

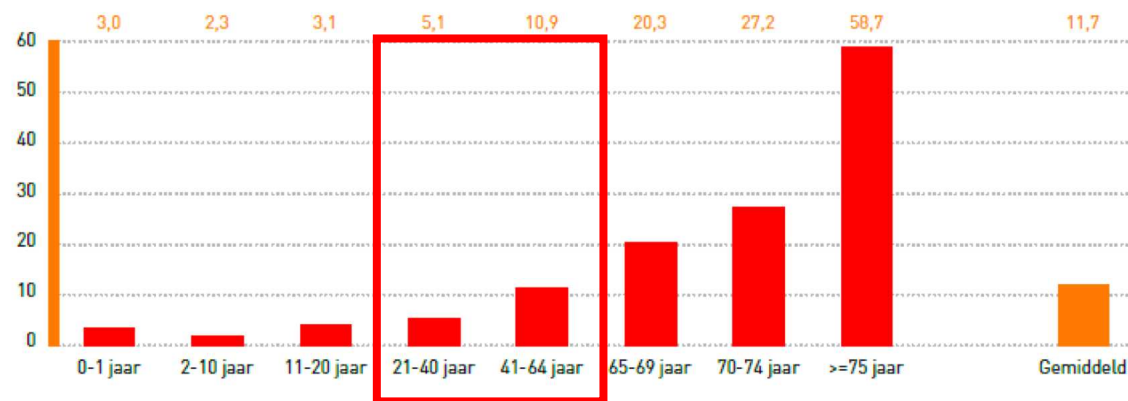


A NCA analysis of approval documents

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Pre-authorization studies and the users of medicines

Number of prescriptions in 2009 in the Netherlands



Bron: Stichting Farmaceutische Kengetallen



Benefit/risk is changing

- Evidence for benefit of several medicines
- Time until benefit is shorter compared to younger adults
- Safety is a problem because of changes in PK/PD
- Nerve system damage is important
- Decrease in kidney function
- Decreased balance
- Decreased thirst etc.



The consequences: HARM frail patients are at risk to be admitted to hospital because of ADR

- Cognitive disturbance (HR 11,9; 3,9-36,3)
- Polymorbidity > 5 (HR 8,7; 3,1-24,1)
- decreased kidney function (HR 3,1; 1,9-5,2)
- not living independently (HR 3,0; 1,4-6,5)
- Polypharmacy (>5 HR 2,7; 1,8-3,9)
- Adherence problems (HR 2,3; 1,4-3,8)





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Is it true that older patients are not studied?

- Which information is available in the SmPC for appropriate prescribing in older persons?
Which information is available in the EPAR for appropriate prescribing in older persons?
What is the compliance with the almost 20 year old ICH E7 guideline?





Methods

- All non-generic products with a European centralised marketing authorisation between 2008 and 2011 with complete dossiers, indicated for diseases in older individuals
- The ICH E7 guideline was summarised in 19 items



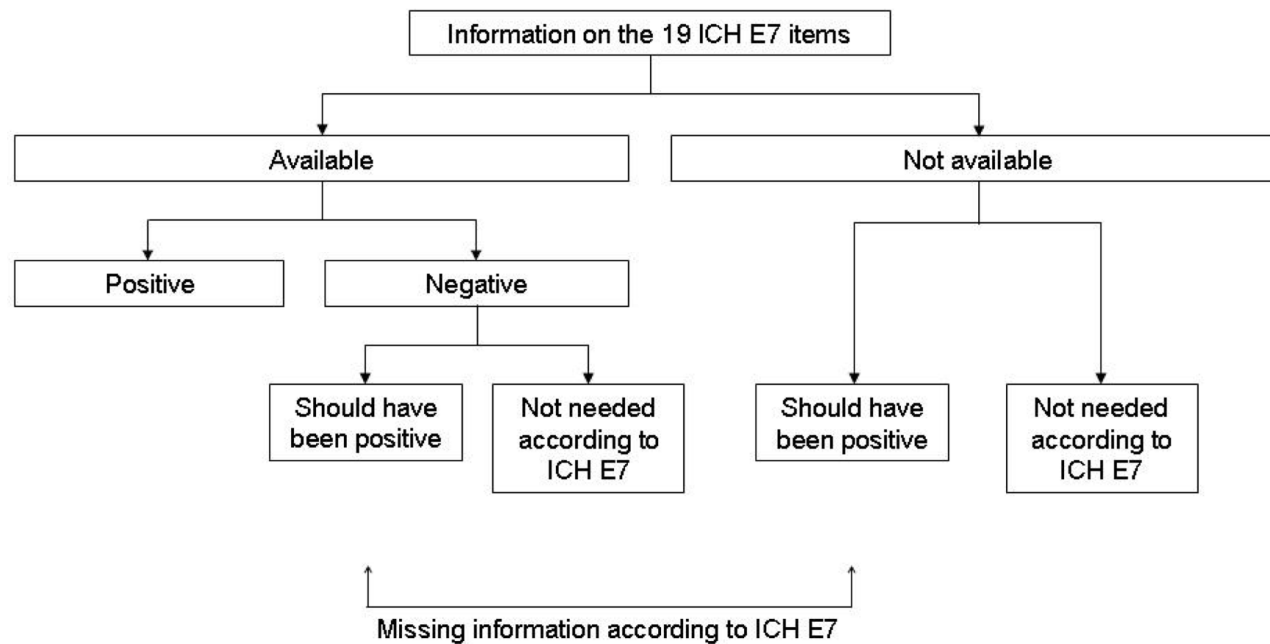


19 items of the ICH E7

- Nature of the studied population (4 items)
 - Inclusion >65 and >75 years
 - Exclusion based on age
 - Exclusions based on common co-morbidity
- Clinical experience in older patients (4 items)
 - Number >65 years
 - Age-related differences for efficacy, dose-response and adverse events
- Pharmacokinetic studies (8 items)
- Drug-drug interaction studies (3 items)



Subdivision of available and missing information

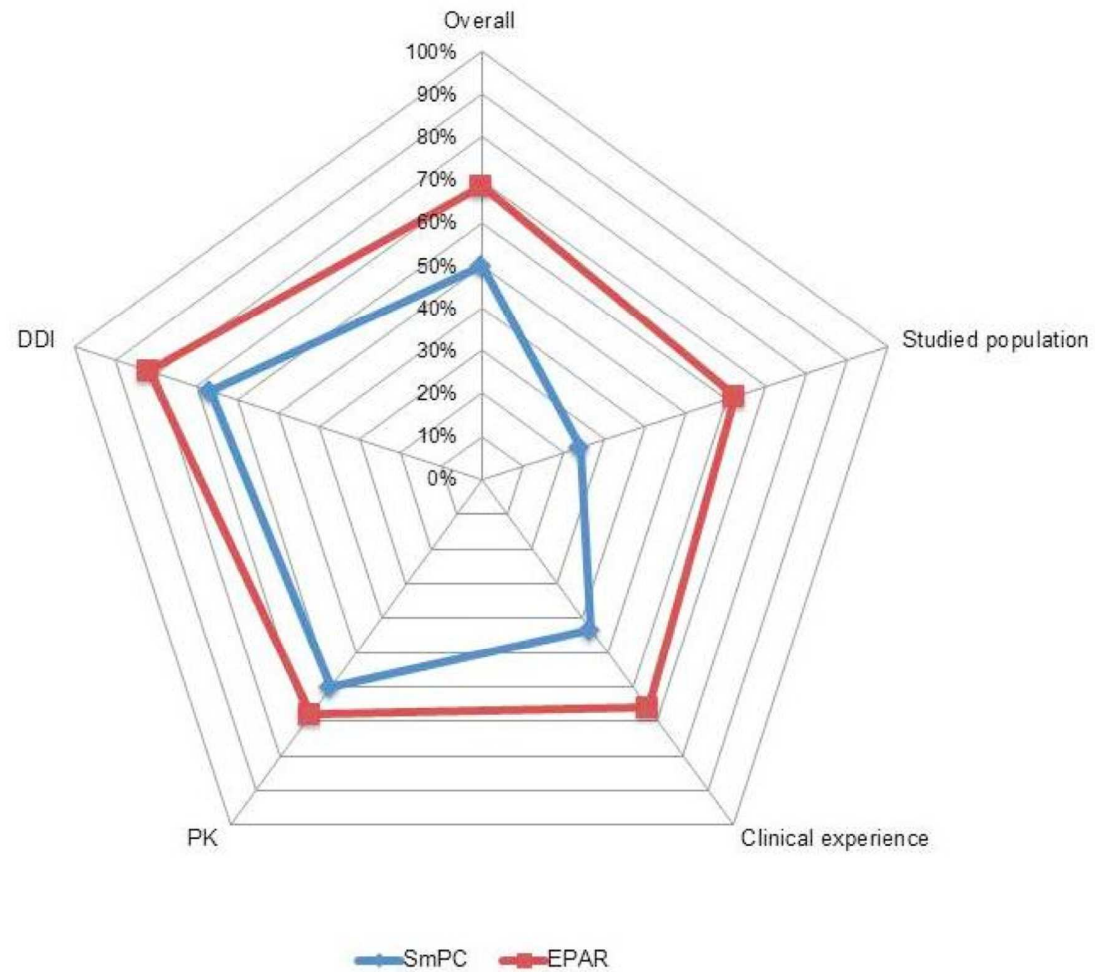


Results

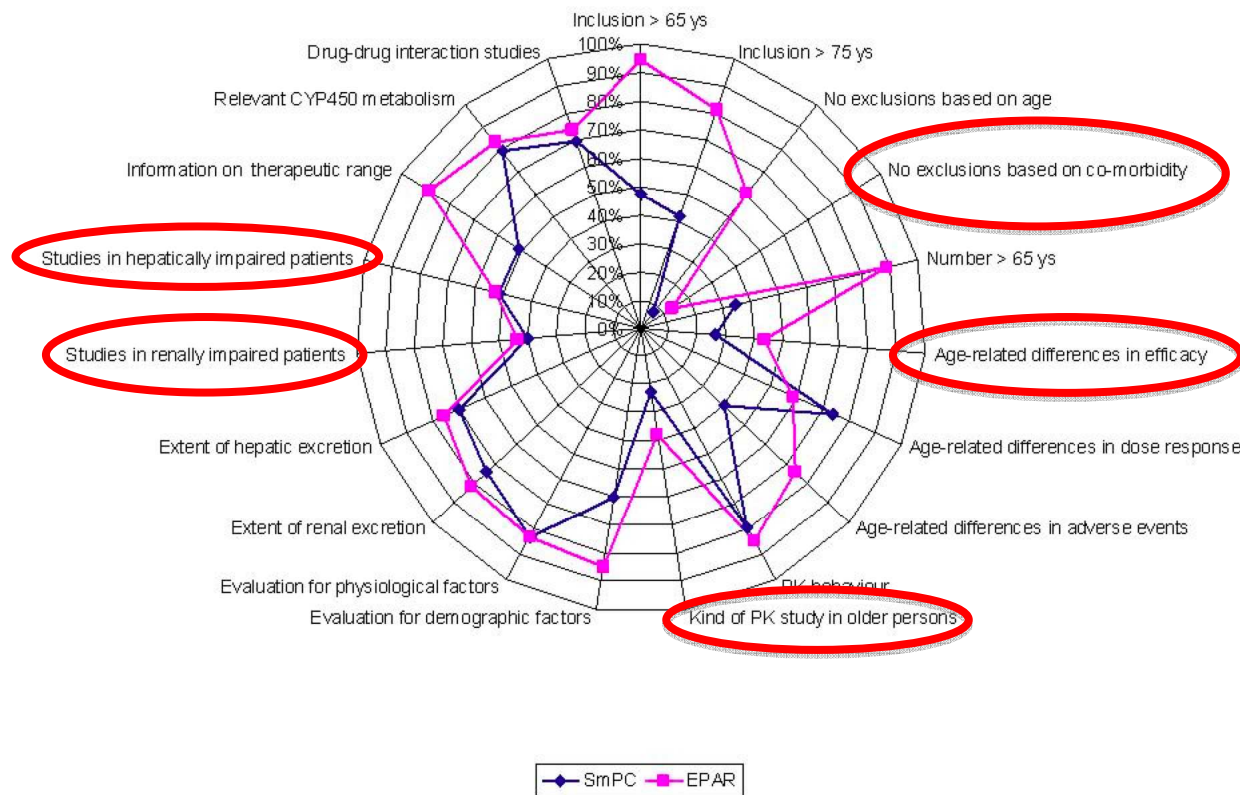
- 53 medicinal products
 - Neoplasms: 12 (23%)
 - Musculoskeletal system/connective tissue: 10 (19%)
 - Circulatory system: 8 (15%)
 - Endocrine, nutritional and metabolic diseases: 5 (9%)
 - Infectious diseases: 5 (9%)
 - Others: 13 (25%)



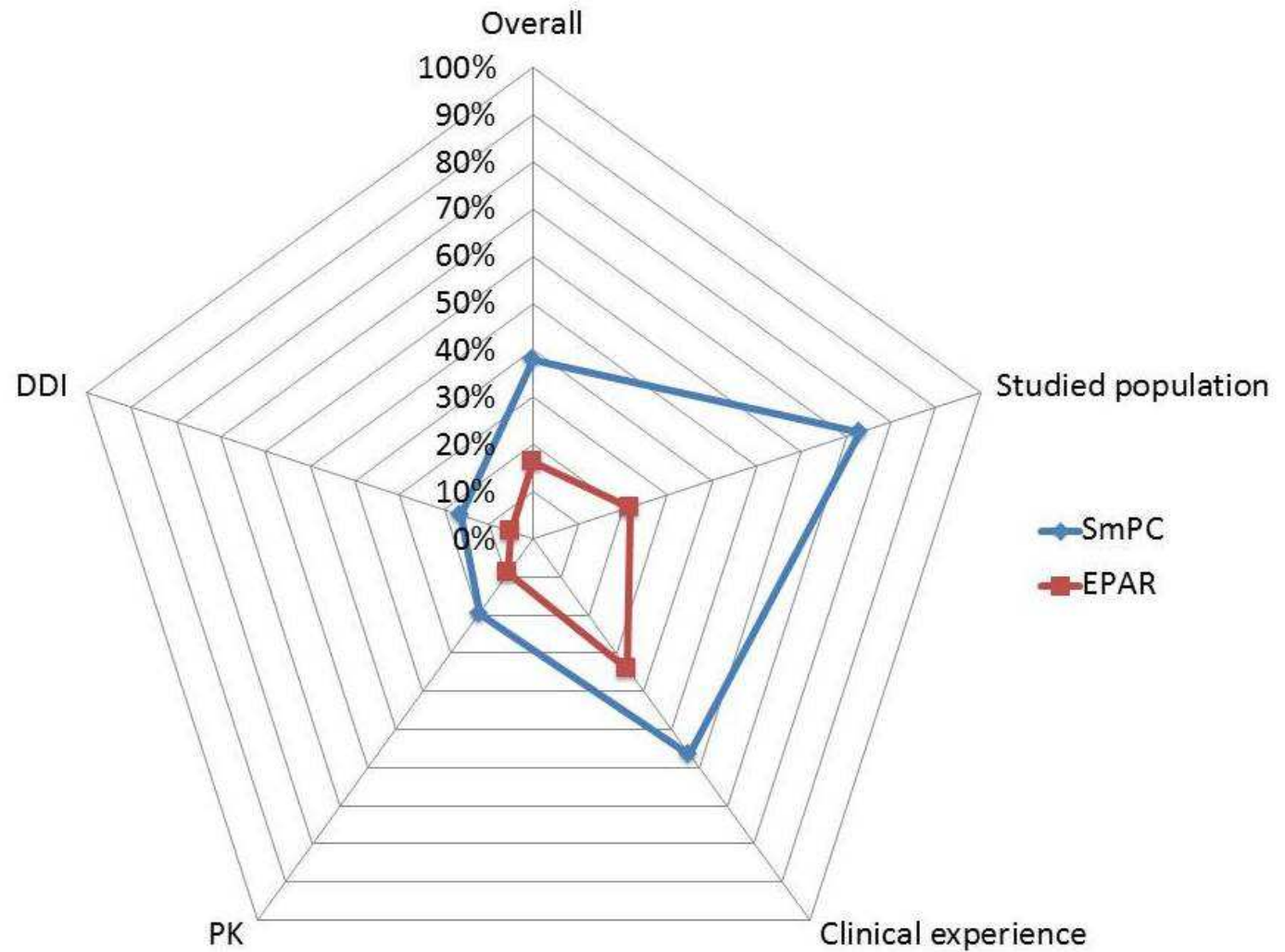
Available, positive information



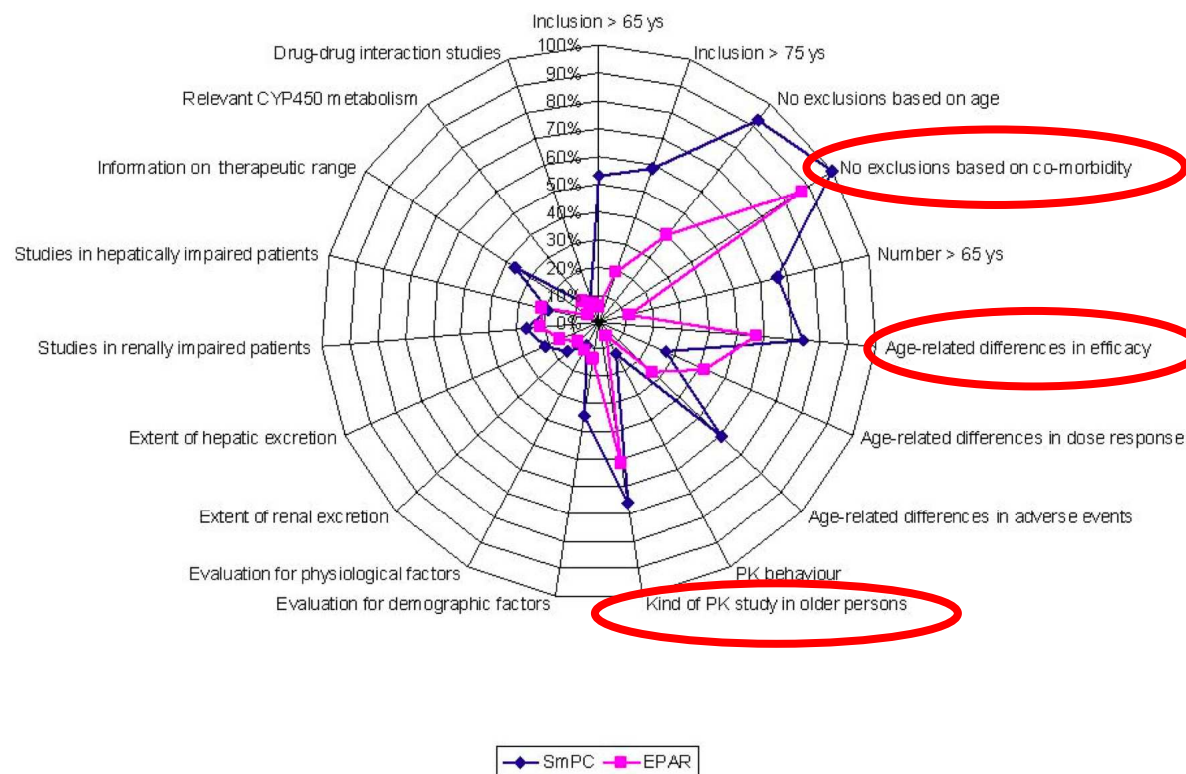
Available, positive information per category



Non-available information that should have been positive



Non-available information that should have been positive per category



Conclusions

- Information on older persons, according to the ICH E7 is relatively high available in the EPARs
- However it is often not present in the SmPC
- Especially information on common co-morbidities, on age-related differences in efficacy and kind of PK study in older persons are lacking





Discussion: is the ICH E7 information what prescribers want?

- Delphi study on the Information of Medicine appropriateness in the Elderly (DIME)
- Regulators found several items less important compared to geriatricians/other experts:
 - The convenience of use for older persons (dosage form and packaging)
 - The extent of renal clearance of the active substances in old persons
 - No exclusion based on concomitant medical conditions common in old persons





What was left out of the final Dime?

- No exclusion based on concomitant medical conditions common in old persons
- A single-dose pharmacokinetic study in young versus old persons





DIME: extra items are needed (total items: 26)

- No exclusion based on concomitant treatment with drugs commonly prescribed for old persons
- The post-marketing data collection in geriatric patients is specified in the Risk Management Plan
- The extent of drug accumulation in old persons
- Information should be available about dosing instructions
- The convenience of use for older persons





DIME: extra items are needed,
especially about safety

- Potential anticholinergic effects
- Potential sedative effects
- Potential orthostatic effects
- Potential effects on the locomotor system
- Potential cardiovascular side effects
- Potential effects on haemostasis
- Important drug-disease interactions



Final item list of the DIME

Information should be available on:	ICH E7	Q&A
Inclusion of patients >65 years in phase III studies	X	
Inclusion of patients >75 years in phase III studies	X	
For drugs used in diseases not unique for, but present in, old persons: inclusion of at least 100 patients >65 years in the phase III studies	X	
For drugs used in diseases characteristically associated with aging (e.g. Alzheimer's disease): the majority of the clinical database consists of geriatric patients	X	
No exclusion of patients on the basis of an upper age cut-off	X	
No exclusion based on concomitant treatment with drugs commonly prescribed for old persons		X
The post-marketing data collection in geriatric patients is specified in the Risk Management Plan		X



Final item list

PHARMACOKINETICS

Information should be available on:	ICH E7	Huisman <i>et al.</i>
A multiple-dose pharmacokinetic study in young versus old persons, if there are age-related differences in pharmacokinetics	X	
The extent of drug accumulation in old persons		X
The extent of renal clearance of the active substances (i.e. parent compound and/or metabolites) in old persons	X	
The extent of hepatic clearance of the active substances (i.e. parent compound and/or metabolites) in old persons	X	
The therapeutic dose range of the drug	X	
The extent of metabolism via or effects on specified CYP450 enzymes	X	
Potential drug-drug interactions, if the therapeutic range of the drug or likely concomitant drugs is narrow, and the likelihood of the concomitant therapy is great	X	

Huisman et al. *Drugs and Aging* 2011; 28: 391-402



Final item list

EFFICACY

Information should be available on:	ICH E7
Age-related differences in efficacy	X
Age-related differences in dose-response	X



Final item list

SAFETY

Information should be available on:	ICH E7	Huisman <i>et al.</i>
Age-related differences in adverse events	X	
Potential anticholinergic effects (e.g. cognitive decline, delirium, blurred vision, urine retention)		X
Potential sedative effects		X
Potential orthostatic effects		X
Potential effects on the locomotor system (e.g. decline of mobility, increased incidence of falls)		X
Potential cardiovascular side effects (e.g. arrhythmias, ischemic effects)		X
Potential effects on haemostasis (e.g. thrombotic effects, bleeding risk)		X
Important drug-disease interactions (e.g. exacerbation of heart failure)		X





Final item list

CONVENIENCE OF USE

Information should be available on:	Huisman <i>et al.</i>	Delphi panel
The convenience of use for older persons (dosage form and packaging)	X	
Information should be available about dosing instructions		X

