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SCIENCE MEDICINES HEALTH

EMA perspective on guidance on medicines for older people

FDA virtual workshop, 23rd March 2021 - **Roadmap to 2030 for New Drug Evaluation in Older Adults**

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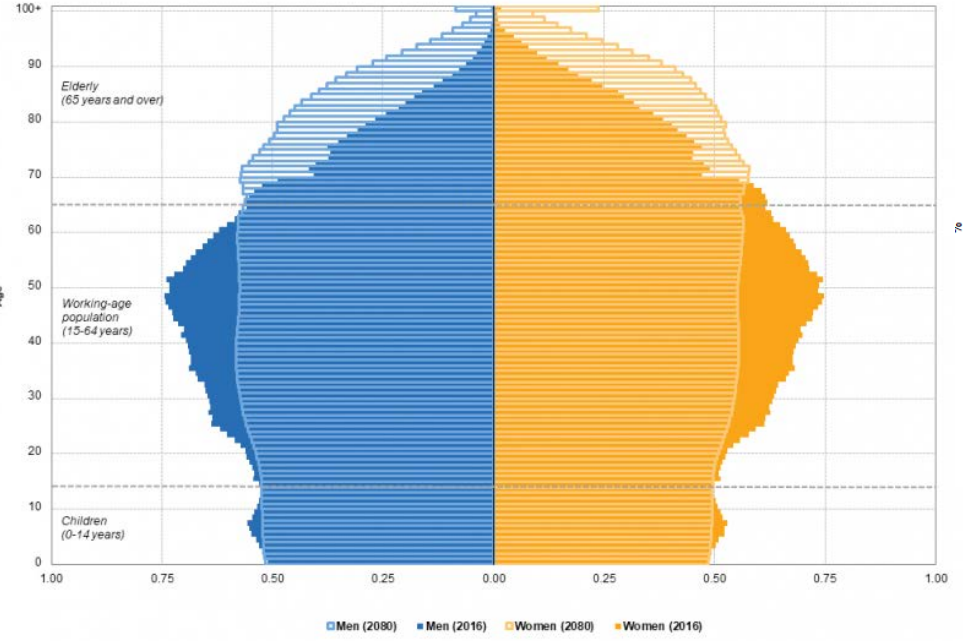
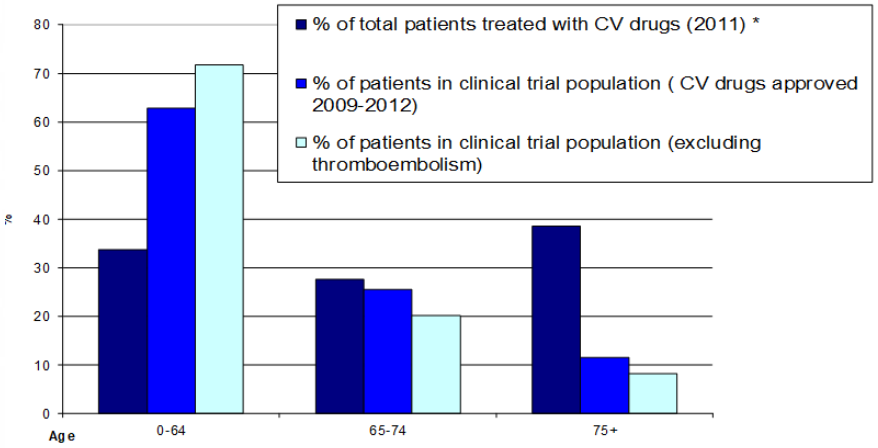
Older patients: hardly a subgroup

EU population pyramid, 2016 and 2080 Source: Eurostat



Cardiovascular drugs



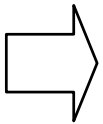
* Extracted from "L'uso dei farmaci in Italia 2011" and Italian census 2011

Source: Cerreta et al *Medicines for older people. Assessment and transparency at the European Medicines Agency regarding cardiovascular and antithrombotic medicinal products*

In 2019, more than one fifth (20.3 %) of the EU-27 population was aged 65 and over

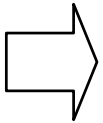
EMA Geriatric Medicines Strategy (2011):

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

Clinical Trials Regulation (EU) No 536/2014

Art 6

Member States will assess… “the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial **represent the population** to be treated…”

Representative: scientifically meaningful rather than equal in quantitative terms

Study on off-label use of medicinal products in the EU (European Commission, 2017)

…"The efficacy and safety of medicines are hardly investigated in elder, multimorbid patients. The **lack of clinical data obtained in elderly** is (still) **a matter of concern.**

Elderly form a **grey area.**

One could argue that medicinal products authorized for adults and used in the elderly is **in principle not off-label unless the SmPC** mentions:

- **upper age ranges**
- special **warnings**
- other **restrictions** for use in the elderly

Information in the EPAR (European Public Assessment Report)

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Adequate data is available for age range?

Frail patients included?

eCTD Module	Age 65-74 number / total number (all ages)	Age 75-84 number / total number (all ages)	Age 85+ number / total number (all ages)
Efficacy and Safety Studies			
Human PK Studies			

Epidemiology

CT inclusion/exclusion criteria

Co-morbidities

Concomitant medication

Safety signals particularly relevant?
(e.g. dizziness, delirium, orthostatic effects, falls, sedation, bleeding, urinary retention, loss of appetite).

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total ADRs				
Serious ADRs – Total				
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				

Appropriately grouped?

dizziness + falls + fractures + syncope reviewed together.

Anticholinergic effects?

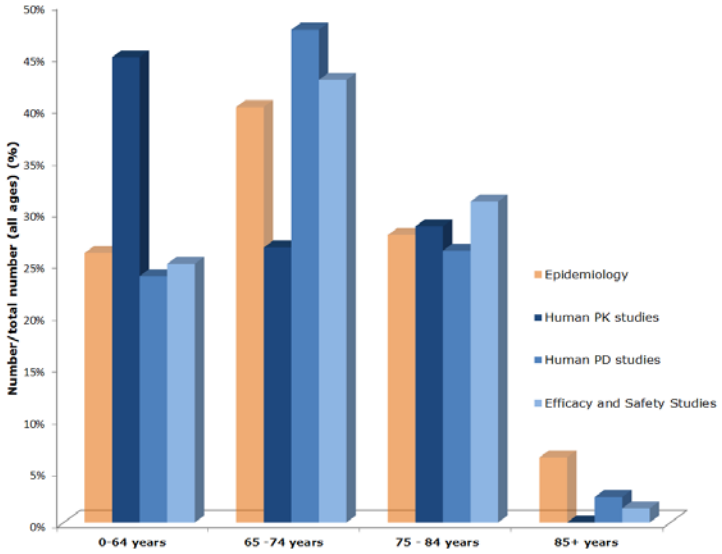
What is the most frequent situation?

Geriatric population is the largest users of medicines, but … **Data and prescriber guidance are usually missing for patients over 75 and/or with comorbidities and co-medications.**

SmPC guideline recommendation	Findings: actual SmPC wording on older patients
4.1 Indication	
It should be stated in which age groups the product is indicated, **specifying age limits**	Very rarely specified (generic "adults" includes elderly) - Indication not restricted
4.2 Posology	
The safety and efficacy have not been established No data are available Limited data are available	Found sometimes, (with age limits >65, 75, 85)
It **should not be used** because of efficacy or safety concerns.	**Other text** commonly used: - the use is not recommended - should be initiated with caution
4.3. Contraindications	
Safety data give rise to concerns Elderly patients have been **excluded** from studies on grounds of safety	Very rarely found
4.4 Warnings	
Patients populations **not studied** in clinical trials	Rarely found

Representativeness?
A cancer example

A prostate cancer drug
All looks well based on age



Sorafenib
(metastatic hepatocellular cancer)

RCT for approval:
Overall Survival gain: 2.8 months
(7.9 to 10.7 months)
population median age 65 years
ECOG: 0 or 1

Medicare data:
No survival gain vs propensity score
matched patients on best supportive care.
Median age: 70
CCI: 2 or more
Survival: 3 months

Prasad, JAMA oncology 2016

Frailty baseline characterization

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Regulatory guidance (**ICH E7**) categorises older patients on the basis of chronological age (65-74; 75-84; 85+).

Chronological age alone is a suboptimal predictor of susceptibility to adverse outcomes.

Is the clinical trial population **representative** of the **real world** population?

Are there any **validated and simple tools** for clinical trials or other clinical investigation (e.g. registry)?

EMA Committee for Medicinal Products for Human Use (CHMP) requested:

- Geriatric Expert Group to draft guidance on **frailty**.
- Quality Working Party to draft guidance of appropriateness of **packaging and formulations**

Points to consider on frailty: Evaluation instruments for baseline characterization of clinical trial populations

Scope: characterise clinical trial population at **baseline**, on **frailty** status, not only chronological age.

– *not* to measure *change*.
– *not* as a *screening* tool.
– *not* as an *outcome* measure.

SPPB (Short Physical Performance Battery) is the preferred tool.

Frailty status may then be used to inform on regulatory decision:

- differences in **benefit / risk** balance?
- specific **post- authorization studies** needed?

Link: https://www.ema.europa.eu/en/physical-frailty-instruments-baseline-characterisation-older-populations-clinical-trials

Reflection paper on the pharmaceutical development of medicines for use in the older population

This reflection paper describes aspects that medicines developers may consider when designing medicines for older people, such as selecting appropriate routes of administration and dosage forms, dosing frequency, excipients, container closure systems, devices and technologies, and user instructions in the product information.

Link: https://www.ema.europa.eu/en/pharmaceutical-development-medicines-use-older-population

Conclusions

- Population enrolled in clinical trials should be representative of the target population.
- A balance between feasibility / risk management/ “noise” needs to be struck
- Assessment of baseline frailty would allow a better characterization of the population enrolled in clinical studies, especially if a different risk-to-benefit ratio is possible.
- Real world evidence tools may offer a source of further insights (ADR underreported).

Evidence based treatment choices

Regulator should assess and inform appropriately

Physician/Applicant should support knowledge gain

Support enrolment of older patients

Develop new research instruments

Report Adverse reactions