

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

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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 cardiology¹²⁻¹⁷ and oncology¹⁸⁻²¹ 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.

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

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.

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 Therapeutic 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 drugs²⁹ 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.

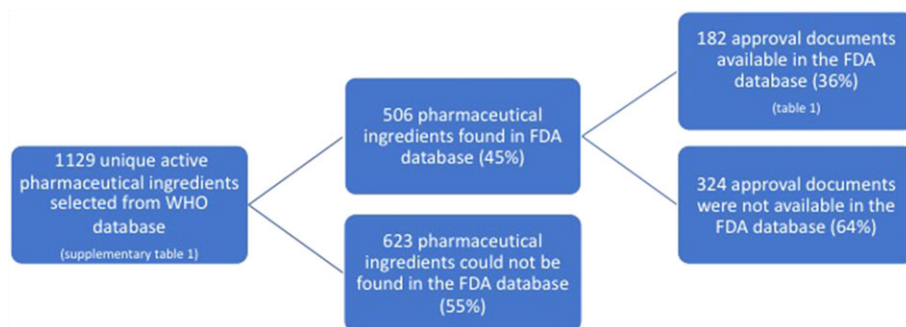


FIGURE 1 Flow diagram of the availability of initial approval documents in the Food and Drug Administration (FDA) database. WHO, World Health Organization

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 |

(Continues)

TABLE 1 (Continued)

| Number | ATC code | Generic product |
|--------|----------|----------------------|
| 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)

TABLE 1 (Continued)

| Number | ATC code | Generic product |
|--------|----------|-----------------|
| 98 | J01MA13 | Trovafloracin |
| 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 |

(Continues)

TABLE 1 (Continued)

| Number | ATC code | Generic product |
|--------|----------|----------------------|
| 147 | N05AX12 | Aripiprazole |
| 148 | N05AX13 | Paliperidone |
| 149 | N05AX14 | lloperidone |
| 150 | N05AX15 | Cariprazine |
| 151 | N05AX16 | Brexiprazole |
| 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 |

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, <i>n</i> (%) | NA | 0 (0) | NA | 0 (0) | 1 (11) | 36 (61) | 44 (64) | 32 (76) | 113 (62) |
| Information on safety with regard to elderly sufficient, <i>n</i> (%) | NA | 1 (100) | NA | 0 (0) | 4 (44) | 19 (32) | 30 (43) | 23 (55) | 77 (42) |
| Information on efficacy with regard to elderly sufficient, <i>n</i> (%) | 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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