

The EMA/EU incentives on Geriatric medicines: lessons learned from paediatrics

with a special focus on quality aspects

Diana van Riet – Nales, Pharm. D.
Vice-chair Quality Working Party (human), European Medicines Agency. London, UK
Coordinator, Medicines Evaluation Board, Utrecht, the Netherlands

AAPS Workshop on " Patient centric drug delivery, product design and development: meeting the requirements in future healthcare", 14 October, Chicago, USA

Agenda

- introduction
- EMA/EU paediatric strategy
- EMA/EU geriatric strategy
- lessons (to be) learned from paediatrics

- *with examples from NL/NO research by assessors groups*

Marketing Authorization(1)

- license to trade a medicinal product manufactured by industry / industrial scale
  - compounded preparations excluded from MA
- issued on basis
  - "paper" review + GMP
- in case of
  - positive benefit/risk
  - consistent & adequate quality ("fit for use")

(1) Directive 2001/83 available at: http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf

B/R (Q)+ for who?

- SmPC : often wide age range
- but older / younger adult patients not the same!(1)
  - older people's bodies distribute and eliminate medicines from the body differently
  - older people are susceptible to a wide range of diseases, including e.g. Alzheimer's disease, heart disease
  - older people often have more than one disease at a time, making it difficult to treat the separate diseases;
  - older people may be weaker, making them vulnerable to disease and the risks associated with medical treatment

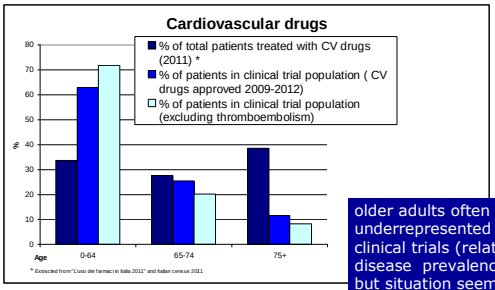
(1) http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000249.jsp&mid=WC0b01ac058004cbb9

General considerations clinical trials

- following ICH E7 and the Q&As, a representative number of patients should be studied pre-authorisation (1)
- older people in many cases main users of a drug
- data should be presented for the entire age spectrum
- population PK or specific PK study including the very elderly should be performed and will help informed prescription

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002875.pdf

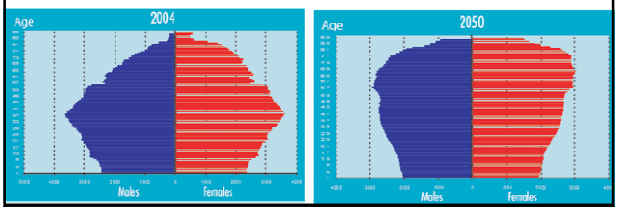
However…
current clinical trials



older adults often underrepresented in clinical trials (relative to disease prevalence), but situation seems to be improving

And….
EU demographics
according Eurostat

>65 years: 84 million in 2008 to around 141 million by 2050



Need for governmental involvement
to assure age appropriate medicines for the elderly !?

Let's take a look what Europe has done for another group of special patients first: children!

Agenda

- introduction
- EMA/EU paediatric strategy
- EMA/EU geriatric strategy
- lessons (to be) learned from paediatrics

Paediatric Regulation (2007)(1)

- result of intensive lobbying to solve the problem of "paediatric orphans"
- argument was that responsibility to bring age appropriate paediatric medicines to the market could not be left to industry alone
- lessons learned from earlier US incentives

(1) Paediatric Regulation available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

Paediatric Regulation

- aim to improve health of children in Europe by
  - facilitating development & availability medicines 0-18 yr
  - ensuring medicines for children are high quality, ethically researched & authorised appropriately
  - improving availability information on use medicines for children
- to be reached without subjecting children to unnecessary trials or delaying authorization medicines adults

Key aspects Paediatric Regulation

- industry should develop Paediatric Investigation Plan (PIP) at early stage new drug development
- PIP subject to agreement by European Medicines Agency's (EMA) Paediatric Committee (PDCO)
- PIP should include information on paediatric formulation(s), strenghts & administration devices
- regulation supported by EU funds for research (e.g KP7)

EU assessment paediatric medicines / PIPS (1)

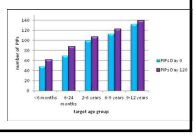
- directive/regulation detailed in other "regulatory documents" as linked to or published on EMA website[1]
- patient centricity > quality aspects
  - all guidelines & Ph. Eur. apply
  - issues requiring further justification /alternative approaches (draft) "guideline on the pharmaceutical development of medicines for paediatric use" [2]
  - background information "reflection paper on formulations of choice for the paediatric population"[3]

(1) http://www.ema.europa.eu
(2) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107908.pdf
(3) http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000087.jsp&mid=WC0b01ac0580025b90

PIP assessment easy job?

?

- preliminary evaluation EMA review process changes to oral paediatric preparations in PIPs
  - 74/152 PIPS age group changed; 58/152 scaling down
  - overall number "oral" PIPs per target age group increased
  - changes in age main driver changes number & nature oral preparations in PIPs
  - changes in pharmaceutical aspects less profound



MA assessment easy job?

?

- existing medicine
- used off label for children >2 yrs old
- applicant recently conducted clinical trials in children confirming off-label use
- applicant applies for a MA variation children >2 yrs
- no age-appropriate paediatric formulation proposed
- appicant states in SMPC **"for children aged below 6 tablets should be crushed and mixed with a ready to use suspension"**

Agenda

- introduction
- EMA/EU paediatric strategy
- EMA/EU geriatric strategy
- lessons (to be) learned from paediatrics

EMA Roadmap to 2015

- takes account changing environment in which to operate
- ensuring EMA vision consistent with/complementary to strategic directions European Commission & Heads of Medicines Agencies
- one of the drivers is challenge stemming from demographic changes as regards population ageing
- agency will undertake "specific efforts to ensure that the needs of older people are taken into account in the development and evaluation of new medicines"

(1) http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf

EMA geriatric strategy vision: 2 principles

medicines used by geriatric patients must be of high quality, and appropriately researched and evaluated.. **for use in this population** ⇨ Evidence based medicine

improve the availability of **information** on the use of medicines for older people ⇨ Informed prescription

18

The approach

- down to earth, achievable actions
  - industry
    - follow guidelines.
    - discuss innovative solutions with the regulators
  - regulators
    - better coordinate activities
    - improve communication to the patient and to the prescriber
- to better use the tools we already have!

Key aspects Geriatric strategy (1)

- *"..identifying gaps in regulatory and scientific knowledge and taking appropriate measures to tackle them" (>research!)*
- definition of strategy; frailty analysis (definition & scales)
- geriatric Needs Survey to identify geriatric activities and instruments (or lack of) at national and European level
- **workshop** on Geriatric Medicines
- provision of **Scientific Advice** during product development
- comments during drafting of **guidelines**
- geriatric **formulations** and adherence

Key aspects Geriatric strategy (2)

- *"..fostering and utilising a relevant experts' pool to address specific issues as requested by the CHMP, making full use of its Working Parties and experts groups where appropriate."*
- establishment of the CHMP Geriatric Advisory group (GEG) (1)
- mandate adopted May 2011 (2)

(1) http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000100.jsp&mid=WC0b01ac0580473f01
(2) http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/06/WC500107028.pdf

Key aspects Geriatric strategy (3)

- *"..ensuring that the development and evaluation of new medicines takes into account specific safety and efficacy aspects related to aging, in accordance with current guidelines, particularly ICH E7"*
- scientific Advice
- peer review comments (EMA)
- AR template (+RMP template)
- SmPC/PL and EPAR to reflect data appropriately
- guideline drafting and revision

Key aspects Geriatric strategy (4-6)

4 "..consideration for the need of specific pharmacovigilance activities"

5 "..ensuring relevant regulatory guidelines contain appropriate guidance on the development and assessment of products to be used in geriatric patients"

6 "..provide advice to applicants on regulatory requirements for the development of products likely to be used in the elderly"

Agenda

- introduction
- EMA/EU paediatric strategy
- EMA/EU geriatric strategy
- lessons (to be) learned from paediatrics

What are paediatric medicines (1)

agreement

- for use children 0-18 yrs
- children do not constitute a homogeneous group (ICH-classification)
- design medicine should be tailored to child's age i.e. age appropriate

For use in children = easy interpretation?

need for extensive retrospective clarifiation decision making process in current SMPCs

Appendix 1

Interpretation of information in section 4.1 and 4.2 of the Summary of Product Characteristics (SPC)

SPC	Comment
Child authorization status	
General statement referring to children	Target age group: 0–18 years
General statement 'Juvenile'	TARGET age group: 0–18 years
'Zuigeling' (sucking child)	target age group: 0–1 year
'Jongvolwassene' (young adult)	Target age group: 16–18 years
'Adolescent'	Target age group: 12–18 years
A recommended dose for a specific age range	Target age group: the specific age range for dosing
A recommended dose for children from 0 until the age of 12 to 17 years and a recommended dose for adults	Target age group: 0–18 years
A recommended dose in mg kg^{-1} without any further information	Target age group: 0–18 years
The medicine can be used from a specific minimum weight	The minimum weight is used to calculate the equivalent minimum age according the Dutch growing curve for girls, lower line

Appendix 1

Continued

SPC	Comment
A minimum age between 0 and 18 years and a minimum weight	The target age groups are only based on the information towards age
The medicine is discouraged for use in children or a specific target age group, nevertheless a recommended dose is given	The child classification according the dosing instruction is applied
A reference to several medicines (e.g. different strengths and dosage forms) and several target age groups, but it is clearly stated which medicine is suitable for which of the target age groups.	Each medicine: only those target age groups which are specific for that medicine; otherwise each medicine all target age groups
The lower target age is not consistent wit the lower ranges of the adapted ICH criteria (e.g. 2.5 years)	The lower age range of the next modified ICH group is applied
Ability to follow the authorized posology ('dose capable')	
The dosage instruction refers to mg/kg, however the medicine contains a fixed quantity of active substance	The medicine is not considered dose capable
Suitability of the dosage form ('suitable')	
Tablets	• A single dose may involve 2 tablets at the maximum • A single dose may involve a halved tablet, if 1) the tablet contains a score line 2) the SPC does not state that the scoring line is for esthaetical reasons only; 3) the SPC does not state that the tablet may only be broken to facilitate the intake of the full dose. • If the SPC reads that the tablet may be pulverized, than the tablet is considered suitable for children from 1 month
Capsules	• If the SPC states that the capsule may be opened, then the capsule is considered suitable for children from 1 month
Suppositories	• A single dose involves one suppository (no halves)
Enemas	• The minimum dosing volume is 5 ml, whereas the maximum dosing volume is 150 ml
Oral liquid preparations	• The maximum dosing volume is 5 ml for children aged below 5 years • The maximum dosing volume is 10 ml for children aged from 5 to 10 years • The minimum single dosing is 0.2 ml

van Riet-Nales DA, de Jager KE, Schobben AF, Egberts TC, Rademaker CM. The availability and age-appropriateness of medicines authorized for children in The Netherlands. Br J Clin Pharmacol. 2011 Sep;72(3):465-73.

What are paediatric medicines (1)

tailored = age appropriate means?

- breaking tablets: uniform weight distribution alone or also ease of breaking?
- best, average, worst, 95% CI etc potential certain age?
  - prolonged release tablet acceptable if 90% will not chew?
- when can children swallow mini-tablets?
  - 2 mm > all from 6 months (1)
  - 3-mm > half from 2 yrs (2)
  - 4-mm > 1 year (3)

(1) Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child. 2012 Jan 17.
(2): Thomson SA, Tuleu C, Wong IC, Keady S, Pitt KG, Sutcliffe AG. Minitablets: new modality to deliver medicines to preschool-aged children. Pediatrics. 2009 Feb;123(2):e235-8.
(3) Unpublished data from pending MEB/UU study

Ease of subdivision of tablets by hand

Ph. Eur. Test on subdivision of tablets does not hold a requirement on the ease of breaking/person who subdivides the tablet

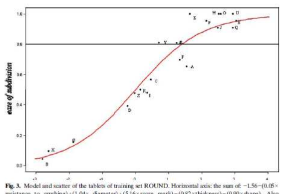


Fig. 3. Model and scatter of the tablets of training set ROUND. Horizontal axis: the sum of: −1.56−(0.05× resistance to crushing)+(1.04× diameter)+(5.16×score mark)−(0.82×thickness)−(0.90×shape). Also shown: horizontal line ease of subdivision=0.800, being the cut-off value for an acceptable ease of subdivision

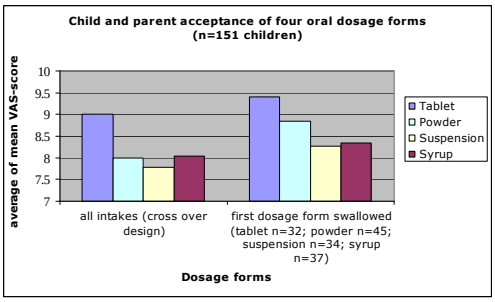
Table III. Sensitivity Analysis of the Parameters of the ROUND Model

Parameter	Statistical significance to the ROUND model (p value)[a]
Resistance to crushing	0
Diameter	1.23e-09
Score mark	5.90e-07
Thickness	1.65e-03
Shape	5.37e-03

[a] The range of theoretically possible p values is 0–1; the closer the p value of a parameter is to 0, the more important its contribution

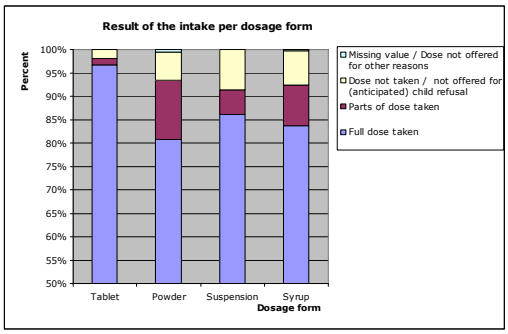
Steen, Frijlink, Schippers, Barends. Prediction of the Ease of Subdivision of Scored Tablets from Their Physical Parameters. AAPS PharmSciTech, Vol. 11, No. 1, March 2010 (# 2010)

all acceptable dosage forms?



Unpublished data from pending MEB/UU study

all acceptable dosage forms?



Unpublished data from pending MEB/UU study

Lessons learned for geriatrics (1)

- definition geriatric population should be clear (age, frailty?) and also clearly described in all the SmPCs
- suitability of clinical geriatric sub-groups to be further considered for quality aspects
- research is essential to fill knowledge gaps
  - methodology and target limits to be defined

What are paediatric medicines (2)

- pharmacy compounded
  - raw material, licensed medicine
- licensed
  - off-label (age, dosing, indication)
  - within label (new, existing)
    - *also really developed for children?*
    - *or rather because of unclear SPC?*

Lessons learned (2)

- categorization issues may complicate stakeholders'discussions
- need for definitions, taxonomy quality aspects
  - which terms?
  - who involved and who takes the lead?
  - liaison with FDA, WHO, etc should be assured!

Lessons learned by who? (3)

- industry when developing paediatric formulation
- PDCO for formulations in PIP?
- EMA Quality Working Party / National authorities
- academia?

Lessons learned (3)

- all parties should closely work together from the beginning
- transfer of information from the beginning is key (websites!)
- different backgrounds should be explored as they are key to positions taken
- the past is not the past: consistent and clear regulatory approaches warranted (retrospective control?)
- training essential to assure good scientist = good regulator = good health care professional

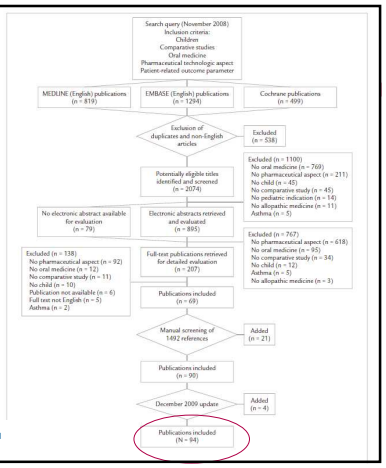
What makes a paediatric medicine age-appropriate? (4)

Aspects considered in Paed GL (1)

- active substance
- route of administration and dosage form
- dosing frequency and modified release preparations
- excipients in the formulation
- patient acceptability (palatability, mixing with food)
- container closure system
- medical device

(1) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107908.pdf

NL systematic review on pharmaceutical aspects in relation to patient outcomes



Van Riet – Nales DA, Schobben AFAM, Egberts ACG, Rademaker CMA. Pharmaceutical technology aspects of oral pediatric drugs and patient outcomes: a systematic literature review. Clin Ther 2010; 5: 924–38.

Children

Table II. Impact of pharmaceutical technologic aspects on patient-related outcomes parameters.[24–28,31–119] Data are number (%) of assessments.

Patient-Related Outcomes Parameter	Pharmaceutical Technologic Aspect: Formulation and Dosage Form (n = 85)	Route and Frequency of Administration (n = 77)	Packaging, Administration Device, and User Instruction (n = 14)	All Assessments (N = 176)*
Patient acceptance	38 (45)	5 (6)	1 (7)	44 (25)
Patient preference	19 (22)	4 (5)	0	23 (13)
Adherence	11 (13)	15 (19)	6 (43)	32 (18)
Clinical efficacy	8 (9)	31 (40)	2 (14)	41 (23)
Side effects and tolerability	8 (9)	22 (29)	0	30 (17)
Administration errors	1 (1)	0	5 (36)	6 (3)

*Two investigations assessed >1 pharmaceutical technologic aspect.

Van Riet – Nales DA, Schobben AFAM, Egberts ACG, Rademaker CMA. Pharmaceutical technology aspects of oral pediatric drugs and patient outcomes: a systematic literature review. Clin Ther 2010; 5: 924–38.

And what a geriatric?

- first step is agreement on aspects to be considered for the quality of geriatric medicines
- which aspects identical to paediatric medicines and which are different?
- key aspect: which information is already available? Where are the knowledge gaps? Need to know for when preparing for a guideline!

aspects already identified

- how to address frailty in trials? frailty or functionality?
  - what does this mean for the quality requirements?
- how to address polypharmacy in trials?
  - adaptation of current quality standards necessary?
- need for caregivers and lower doses
- elderly may be unwilling
  - suitability paediatric formulations for the elderly?
- different ADME? central pharmacokinetics?

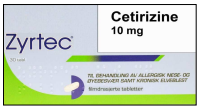
Health literacy, impaired vision
regulatory requirements may help

432. Improved Drug Packaging Design Can Improve Patient Safety

Laura W Bakke,[1] Sigurd Hortemo,[2] Tor Endestad,[1] Steinar Madsen.[2] [1]*Insitute of Psychology, University of Oslo, Oslo, Norway;* [2]*Norwegian Medicines Agency, Oslo, Norway.*

Objectives: The objective of this study was to test if a new standardized drug packaging design could improve recognition and discrimination of drug packages.

Results: The important measures in a mental rotation task are accuracy (percent correct answers) and reaction time. With the new design, overall accuracy in the older group improved from 52 to 82% ($p < 0.001$) and in the young group from 79 to 94% ($p < 0.001$). In the older group, the accuracy improved from 44% to 86% ($p < 0.001$) when comparing packages with the same active ingredient. In both groups, overall reaction time decreased from 1,154 to 1,005 ms ($p < 0.001$).



Bakke et al, Pharmacoepidemiology Drug Safety 2012; 21: (suppl 3) 205

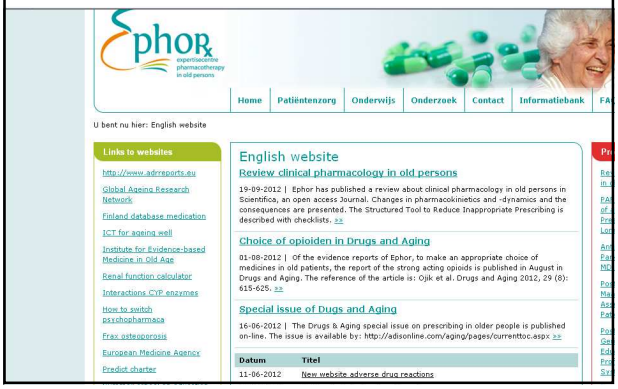
Reality for children and the elderly: holistic view needed

- not all problems related to the use of a medicine can be solved through regulatory incentives
  - the specific formulation is not (fully) reimbursed because it is more expensive than the (younger) adult formulation
    - to involve HTA from the start?
- aspects may have a link with, but not only due to age (hand force, willingness)

Reality for children and the elderly: many stakeholders
-- know who is doing what and also planning to do what

- authorities e.g
  - Geriatric Expert Group (EMA)
  - Expert Group Practical Experiences (MEB)
    http://www.cbg-meb.nl/CBG/nl/over-ons/netwerk/expertgroepen/default.htm
  - regulatory science e.g. medication use for the elderly (MEB/RIVM/UU, NL)
- patients e.g.
  - AGE platform Europe (AGE) http://www.age-platform.eu/en/about-age
- health care professionals e.g.
  - European Union Geriatric Medicine Society (EUGMS)
    http://www.eugms.org/

Expertisecentre PHarmacotherapy in Old peRsons (EPHOR) http://ephor.artsennet.nl/English-website.htm



Conclusion

- patient centricity is key in Europe
- paediatric and geriatric development issues not the same i.e. paediatric guideline will not consider geriatric medicines
- appropriate geriatric medicine development is a shared responsiblity of industry, academia, regulators, patients: more research is needed
- respect good regulatory practice but assure a balanced approach between new and existing medicines

Thank you for your attention

da.v.riet@cbg-meb.nl

Acknowledgements

Paul Jansen, EPHOR/GEG

Francesca Cerreta, EMA

Steiner Madsen, Norwegian Medicines Agency