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ORIGINAL ARTICLE

Under-representation of elderly in clinical trials: An analysis of the initial approval documents in the Food and Drug Administration database

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Aims: To evaluate the availability of pharmacokinetic, safety and efficacy analyses specifically targeted at elderly, prior to the authorization of drugs.

Methods: A cross-sectional, structured review of publicly available initial approval documents of Food and Drug Administration-approved drugs was performed. The 10 most frequently on-label prescribed drug classes, drugs with known pharmacokinetic differences in the elderly or drugs that are relatively contraindicated in elderly (e.g. anticholinergics or benzodiazepines) were included in the analyses.

Results: In total, 1129 unique active pharmaceutical ingredients were found eligible for the analyses, of these, 506 were found in the Food and Drug Administration database (45%). The initial approval documents were available for 182 drugs. For the majority of the drugs, the initial approval documents in the database showed information on pharmacokinetics in elderly (n = 113; 62%). Furthermore, over time, the availability of information with regard to elderly increased statistically significantly from 0% in the period 1970–1979 to 76% for the period 2010–2018. Information on safety and efficacy was less frequently present, i.e. 42% and 45%, respectively and, moreover, the availability of information did not improve over time.

Conclusion: The under-representation of elderly in clinical trials thereby challenging the external validity of benefit/risk assessments of launched drugs was confirmed. Priority should be given to a study population that is representative for the target population.

KEYWORDS

clinical trials, efficacy, elderly, pharmacokinetics, safety

1 | INTRODUCTION

The elderly represent a fast-growing majority of the population in the Netherlands and worldwide.[1,2] In Europe, 25% of the population is aged 60 years or over and is expected to grow to 35% in 2050.[3] Importantly, the representation of older people in clinical drug trials requires special attention, as it is known that pharmacokinetics and pharmacodynamics (and hence efficacy and safety) substantially change after the age of 75 years; albeit, not all drugs are similarly affected leading to increased variability in drug levels.[4] In literature, different physiological

The authors confirm that the PI for this paper is Rikje Ruiter.

parameters are discussed to affect absorption, distribution, metabolism and excretion of drugs during aging. For example, sarcopenia and increased percentage of fat tissue results in a different distribution volume.[5] With regard to metabolism, the total liver mass reduces with age and there is a lower capacity for phase 1 reactions through the cytochrome P-450 enzymes.[6,7] In contrast, conjugation reactions are not affected by ageing.[5] Also, the hepatic blood flow is lower, which results in a reduced first pass effect.[8] The renal function diminishes with age: there is reduced renal blood flow, diminished glomerular filtration rate and a reduced renal tubular secretory function.[5] It is generally accepted that of the pharmacokinetic parameters, absorption is least affected by age.[5] Pharmacodynamic changes in the elderly are the consequence of diminished reserve capacity or diseases of organ systems and changes in receptor number and affinity.[5] In addition, comorbidity associated polypharmacy is more common among elderly and consequently the risk of interactions as well as adverse drug reactions is higher.[9] These age-related differences may give rise to age-specific risk/benefit ratios for drugs in elderly.

The elderly consume the majority of prescribed medications and carry the largest burden of chronic diseases.[10] Their representation in clinical trials should reflect this. For this reason, in 1993, the International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use issued the ICH E7 guideline for the carrying out of studies in the geriatric population, stating that the trial population should represent the population that will consume the drug and should include a minimum percentage of older participants. The ICH E7 guideline was endorsed, among others, by the Food and Drug Administration (FDA) and pharmaceutical companies.[11] Nevertheless, previous reports described that elderly are generally under-represented in clinical studies in cardiology[12-17] and oncology[18-21] as they are excluded due to older age, multimorbidity or polypharmacy. Descriptive studies showed that in 30–40% of the original research papers in major medical journals, elderly people were excluded without justification.[22,23] Recent investigations carried out to evaluate the adherence to the ICH E7 guideline, showed that the proportion of the elderly in clinical trials is unacceptably low (1–9% in trials involving diseases not unique to old age).[24] This was confirmed by an evaluation of the clinical trial database (clinicaltrials.gov).[25] However, no investigation has systematically reviewed the available information on publicly available database of health care regulators.

In this study, we aimed to evaluate the availability of pharmacokinetic, safety and efficacy analyses specifically targeted at the elderly, prior to the authorization of the most frequently prescribed drug classes during the past years.

What is already known about this subject

- Under-representation of elderly in clinical trials has been described earlier, thereby challenging the external validity of benefit/risk assessments of launched drugs.
- Pharmacokinetic differences in the elderly may give rise to differences in safety and efficacy. Therefore, it is pivotal include geriatric patients in clinical trials of medical substances.

What this study adds

- This is the first cross sectional, structured research on availability of pharmacokinetic, safety and efficacy analyses of the publicly available initial approval documents of Food and Drug Administration-approved drugs.
- For the majority of the drugs, the initial approval documents showed information on pharmacokinetics in elderly, but information on safety and efficacy was missing.

2 | METHODS

2.1 | Design

A cross-sectional, structured assessment of publicly available initial approval documents of FDA-approved drugs was performed. To obtain marketing authorization for newly developed drugs, companies are required to deliver quality, safety and efficacy information about the drug.

2.2 | Drugs of interest

The following initial approval documents were assessed: those of frequently on-label prescribed drug classes, those of drugs with known pharmacokinetic differences in the elderly, or those of drugs that are relatively contraindicated in elderly (e.g. anticholinergics or benzodiazepines). The following most frequently described drug classes were selected: antihypertensive drugs, medication for pain, drugs used for mental health or nervous system disorders, antibacterial drugs, lipid regulators, glucose lowering drugs, respiratory drugs, antiulcer drugs and thyroid therapies based on IQVIA.[26] Furthermore, drugs with known large or small volumes of distribution and/or high or low hepatic clearance or renal excretion were included.[4] Last, drugs with relative contraindications in elderly (e.g. anticholinergics or benzodiazepines).[27]

2.3 | Assessment of information on pharmacokinetics, safety and efficacy

For these drug classes all available medical substances were extracted in December 2017 from the World Health Organization Anatomical Therapeutical Chemical Classification (ATC) index 2018.[28] All drugs selected for the analyses were included in Table S1. Subsequently, using the FDA drug database, initial approval documents were retrieved for all

selected drugs[29] during the period December 2017–March 2018. When initial approval documents were available, these were evaluated for availability of data on pharmacokinetics, efficacy and safety analyses. The availability of analyses in the geriatric population was assessed as sufficient or insufficient, based on thorough assessment of the complete initial approval document. Information was deemed sufficient if information on pharmacokinetics, efficacy and safety was present in adequate numbers (e.g. representative of the target population). *Adequate* was assessed in concordance with the ICH7 guideline: "geriatric patients should be included in the Phase 3 database (and in Phase 2, at the sponsor's option) in meaningful numbers." With regard to pharmacokinetic studies it is stated in the ICH7 guideline that "a pilot trial of limited size conducted under steady-state conditions to look for sizable differences between older and younger subjects or patients" can be performed and "a larger, single-dose pharmacokinetic study of sufficient size to permit statistical comparisons between geriatric and younger subjects' or patients' pharmacokinetic profiles is also acceptable." A pharmacokinetic screening approach as described in the ICH7 guideline was also deemed adequate.

Furthermore, the year of initial marketing approval was extracted. One researcher (Ri.R.) performed the inclusion and assessments. In case of uncertainty, a second researcher (Ro.R.) was consulted. A random sample of 10% (n = 18) was selected and double checked by the second researcher (Ro.R.), to ensure correct assessment of adequateness. Outcomes were numbers (%) of initial approval documents that contained adequate data on pharmacokinetics, efficacy and safety analyses.

2.4 | Statistical analyses

To assess whether the percentage of available initial approval documents significantly increased during a certain time frame, χ^2 test statistics were used, considering $P < .05$ statistically significant. Analyses were performed using SPSS statistics version 23.

3 | RESULTS

In the ATC database, 1129 unique active pharmaceutical ingredients were found for the analyses (Table S1). Of these, 506 medical substances were found in the FDA database (45%). The majority consisted of drugs for mental health or nervous system disorders (n = 132; 26%); followed by antibacterial drugs (n = 101; 20%) and respiratory drugs (n = 86; 17%). Seventy-one antihypertensive drugs were found (14%) and 39 glucose-lowering drugs (8%). All other drugs each comprised <5% of the total amount of drugs found in the FDA database (Figure 1).

Of the 506 medical substances, 182 (36%) initial approval documents were available (Table 1). Of these, the majority were drugs for mental health or nervous system disorders (n = 51; 28%); followed by glucose-lowering drugs (n = 32; 18%) and antibacterial drugs (n = 22; 12%). Twenty-one antihypertensive drugs were found (12%), 16 lipid-lowering drugs (9%) and 15 respiratory drugs (8%). Antiulcer drugs comprised 7% (n = 13) and all other drugs each comprised <5% of the total amount.

For the majority of the drugs, the initial approval documents in the database did show information on pharmacokinetics in elderly (n = 113; 62%). For 1 drug, it was explicitly stated that information on pharmacokinetics, safety and efficacy in elderly was not applicable (ivacaftor). Furthermore, over time, the availability of information on pharmacokinetics in elderly increased statistically significantly from zero in the period 1979–1979 to 76% (n = 32) in the period 2010–2018 (p = .02; Table 2). For safety and efficacy information in elderly, detailed information was present in respectively 77 and 81 documents (42% and 45%). In addition, the availability of information on safety and efficacy in elderly did not improve over time (p = 0.13 and 0.11, respectively).

4 | DISCUSSION

In this study the availability of pharmacokinetic, safety and efficacy analyses specifically targeted at the elderly, prior to the authorization of the most frequently prescribed drug classes was evaluated. Based on the available initial approval documents, it was concluded that 62% of the FDA documents included reports on pharmacokinetic analyses, and 42 and 45% on safety and efficacy analyses in the elderly. For the majority of the drugs, the initial approval documents were not available in the database; however, over time, the percentage of available initial approval documents, as well as the information on pharmacokinetics increased significantly. With regard to crucial data on safety and efficacy, presence of information specifically on elderly was insufficient and did not increase over time.

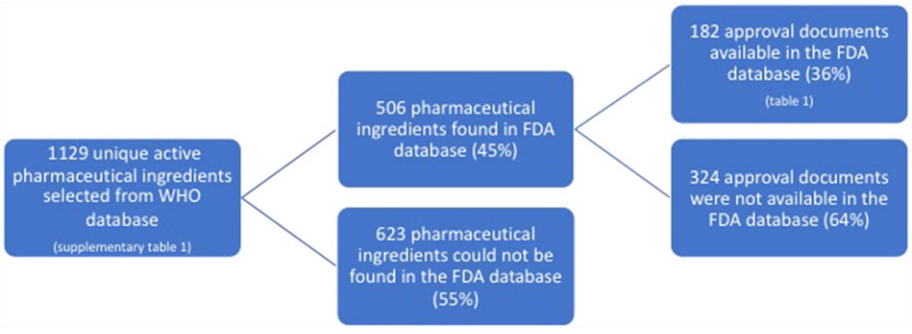

FIGURE 1 Flow diagram of the availability of initial approval documents in the Food and Drug Administration (FDA) database. WHO, World Health Organization

TABLE 1 Overview of the 182 substances included in the analyses (sorted on ATC code)

Number	ATC code	Generic product
1	A02BA01	Cimetidine
2	A02BA02	Ranitidine
3	A02BA03	Famotidine
4	A02BA04	Nizatidine
5	A02BB01	Misoprostol
6	A02BC01	Omeprazole
7	A02BC02	Pantoprazole
8	A02BC03	Lansoprazole
9	A02BC04	Rabeprazole
10	A02BC05	Esomeprazole
11	A02BC06	Dexlansoprazole
12	A02BX02	Sucralfate
13	A02BX05	Bismuth subcitrate
14	A10AB01	Insulin (inhalation)
15	A10AB02	Insulin (glargine)
16	A10AB03	Insulin (inhalation)
17	A10AB06	Insulin glulisine
18	A10AD04	Insulin lispro
19	A10AD06	Insulin degludec and insulin aspart
20	A10AE04	Insulin glargine
21	A10AE05	Insulin detemir
22	A10AE06	Insulin degludec
23	A10BA02	Metformin
24	A10BB02	Chlorpropamide
25	A10BB07	Glipizide
26	A10BB12	Glimepiride
27	A10BF01	Acarbose
28	A10BG01	Troglitazone
29	A10BG02	Rosiglitazone
30	A10BG03	Pioglitazone
31	A10BH01	Sitagliptin
32	A10BH03	Saxagliptin
33	A10BH04	Alogliptin
34	A10BH05	Linagliptin
35	A10BJ01	Exenatide
36	A10BJ02	Liraglutide
37	A10BJ03	Lixisenatide
38	A10BJ04	Albiglutide
39	A10BJ05	Dulaglutide
40	A10BJ06	Semaglutide
41	A10BK01	Dapagliflozin
42	A10BK02	Canagliflozin
43	A10BK03	Empagliflozin
44	A10BX03	Nateglinide
45	A10BX05	Pramlintide
46	C03DA04	Eplerenone
47	C03XA01	Tolvaptan
48	C03XA02	Conivaptan
49	C04AB01	Phentolamine
50	C07AB09	Esmolol
51	C07AB12	Nebivolol
52	C07AG02	Carvedilol
53	C08CA01	Amlodipine
54	C08CA02	Felodipine
55	C08CA03	Isradipine
56	C08CA16	Clevidipine
57	C09AA02	Enalapril
58	C09AA03	Lisinopril
59	C09AA10	Trandolapril
60	C09AA13	Moexipril
61	C09CA02	Eprosartan
62	C09CA03	Valsartan
63	C09CA04	Irbesartan
64	C09CA06	Candesartan
65	C09CA07	Telmisartan
66	C09CA08	Olmesartan medoxomil
67	C09CA09	Azilsartan medoxomil
68	C09XA02	Aliskiren
69	C10AA01	Simvastatin
70	C10AA02	Lovastatin
71	C10AA03	Pravastatin
72	C10AA04	Fluvastatin
73	C10AA05	Atorvastatin
74	C10AA06	Cerivastatin
75	C10AA07	Rosuvastatin
76	C10AA08	Pitavastatin
77	C10AB05	Fenofibrate
78	C10AB11	Choline fenofibrate
79	C10AC04	Colesevelam
80	C10AX09	Ezetimibe
81	C10AX11	Mipomersen
82	C10AX12	Lomitapide
83	C10AX13	Evolocumab
84	C10AX14	Alirocumab
85	G04BD07	Tolterodine
86	H03AA01	Levothyroxine sodium
87	J01AA12	Tigecycline
88	J01DD15	Cefdinir
89	J01DD16	Cefditoren
90	J01DE01	Cefepime
91	J01DH02	Meropenem
92	J01DH03	Ertapenem
93	J01DH04	Doripenem
94	J01DI02	Ceftaroline fosamil
95	J01FA13	Dirithromycin
96	J01FA15	Telithromycin
97	J01MA12	Levofloxacin

(Continues)

(Continues)

TABLE 1 (Continued)

Number	ATC code	Generic product
98	J01MA13	Trovafloxacin
99	J01MA14	Moxifloxacin
100	J01MA15	Gemifloxacin
101	J01MA16	Gatifloxacin
102	J01XA03	Telavancin
103	J01XA04	Dalbavancin
104	J01XA05	Oritavancin
105	J01XD02	Tinidazole
106	J01XX08	Linezolid
107	J01XX09	Daptomycin
108	J01XX11	Tedizolid
109	M01AH01	Celecoxib
110	N02AA05	Oxycodone
111	N02AB03	Fentanyl
112	N02AX06	Tapentadol
113	N02BG08	Ziconotide
114	N02CC02	Naratriptan
115	N02CC03	Zolmitriptan
116	N02CC04	Rizatriptan
117	N02CC05	Almotriptan
118	N02CC06	Eletriptan
119	N02CC07	Frovatriptan
120	N03AF02	Oxcarbazepine
121	N03AF03	Rufinamide
122	N03AF04	Eslicarbazepine
123	N03AG04	Vigabatrin
124	N03AG06	Tiagabine
125	N03AX11	Topiramate
126	N03AX14	Levetiracetam
127	N03AX15	Zonisamide
128	N03AX16	Pregabalin
129	N03AX18	Lacosamide
130	N03AX22	Perampanel
131	N03AX23	Brivaracetam
132	N04 BC04	Ropinirole
133	N04 BC05	Pramipexole
134	N04 BC06	Cabergoline
135	N04 BC07	Apomorphine
136	N04 BC09	Rotigotine
137	N04BD02	Rasagiline
138	N04BD03	Safinamide
139	N04BX01	Tolcapone
140	N04BX02	Entacapone
141	N05AE04	Ziprasidone
142	N05AE05	Lurasidone
143	N05AH03	Olanzapine
144	N05AH04	Quetiapine
145	N05AH05	Asenapine
146	N05AX08	Risperidone
147	N05AX12	Aripiprazole
148	N05AX13	Paliperidone
149	N05AX14	Iloperidone
150	N05AX15	Cariprazine
151	N05AX16	Brexpiprazole
152	N05AX17	Pimavanserin
153	N05BA09	Clobazam
154	N05CF02	Zolpidem
155	N05CF03	Zaleplon
156	N05CF04	Eszopiclone
157	N05CH02	Ramelteon
158	N05CH03	Tasimelteon
159	N05CM18	Dexmedetomidine
160	N05CM19	Suvorexant
161	N06AB04	Citalopram
162	N06AB10	Escitalopram
163	N06AX17	Milnacipran
164	N06AX21	Duloxetine
165	N06AX23	Desvenlafaxine
166	N06AX24	Vilazodone
167	N06AX26	Vortioxetine
168	R01AA04	Phenylephrine
169	R01AD13	Ciclesonide
170	R03AC13	Formoterol
171	R03AC18	Indacaterol
172	R03AC19	Olodaterol
173	R03BB04	Tiotropium bromide
174	R03BB05	Aclidinium bromide
175	R03BB07	Umeclidinium bromide
176	R03DC03	Montelukast
177	R03DX05	Omalizumab
178	R06AX17	Ketotifen
179	R06AX24	Epinastine
180	R06AX27	Desloratadine
181	R07AX01	Nitric oxide
182	R07AX02	Ivacaftor

(Continues)

TABLE 1 (Continued)

Our results are in line with earlier studies on under-representation of the elderly in (pre-authorization) trials and published reports.[12,13,18,22-25] It was reported that only 3 of the 155 clinical trials on 4 widely prescribed drugs were exclusively designed for patients aged 65 years and older.[30] Moreover, a recent assessment of all performed clinical trials in 2012 revealed that only 2% of the randomized controlled trials were designed for elderly aged 65 and over.[31]

Unfortunately, we have shown that despite efforts to include elderly patients in clinical drug trials, under-representation of elderly patients is still present, which challenges the external validity of benefit/risk assessments of launched drugs and leads to the phenomenon of off label prescribing in old patients.[32] With regard to elderly, adequate representation of the targeted population in clinical trials is

TABLE 2 Availability of information on pharmacokinetics, safety or efficacy with regard to elderly in the initial approval documents in the Food and Drug Administration database for the 10 most frequently prescribed drug classes, drugs with known large or small volumes of distribution, and/or high or low hepatic clearance or renal excretion, or which are relatively contraindicated in elderly per time period

	Before 1950	1950–1959	1960–1969	1970–1979	1980–1989	1990–1999	2000–2009	2010 onwards	Total
Number of available initial approval documents	0	1	0	2	9	59	69	42	182
Information on pharmacokinetics with regard to elderly sufficient, *n* (%)	NA	0 (0)	NA	0 (0)	1 (11)	36 (61)	44 (64)	32 (76)	113 (62)
Information on safety with regard to elderly sufficient, *n* (%)	NA	1 (100)	NA	0 (0)	4 (44)	19 (32)	30 (43)	23 (55)	77 (42)
Information on efficacy with regard to elderly sufficient, *n* (%)	NA	1 (100)	NA	0 (0)	4 (44)	20 (34)	32 (46)	24 (57)	81 (45)

NA, not available.

of pivotal importance as pharmacokinetic differences may give rise to differences in safety and efficacy. However, there are differences in opinion on this issue between EU countries leading to differences in clinical trial regulations and practice in older people, further complicating the adequate inclusion of elderly in clinical trials.[16] Efforts have been made to overcome the underrepresentation of the elderly in clinical research. The updated ICH E7 guideline emphasizes the need for additional short- and long-term safety data, adapted age-specific endpoints and subjective outcomes such as quality of life. Moreover, the population under research should reflect the population at which the drug under investigation is aimed. Unfortunately, no specific percentage can be given as the percentage of elderly in the target population differs per drug. Nevertheless, efforts should be made to include patients aged >80 years with different degrees of comorbidity and frailty.[33] For example, it was recommended to include older people in phase 1 clinical trials on gynaecological cancers, as they have similar toxicity profiles compared to their younger counterpart.[34] However, including elderly in clinical trials remains challenging: given the presence of protocol restrictions (e.g. exclusion criteria on age, polypharmacy and multimorbidity), many elderly must be screened before 1 study participant can be enrolled.[30]

One of the major drawbacks of this study is that it could not be verified which specific older patients in terms of age, ethnicity, sex and comorbidities were included in the clinical trials. This is important as the elderly population included in the assessed initial approval documents could have consisted of relatively healthy elderly with 1 disease, thus not being representative of the target population of elderly which the drugs are using namely those elderly with multiple comorbidities and polypharmacy.[33] Furthermore, the presence of information on pharmacokinetic studies could only be quantitatively assessed and not qualitatively. The available information was highly variable per assessed molecular entity; for example, different definitions of *elderly* were used, and information on *numbers* of elderly in clinical trials was missing frequently. As noticed in the methods section, the ICH7 guideline was used to deem whether numbers of included elderly were adequate, a random sample (10%) of the assessed reports was double checked to verify correct assessment of adequateness. Also, pages of the assessed initial approval reports were regularly withdrawn for confidentiality reasons of the submitting company. Furthermore, there is no way to determine whether all data submitted to the FDA are available in the online published documents. Lastly, not all pharmaceutical ingredients were found as drugs in the FDA database, which probably leads to nondifferential misclassification.

To our knowledge, this is the first study to assess the presence of information on pharmacokinetics, safety and efficacy in initial approval documents accessible in the FDA database. During the period 1927–2013, a total of 1453 drugs obtained FDA approval and the FDA still approves dozens of drugs each year.[35] However, an analysis on the availability of pre-authorization information on pharmacokinetics, safety and efficacy in elderly in the FDA database has not yet been performed. In a methodological guideline on the use of FDA documents for evidence syntheses, the benefit of using aggregated clinical trial information from FDA documents for the interpretation of data was emphasized, as it is less biased than published trial information.[36] Nevertheless, since 2010, there is still insufficient data available on safety and efficacy of the most frequently prescribed drugs in the elderly. Knowing that older people account for the majority of all drug consumers, priority should be given to clinical research with a study population that is representative for the actual patient population.[10]

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Ri.R., J.B. and Ro.R. designed the study. Ri.R. and Ro.R. performed the analyses. Ri.R., J.B. and Ro.R. wrote the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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