Regulatory Perspectives on Developing Drug Products for Older Adults in the United States

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Disclaimer

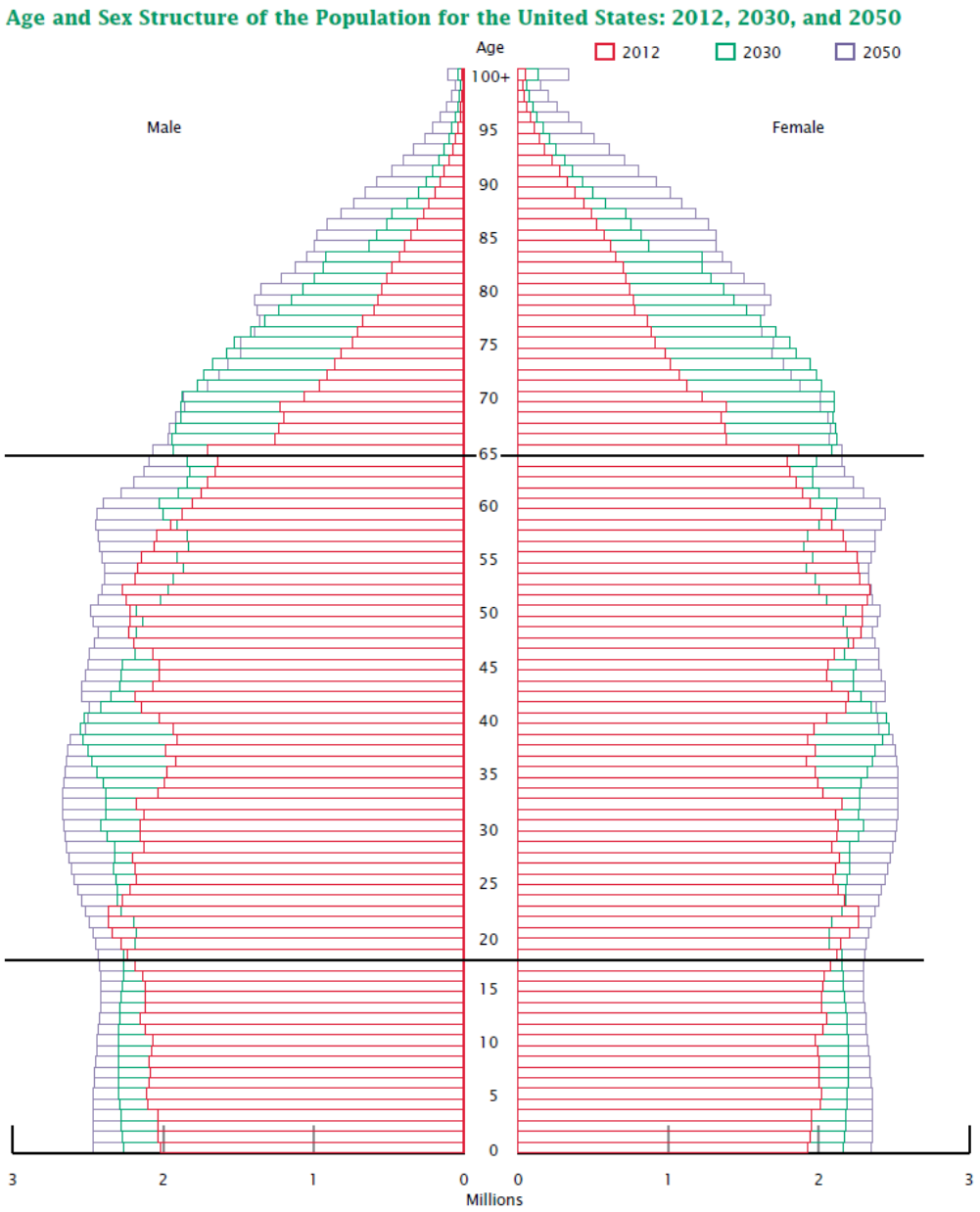
- **This presentation reflects the views and opinions of the presenter and does not represent the views, opinions, and policies of the Food and Drug Administration.**
- **This presenter declares no conflict of interest.**

Outline

- Demographics and background
- Development of regulations, guidelines, and guidances in the US
- Older adults in clinical trials
- Regulatory development in other regions
- Take-home messages
- Acknowledgements

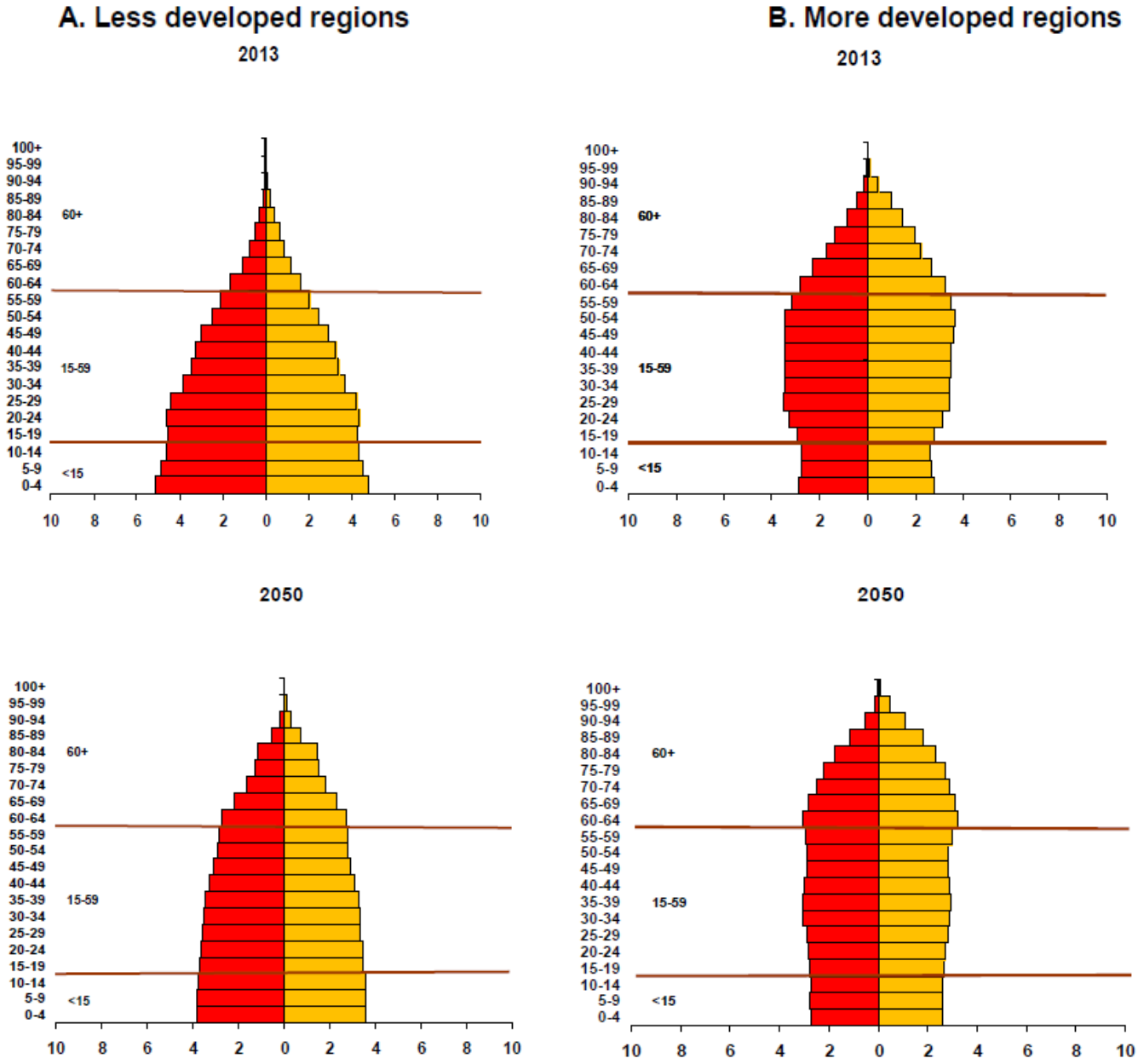
3

The US Is Aging



Klotz. *Drug Metab Rev* 2009

The World Is Aging

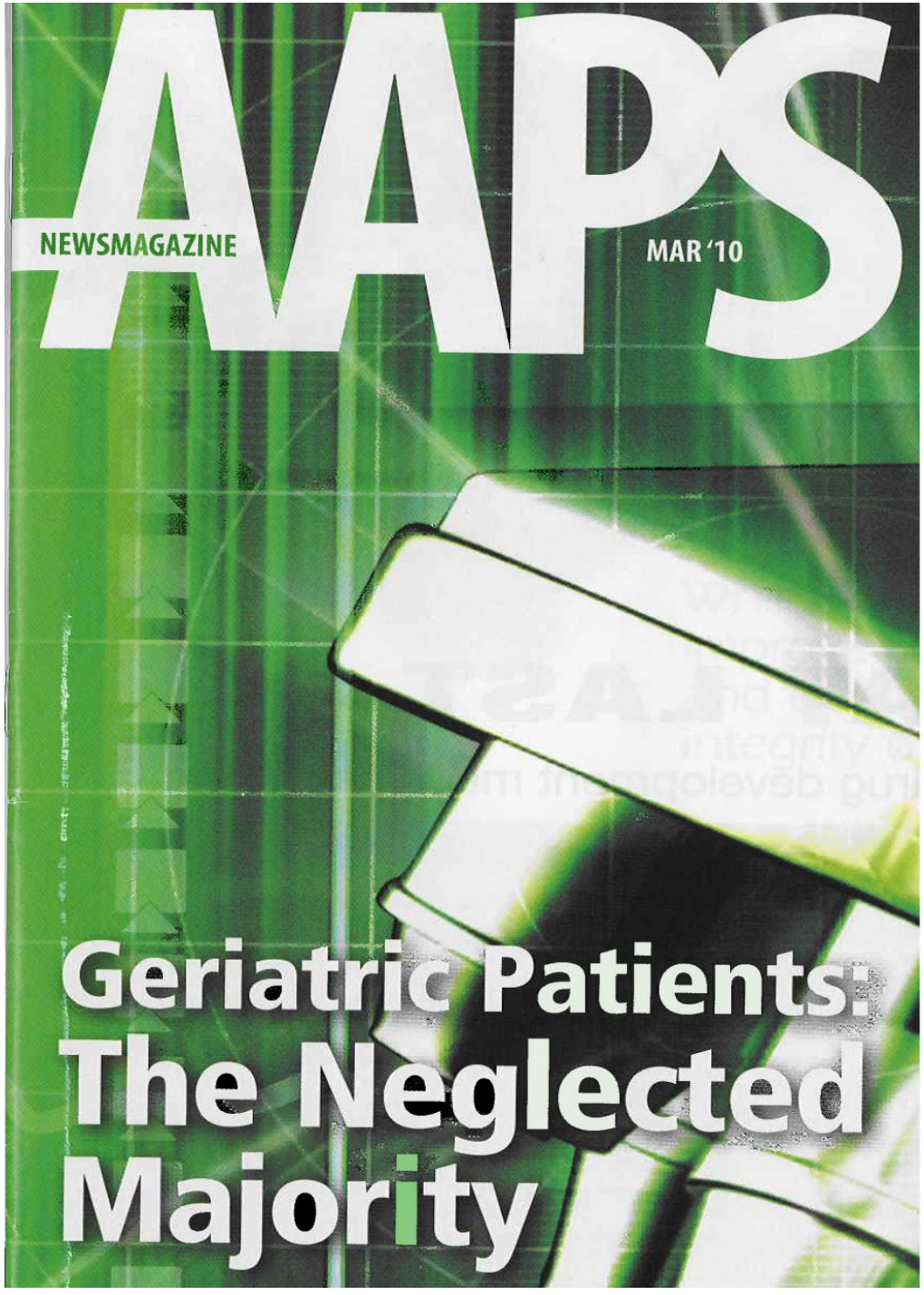


United Nations,
World Population Ageing 2013

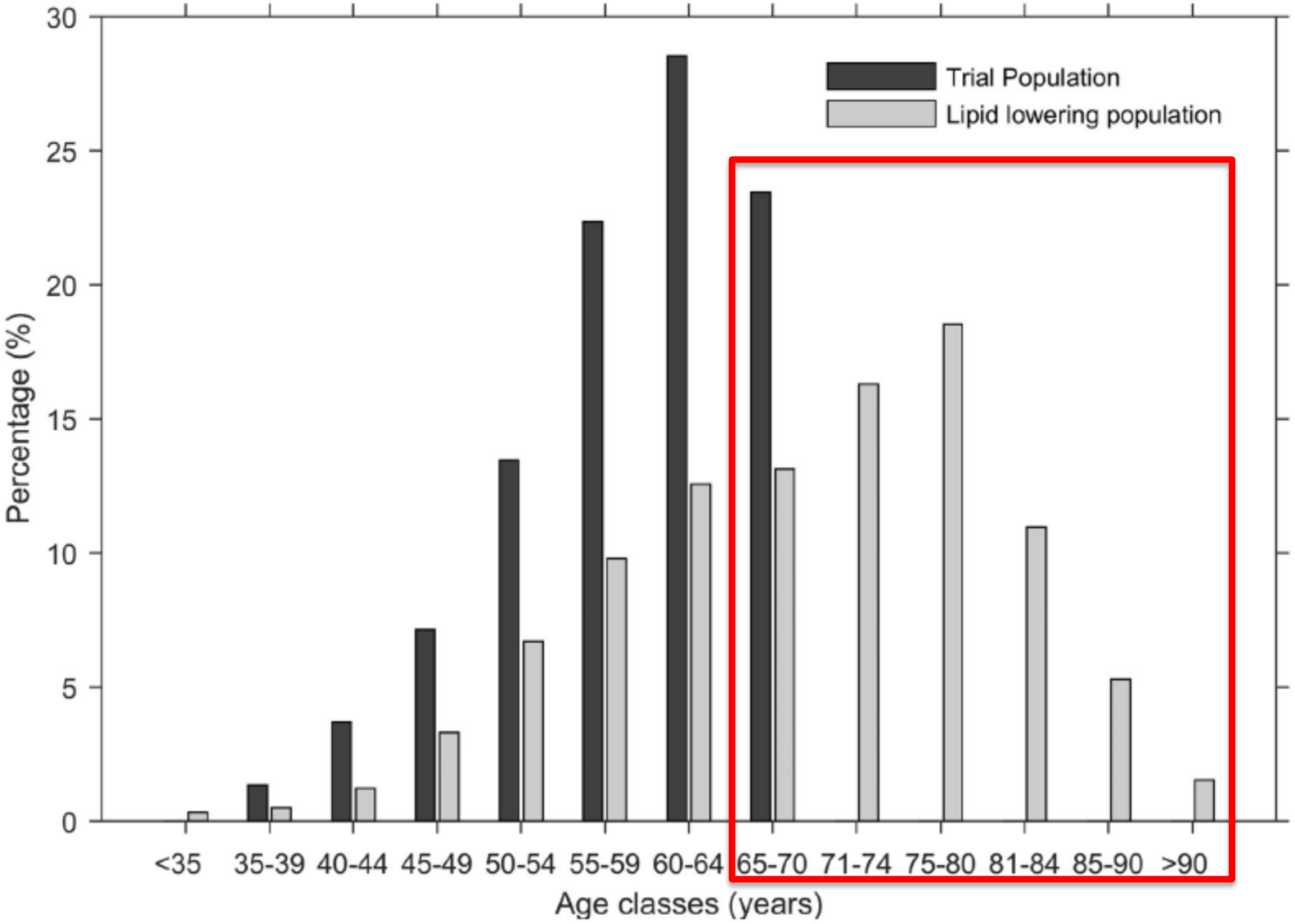
Prescription Drug Consumption (≥ 65 years)

Year	Population, million	Population, %	Rx Consumption, %
US			
2000	35	12.4	25
2030	71	20	40
World			
2030	973	12	-
2050	-	20	-

Schwartz & Abernethy *Clin Pharmacol Ther* 2009;
An Aging World: 2015, US Census Bureau


AAPS
NEWSMAGAZINE
MAR '10
Geriatric Patients:
The Neglected
Majority

Simvastatin Trial Patients Differ from Actual Patients



Schlender et al. *Eur J Pharm Sci* 2018

Regulatory Development in the US

Geriatric Data Required since Enactment of NDA Content and Format Regulation

21 CFR Ch. I (4-1-86 Edition)
Subpart B—Applications

§ 314.50 Content and format of an application.

(5) *Clinical data section.* A section describing the clinical investigations of the drug, including the following:

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT

OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION July 1988

C. Clinical Pharmacology [21 CFR 314.50(d)(5)(i)]

1. Types of studies to be included in this section are:

a. Studies of absorption, distribution, metabolism, and excretion (ADME studies). The full reports of bioavail ability and pharmacokinetic studies are included in the Human Pharmacokinetic and Bioavailability Section [21 CFR 314.50(d)(3)], but the Clinical Pharmacology section should summarize those results, emphasizing findings of particular importance to the design of clinical trials, the basis for dosage selection, and optimal use of the drug. The section should include investigations of drug-drug interactions (effects on the pharmacokinetics of the new drug by another drug or on the pharmacokinetics of any other drug by the new drug) and investigations of effects of other diseases or conditions (renal disease, hepatic disease, hypochlorhydria) or demographic characteristics (age, race, sex) on pharmacokinetics. Pharmacokinetic implications of blood level determinations carried' out during controlled or uncontrolled trials, including phase 3 "pharmacokinetic screen" measurements, should be considered in this section.

to dose-interval, to duration of treatment, to cumulative dose or dose-exposure time product in some cases, to demographic characteristics such as age, or to other baseline features, such as renal function, and to blood level, if blood level data are available. As in the case of similar analyses of effectiveness, minor differences should be described but need not be analyzed with rigorous statistical methods. It is substantial differences, potentially useful to the prescribing physician, that are sought in such analyses. If a finding of "no difference," e.g., no evidence of an increasing rate of an important adverse event with age, is considered important or a potential labeling claim, there should be an analysis of the statistical power or confidence limits of the finding.

US Guideline

GUIDELINE FOR THE STUDY OF DRUGS LIKELY TO BE USED IN THE ELDERLY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

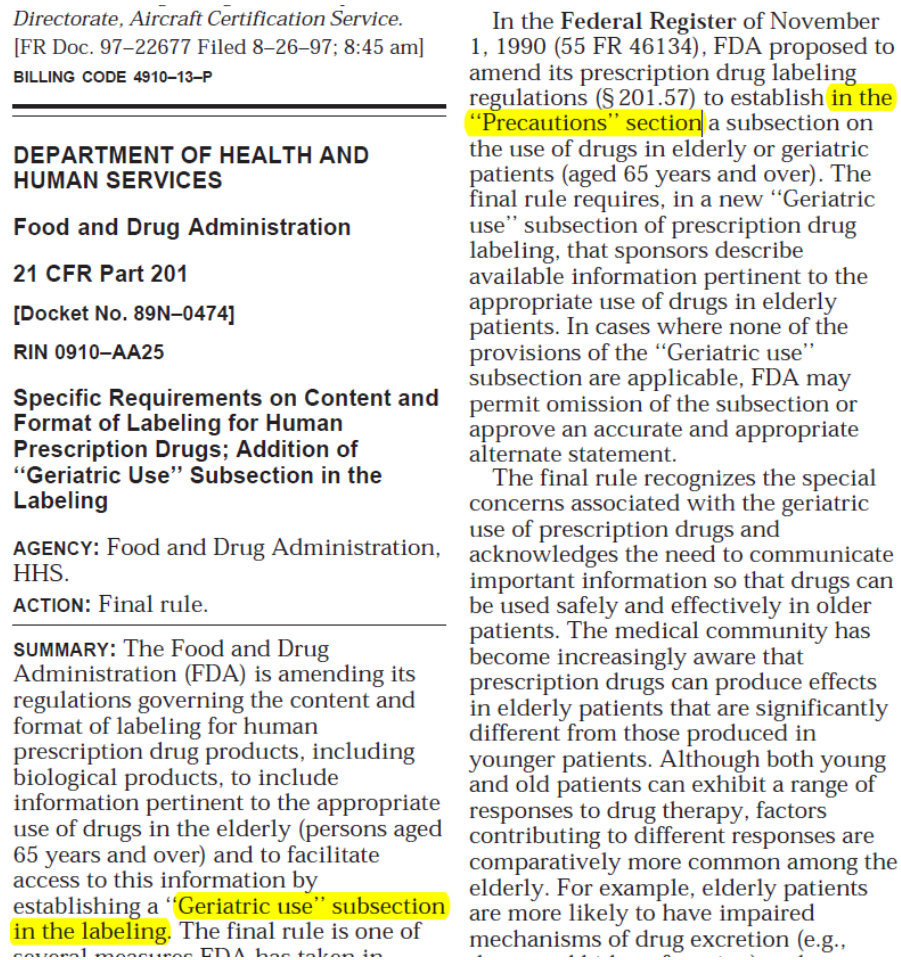
1989 ed

- Drugs should be studied in all age groups, including the geriatric, for which they will have significant utility.
- Attempt to include > 75 years and concomitant illnesses
- PK studies for:
  - renal impairment
  - hepatic impairment
  - PK screen
  - drug-disease and drug-drug interactions
- PD studies

ICH E7 Guideline

- Arbitrary geriatric population ≥ 65 years; important ≥ 75 years
- Suggested to include "meaningful number" of geriatric patients in Phase 3 (and Phase 2 optional) trials
- Disease not unique to, but present in older adults, a minimum of 100 patients to detect difference
- Drug interaction studies (CYP isozymes)
- Updated with Q&A

Geriatric Use Subsection in Precaution



Directorate, Aircraft Certification Service.
[FR Doc. 97–22677 Filed 8–26–97; 8:45 am]
BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 89N–0474]

RIN 0910–AA25

Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format of labeling for human prescription drug products, including biological products, to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and over) and to facilitate access to this information by establishing a "Geriatric use" subsection in the labeling. The final rule is one of several measures FDA has taken in

In the **Federal Register** of November 1, 1990 (55 FR 46134), FDA proposed to amend its prescription drug labeling regulations (§ 201.57) to establish in the "Precautions" section a subsection on the use of drugs in elderly or geriatric patients (aged 65 years and over). The final rule requires, in a new "Geriatric use" subsection of prescription drug labeling, that sponsors describe available information pertinent to the appropriate use of drugs in elderly patients. In cases where none of the provisions of the "Geriatric use" subsection are applicable, FDA may permit omission of the subsection or approve an accurate and appropriate alternate statement.

The final rule recognizes the special concerns associated with the geriatric use of prescription drugs and acknowledges the need to communicate important information so that drugs can be used safely and effectively in older patients. The medical community has become increasingly aware that prescription drugs can produce effects in elderly patients that are significantly different from those produced in younger patients. Although both young and old patients can exhibit a range of responses to drug therapy, factors contributing to different responses are comparatively more common among the elderly. For example, elderly patients are more likely to have impaired mechanisms of drug excretion (e.g.,

- **Older adults are main users of medications. They are more prone to drug effects and adverse drug reactions.**
- **The FDA established the "Geriatric Use" subsection as part of the Precaution section of labeling for human prescription drug and biological products to provide pertinent information on the use of these products in older adults (≥ 65 years).**

Federal Register August 27, 1997 (62 FR 45313)

The "Demographic Rule"

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312 and 314

[Docket No. 95N–0010]

Investigational New Drug Applications and New Drug Applications

AGENCY: Food and Drug Administration, HHS.

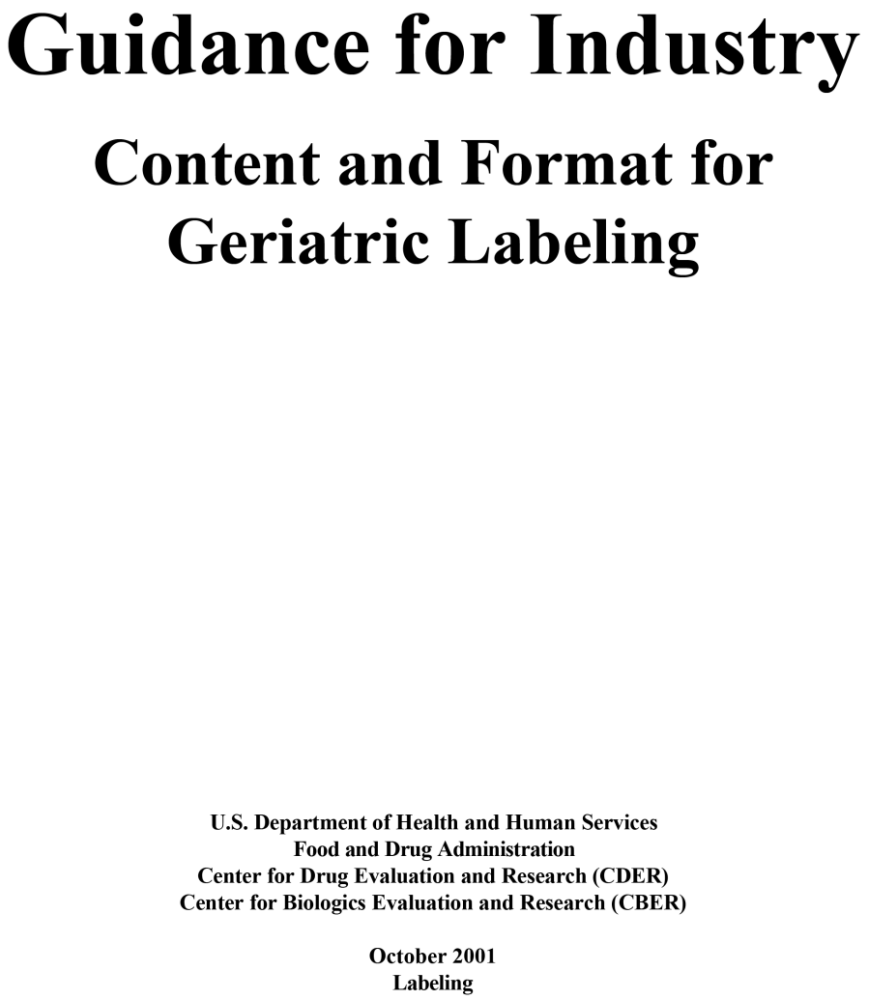
ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations pertaining to new drug applications (NDA's) to clearly define in the NDA format and content regulations the requirement to present effectiveness and safety data for important demographic subgroups, specifically gender, age, and racial subgroups. FDA also is amending its regulations pertaining to investigational new drug applications (IND's) to require sponsors to tabulate in their annual reports the numbers of subjects enrolled to date in clinical studies for drug and biological products according to age group, gender, and race. This action is intended to alert sponsors as early as possible to potential demographic deficiencies in enrollment that could lead to avoidable deficiencies later in the NDA submission. This rule does not address the requirements for the conduct of clinical studies and does not require sponsors to conduct additional studies or collect additional data. It also does not require the inclusion of a particular number of individuals from specific subgroups in any study or overall. The rule refers only to the presentation of data already collected.

DATES: Effective August 10, 1998. Submit written comments on the information collection provisions of this final rule by April 13, 1998.

Federal Register 1998;63:6854-6862

Guidance on Geriatric Labeling


Guidance for Industry

Content and Format for Geriatric Labeling

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2001
Labeling

- **This guidance discusses:**
  - **Who should submit revised labeling**
  - **Implementation dates**
  - **Description of the regulation and optional standard language in proposed labeling**
  - **Content and format for geriatric labeling**
  - **Applicability of user fees to geriatric labeling supplements**

Move "Geriatric Use" to Section 8.5

(1) Prescription drug labeling described in §201.100(d) must contain the specific information required under §201.57(a), (b), and (c) under the following headings and subheadings and in the following order:

Highlights of Prescribing Information
- Product Names, Other Required Information
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

Full Prescribing Information: Contents

Full Prescribing Information
- Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 Dosage Forms and Strengths
- 4 Contraindications
- 5 Warnings and Precautions
- 6 Adverse Reactions
- 7 Drug Interactions
- 8 Use in Specific Populations
  - 8.1 Pregnancy
  - 8.2 Labor and delivery
  - 8.3 Nursing mothers
  - 8.4 Pediatric use
  - 8.5 Geriatric use
- 9 Drug Abuse and Dependence
  - 9.1 Controlled substance
  - 9.2 Abuse
  - 9.3 Dependence
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology
  - 12.1 Mechanism of action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 Nonclinical Toxicology
  - 13.1 Carcinogenesis, mutagenesis, impairment of fertility
  - 13.2 Animal toxicology and/or pharmacology
- 14 Clinical Studies
- 15 References
- 16 How Supplied/Storage and Handling
- 17 Patient Counseling Information

71 FR 3986, Jan. 24, 2006; CFR Title 21, Sec. 201.56

Guidance for Industry

Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements

Section 8.5

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2013
Labeling

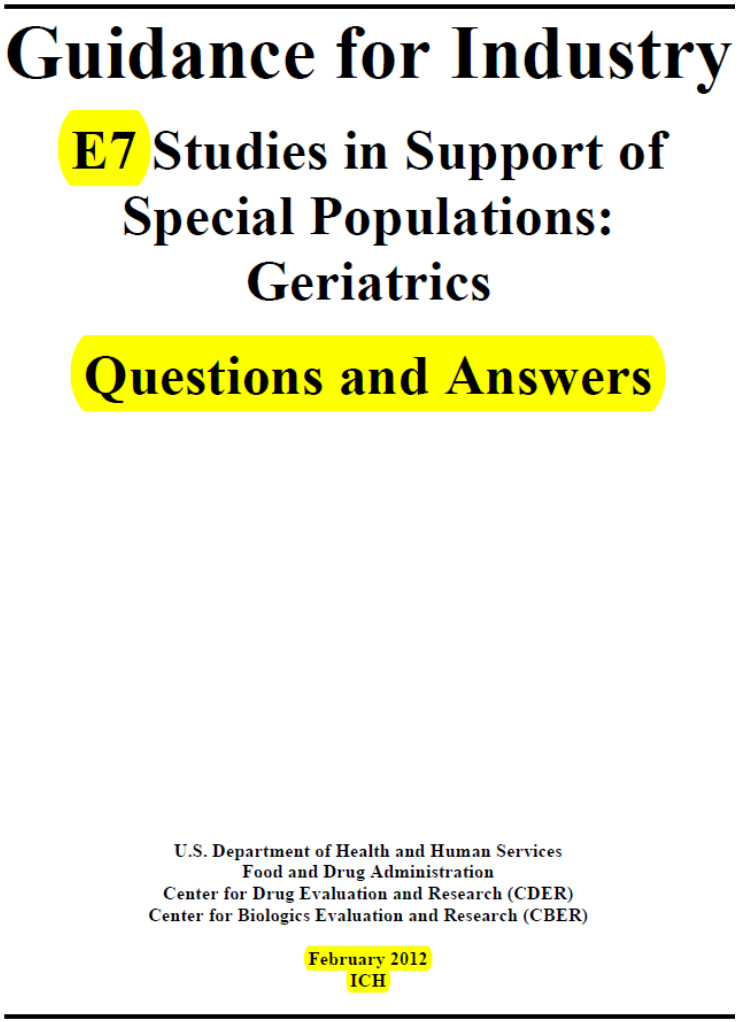
Contains Nonbinding Recommendations

APPENDIX C — Reorganizing Labeling Sections

Location in Old Format	→	Location in FPI in PLR Format
Boxed Warning	→	Boxed Warning
Description	→	Description
Clinical Pharmacology	→	Clinical Pharmacology
Indications and Usage	→	Indications and Usage
Contraindications	→	Contraindications
Warnings	→	Warnings and Precautions
Precautions		
General	→	Warnings and Precautions
Information for Patients	→	Patient Counseling Information
Laboratory Tests	→	Warnings and Precautions
Drug Interactions	→	Drug Interactions
Drug/Laboratory Test Interactions	→	Warnings and Precautions
Carcinogenesis, Mutagenesis, Impairment of Fertility	→	Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)
Pregnancy	→	Use in Specific Populations (Pregnancy)
Labor and Delivery	→	Use in Specific Populations (Labor and Delivery)
Nursing Mothers	→	Use in Specific Populations (Nursing Mothers)
Pediatric Use	→	Use in Specific Populations (Pediatric Use)
Geriatric Use	→	Use in Specific Populations (Geriatric Use)
Adverse Reactions	→	Adverse Reactions
Drug Abuse and Dependence	→	Drug Abuse and Dependence
Overdosage	→	Overdosage
Dosage and Administration	→	Dosage and Administration
How Supplied	→	Dosage Forms and Strengths
	→	How Supplied/Storage and Handling
Animal Pharmacology and/or Animal Toxicology	→	Nonclinical Toxicology (Animal Toxicology and/or Pharmacology)
Clinical Studies	→	Clinical Studies
References	→	References

PLR = Physician Labeling Rule

ICH E7 Update



- 100 patients are unlikely to be sufficient (aging Baby Boomers); include representative number of older adult patients
- Present data for 4 age groups to assess consistency of treatment efficacy and safety with non-older adult patients:
  - < 65
  - 65 – 74
  - 75 – 84
  - ≥ 85
- Emphasize studying patients ≥ 75 years of age.
- Avoid arbitrary upper age limits in clinical trials.
- Encourage inclusion of patients with concomitant illnesses.
- Prefer inclusion of older adult patients in the pivotal Phase 3 trials, not in separate trials.
- Study PK of older adult patients:
  - Entire spectrum of the older adult patient population to identify age-related differences not explained by other factors (renal and weight)
  - If enough number of patients in different age ranges (including patients ≥ 65 and ≥ 75 years) is included in the clinical trials, then population PK analysis could provide such data.
  - Or, a specific PK study comparing non-older adult and older adult participants in the same study (matched for relevant covariates such as weight and sex) could be performed.

Cerreta et al. *J Nutr Health Aging* 2015

FDASIA's Section 907

SEC. 907. REPORTING OF INCLUSION OF DEMOGRAPHIC SUBGROUPS IN CLINICAL TRIALS AND DATA ANALYSIS IN APPLICATIONS FOR DRUGS, BIOLOGICS, AND DEVICES.

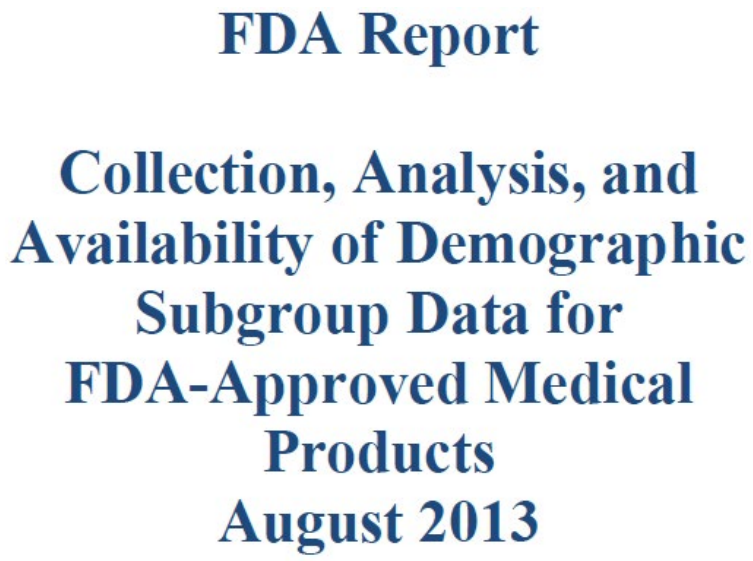
(a) REPORT.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this Act, the Secretary, acting through the Commissioner, shall publish on the Internet Web site of the Food and Drug Administration a report, consistent with the regulations of the Food and Drug Administration pertaining to the protection of sponsors' confidential commercial information as of the date of enactment of this Act, addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to the Food and Drug Administration, and shall provide such publication to Congress.

FDASIA = Food and Drug Administration Safety and Innovation Act
In 2012, the Section 907 of FDASIA directed the FDA to issue a report within 1 year and an action plan in the following year to Congress.

PUBLIC LAW 112–144—JULY 9, 2012 126 STAT. 1093

The 2013 FDA Report to Congress



- **Describes the demographics and subset analyses for 72 approved applications in 2011 from:**
  - **CDER (24 drugs + 6 biologics)**
  - **CBER (5 biologics)**
  - **CDRH (37 devices)**

U.S. Department of Health and Human Services
Food and Drug Administration

The 2014 FDA Action Plan to Congress

- **Has 3 priorities:**
  - **Quality: improve the completeness and quality of demographic subgroup data analyses**
  - **Participation: identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation**
  - **Transparency: making demographic subgroup data more available and transparent**
- **To include the subgroup data analyses in:**
  - **product labeling**
  - **information distributed to patients and healthcare providers**

Make Clinical Trial Data Available that Supported NDA Approval

WHAT IS THE PURPOSE OF DRUG TRIALS SNAPSHOTS?

Drug Trials Snapshots provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. The information provided in these Snapshots also highlights whether there were any differences in the benefits and side effects among sex, race and age groups. Drug Trials Snapshots is part of an overall FDA effort to make demographic data more available and transparent.

HOW TO USE SNAPSHOTS:

Each Snapshot contains information about the drug in a question and answer format. At the end of each section of the Snapshot, there is a shaded bar with the words "MORE INFO". Click the "MORE INFO" bar for more technical and detailed content. At the bottom of each Snapshot, there is a link to the drug's Package Insert as well as the medical review.

LIMITATIONS OF SNAPSHOTS:

The Snapshot is intended as one tool for consumers to use when discussing a drug's risks and benefits with their physician. Do not rely on Snapshots alone to make decisions regarding medical care. Do not use Snapshots to substitute for advice from your health care professional. Conclusions regarding how effective and safe a drug is among different sex, race, and age groups cannot always

Download PDF

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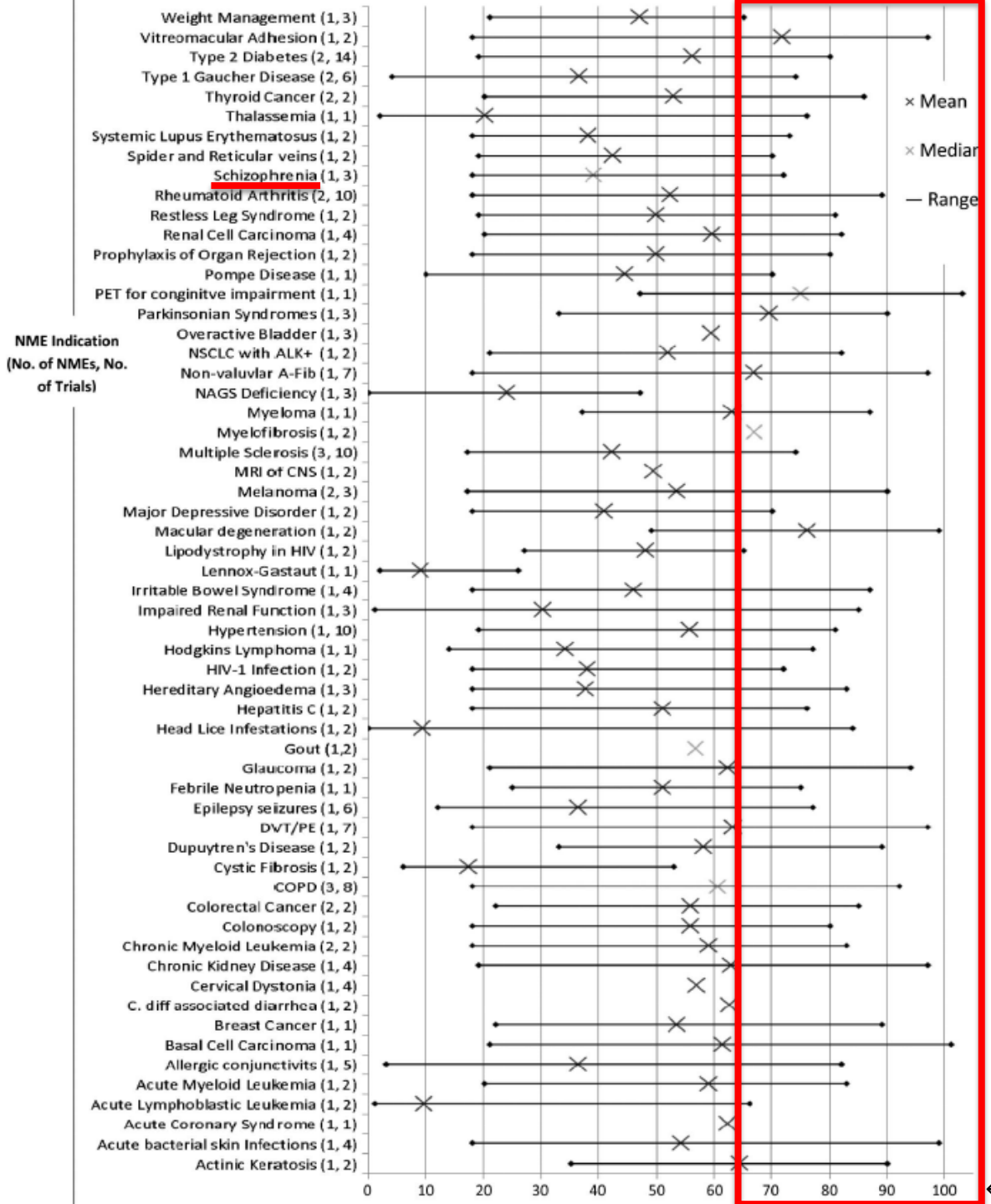
https://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

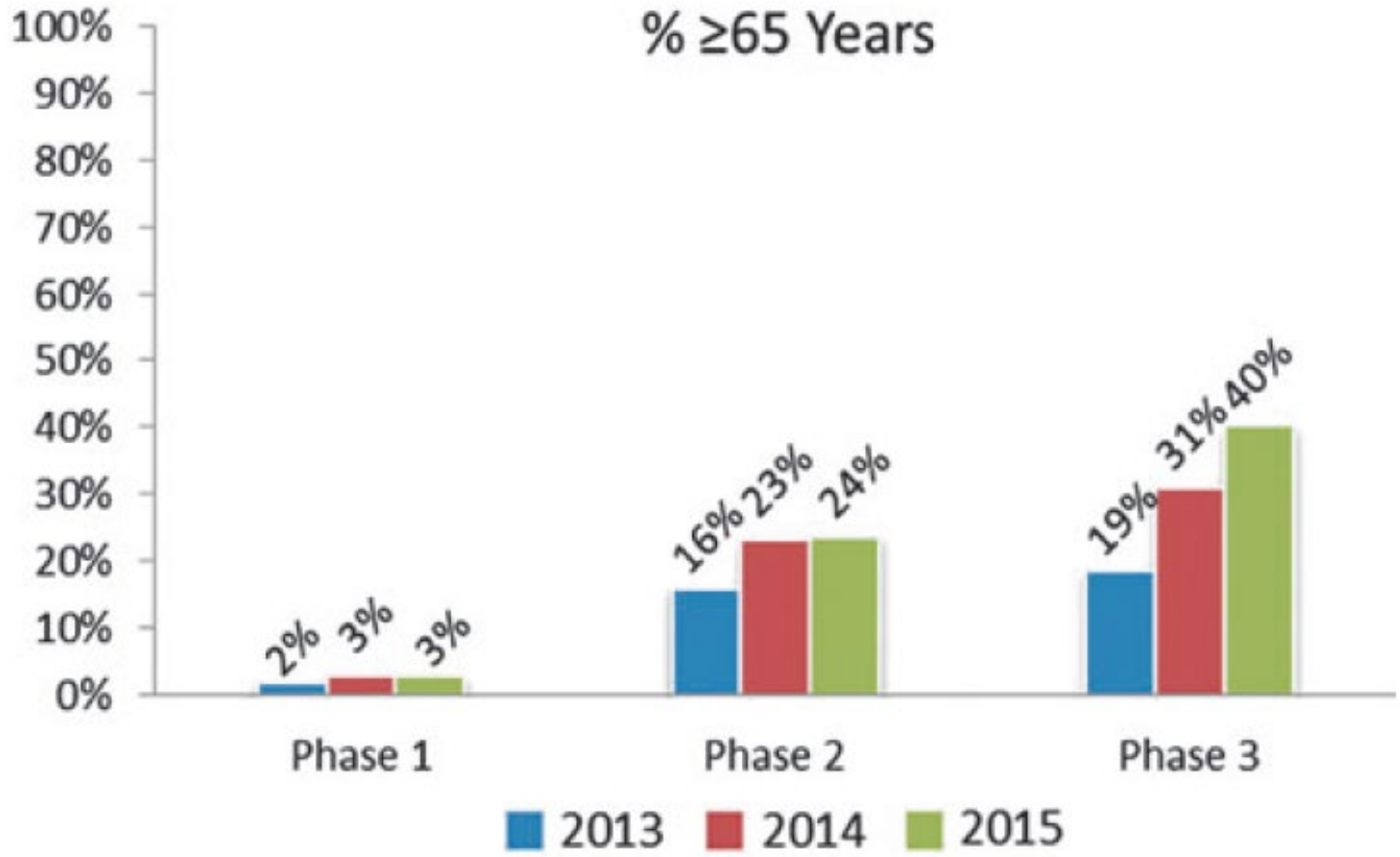
Older Adults in Clinical Trials



Age Range of Study Participants by New Molecular Entity's Indication 2010 – 2012

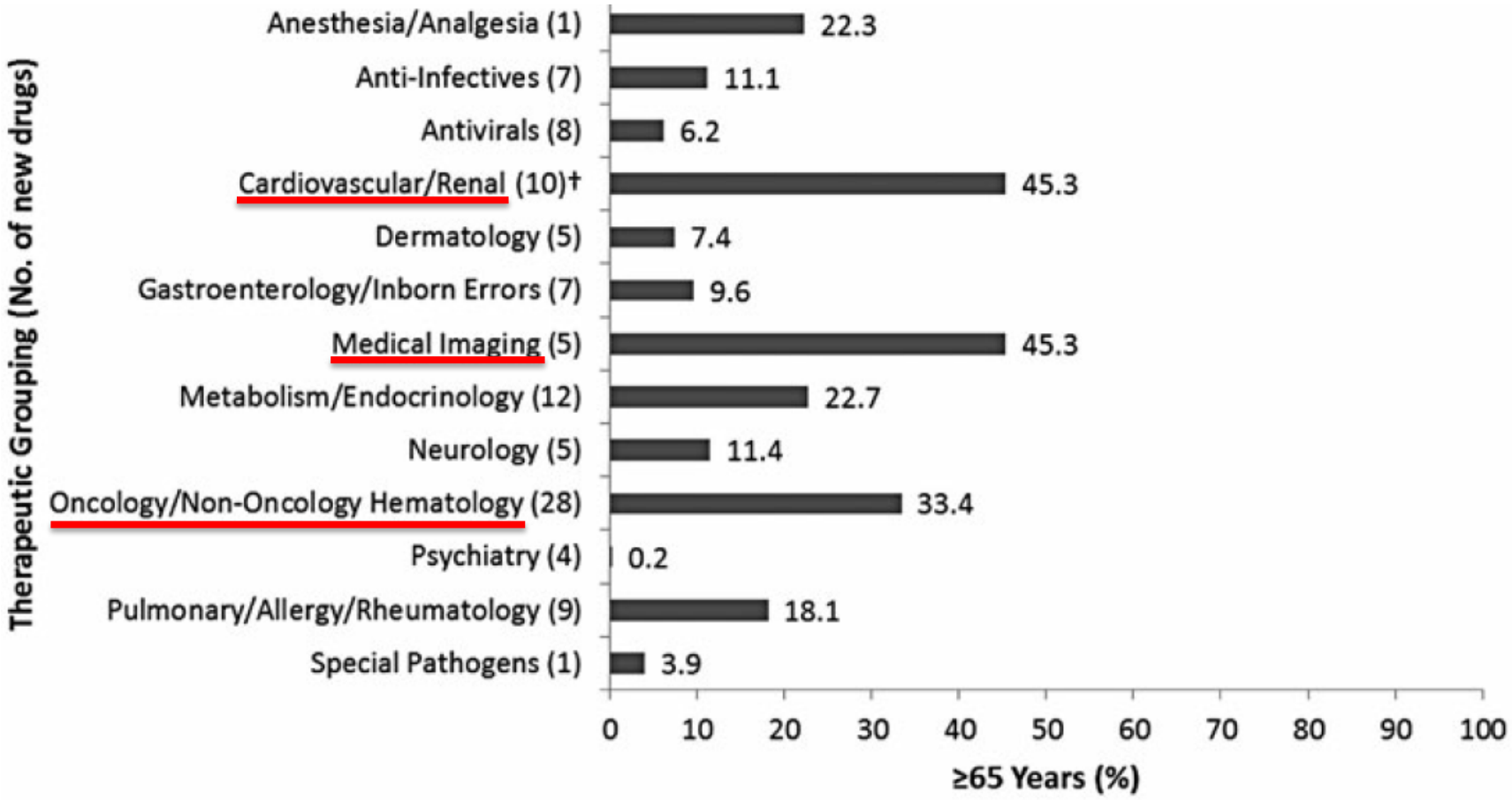
Eshera et al. *Am J Ther* 2015

Age of Clinical Trial Participants



Chen et al. *J Womens Health (Larchmt)* 2018 (modified)

% Older Adult in New Drug Trials 2013 – 2015



Chen et al. *J Womens Health (Larchmt)* 2018

Select Approved Oncologic New Molecular Entities 2008 – 2017

Figure 5 Enrollment by age groups in trials for select oncology drugs approved between 2008 and 2013. Includes subject-level data from

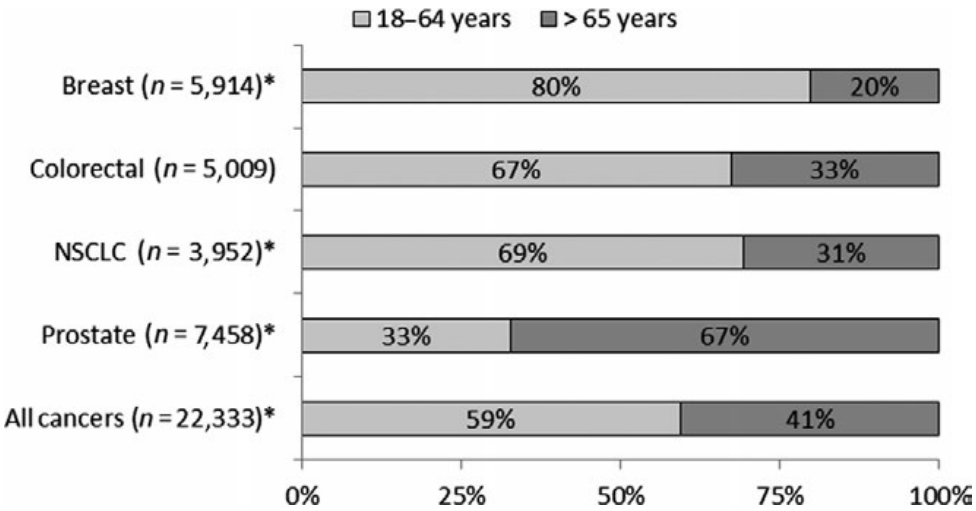


Table 2 Demographic subgroup composition of clinical trial participants with data from Drug Trials Snapshots for select oncology drugs approved between 2014 and 2017

	% Participants			
Demographic subgroup	Breast cancer (*n* = 833)	Colorectal cancer (*n* = 800)	NSCLC (*n* = 1,979)	All cancers (*n* = 3,612)
Age[a]				
17–64 years	56	56	65	61
≥65 years	44	44	35	39

Ramamoorthy et al. *Clin Pharmacol Ther* 2018 (modified)

Regulatory Development in Other Regions

- Besides the ICH E7 and ICH E7 update

EMA's Efforts to Care for Older Adults

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2011
EMA/CHMP/137793/2011

EMA geriatric medicines strategy

1. Introduction

The Agency's Road Map to 2015 takes into account the changing environment in which the Agency will have to operate over the next four years, ensuring that its vision is consistent with, and complementary to, strategic directions provided by the European Commission and Heads of Medicines Agencies.

- **2 strategies:**
  - **Evidence based medicine**
    - **Approved drugs are supported by relevant data on benefit-risk balance.**
  - **Informed Rx**
    - **Improve availability of information to patients and prescribers**

Cerreta et al. *N Engl J Med* 2012

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2015
EMA/CHMP/778709/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Draft

Draft agreed by Frailty PtC drafting Group	March 2015

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017,
EMA/CHMP/QWP/292439/2017 Rev.: 4.0

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

Draft

Draft reflection paper agreed by QWP	February 2017

Japanese Pharmaceutical and Medical Devices Agency

- No additional strategy to the development of drug products for older adults.[¶]
- The Japanese population is aging faster than other countries such as Italy, Germany, UK, and US.
- PMDA workers recognize the underrepresentation of older adults especially ≥ 75 years of age in clinical trials.[§]
- A PMDA working group is evaluating on the insufficient clinical study data in older adults for approved drug products.

[¶]De Spiegeleer et al. *Ageing Res Rev* 2016; [§]Asahina et al. *J Nutr Health Aging* 2014; World Population Ageing 2015, United Nation

Take-home Messages

- **Persons ≥ 65 years of age will be the fastest growing segment of population for the next 4 decades in the US. The segment of population ≥ 85 years of age increases even faster and will triple by 2060.**
- **Older adults are main users of medications.**
- **The 1989 US guideline, ICH E7, and ICH E7 update guide the conduct of clinical trials for older adults.**
- **The 2001 US labeling guidance guides the labeling for the use of prescription drug and biological products in older adults.**

Take-home Messages (continued)

- **FDASIA's Section 907 directed the FDA to publish an Action Plan to enhance the collection and availability of demographic subgroup data for medical products.**
- **Underrepresentation of older adults in clinical trials is common across multiple therapeutic areas. However, signs of improvement for this issue are emerging.**
- **Besides the ICH E7 and its update:**
  - **the EMA has geriatric medicine strategy, points to consider on frailty, and reflection paper on pharmaceutical development to care for older adults.**
  - **the PMDA has a working group on evaluating the sufficiency of clinical data in older adults for approved drug products.**

Acknowledgements

- Office of Clinical Pharmacology's Geriatrics Scientific Interest Group
- OCP's DCP2ers
- OCPers (current and former)
- Older adult relatives and friends

Darrell R Abernethy, MD, PhD
1949 – 2017

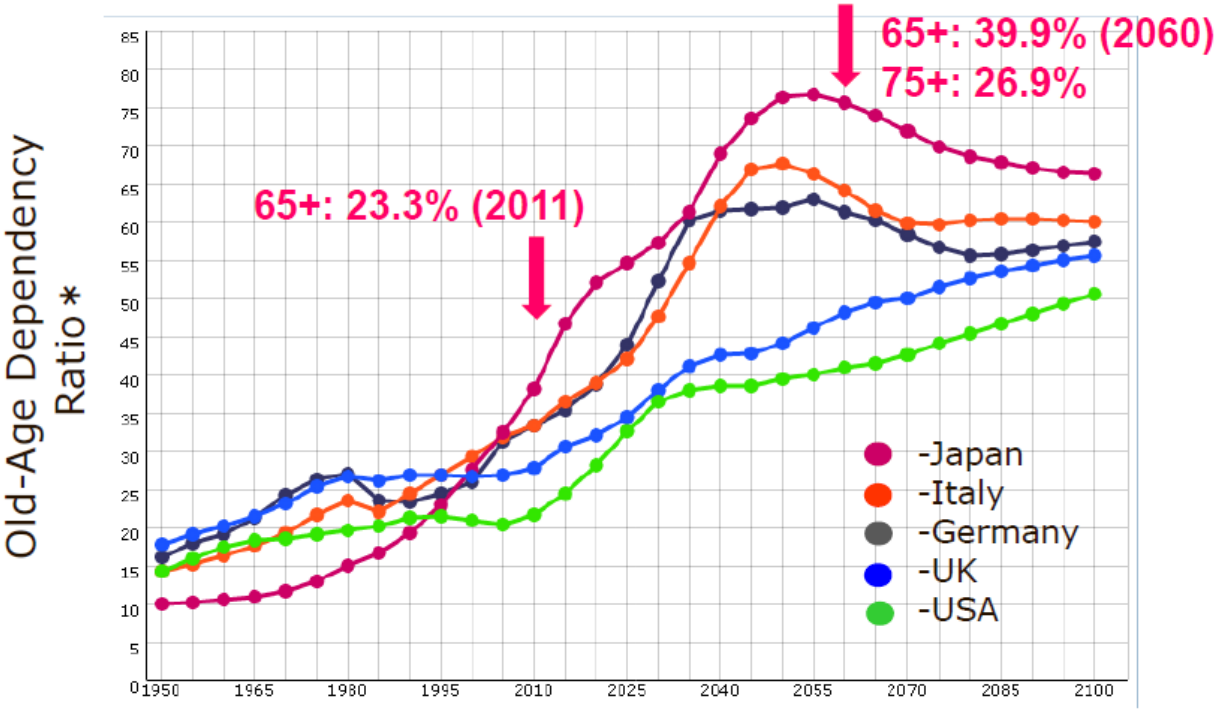
Internist, Clinical Pharmacologist, and Geriatrician

Backup

Selected Guidances on Developing Drug Products for Older Adults

- Food and Drug Administration: Guidance for Industry: Guideline for the Study of Drugs Likely to Be Used in the Elderly. 1989. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072048.pdf
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH E7: Guideline for Industry: Studies in Support the of Special Populations: Geriatrics. 1994. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073131.pdf
- Food and Drug Administration: Guidance for Industry: Content and Format for Geriatric Labeling. 2001. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075062.pdf
- 52. Food and Drug Administration Safety and Innovation Act. Public Law 112–144, July 9, 2012. www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf
- FDA Report: Collection, analysis, and availability of demographic subgroup data for FDA-approved medical products. 2013. ww.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf
- FDA report: FDA action plan to enhance the collection and availability of demographic subgroup data. 2014. www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf
- Drug Trials Snapshots https://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm
- Food and Drug Administration: Webpage on Guidances for Drugs https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- Food and Drug Administration: Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. 1998. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf
- Food and Drug Administration: Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. 2005. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf
- Food and Drug Administration: Guidance for Industry: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments. Draft Guidance, 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614401.pdf
- Food and Drug Administration: Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations. Draft Guidance, 2019. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631941.pdf
- Food and Drug Administration: Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs — General Considerations. Draft Guidance, 2019. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631943.pdf
- Food and Drug Administration: Guidance for Industry: Bioanalytical Method Validation. 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf
- Food and Drug Administration: Biologics development https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/default.htm
- Food and Drug Administration: Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. Draft Guidance 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf
- Food and Drug Administration: Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. 2014. https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf
- Food and Drug Administration: Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Draft Guidance 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf
- Food and Drug Administration: Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. Draft Guidance, 2010. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf
- Food and Drug Administration: Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. 2003. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf
- Food and Drug Administration: Guidance for Industry: Population Pharmacokinetics. 1999. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf
- Food and Drug Administration: Guidance for Industry: In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies. Draft Guidance, 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf
- Food and Drug Administration: Guidance for Industry: Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications. Draft Guidance, 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
- Food and Drug Administration: Guidance for Industry: Physiologically Based Pharmacokinetic Analyses — Format and Content. 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf
- Food and Drug Administration: Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance, 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM612697.pdf
- Food and Drug Administration: Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2006. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf
- Food and Drug Administration: Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf
- Food and Drug Administration: Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2006. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf
- Food and Drug Administration: Human Factors and Medical Devices https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm

高齢化の現状と将来

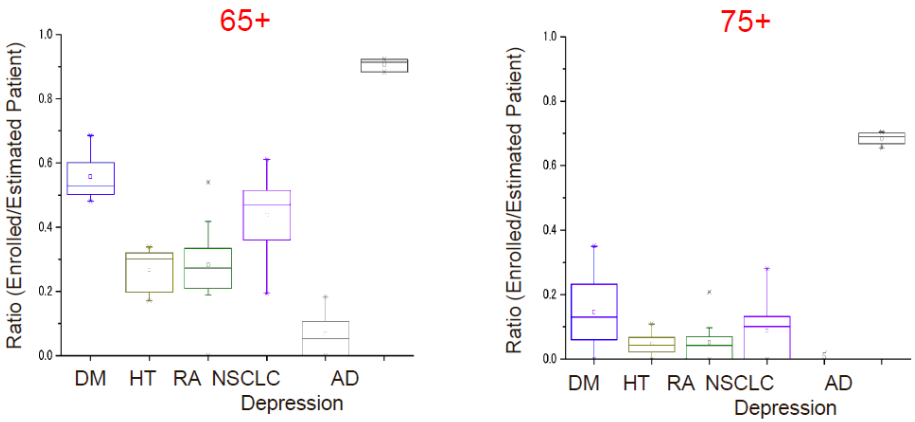


＊老年人口指数：生産年齢人口（15～64歳）に対する65歳以上の高齢者人口の比率

United Nations, Department of Economic and Social Affairs, Population Division (2011): World Population Prospects: The 2010 Revision. New York

Older Adults in Japanese Clinical Trials

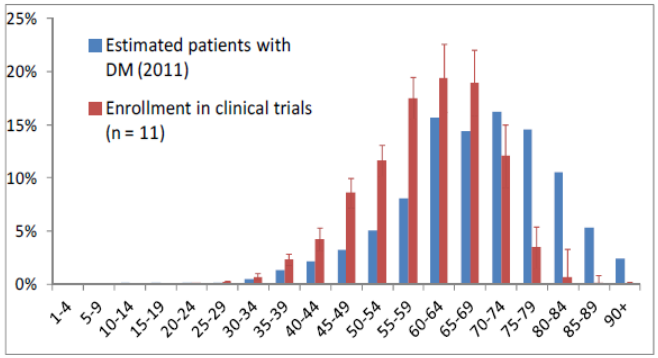
Ratio of Enrolled elderly (65+, 75+) to Estimated Patient in Japan



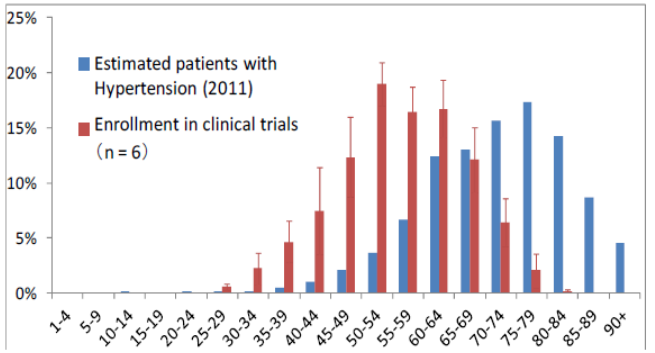
Boxes: median values (horizontal rule) with 25th and 75th percentiles (top and bottom of box)
Error bars: 10th and 90th percentiles

Representation of the elderly in clinical trials (DM, HT)

DM



HT



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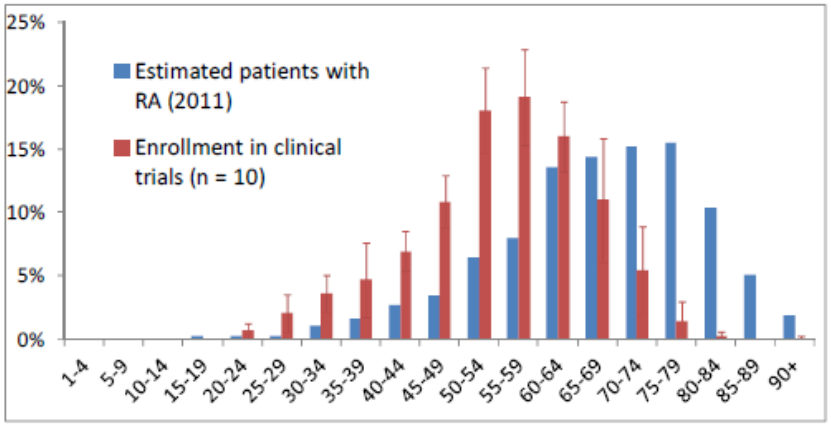
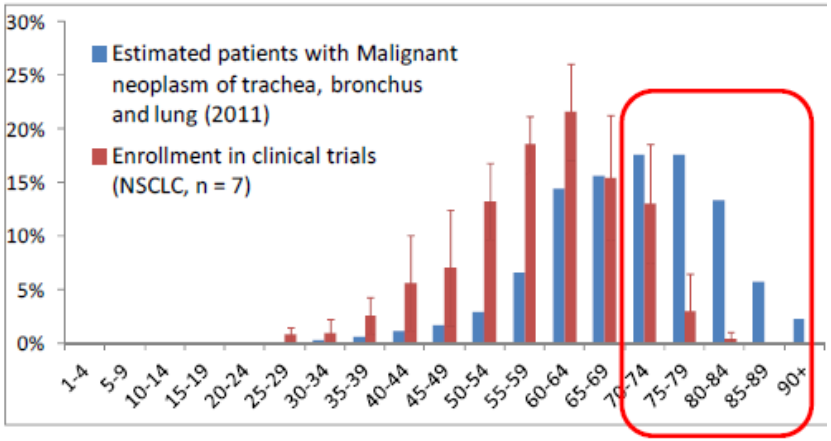
https://www.pmda.go.jp/files/000197716.pdf

Representation of the elderly in clinical trials (RA, NSCLC, Depression, AD)

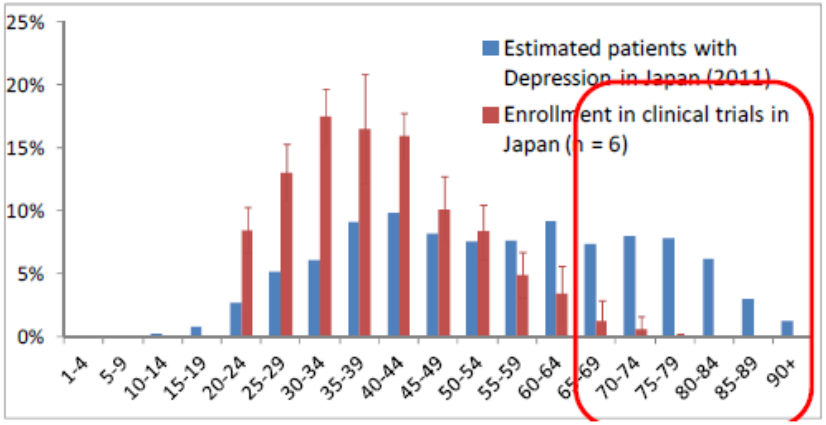
RA



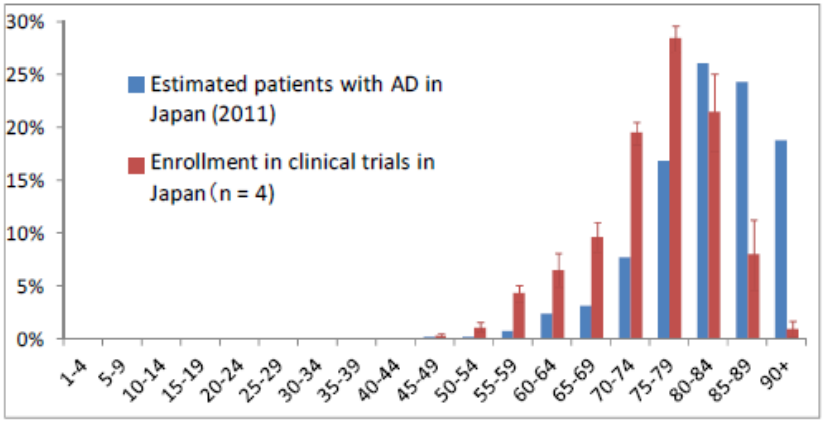
NSCLC



Depression



AD



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https://www.pmda.go.jp/files/000197716.pdf

Assessing and Communicating Heterogeneity of Treatment Effects for Patient Subpopulations: Challenges and Opportunities

8:15 A.M. – 4:30 P.M. (REGISTRATION BEGINS AT 7:30 A.M.)
NOVEMBER 28, 2018
FDA WHITE OAK CAMPUS, BLDG. 31, THE GREAT ROOM (1503 B & C)

Hosted by Johns Hopkins Center of Excellence in Regulatory Science and Innovation (JH-CERSI) and the Food and Drug Administration (FDA)

ABOUT

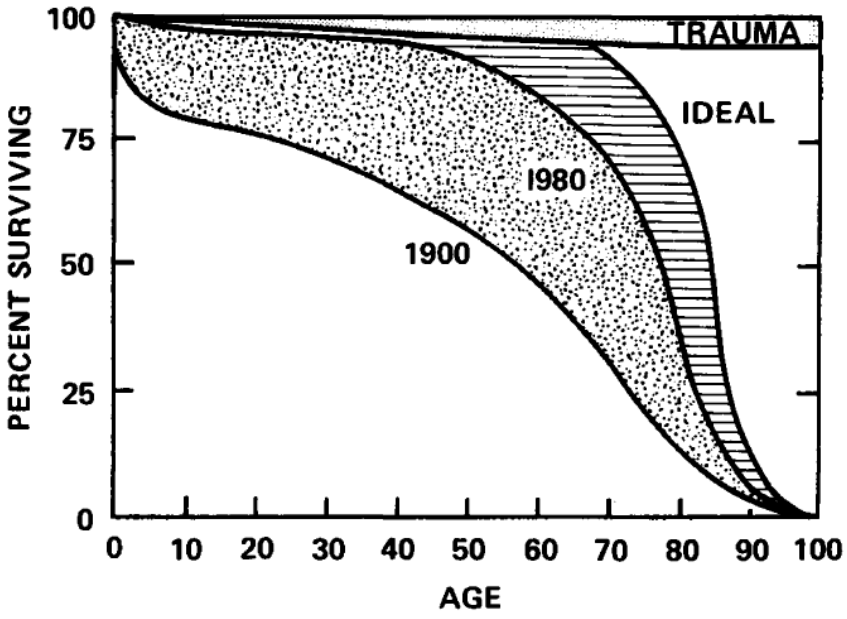
Heterogeneity of treatment effects (HTE) is the variation in how individuals respond to a treatment. This is a vital and yet underexplored concept of importance to regulators, manufacturers, payors, healthcare providers, academic researchers, and patient and consumer advocacy groups. HTE is of high relevance to the FDA for product approval, labelling, and post-marketing surveillance. We propose a stimulating symposium comprised of talks and panel discussions by leading experts that engages various stakeholders in how to assess and communicate HTE.

The symposium will focus on the following topics:

- Major sources of HTE including subpopulations (e.g., sex, race, pediatric and geriatric populations)
- HTE considerations in study design and statistical analysis
- How HTE may be communicated to stakeholders via various avenues such as drug trial snapshots and labeling.

Compression of Morbidity

- **The eventual goal of healthy aging and drug therapy should be the compression of morbidity to the end of life.**



Fries *N Engl J Med* 1980; Myint et al. *BMJ* 2012