for the selected suspected or interacting ambroxol and/or bromhexine –containing products should be provided. Causality assessment should be performed for serious cases

- For Mucosolvan alone, 256 cases required a causality assessment

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Example Question 5

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"Please provide a benefit/risk balance evaluation of ambroxol and/or bromhexine-containing medicinal products, in each of their licensed indications. Based on the responses to the above questions, this should consider how the benefit risk balance may differ according to age, separating the populations of 0-6 years old, 6-12 years old and 12 years of age and older."

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Example Mucosolvan

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- 3 indications
  - Secretolysis
  - Infant respiratory distress syndrome
  - Prophylaxis of post-operative complications
- 3 age groups

→ 9 sub-sections of Benefit/Risk assessment

Prerequisite: stratification of both efficacy and safety data according to these sub-groups

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….for one single indication

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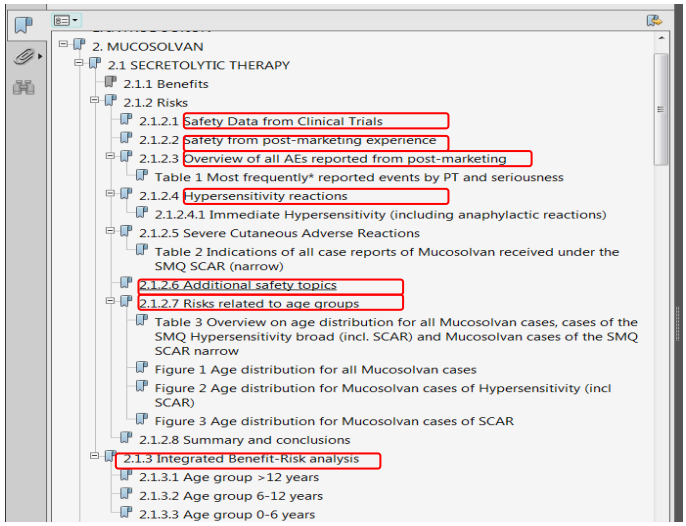

Response in a nutshell

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The result of the analysis of the safety-related aspects revealed no new or undue risks to patients

The benefit/risk balance was considered positive for all products, indications and age groups

Clinical data were transparently described, including the given limitations for studies from the pre-ICH/GCP era

It was pointed out that post-Marketing experience was considered an essential part of the available data

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AFTER SUBMISSION WITHIN THE GIVEN TIMELINE…

Assessment of the Rapporteur and Co-Rapporteurs

AT: positive position; acknowledged the situation for these mature registered products

BE: negative position concerning all products independently from indications and age groups

PT: position in between but tendency more in favour with certain limitations (e.g. age groups, labelling)

List of outstanding issues, 11 Sep 2014

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- …provide further justification supportive of a positive benefit risk in the secretolytic indication in each of the paediatric sub-populations i.e. 0-2, 2-6 and 6-12 years of age…
- … provide proposals and justifications for further risk minimisation measures for each of the approved indications..
- Plus various detailed questions around the SCAR topic

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Timetable

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Procedural step	Date	Comments
PRAC List of outstanding issues (1st LoOIs)	15.09.2014	
PDCO opinion	10.10.2014	On safety + efficacy for paediatric use → based on request from PRAC
Submission of response to 1st LoOIs	20.10.2014	

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THE ORAL EXPLANATION MEETING

December 2nd 2014

Why did we ask for this meeting?

Topics:

- SCARs - Relationship to AX & BX use
- Post-operative Pulmonary Complications (PPC) in adults - Positive benefit/risk of AX
- Secretolytic indication – Paediatric use
- Efficacy and safety of AX/BX
- Proposed Risk Minimisation Measures

7 BI participants and 1external expert (on SCAR)

At the EMA

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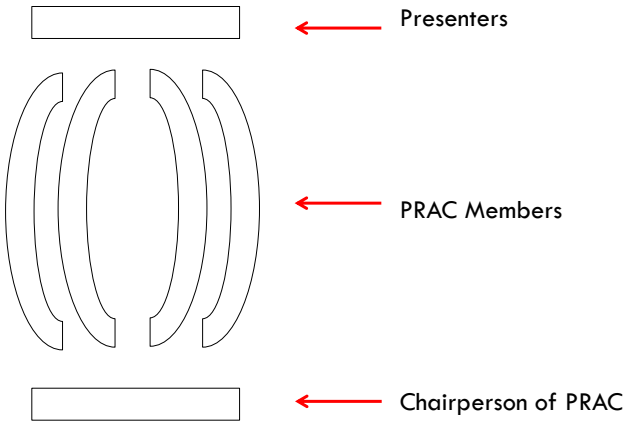

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Procedural aspects

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Welcome + explanations by Chairperson of the PRAC (Dr. June Raine) how the meeting will be held
→ Introduction of the company's participants
→ Presentation: 20 minutes (our presentation was a few minutes longer)
→ Q&A section : 10 minutes (actually it took 1 hour in our case)

After the Meeting
- Administrative person will bring you back to the waiting room

Debriefing session with (Co-)Rapporteurs:
- Outcome in our case not yet conclusive
- SCARs: discussion still ongoing but rather in the direction that it must be included as side effect
- Age groups/indications: still under discussion

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Information about PRAC Referral to the public

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/01/news_detail_002246.jsp&mid=WC0b01ac058004d5c1

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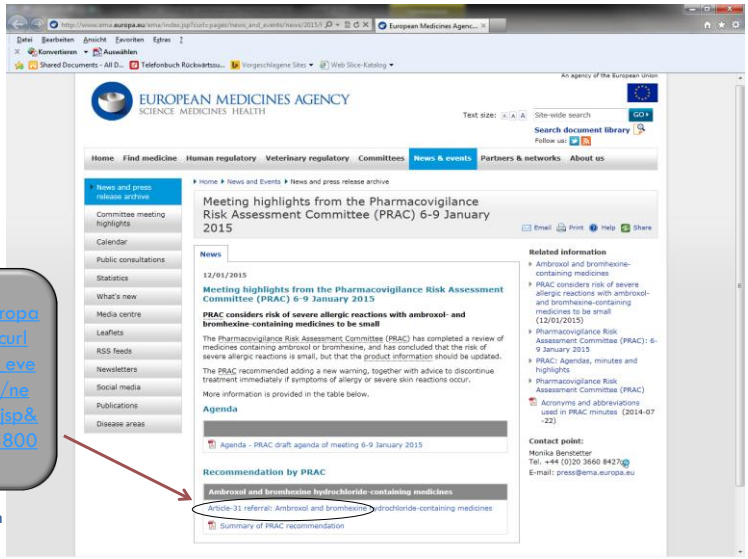

Press reactions

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Ambroxol/Bromhexin: EMA vertagt auf 2015

Berlin - Die Europäische Arzneimittelagentur (EMA) entscheidet in diesem Jahr nicht mehr über das Nutzen/Risiko-Profil vom Ambroxol und Bromhexin. Die ursprünglich für September angesetzte und dann auf Dezember verschobene Entscheidung des Pharmakovigilanzausschuss für Risikobewertung (PRAC) wurde auf Januar verlegt. Offenbar konnte Boehringer die Experten bei der Anhörung beeindrucken.

Obviously, BI could impress the experts at the oral hearing.

Am vergangenen Mittwoch hatte im Rahmen einer Anhörung Boehringer seine Argumente noch einmal vorgetragen. Der Hersteller des Originalpräparats Mucosolvan ist vom positiven Nutzen/Risiko-Profil von Ambroxol und Bromhexin überzeugt.

PRAC recommendation - Conclusions

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- -…there is a reasonable possibility of a risk of SCARs associated with ambroxol and bromhexine.
- … ambroxol and bromhexine are associated with an increased risk of hypersensitivity reactions.
- … risk of SCARs should be addressed by its inclusion in the product information accompanied by a warning in order for patients and caregivers to recognise the prodromes of SCARs and discontinue treatment immediately in the event of such signs.
- the available data were insufficient to justify new age restrictions.

The Committee … concluded that the benefit-risk balance of ambroxol- and bromhexine-containing medicinal products remains favourable …. (22 of 31 votes)

CMDh position - Conclusions

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The CMDh … **agrees with the overall scientific conclusions by the PRAC** and reached the position that the marketing authorisations for ambroxol- and bromhexine-containing medicinal products should be varied

Position reached by a majority of 19 out of 28 votes Icelandic + Norwegian CMDh members agreed with position

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Status today…

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Lessons learned

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General

- Don‘t underestimate the enormous pressure on the organisation
- Large resource and financial impact
- Everthing will take more time than you expected

Project Management

- Get started immediately
- Assign clear responsibilities and leadership roles
- Perform regular weekly Core Team meetings
- Make sure you get the resources you need
- Strategy first!

Lessons learned (cont'd)

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Internal Communication/ Information

- Immediately involve all people you might need
- Inform your colleagues in the countries regularly on the status

External Communication

- Prepare Q&A papers + reactive press statements
- Establish a good communication channel with EMA contact person

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Lessons learned (cont'd)

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Administrative aspects

- Train the authors to avoid unnecessary work afterwards (e.g. references to be filled in the eTOC)
- Install a dedicated Shareroom for handling of huge data packages, work on the same documents
- Consolidation of draft documents by one person
- Plan enough time for Management Review and submisssion process

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Lessons learned (cont'd)

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Oral Explanation Meeting

- Time is precious: focus on the most important topics
- Consider already upfront any possible questions that the PRAC may have and be prepared to answer
- Pre-define the roles of active partcicpants and perform rehearsals with all speakers
- Bring paper copies of all response documents

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Efforts in numbers

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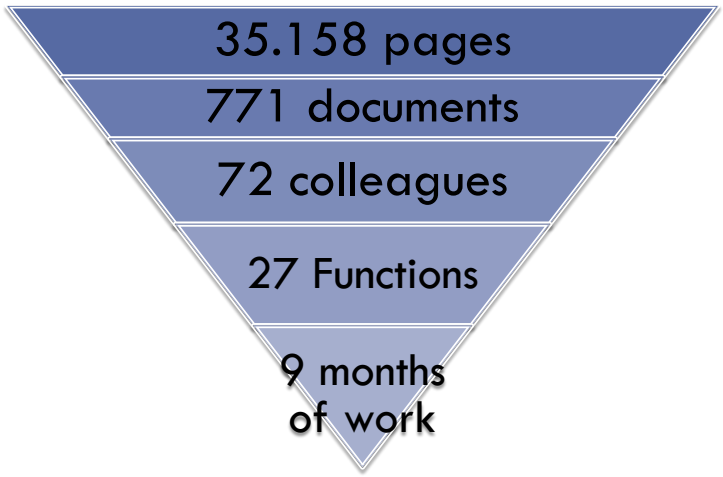

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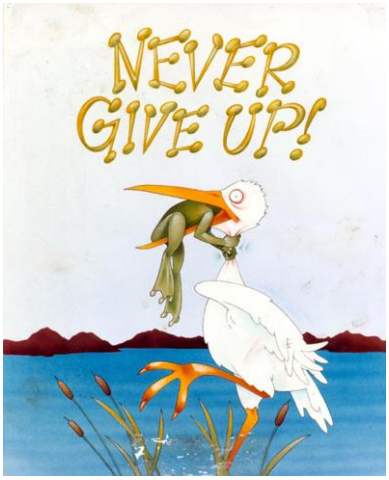
NEVER
GIVE UP!