



# AGES

Österreichische Agentur für Gesundheit  
und Ernährungssicherheit GmbH

*Gesundheit. Ernährung. Sicherheit.  
Unsere Verantwortung.*

# **“Kinderarzneimittel” Verpflichtungen der Zulassungsinhaber**

AGES-Gespräch

19. November 2007

Dr. Christa Wirthumer-Hoche  
AGES PharmMed, Wien

# Paediatric Regulation EC-1901/2006



- **Gesetzliche Grundlagen der Verordnung über Kinderarzneimittel, speziell in Hinblick auf die Verpflichtungen des Zulassungsinhabers**
- **Leitlinie zur verpflichtenden Übermittlung von Daten für Kinderarzneimittel**

# Spirit of the Paed. Regulation



To create data –

- Collect data for already authorised products
  - Art. 45 – 26 Jan. 2008
  - Art. 46
- since 26 July 2008 each new application for a new MP has to have a PIP for each indication (Art.7),
- from 26 Jan. 09 onwards – variations, line extensions (Art. 8)

# Main pillars of the Regulation

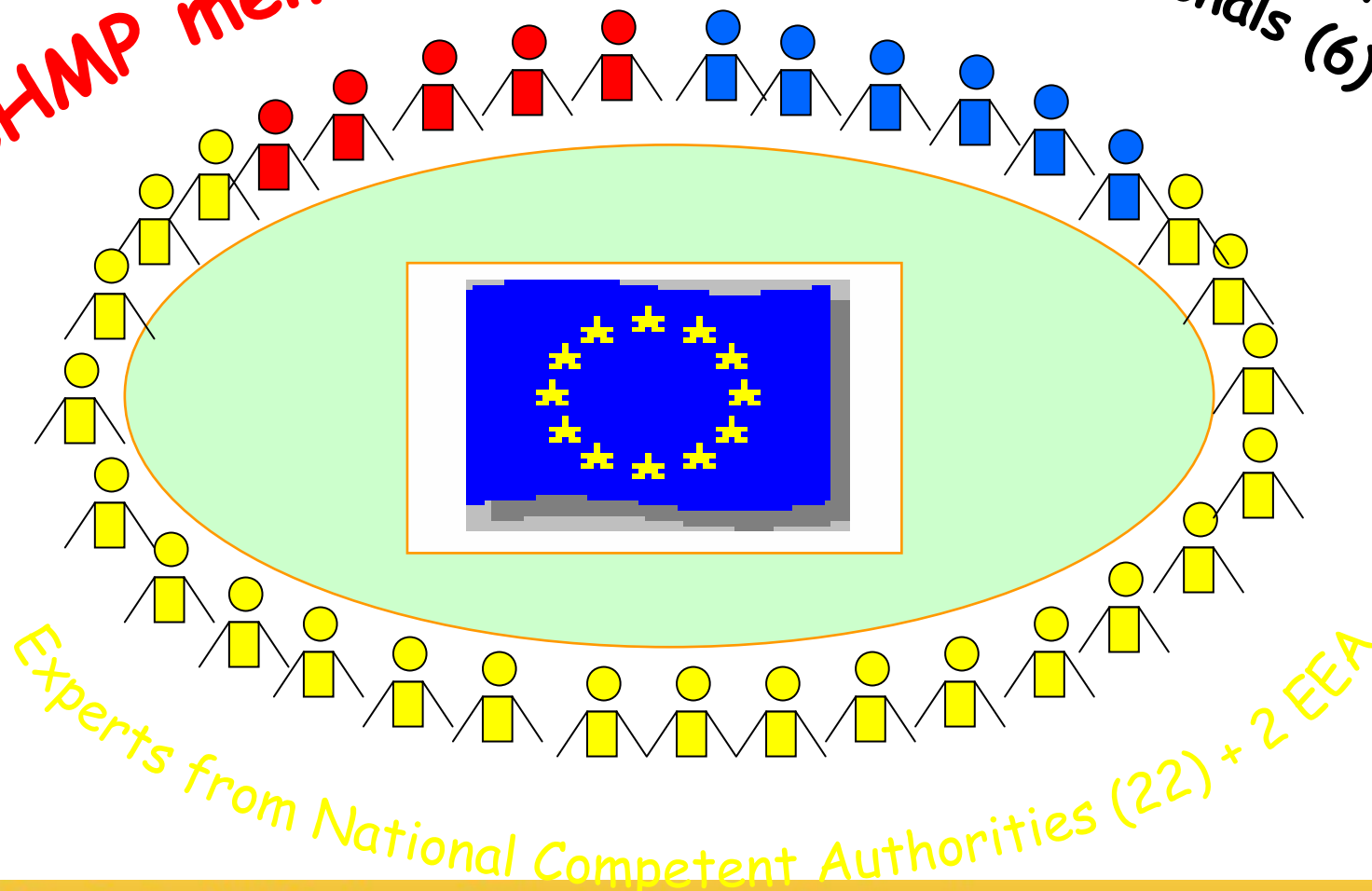


- Creation of a Paediatric Committee
- Measures for patented MPs
- Measures for off-patent MPs

# Paediatric Committee (PDCO)

CHMP members (5)

Patient/family and health-care professionals (6)



# Paediatric Committee - tasks



- Opinions
  - PIP
  - Waiver
  - Deferral
- Compliance (on request)
- S/E/Q/ of data from PIP (on request)
- Inventory of therapeutic needs
- Advice on EU paediatric clinical trials network

# Requirement

- „An application for MA under Art 6 of Dir 2001/83/EC in respect of a MP for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes one of the following:
  - Results of all studies performed and details of all information collected in compliance with an agreed PIP
  - Decision of the Agency granting a product-specific waiver
  - Decision of the Agency granting a class waiver
  - Decision of the Agency granting a deferral

# Requirement

- Not for: generics, well-established use, homeopathic or herbal products
- Not to delay MA in adults
  - Deferrals
- No unnecessary clinical or other trials in paediatric population
  - Waivers

# Compliance check

- **NCA: Set up and manage new aspects of national procedures, in particular**
- **a) validation** of applications for MA and for Extensions/Variations
  - This is to ensure that applications submitted include the necessary documents and or results in keeping with obligations of Articles 7 and 8. There is a clear responsibility on the NCA not to validate applications that do not include either results in compliance, or a deferral or a waiver of the paediatric development.
  - As a consequence, current validation procedures would have to be amended, and scientific staff would need to be involved.

- *The new validation and compliance check systems must be in place by 26 July 2008 when the obligation relating to new marketing authorisations comes into force*
- **26 July 2008**  
Obligation to submit results of studies according to agreed PIP with applications for Marketing Authorisation (new products)  
Or decision granting a waiver or deferral
- **26 January 2009**  
Obligation to submit results of studies according to agreed PIP with application for new indications, new routes of administration, new pharmaceutical forms  
Or decision granting a waiver or deferral

# Patent protected MPs

- For yet unauthorised Products  
Patent protected products  
Obligation to submit results of agreed PIP at time of  
MA or variation  
Reward: 6 months extension of the SPC (patent  
protection)

# For Orphan Drugs



15 – 20 % of rare disease affect children only,  
55% affect adults and children

Reward – 2 years of market exclusivity added to  
existing 10 years

Compliance with the PIP necessary

# For off-patent products

- Medicinal products NOT covered by a patent or supplementary protection certificate
- Optional procedure
  - Need for an agreed PIP
  - No need for MA in all Member States
  - Brand name may be retained
  - 10 years of data protection:  $(8+2) + 1$

# PUMA



# PUMA vs MA

- Same legal basis
  - Stand alone application
  - or*
  - Abridged application with cross reference to adult product
- Covers (only) paediatric indication(s) and formulation(s)
- Optional but need for agreed PIP and compliance

# Paediatric Symbol

- Ensure that **the Symbol**, chosen by the Commission, is included
  - on the packaging of all MPs with a paediatric indication,
  - with a modification of PL to add the explanation of the symbol (Article 32).
- The symbol should be present on the labelling of **products already authorised and new products**, whichever the authorisation route (national as well as MRP / DCP) *within 2 years of the publication of the symbol by the European Commission.*
- This involves a potential review of all authorised MPs to identify at national level which products have a paediatric indication. (4.1 in combination with 4.2 in SPC?)

# Paediatric Symbol

- Survey on existing paediatric and non-paediatric symbols in the Community
  - « P » blocked for POM in UK, ...
- Experience with other symbols showed risk for misleading interpretations



take in the morning (?)  
increases photosensitivity (?)

- Perception of symbols differs between cultures
- ➔ One single paediatric symbol for all age groups???
- Flexible symbol according to age group or weight???

# Paediatric Regulation

Art 45:

“By 26 January 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.

The competent authority shall, as appropriate, update the SPC, and PL and shall vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and their implications for marketing authorisations concerned.

The Agency (EMA) shall coordinate the exchange of information”

# Receive from MAHs all existing paediatric studies/trials



already performed (*before 26 January 2008*).

- In addition, further studies to be performed will be submitted on an ongoing basis *within 6 months of completion*.
- Studies should be submitted to NCAs for assessment in the MSs where the MP is authorised.
- This activity has been anticipated and is partly covered by the current paed. worksharing exercise but the scope is now wider (Articles 45 and 46).
- Collecting this information and assessing will require resources although work sharing is intended to avoid multiplication of assessment.

# Duty of the NCAs

- **Perform a survey of use** and collect data on use of medicinal products in children with a view to identifying paediatric needs.
  - *Member States should collect this information and communicate it to the EMEA within 2 years, i.e. before 26 January 2009 (Article 42).*

How are NCAs and EMEA now collecting data on MPs with paediatric use?



Medicinal Products with paediatric use

MAH:  
EU-MS/EEA:

<MAH>  
Austria

Name of the product authorised nationally; in case of MRP/DCP name of the medicinal product in the RMS is possible

pharmaceutical form in English (according to the "Standard Terms" if applicable)

Marketing authorisation number in the relevant Member State

if applicable

Name of the medicinal product

Strength

Pharmaceutical form

Active Substance(s)  
*Herbal MPs should be indicated (HERB)\**

Marketing Authorisation Number

MRP/DCP-No.

Fentanyl "MAH"  
Risperidon "MAH"

Enter strength of the medicinal product, use one line for each strength if more than one strength is authorised

oral patch  
tableted tablet

Name of the active substance(s) in English as stated in the SPC; if more than one active substance included (fixed combination) state within one line

XX/H/0123/01  
XX/H/0111/01

if information about paediatric use is available in 4.1 and/or 4.2 of the SPC, enter "Y" for YES, "N" for NO otherwise; if "Y" is entered, please enclose the relevant wording in annex II.

Ondansetron "MAH"  
Paracetamol "MAH"

1 mg/ml  
200 mg/5 ml

solution for injection  
oral solution

Oral  
diclofenac sodium  
Paracetamol

XX/H/0122/01  
XX/H/0129/01

Didofenac "MAH"  
Finasterid "MAH"

3%  
5 mg

gel  
film coated tablet

Diclofenac sodium  
Finasteride

1-33333  
1-99999

XX/H/0777/01  
XX/H/0222/01

\*In case of a herbal MP, further information is needed.

\*\* If information about paediatric use is available in 4.1 and/or 4.2 please enclose the relevant wording in annex II.

Medicinal Products with paediatric use

<b>Paediatric use</b> for specific age groups (neonate, infant, child, adolescent) (SPC 4.1 and/or 4.2) Y/N - see footnote,**	ATC-Code has to be stated in each case  <b>ATC-Code</b> (7-digit)	Studies already submitted Y/N If YES - provide a declaration (Annex I)	Studies not yet submitted Y/N if YES - complete the next 2 columns	EudraCT Number if applicable  Studies not yet submitted Study number	
	N02AB03		Y	Transdermal fentanyl in children with cancer pain	20XX-0X-XXX-8
	N05AX08		N	-	-
	A04AA01		Y	Ondansetron in children with post-operative nausea and vomiting (PONV)	20XX-0X-XXX-9
	N02BE01		N	-	-
N	M02AA15	N	Y	Mild to moderate pain and inflammation of muscles, joints, periarticular structures in children	20XX-0X-XXX-6
N	G04CB01	N	N	-	-

Information about paediatric use is available in 4.1 and/or of the SPC, enter "Y" /YES, "N" for NO otherwise; if "Y" is entered, please enclose the relevant wording in annex II.

if studies on the paediatric population had been submitted in the past, enter "Y" for YES, "N" for NO otherwise; if "Y" is entered, please provide a declaration in annex I.

if studies in the paediatric population had been conducted, and had not been submitted so far, enter "Y" for YES, "N" for NO otherwise.

EudraCT Number if applicable

\*In case of a herbal MP, further information is needed.

\*\* If information about paediatric use is available in 4.1 and/or 4.2 please enclose the relevant wording in annex II.



# Annex I – MAH declaration



## Subject:

**Declaration concerning paediatric studies already submitted to the NCAs, (Art. 45)**

We *[MAH]* confirm that **all products authorised in *[EU-Member-State]* are listed** in the table submitted to the NCA, **independent of whether paediatric use is granted or not** and/or paediatric studies are available, already submitted or have yet to be submitted.

We further confirm to the best of our knowledge, that all paediatric studies available have been submitted already. These products are indicated in the template ("Studies already submitted" indicated with YES).

These studies are available on request by the National Competent Authority within 3 days at the latest.



# Guidance concerning submission of inf. about MPs as requested by the Paed. Reg.



- Each MAH has to fill in the template for all their national approved MPs (including MRP and DCP) subdivided for each MS in English language.
- The **template** with the **Annex I** and the **Annex II** if applicable has to be sent to each NCA in electronic format only where the MP is authorised.
- Therefore the NCAs will dedicate a mailbox or e-mail address. A list of these addresses for each NCA will be published on the CMD-h website.

Guidance concerning submission of inf.  
about MPs as requested by the Paed. Reg.



AGES PharmMed:

[kinderarzneimittel@ages.at](mailto:kinderarzneimittel@ages.at)

MAHs should send a copy of all the templates to EMEA:

[paedstudies@emea.europa.eu](mailto:paedstudies@emea.europa.eu)

It is recommended that MAHs send to EMEA also an overview of their products with information about the studies not yet submitted, in addition to the information in the templates. This will facilitate the EU worksharing procedure and the appointment of Rapporteurs.

# Deadlines



- 26 Jan 2008
  - For the line listing and the Annex I & II,
  - *but*
- 26 April 2008
  - For annex II
    - Deadline only in connection with Art .45, there is no deadline in the Reg. concerning all the other addition paediatric information

# Products / studies concerned



- The requirements laid down in Art.45 & 46 relate to all authorised medicinal products without exception.
  - Including generics, well-established use, homeopathic MPs
- The information / studies have to be submitted to each NCA where the product is authorised, regardless of the place of conduct of the trial.
- Paediatric studies means any studies including patients aged < 18 years, including those with both adult and paediatric patients.

# Worksharing

- For nationally authorised MPs (incl. MRP & DCP), irrespective of whether paediatric use was authorised
  - the line listing has to be forwarded to NCA, but not the studies by 26 January 2008
  - The studies will have to be forwarded to the Rapporteur, once appointed, according to priorities set up within the Worksharing exercise in the next 6 months.
  - The coordination of the Paediatric worksharing project will be done by the CMD-h/EMA subgroup on Paediatric Regulation.

# Why worksharing?

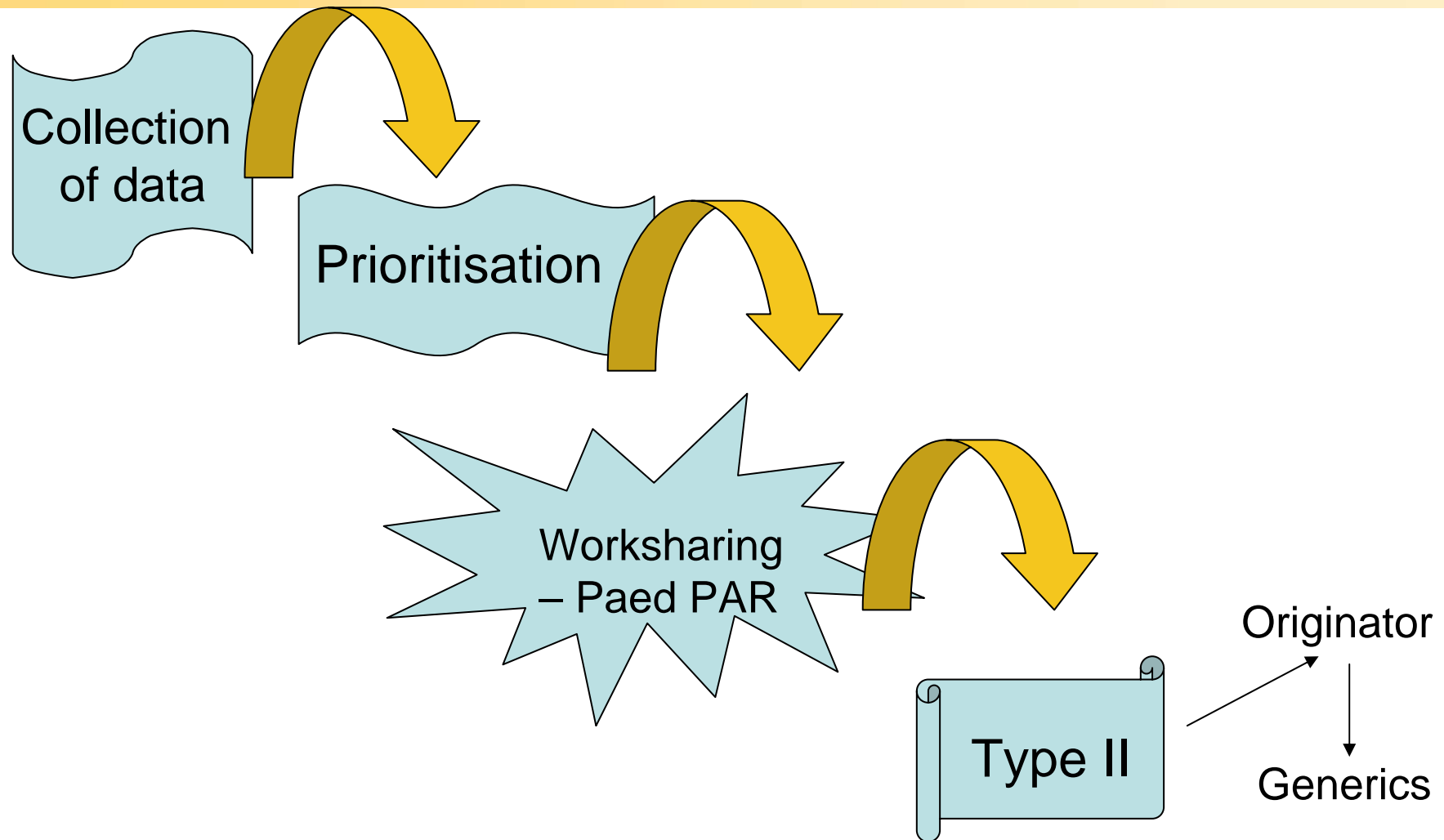
- Consistent approach needed for products approved via national, MRP/DCP & CP
- Duplication in assessment of the same set of data is a waste of resources
- NCAs are part of a network; this network is strengthened by cooperation; benchmarking is instrument to build trust
- It is in the interest of public health (for patients and health professionals) to harmonise information for all products on the European market

# EU Worksharing procedure on paediatric data



- Proposal for Worksharing agreed in HMA-hum meeting Iceland 24 February 2005
- Assessment of first wave started around September 2005
- Lists of products (MRP and nationally approved) selected
  - 1<sup>st</sup> wave finalised, variations awaited
  - 2<sup>nd</sup> wave ongoing
- Assessment of the studies submitted by MAH according Art. 45

# Procedure – Paed data assessment



## 1.) Sind alle zugelassenen Arzneispezialitäten betroffen?

- *Ja, es sind alle zugelassenen Arzneispezialitäten betroffen. Die Anforderung gilt für alle Arzneispezialitäten unabhängig vom Zulassungsverfahren (rein national, MRP/DCP oder zentrales Zulassungsverfahren) und der Art der Arzneispezialität (inklusive Generika, Homöopathika und apothekeneigene Arzneispezialitäten).*

## ***1.a.) Wie ist die Vorgangsweise für zentral zugelassene Produkte?***

- *Eine Auflistung aller zentral zugelassenen Produkte muss der EMEA übermittelt werden.*

## ***1.b.) Muss für apothekeneigene Arzneispezialitäten auch jeweils eine Kopie an die EMEA geschickt werden?***

- *Nein, nur an die AGES PharmMed, da es sich bei apothekeneigenen Arzneispezialitäten um national spezifische Zulassungen handelt.*

## 2.) Welche Dokumente müssen übermittelt werden?

- *Folgende Dokumente müssen übermittelt werden:*
  - *Tabelle*
  - *Annex I – falls zutreffend*
  - *Annex II – falls zutreffend*

*Zu finden sind diese Formblätter sowohl in unveränderbarer Form (.pdf), als auch in veränderbarer Form (.doc bzw. .xls) auf der Website der AGES PharmMed ([www.ages.at](http://www.ages.at)).*

## 3.) Muss die Tabelle in englisch oder in deutsch ausgefüllt werden?

- *Die Tabelle muss in englisch ausgefüllt werden, der Annex II (SPC 4.1 und/oder 4.2) in deutscher Sprache – falls es sich um ein rein national zugelassenes Produkt handelt; in Englisch dann, wenn es sich um ein Produkt handelt, das im MRP/DCP-Verfahren zugelassen wurde.*

## 4.) An welche Adresse müssen die Dokumente elektronisch geschickt werden?

- *Die Auflistungen (Tabelle, Annex I und Annex II – falls zutreffend) betreffend alle in Österreich zugelassenen Arzneyspezialitäten müssen an folgende Mailadressen geschickt werden:*

*AGES PharmMed:*                      [kinderarzneimittel@ages.at](mailto:kinderarzneimittel@ages.at)

*EMA:*    [paediatrics@emea.europa.eu](mailto:paediatrics@emea.europa.eu)

## 5.) Bis wann müssen die Dokumente übermittelt werden?

- *26.01.2008 – Deadline für die Übermittlung der Tabelle und Annex I.*

*Die gesetzliche Frist für die Übermittlung der Information bezüglich abgeschlossener Studien, die noch nicht übermittelt wurden ist der 26.01.2008.*

*Nach Absprache im CMD wurde folgende Vereinbarung getroffen: Annex II sollte auch gemeinsam mit der Tabelle und dem Annex I übermittelt werden, kann jedoch bis 26.04.2008 nachgereicht werden.*

## 6.) Müssen die Studien zeitgleich mit der Tabelle übermittelt werden und an wen?

- *Die Tabelle muss der nationalen Behörde bis 26.01.2008 übermittelt werden – eine Kopie geht an die EMEA! Zu diesem Zeitpunkt müssen die Studien noch nicht übermittelt werden.*

*Die Studien müssen dem Rapporteur direkt übermittelt werden, der innerhalb einer Frist von 6 Monaten – also bis 26.07.2008 – im Rahmen des „Paediatric Worksharing Project“ benannt wird.*

*Die Koordination des „Paediatric Worksharing Project“ wird von der CMD-h/EMEA Arbeitsgruppe durchgeführt. Der Zulassungsinhaber wird schriftlich informiert, welcher EU-Mitgliedsstaat als Rapporteur fungiert.*

## 7.) Welche Bedingungen müssen erfüllt sein, damit eine Studie als pädiatrische Studie gilt?

- *Eine Studie gilt dann als pädiatrische Studie, wenn die Probanden Kinder unter 18 Jahre sind, aber auch dann, wenn Kinder und Erwachsene an der Studie teilgenommen haben.*

- 8.) Müssen nur jene Studien gemeldet werden, die in dem Land durchgeführt wurden, in dem die Arzneispezialität zugelassen ist?**
- *Die Informationen betreffend Studien müssen jeweils der nationalen Behörde des Landes mitgeteilt werden, in dem das Produkt zugelassen ist – unabhängig davon, in welchem Land die Studie durchgeführt wurde.*

**Danke!**



**AGES**

Österreichische Agentur für Gesundheit  
und Ernährungssicherheit GmbH



*Gesundheit. Ernährung. Sicherheit.  
Unsere Verantwortung.*

**[www.ages.at](http://www.ages.at)**