

Bridging the Gap – Promoting Safe and Effective Drug Use in Geriatric Patients

- **Inclusion of Geriatric Patients in Clinical Studies**
- **Communicating Information about Use of Drugs in Geriatric Patients in Labeling**

Disclaimer



- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
- Photographs in this presentation are from the CDC's *"The State of Aging and Health in America 2013."*

Overview of Webinar: 4 Parts



1. History of FDA's Geriatric Clinical Data Initiatives for Human Prescription Drugs¹
2. Inclusion of Older Adults in Cancer Clinical Trials²
3. Geriatric Information in Human Prescription Drug Labeling¹
4. Prescription Drug Labeling Resources¹

¹ **Eric Brodsky, M.D.:** *Associate Director, Labeling Policy Team, Office of New Drug Policy, Office of New Drugs (OND), CDER, FDA*

² **Harpreet Singh, M.D.:** *Director, Division of Oncology 2, Office of Oncologic Diseases, OND, CDER, FDA and Acting Associate Director for Cancer in Older Adults and Special Populations, Oncology Center of Excellence, FDA*

PART #1:
**History of FDA's Geriatric Clinical
Data Initiatives for Human
Prescription Drugs**

Eric Brodsky, M.D.

Associate Director, Labeling Policy Team, ONDP, OND, CDER, FDA

Part #1: Learning Objectives

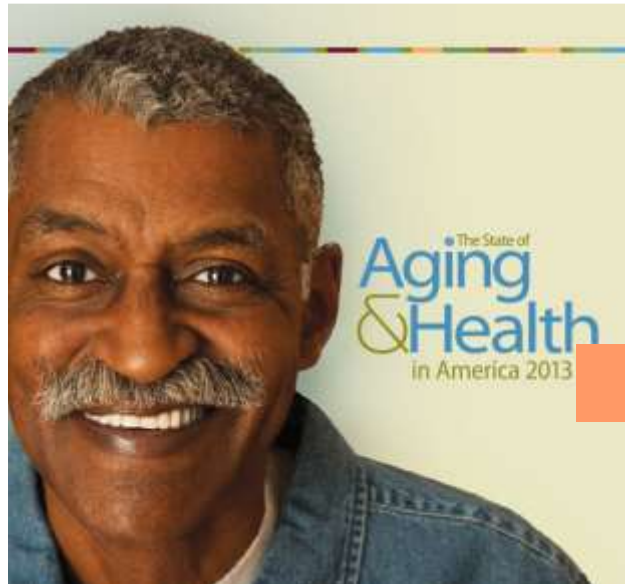


- Discuss the geriatric¹ population in the United States
- Provide an overview of the history of FDA's geriatric clinical data initiatives



¹ Geriatric patients are defined as patients 65 years of age and older

Prescription Drug Use Among Geriatric Patients in the United States



Geriatric Population In the U.S. Increasing



- 2010 Census: 40 million Americans aged 65 years or older (13% of population)¹
- 2030 estimated: 72 million Americans aged 65 years or older (20% of population)²
- According to the CDC, *“The growth in the number and proportion of older adults is unprecedented in the history of the United States”*²
 - Longer life span
 - Aging baby boomers

¹ www.census.gov

² *“The State of Aging and Health in America 2013.”* Atlanta, GA: CDC, Department of Health and Human Services; 2013. Available at <https://www.cdc.gov/aging/pdf/State-Aging-Health-in-America-2013.pdf>

Considerations When Prescribing Prescription Drugs to Geriatric Patients

- Comorbidities
- Organ function (e.g., renal function)
- Consequences of adverse reactions
- Differences in safety and effectiveness
- Concomitant drug therapies



Polypharmacy in Geriatric Patients

A prospective cohort study of community-dwelling adults 62 to 85 years old assessed concurrent use of ≥ 5 prescription drugs:

- 2010-2011: 36% (n = 2,206)

¹ Quato, D. et al. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. *JAMA Intern Med.* 2016;176(4):473-482.

History of FDA's Geriatric Clinical Data Initiatives



History of Geriatric Clinical Data Initiatives (1 of 4)



- **1998:** FDA required NDA holders¹ and, subsequently, recommended that BLA holders² present safety and efficacy data based on age in their applications
- **2012:** FDA reaffirmed importance of obtaining geriatric data, across the entire full age range of the geriatric population³

NDA = New Drug Application; BLA = Biologic License Application

¹ Preamble of the demographic rule (21 CFR 314.50(d)(5); 63 FR 6854) published February 11, 1998

² See the guidance for industry and FDA staff *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016).

³ See the ICH guidance for industry *E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers* (February 2012).

History of Geriatric Clinical Data Initiatives (2 of 4)



- **2012:** FDASIA¹ directed FDA to report on the inclusion of age subgroups in clinical studies and the analysis of subgroups in NDAs and BLAs
- **2013:** FDA's Good Review Practice document on the review of IND applications discouraged arbitrary upper age limits for trial entry

IND = Investigational New Drug (IND)

¹ The Food and Drug Administration Safety and Innovation Act.

² *Good Review Practice: Clinical Review of Investigational New Drug Applications* (December 2013)



History of Geriatric Clinical Data Initiatives (3 of 4)

2013: *FDA's Report on the Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products:*¹

- Analyzed geriatric data for 35 approved prescription drugs and biological products in 2011
- Percentage of geriatric patients in clinical studies tended to reflect disease prevalence in geriatric patients
 - SLE (2% were ≥ 65 years old)
 - Age-related macular degeneration (88% were ≥ 65 years old)

SLE = Systemic Lupus Erythematosus

¹ FDA Report. *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*. August 2013 at <https://www.fda.gov/media/86561/download>

History of Geriatric Clinical Data Initiatives (4 of 4)



2014: *FDA Action Plan to Enhance the Collection and Availability of Demographic Data*¹

- Drug Trials Snapshots
- Consistently communicate meaningful information on demographic subgroups in labeling

2019: *FDA's Enhancing the Diversity of Clinical Trial Populations* guidance:²

- Recommended approaches to broaden eligibility and increase enrollment of underrepresented populations in clinical studies (when appropriate)

¹ FDA's Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data at <https://www.fda.gov/media/89307/download>

² Draft guidance for industry: *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic.

DRUG TRIALS SNAPSHOTS



- Since 2015, Drug Trials Snapshots:¹
 - Demographic groups who participated in clinical trials
 - CDER's NMEs and new biological products
- Includes subgroup analyses in demographic groups (e.g., patients less than 65 years old vs. patients 65 years of age and older)

NMEs = new molecular entities

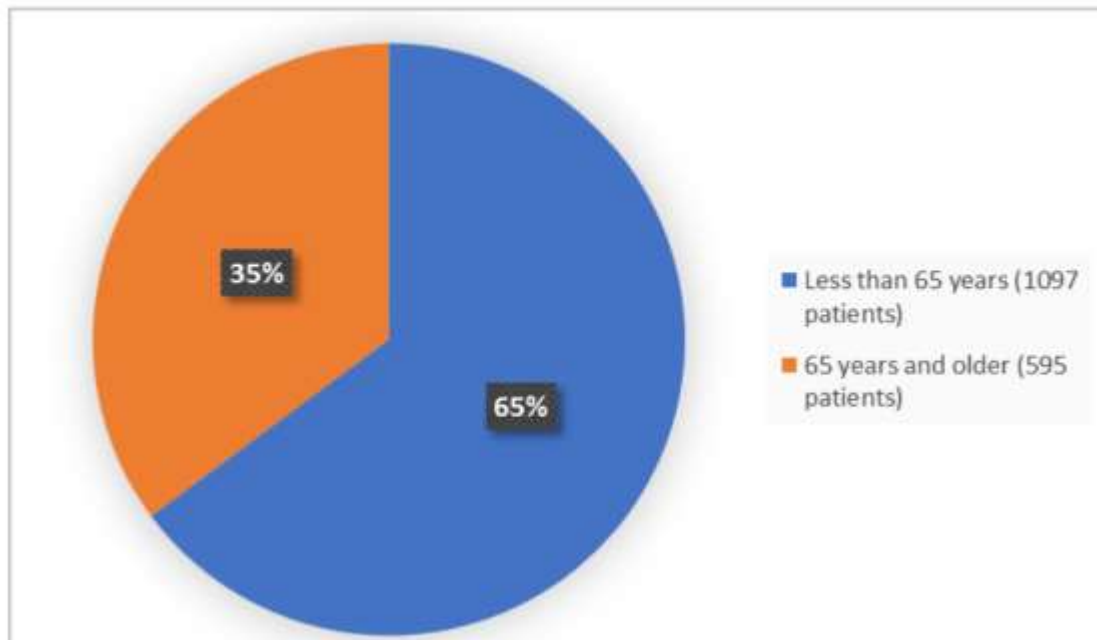
¹ Drug Trials Snapshots: <https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots>

Drug Trials Snapshot: DAYVIGO (lemborexant tablets)



[approved for the treatment of adults with insomnia]

Figure 3. Demographics by Age (efficacy population)



Drug Trials Snapshots: Percentage of Geriatric Patients in Novel Drug Trials¹

Year	Novel Drugs Approved by CDER	Total Number of Patients in Key Clinical Trials ²	Patients 65 Years of Age and Older (%)
2019	48	49,000	36%
2018	59	44,000	15%
2017	46	59,000	32%
2016	22	31,000	21%
2015 ³	45	106,000	37%

¹ Drug Trials Snapshots: <https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots>

² Key trials were trials that provided primary support for the approval of these novel drugs.

³ In 2015, 37%, 15%, and 6% of the study participants in the key clinical trials supporting approval of novel drugs were ≥ 65 years of age, ≥75 years of age, and ≥85 years of age, respectively.

Part 1: Challenge Question #1



Which of the following is **NOT** true about FDA's Drug Trials Snapshots?

1. Includes subgroup efficacy data by age groups
2. Includes subgroup safety data by age groups
3. Includes updated geriatric data from trials completed after approval
4. Includes percentage of geriatric patients in key clinical trials

PART #2: Inclusion of Older Adults in Cancer Clinical Trials

Harpreet Singh, M.D.

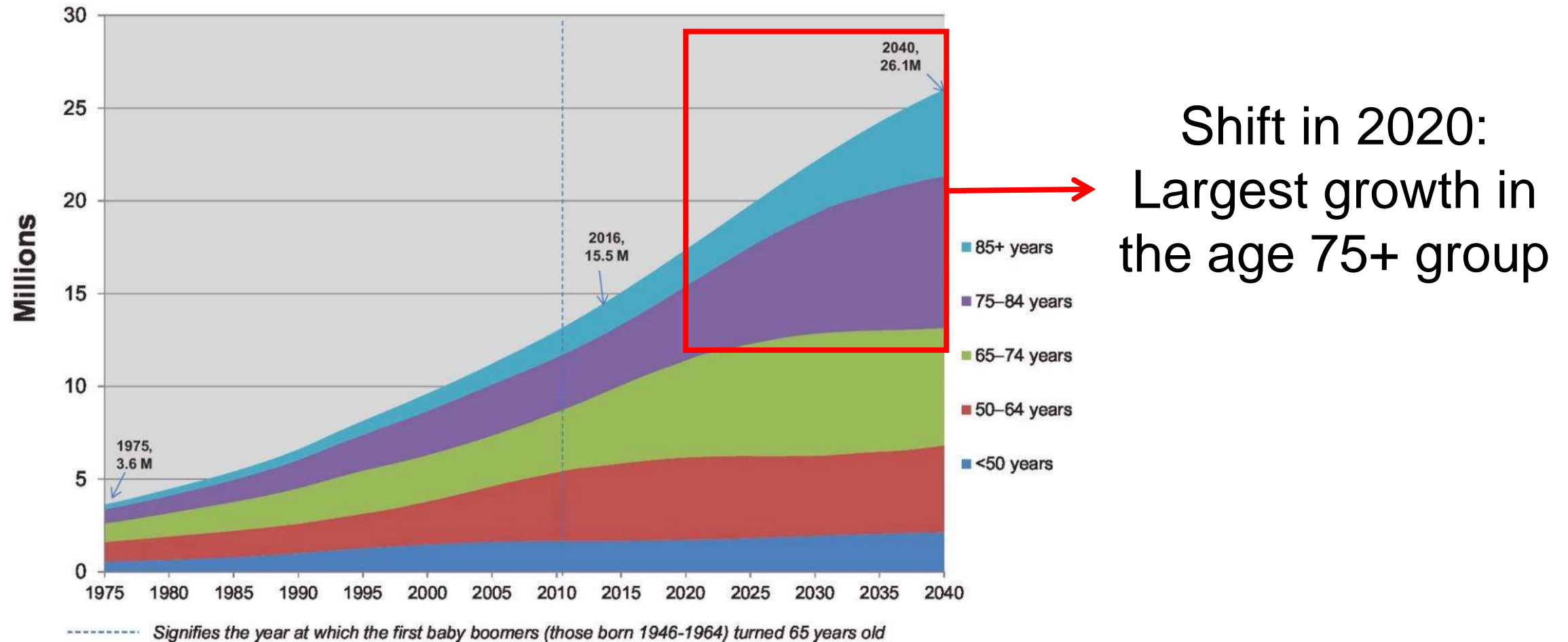
Director, Division of Oncology 2, Office of Oncology Diseases, OND, CDER, FDA and Acting Associate Director for Cancer in Older Adults and Special Populations, Oncology Center of Excellence, FDA

Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.

Projected Rise in Cancer Prevalence

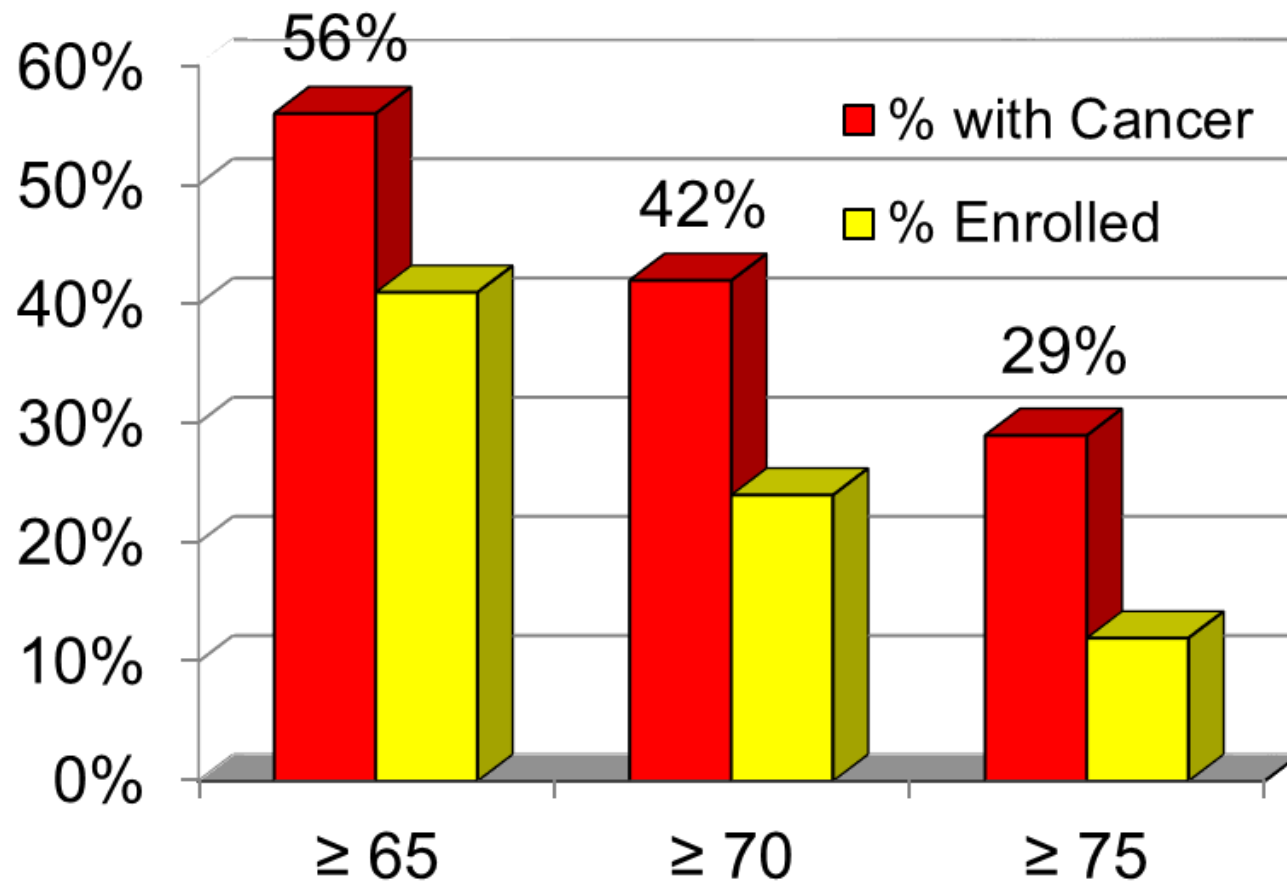
Estimated Cancer Prevalence by Age in the US (1975-2040)



Persistent Under-representation of Older Adults

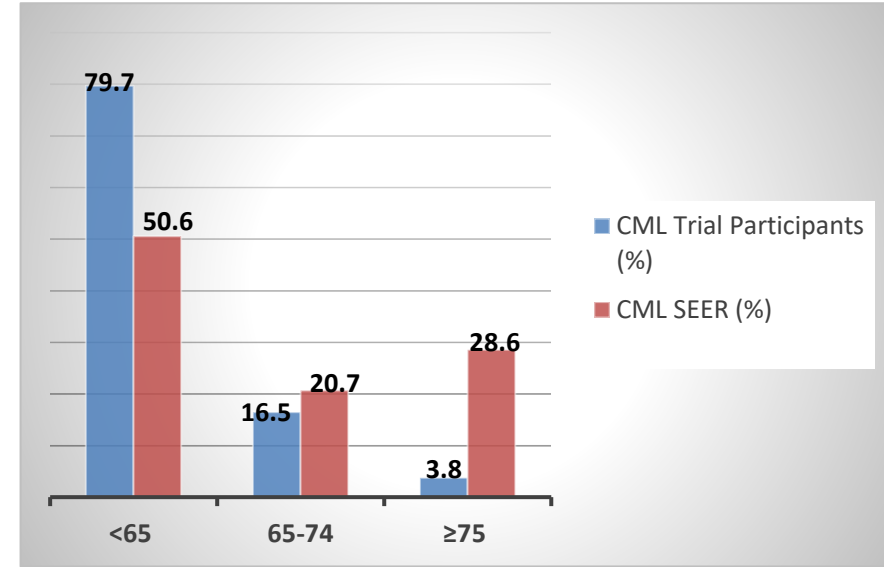
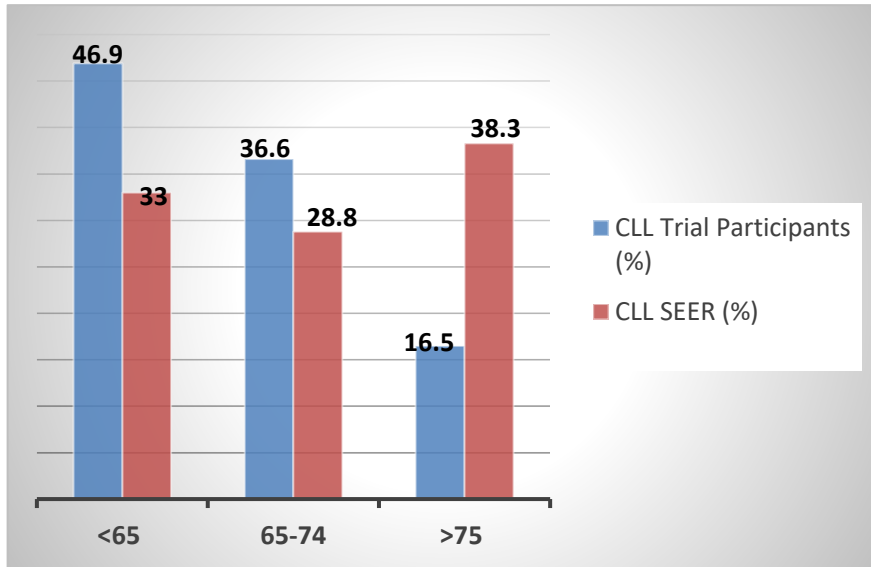
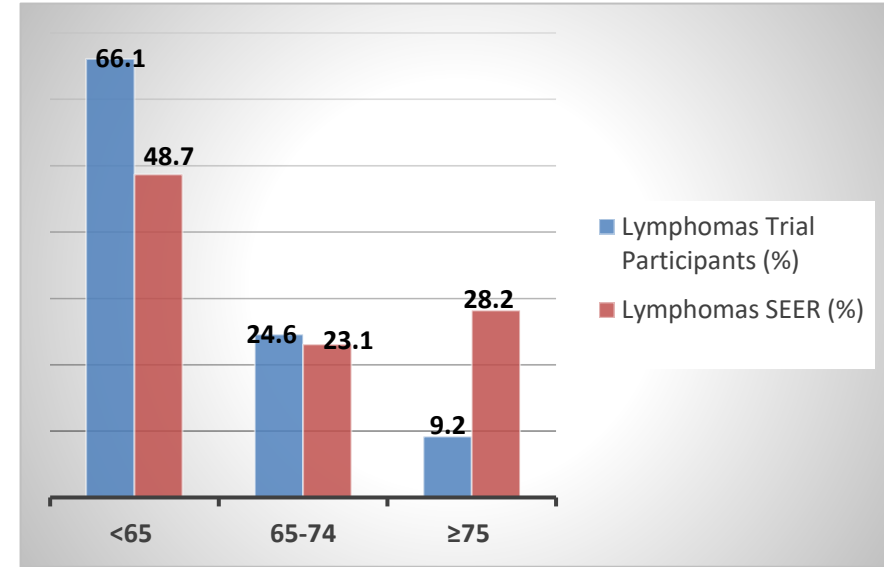
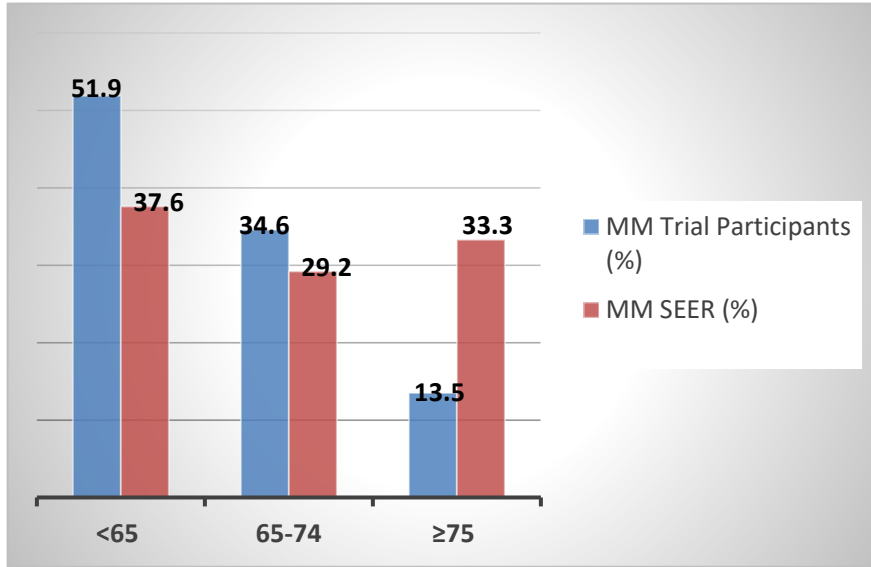
- 10-yr perspective (2005-2015)
- 105 FDA oncology trials
- 224,766 patients

Disparity is Greatest for Patients Age ≥ 75



Singh et al, ASCO Annual Meeting, 2017

Patients Enrolled on FDA trials Compared with New Cases by Age Group



*Includes 5% of patients enrolled on Hodgkin's Lymphoma trials

Biologic Rationale for Inclusion of Older Adults

PK

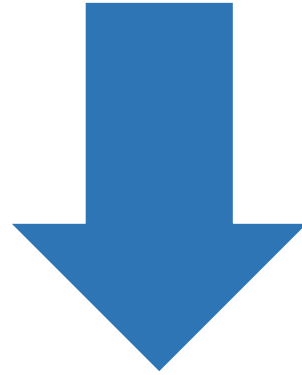
- Intrinsic Factors (i.e. renal and hepatic function) – Increased Number of Comorbidities
- Extrinsic Factors (i.e. Drug-drug Interactions) - Concomitant medication

PD

- Adverse events
- Desirable effects
- Efficiency of compensatory mechanisms

Goal of Geriatric Oncology

Improve the **evidence** base for treating older adults with cancer

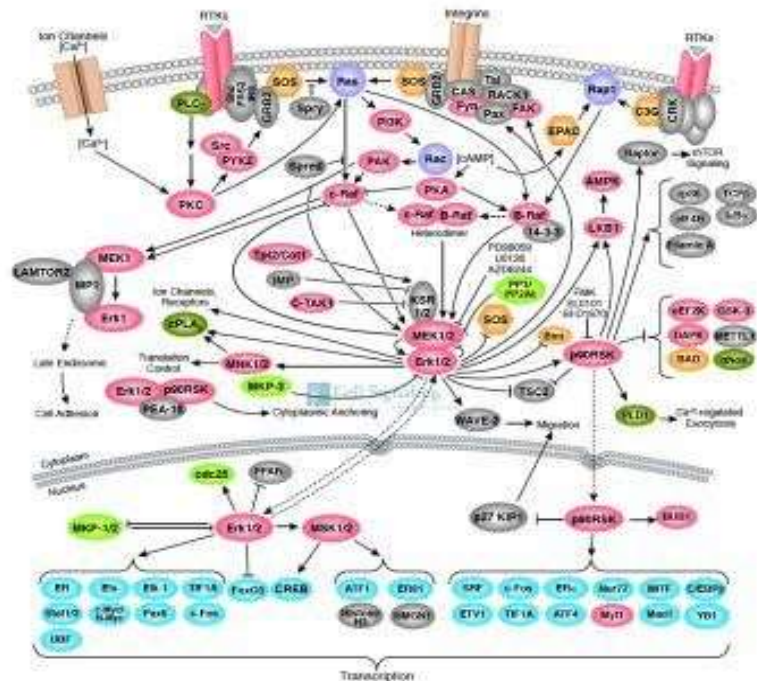


Improve the **quality of care** received by older adults with cancer

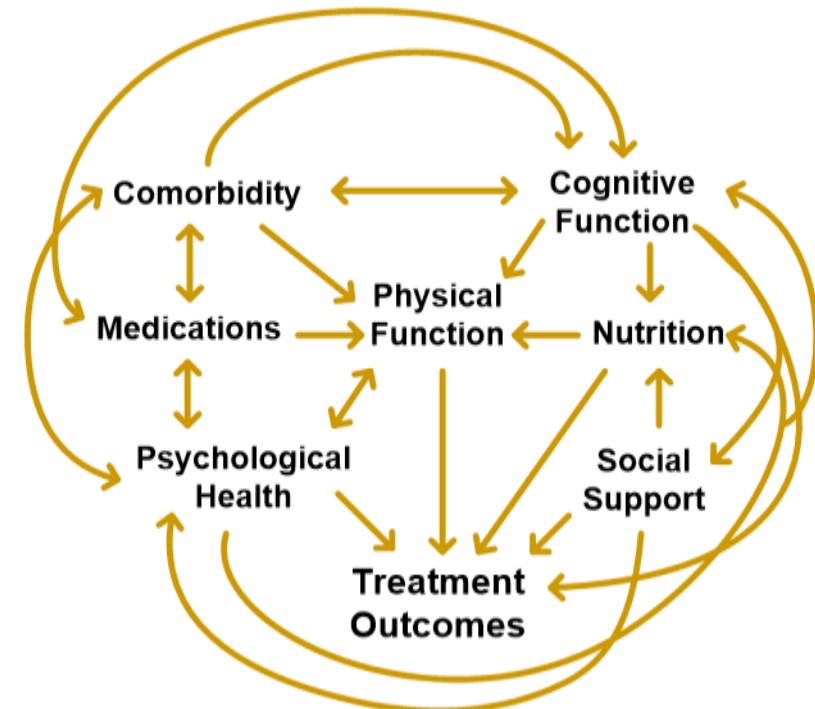
Extrapolation of Data from Younger Patients is Inadequate

Personalized medicine will require trials that address patient heterogeneity

Tumor-centric



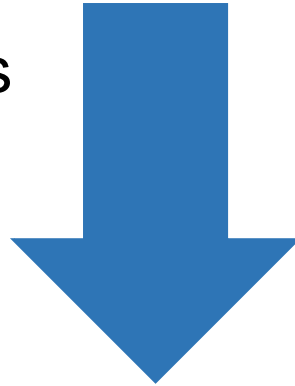
Patient-centric



Opportunities for Systematic Change

Multi-stakeholder engagement

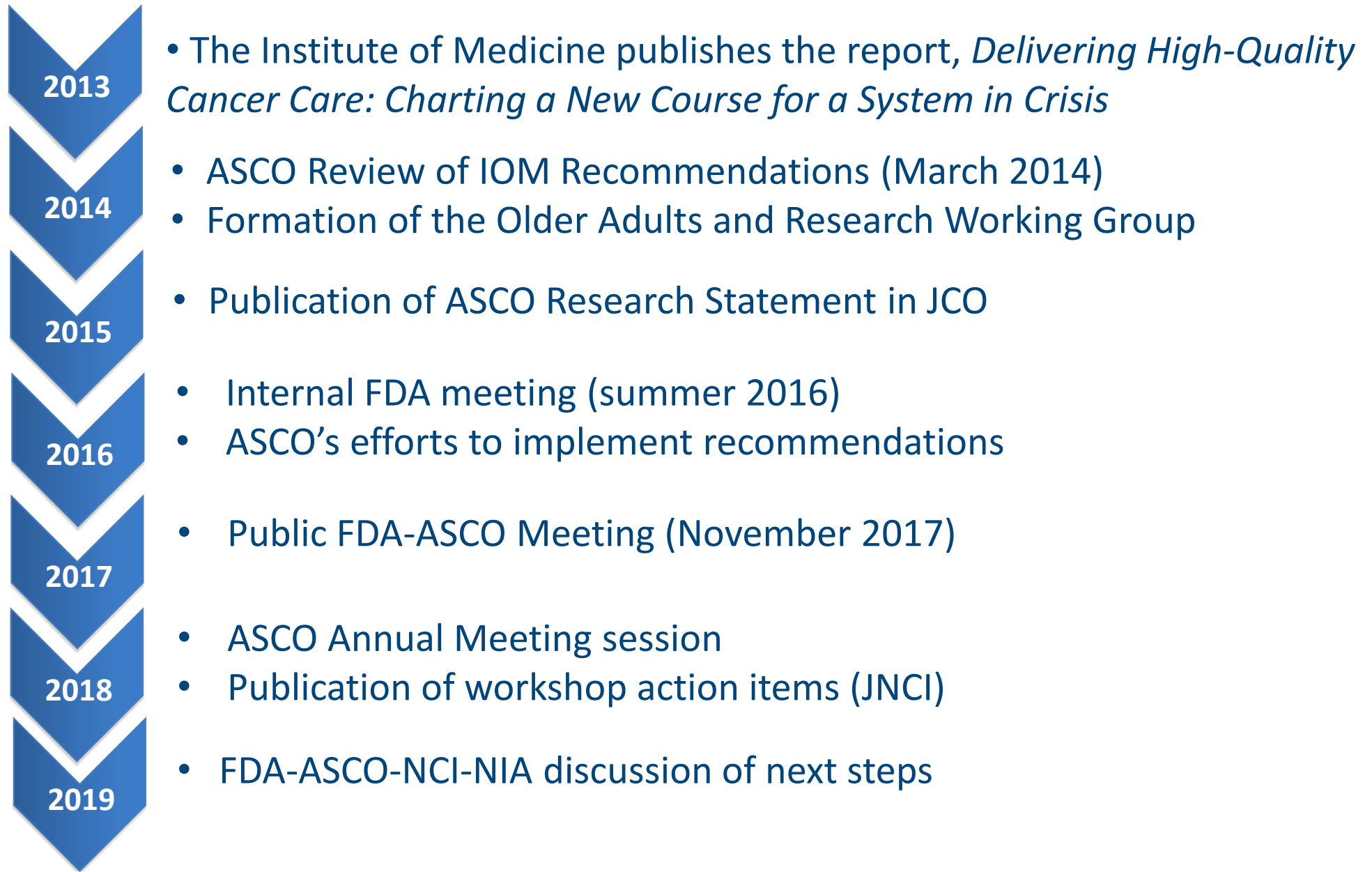
Systematic actions



A culture change

Evidence gap is closed rapidly

Efforts to Improve the Evidence Base Timeline



Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement

Recommendation
To improve the conduct of research
Use clinical trials to improve evidence for treating older adults with cancer
Leverage research designs and infrastructure for generating evidence on older adults with cancer
To improve the research environment
Increase FDA authority to incentivize and require research involving older adults with cancer
Increase clinicians' recruitment of older adults with cancer to clinical trials
Use journal policies to improve researchers' reporting of age distribution and health risk profiles of research participants

Commentary: Expanding the Evidence Base in Geriatric Oncology: Action Items From an FDA-ASCO Workshop

Laura A. Levit, Harpreet Singh, Heidi D. Klepin, Arti Hurria

Action Items:

1. Increase enrollment of older adults on trials (trial design, eligibility, access)
2. Collect more information on older adults from treatment trials
3. Expand the use of real-world data in research on older adults
4. Strengthen the collaboration between stakeholders to develop advocacy and policy solutions

JNCI J Natl Cancer Inst (2018) 110(11): djy169

Doi: 10.1093/jnci/djy169

First published online October 17, 2018

Commentary

Opportunities for Systematic Change: Sponsors

- Implement the ASCO-FDA-Friends of Cancer Research eligibility criteria recommendations
- Expand access to clinical trials in community settings
 - Decentralizing clinical trials efforts underway
- Engage social and behavioral scientists, patient advocates, geriatricians and geriatric oncologists during trial design

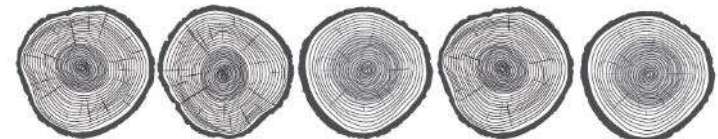
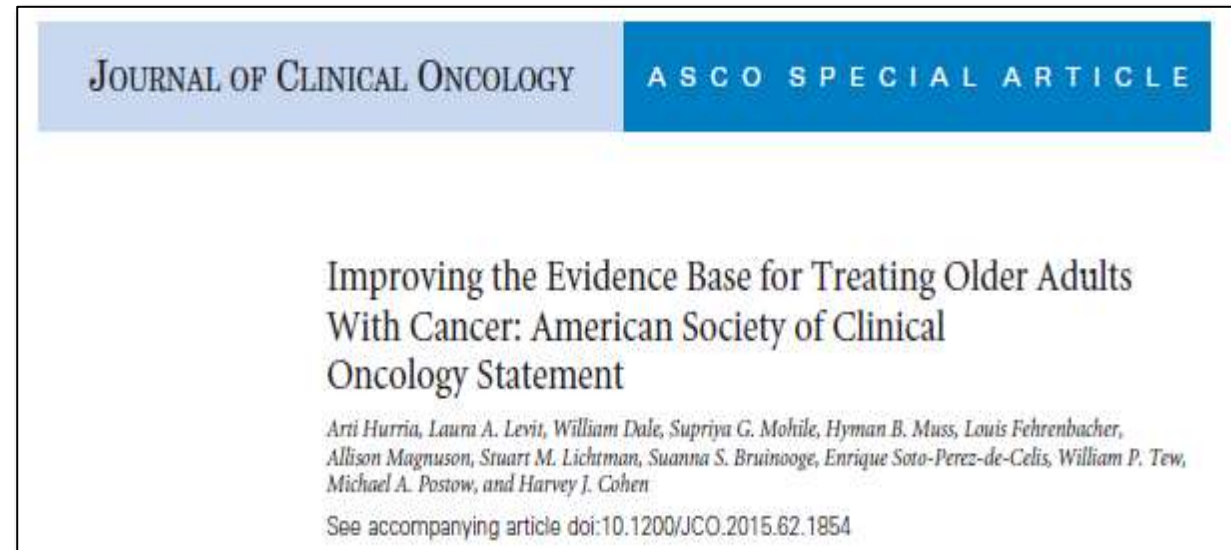
Efforts to Translate Recommendations into Action: FDA

- Routinely working with sponsors during the planning process for IND applications.
- Developing oncology-specific guidance on increasing the enrollment of older adults on trials and collecting appropriate data.
- Supporting “root cause” analyses to understand the lack of physician recruitment of older adults to trials.
- Conducting analyses that compare recruitment in oncology clinical trial to other diseases and to other countries.
- Considering post-marketing commitments where appropriate to obtain more data on older adults.

PROJECT SILVER

Key Objective: Improving the evidence base for treating older adults with cancer

- Regulatory Policy
- Advocacy and Outreach
- Global Engagement
- Research & Publications



FDA Guidance on Inclusion of Older Adults

1997	Guidance for the Study of Drugs Likely to Be Used in the Elderly
2012	Guidance for Industry: E7 Studies in Support of Special Populations
2019	Enhancing the Diversity of Clinical Trial Populations
2020	Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies (OCE)
2020	DRAFT Geriatric Labeling Guidance (OND)
2020	DRAFT Inclusion of Older Adults in Cancer Clinical Trials (OCE)

FDA Guidance for Industry

Eligibility Criteria

Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

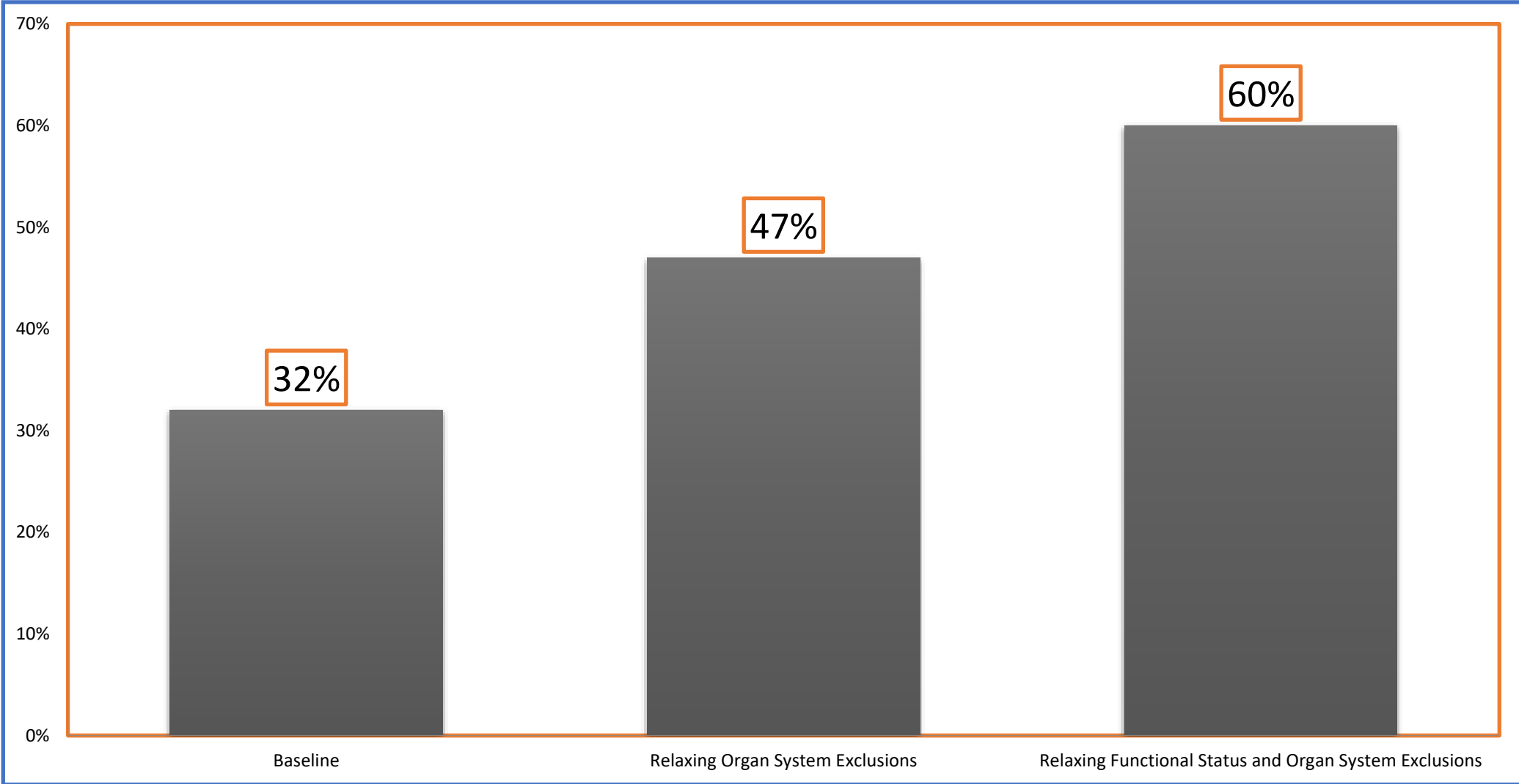
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Julia Beaver at 240-402-0489 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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

March 2019
Clinical/Medical

Predicted enrollment of older adults when exclusion criteria are relaxed



Modified from Lewis J.H et al .Journal of Clinical Oncology 21, no. 7 (April 2003) 1383-1389.

The following quote is attributed to Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-encourages-inclusion-older-adult-patients-cancer-clinical-trials>

“Enrolling a broad representation of patients in clinical trials is an important tenet of clinical research as it facilitates a better understanding of the drug’s benefits and risks across the patient population likely to take the drug. However, because cancer incidence increases with age, and given the aging U.S. population, it’s particularly important now more than ever to ensure that older adults are also enrolling in cancer clinical trials.

“Unfortunately, adults aged 65 years and older, and especially those over 75 years old, are currently underrepresented in cancer clinical trials despite accounting for a growing segment of the cancer patient population.

“This has been a persistent issue in oncology and the FDA is engaged with stakeholders to improve the representation of older adults in cancer clinical trials. That is why today, we are providing recommendations on increasing the enrollment of older adults in cancer clinical trials, when appropriate.

Inclusion of Older Adults in Cancer Clinical Trials

Draft Guidance for Industry

MARCH 2020

[Download the Draft Guidance Document](#)

[Read the Federal Register Notice](#)

Adequate representation of older adults is necessary to determine benefit-risk of cancer therapeutics in this population

- **Early clinical development**
 - Enroll older adults in early phase trials, study drug-drug interactions
- Clinical trials
 - Trial design, recruitment strategies, collect additional information, safety monitoring strategies, reporting in discrete age groups
- **Collection of post marketing data through additional trials, registries, and/or real world data**


General Recommendations

- Include a representative population including those with frailty
- Strategy for inclusion informed by
 - Prevalence of the condition (breast, lung, colon, DLBCL, MM)
 - Diagnosis and treatment patterns
 - Prior relevant studies
 - Expected differences in safety and efficacy outcomes

Early Clinical Development



- Enroll older adults in early phase studies to inform dose selection
- Evaluate drug-drug interactions early

Action Item  Evaluate demographics of early phase trials

Clinical Trials with Registration Intent



Trial Design

- Flexible approaches to trial design
- Consider patient perspectives for trial design including endpoints

Recruitment Strategies

- Consider geography of clinical trial sites
- Format and content of informational material
- Accommodations needed for impairments
- Caregiver support
- Discuss specific goals for enrollment with investigators
- Consider recruiting investigators with expertise in care of older adults with cancer

Clinical Trial Assessments/Reporting

- Collect information on elements from geriatric assessments tools if feasible
- Develop and report more discrete age groups (65-69, 70-74, 75-79, 80+)
- More detailed labeling in Geriatric Use Section (see example below)

8.5 Geriatric Use

Of 284 patients who received PIQRAY in the SOLAR-1 trial, 117 patients were ≥ 65 years of age and 34 patients were ≥ 75 years of age. In patients treated with PIQRAY plus fulvestrant, there was a higher incidence of Grade 3-4 hyperglycemia in patients ≥ 65 years of age (44%) compared to patients < 65 years of age (32%). No overall differences in effectiveness of PIQRAY were observed between patients ≥ 65 years of age compared to younger patients. There are an insufficient number of patients ≥ 75 years of age to assess whether there are differences in safety or effectiveness.

Post Market Considerations



- Ideally, adequate information on older adults should be captured in the premarket clinical trials
- If older adults are not adequately represented, it may be appropriate to develop a plan to collect data on older adults in the postmarket setting.
- **This could be accomplished with post-marketing trials examining a broader population, or through collection of real world data in an observational study or registry.**
- In certain situations, FDA may require postmarket studies and clinical trials.
- Sponsors should prospectively discuss their plan for collecting additional information in the postmarket setting with the CDER or CBER review division or office.
- Postmarket data may provide clinically useful information, that when appropriate, **can be added to the geriatric use section of the labeling.**

Geriatric Use Labeling

“Per 21CFR 201.57, specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients”

8.5 Geriatric Use

Of the 182 patients treated with IMFINZI in patients with urothelial carcinoma, 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15% (17/112) and was 12% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older.

Of the 476 patients treated with IMFINZI in the PACIFIC study, 45% were 65 years or older, while 7.6% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients. The PACIFIC study did not include sufficient numbers of patients aged 75 years and over to determine whether they respond differently from younger patients.

Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology

Supriya G. Mohile, William Dale, Mark R. Somerfield, Mara A. Schonberg, Cynthia M. Boyd, Peggy S. Burhenn, Beverly Canin, Harvey Jay Cohen, Holly M. Holmes, Judith O. Hopkins, Michelle C. Janeloins, Alok A. Khorana, Heidi D. Klepin, Stuart M. Lichtman, Karen M. Mustian, William P. Tew, and Arti Hurria

- 1. Do Geriatric Assessments (GA)**
- 2. Include Essential GA Domains**
- 3. Conduct (non-cancer) Prognostication**
- 4. Enact GA-Guided, Targeted Interventions**



PROJECT SILVER

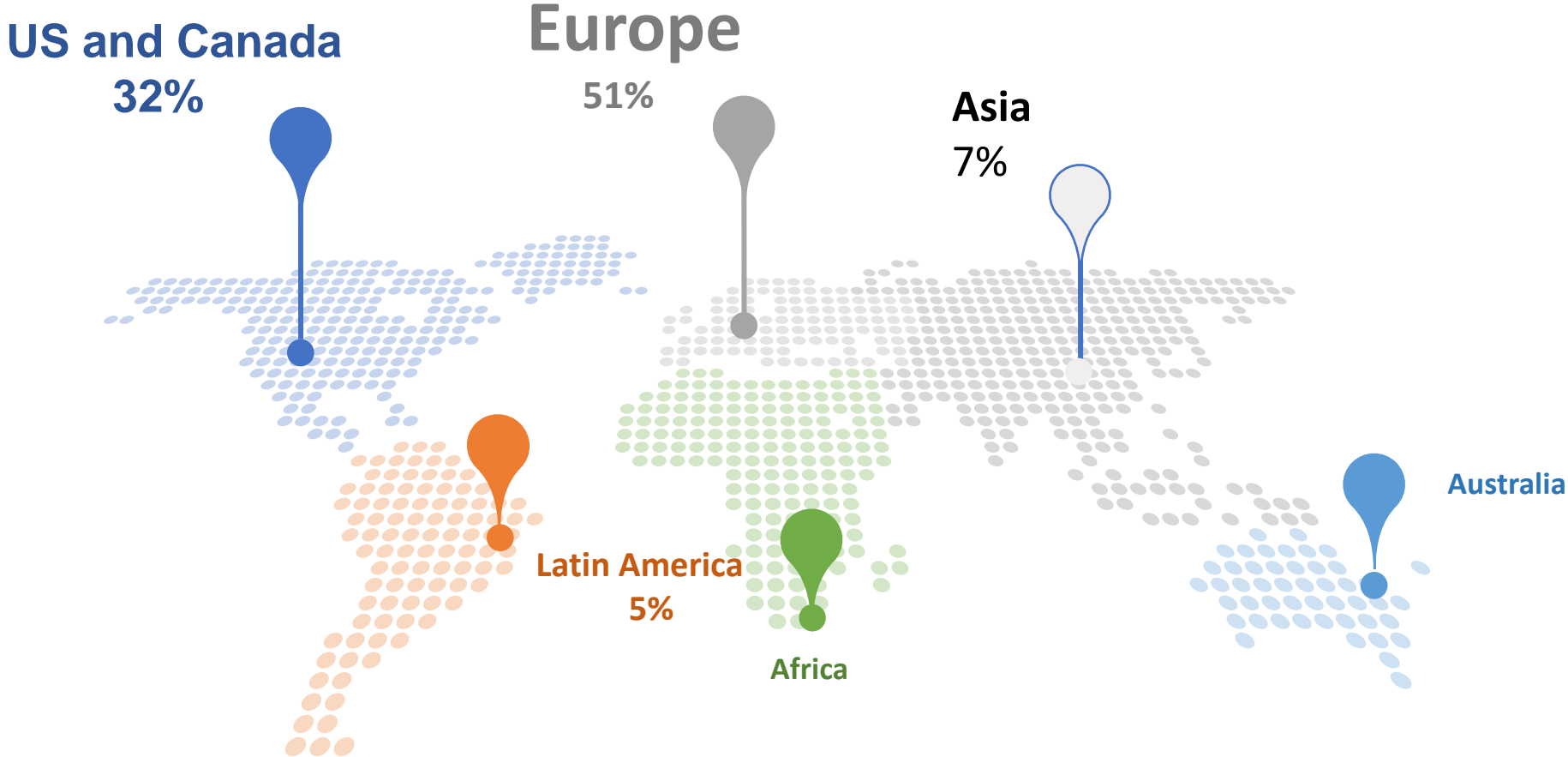
Global Regulatory Strategy

ASCO 2020 Educational Session
Globalization of Geriatric Oncology

Oncology Drug Development is Global

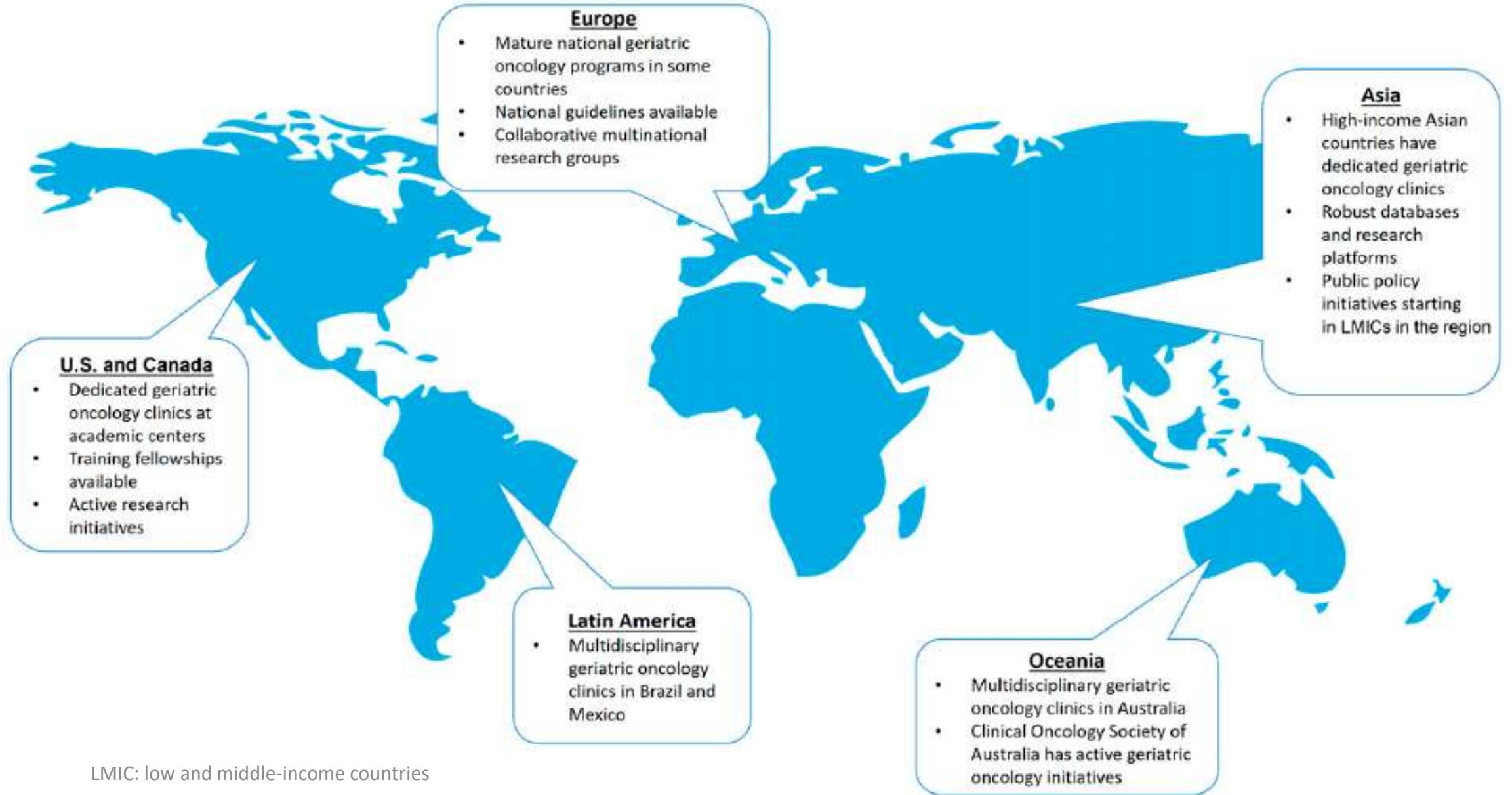
- Pivotal trials are increasingly international
- Older adults a growing segment of our global population of patients with cancer
- Remain underrepresented in oncology trials
- Global regulatory strategies to increase evidence base for older adults are imperative

Global Enrollment of Older Adults in Cancer Registration Trials: A 10 year FDA experience



Global enrollment of older adults in oncology trials (n>170,000), reviewed enrollment of patients≥65 ~ Presented at ASCO 2017

Global Geriatric Oncology Initiatives

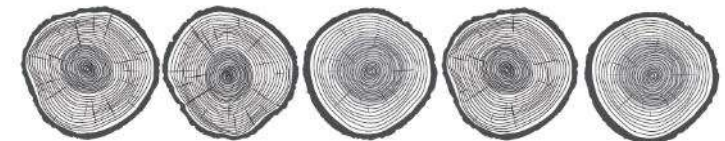


LMIC: low and middle-income countries

Project SILVER - Global Outreach

- Comprehensive global regulatory effort to improve the evidence base for older adults with cancer
- **Identify liaisons through Project ORBIS for SILVER***
- Discuss key applications in specific disease areas which heavily impact older adults
- Consider more detailed labeling information
- Collectively gather post market data (registries, RWD)

*SIOG Taskforce pending



PROJECT SILVER – Global Engagement

INTERNATIONAL GENEVA / GENÈVE INTERNATIONALE

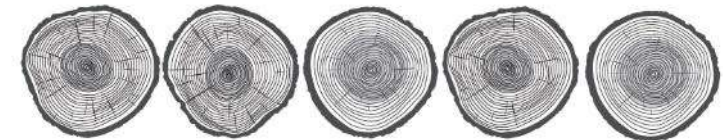
**IFA and SIOG jointly host a landmark global dialogue
on the ageing population with cancer**

Meeting the needs of older cancer patients

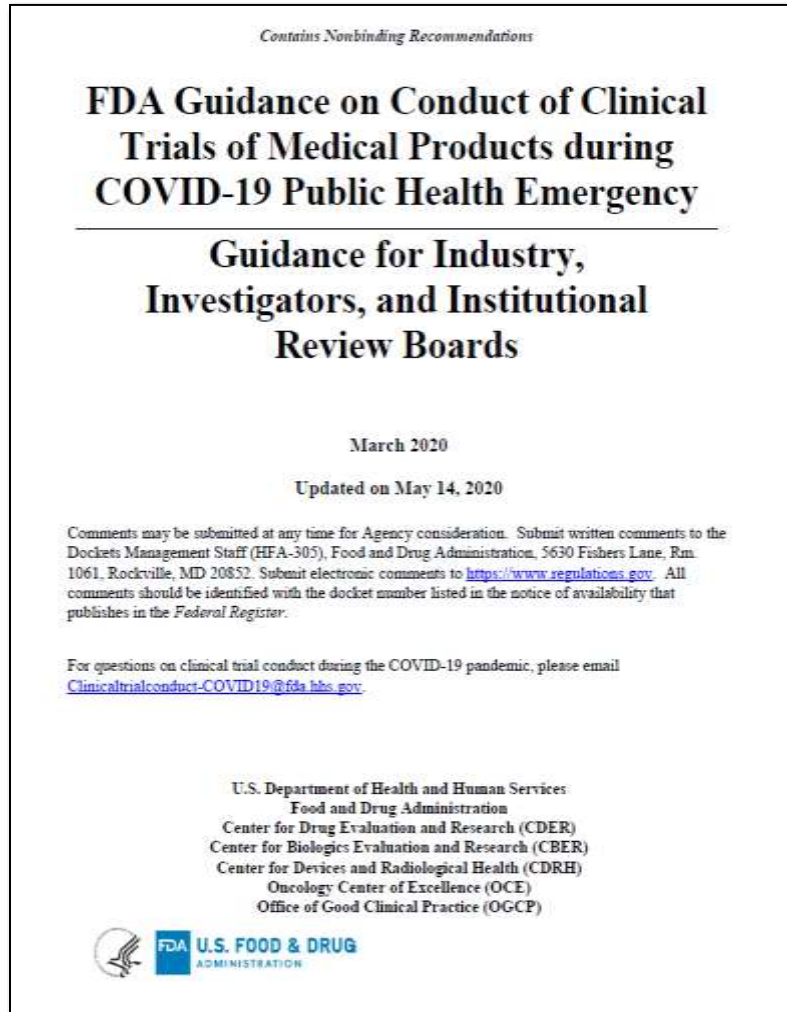
*Age increases
cancer risk,
and the world's
population is
rapidly ageing,
meaning a steep
rise in the number
of older people
with cancer
is inevitable.*



November 2019, United Nations



COVID Guidances- Rapid Dissemination of Information



FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic

Initial release date: March 19, 2020

Multiple updates:

Most Recent July 2, 2020

COVID-19 Guidances are **Expedited**

- Released without Public Comment

Considerations for Ongoing Trials

- **Safety is paramount**- Modifications to trials should assure safety
- **Engage with IRB/IEC** on continued accrual, drug administration and trial participation
- **Alternative offsite methods** for safety assessments and site monitoring
 - Technology to facilitate remote data collection and monitoring
- **Alternative secure delivery methods of IP** can be explored
- **Clarifies Reporting Requirements and Interactions with FDA and IRBs**
 - **COVID-19 screening as a part of health care** does not need to be reported as a protocol amendment unless data is part of the research objective(s)
 - **Protocol modifications to protect life and well-being may be implemented before IRB/FDA approval.** (reporting required afterward)
 - **Document COVID-19 Contingency Measures**

Barriers to Clinical Trial Participation

- Geographic/logistical barriers
 - Clinical trials are not conducted where older adults live (rural US)
 - If the clinical trial site is local, older adults often require assistance in getting to their appointments
 - Clinical trials typically require more healthcare interactions than standard of care
- Caregiver support often required for transportation and advocacy
- Desire for treatment with “home” physician
 - There may be preference for treatment with known, community based physician

Elements of Decentralized Trials Which Address Current Barriers

- Alternative off-site methods for safety assessments and monitoring → [local labs/imaging](#)
- Technology to facilitate remote data collection and monitoring → [telemedicine visits \(phone/video\)](#)
- Alternative secure delivery methods of investigational products → [shipping oral drugs, administering IV drugs locally where feasible](#)
- Obtaining remote consent

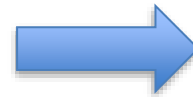
Potential Lessons “Silver Linings” from COVID-19

- Calls to make clinical trials more patient centered pre-dated COVID-19 → FDA’s efforts and support longstanding
 - “Decentralize” Clinical Trials
 - Bring trial assessments to where patients live
 - Take Advantage of Digital Health Technology
 - Learn from “Real-World” Data → Older adults heavily impacted by COVID-19

COVID-19 Evidence Accelerator



National Academies Workshops



Lessons Learned from COVID-19
~ silver linings to influence Project SILVER

NASEM Workshop Q1 2021

Project Title - Improving the Evidence Base for Treating Older Adults with Cancer:

Exploring Root Causes and Bridging the Knowledge Gap Workshop

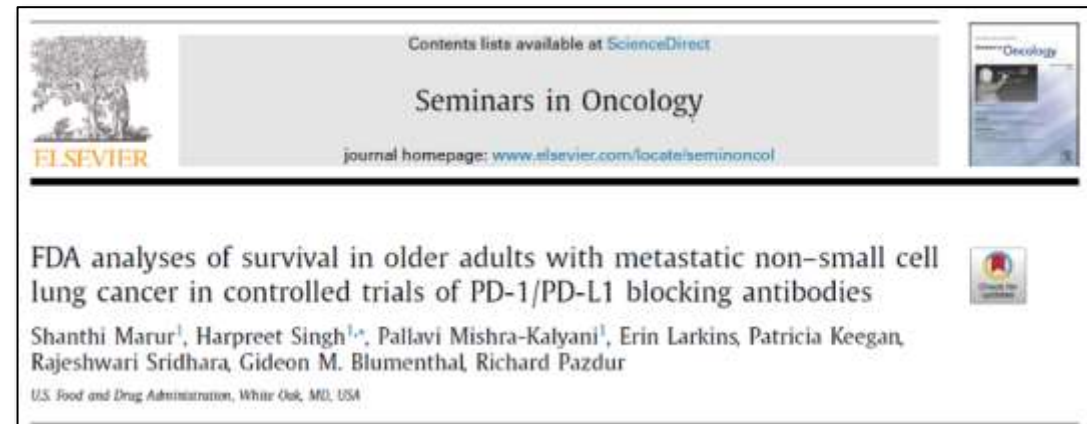
Research & Publications

Perspectives

Enrollment of older adults on oncology trials: An FDA perspective☆

Harpreet Singh*, Julia A. Beaver, Geoffrey Kim, Richard Pazdur

Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States



Contents lists available at ScienceDirect

ELSEVIER

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

FDA analyses of survival in older adults with metastatic non-small cell lung cancer in controlled trials of PD-1/PD-L1 blocking antibodies

Shanthi Marur¹, Harpreet Singh^{1,*}, Pallavi Mishra-Kalyani¹, Erin Larkins, Patricia Keegan, Rajeshwari Sridhara, Gideon M. Blumenthal, Richard Pazdur

U.S. Food and Drug Administration, White Oak, MD, USA

COMMENTARY

Expanding the Evidence Base in Geriatric Oncology: Action Items From an FDA-ASCO Workshop

Laura A. Levit, Harpreet Singh, Heidi D. Klepin, Arti Hurria

JNCI J Natl Cancer Inst (2018) 110(11): djy169

doi: 10.1093/jnci/djy169
First published online October 17, 2018
Commentary

Progress Through Collaboration: An ASCO and U.S. Food and Drug Administration Workshop to Improve the Evidence Base for Treating Older Adults With Cancer

Harpreet Singh, MD, Arti Hurria, MD, and Heidi D. Klepin, MD, MS

original reports Outcomes of Older Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-Negative Metastatic Breast Cancer Treated With a CDK4/6 Inhibitor and an Aromatase Inhibitor: An FDA Pooled Analysis

Lynn J. Howie, MD¹; Harpreet Singh, MD¹; Erik Bloomquist, PhD¹; Suparna Wedam, MD¹; Laleh Amiri-Kordestani, MD¹; Shenghui Tang, PhD¹; Rajeshwari Sridhara, PhD¹; Jacqueline Sanchez, MA¹; Tatiana M. Prowell, MD¹; Paul G. Kluetz, MD¹; Belinda L. King-Kallimanis, PhD¹; Jennifer J. Gao, MD¹; Amna Ibrahim, MD¹; Kirsten B. Goldberg, MA¹; Marc Theoret, MD¹; Richard Pazdur, MD¹; and Julia A. Beaver, MD¹

853.MYELOMA: THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

FDA Analysis of Survival Outcomes in Older Adults with Relapsed-Refractory Multiple Myeloma (RRMM) Treated with Novel Drug Regimens

Bindu Kanapuru, MD, Susan Jin, Kunthel By, Theresa Carioti, Yuan-Li Shen, PhD, Rajeshwari Sridhara, PhD, Nicole J Gormley, MD, Ann T. Farrell, MD, Richard Pazdur, MD

PART #3:

Geriatric Information in Human Prescription Drug Labeling

Eric Brodsky, M.D.

Associate Director, Labeling Policy Team, Office of New Drug Policy,
Office of New Drugs, Center for Drug Evaluation and Research, FDA

Disclaimer



- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
- Photographs in this presentation are from the CDC's *"The State of Aging and Health in America 2013."*

Part 3: Learning Objectives



Discuss the key concepts in the *Geriatric Labeling Draft Guidance*:¹

- How to incorporate geriatric information in labeling
- Omitting, revising, and/or updating geriatric information in labeling



¹ Draft guidance for industry, *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020) (referred to as the Geriatric Labeling Draft Guidance herein). When final, this guidance will represent the FDA's current thinking on this topic.

Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Eric Brodsky at 301-796-0855, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

Geriatric Labeling Draft Guidance

- Assist applicants of human prescription drugs in determining the appropriate placement and content of geriatric use information in labeling
- Replaces the guidance for industry, *Content and Format for Geriatric Labeling* (October 2001), and provides additional examples of geriatric use statements in labeling

Definition of “Geriatric Patients” in Labeling



- FDA received a variety of suggestions for age designations before the Geriatric Labeling Rule was finalized in 1997¹
- For the purposes of prescription drug labeling, the geriatric population is defined as patients 65 years of age and older²
- Additional age cut-off points may be needed within the geriatric population for subgroup effectiveness and safety analyses (e.g., 65 to 74, 75-84, and 85 years of age and older)

¹ See the preamble of the final rule, “Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of ‘Geriatric Use’ Subsection in the Labeling,” (21 CFR 201; 62 FR 45313, 45316) published August 27, 1997.

² 21 CFR 201.57(c)(9)(v)(A)

Geriatric Labeling Draft Guidance: Three Scenarios



Drug is **approved** for:

First

- Use in adult patients (including geriatric patients)^{1,2} (**focus of today's discussion**)
- A geriatric-specific indication:³ For a specific indication, **Second** drug is indicated for use only in geriatric patients¹ and not in adult patients less than 65 years old) (very rare)

Drug is **not approved** in geriatric patients but approved in younger adults (uncommon)

Third

¹ A drug may be approved in all geriatric patients or a subset of the geriatric population

² 21 CFR 201.57(c)(9)(v)(B); ³ 21 CFR 201.57(c)(9)(v)(A)

Drug is Approved for Use in Adult Patients (Including Geriatric Patients): *Geriatric Use Subsection*



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 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Geriatric Use Subsection

Geriatric Exposure Data in *Geriatric Use* Subsection



- Generally recommend including geriatric exposure data in beginning of *Geriatric Use* subsection¹

- Geriatric exposure data:
 - Required when information was sufficient to detect differences in safety and/or effectiveness between geriatric and younger adult patients and there were no observed differences in safety and/or effectiveness²
 - Recommended in all other situations

- Alternative age cutoff points may be permitted³

¹ However, information on specific risks associated with the use of the drug in geriatric patients and/or recommendations on specific monitoring in geriatric patients may appear before the drug exposure information.

² Under this scenario, this subsection *must* include the percentage of patients ≥ 65 years of age and the percentage of patients ≥ 75 years of age (or the total number of patients ≥ 65 years of age and the total number of patients ≥ 75 years of age) in the clinical studies of the drug. See 21 CFR 201.57(c)(9)(v)(B)(2)

³ If the FDA determines that such age cutoff point(s) are accurate and appropriate. See 21 CFR 201.57(c)(9)(v)(F).

Examples of Geriatric Exposure Data in Geriatric Use Subsection¹



- “Of the total number of DRUG X-treated patients in these studies, n (x%) were 65 to 74 years of age, n (y%) were 75 to 84 years of age, and n (z%) were 85 years of age and older.”
- “Of the total number of DRUG X-treated patients in clinical studies for Disease A, n (y%) were 65 to 74 years of age, and n (z%) were 75 years of age and older [see *Clinical Studies (14)*].”
- “Of the total number of DRUG X-treated patients in these studies, n (y%) were 65 years of age and older, while n (z%) were 75 years of age and older.”

¹ The *Geriatric Use* subsection can also include information on the total number of geriatric patients in the clinical studies. For example: “There were n patients 65 years of age and older in the clinical studies for Disease A, Disease B, and Disease C [see *Clinical Studies (14.1, 14.2, 14.3)*].”

Develop Labeling Based on Sufficiency of Information To Detect Differences in Safety and/or Effectiveness Between Geriatric and Younger Adult Patients

- ***Insufficient*** information to detect differences in safety and/or effectiveness between geriatric and younger adult patients
- ***Sufficient*** information to detect differences in safety and/or effectiveness between geriatric and younger adult patients and:
 - Differences observed
 - No differences observed

**Insufficient information to detect
differences in safety and/or
effectiveness between geriatric and
younger adult patients:
Geriatric Use Subsection**

Insufficient Information To Detect Differences in Safety and/or Effectiveness in Geriatric Patients Compared to Younger Adults – Required Statement¹

“Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.”

¹ 21 CFR 201.57(c)(9)(v)(B)(1)

Insufficient Information To Detect Differences in Safety and/or Effectiveness in Geriatric Patients Compared to Younger Adults – Alternative Permissible Statement¹

“Clinical studies of DRUG X did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.”

¹ Alternative permissible statement if FDA determines statement is accurate and appropriate. See 21 CFR 201.57(c)(9)(v)(F).

Insufficient Information To Detect Differences in Safety and/or Effectiveness in Geriatric Patients Compared to Younger Adults (*Disease/Condition Primarily Occurs in Younger Adult or Pediatric Patients*)

- Sometimes a drug is approved for adult patients (including geriatric patients) but there is limited or no experience in geriatric patients because the disease primarily occurs in younger adult or pediatric patients
- Consider following alternative statement in *Geriatric Use* subsection:
 - “Disease A is largely a disease of pediatric and young adult patients. Clinical studies of DRUG-X did not include patients 65 years of age and older.”

**Sufficient information to detect
differences in safety and/or
effectiveness between geriatric and
younger adult patients:
*Geriatric Use Subsection***

***Sufficient Data:*¹ No Observed Differences in Safety and/or Effectiveness in Geriatric Patients Compared to Younger Adults**

- “No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.”²
- “No overall differences in safety or effectiveness of DRUG X have been observed between patients 65 years of age and older and younger adult patients.”³

¹ Data is *sufficient* to detect differences in safety and/or effectiveness between geriatric and younger adult patients. See 21 CFR 201.57(c)(9)(v)(B).

² Required regulatory statement. See 21 CFR 201.57(c)(9)(v)(B)(2).

³ Alternative permissible statement if FDA determines statement is accurate and appropriate. See 21 CFR 201.57(c)(9)(v)(F).

***Sufficient Data:*¹ Observed Differences in Safety and/or Effectiveness in Geriatric Patients Compared to Younger Adults²**

Geriatric Use subsection must² contain a summary of observed differences in geriatric and younger adult patients:

- Responses:
 - Reduced effectiveness
 - Unique adverse reactions
 - Adverse reactions with greater frequency or severity
- Specific monitoring
- Dosage Recommendations

¹ Data is *sufficient* to detect differences in safety and/or effectiveness between geriatric and younger adult patients. See 21 CFR 201.57(c)(9)(v)(B); ² 21 CFR 201.57(c)(9)(v)(B)(3).

***Sufficient Data Example:*¹ Observed Differences in Effectiveness in Geriatric Patients Compared to Younger Adults²**

“The **overall response rates** in DRUG-X-treated adult patients < 65, 65-75, and ≥ 75 years of age were 25%, 20%, and 15%, respectively. In comparison, the overall response rate for placebo-treated patients in each of these subgroups was 10%.”

¹ Data is *sufficient* to detect differences in safety and/or effectiveness between geriatric and younger adult patients. See 21 CFR 201.57(c)(9)(v)(B); ² 21 CFR 201.57(c)(9)(v)(B)(3).

Sufficient Data: Observed Differences in Effectiveness in Geriatric Patients Compared to Younger Adults

8.5 Geriatric Use

safety

...
No overall difference in safety of DRUG-X have been observed between patients 65 years of age and older and younger adult patients.

Of the 542 patients with metastatic or recurrent NSCLC randomized to DRUG-X in combination with drugoxide-a, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 270 patients less than 65 years of age compared to 0.73 (95% CI: 0.56, 0.95) in the 272 patients 65 years of age and older.

effectiveness

Sufficient Data Example:¹ Observed Differences in Safety in Geriatric Patients Compared to Younger Adults²



“In patients ≥ 65 years of age, consider premedication with drug-a before DRUG-X use [see *Dosage and Administration (2.x)*]. In DRUG-X-treated patients, the incidence of \geq Grade 3 **nausea and vomiting** was 10%, 35%, and 40% in adult patients < 65 , 65-75, and ≥ 75 years of age, respectively [see *Adverse Reactions (6.1)*]. In comparison, in placebo-treated patients, \geq Grade 3 **nausea and vomiting** occurred in 1–3% of patients in the three subpopulations.”

¹ Data is *sufficient* to detect differences in safety and/or effectiveness between geriatric and younger adult patients. See 21 CFR 201.57(c)(9)(v)(B); ² 21 CFR 201.57(c)(9)(v)(B)(3).

Sufficient Data: Observed Differences in Safety in Geriatric Patients Compared to Younger Adults



8.5 Geriatric Use

effectiveness

... No overall differences in effectiveness of DRUG-X have been observed between patients ≥ 65 and older and younger adult patients.

There was a higher incidence of serious adverse reactions in patients ≥ 65 years of age than in patients < 65 years of age (35% vs. 22%, respectively). The serious adverse reactions most frequently reported in patients ≥ 65 years of age were related to myelosuppression and consisted of neutropenia (10%), thrombocytopenia (7%), and anemia (7%) [see Adverse Reactions (6.1)].

safety

Pool or Do Not Pool



For All Approved Adult Indications Include Statements Comparing Safety and Effectiveness Between Geriatric and Younger Adult Patients

8.5 Geriatric Use

...

Disease-A

[[Include exposure]] No overall differences in safety or effectiveness of DRUG X have been observed between patients 65 years of age and older and younger adult patients.

Disease-B

[[Include exposure]] Clinical studies of DRUG X did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Two Separate Statements
(pooling not appropriate)

For All Approved Adult Indications Include Statements Comparing Safety and Effectiveness Between Geriatric and Younger Adult Patients

Pooled data from studies
from all two diseases

8.5 Geriatric Use

Of the total number of DRUG X-treated patients in clinical studies in **Disease A and Disease-B**, n (y%) were 65 years of age and older, while n (z%) were 75 years of age and older [see *Clinical Studies (14.1, 14.2, and 14.3)*]. No overall differences in safety or effectiveness of DRUG X have been observed between patients 65 years of age and older and younger adult patients with Disease A and Disease-B.

Additional Information to Include in the *Geriatric Use* Subsection



Specific Risks, Safety Concerns, and Specific Monitoring in Geriatric Patients: *Geriatric Use* Subsection



Geriatric Use subsection must include:¹

- Specific risks or safety concerns associated with the use of the drug in geriatric patients
- Specific monitoring in geriatric patients

May Include Risk Mitigation Prior to Exposure (Observed Differences in Safety in Geriatric Patients Compared to Younger Adults)

8.5 Geriatric Use

Assess renal function more frequently in DRUG-X-treated geriatric patients because there is a greater risk of DRUG-X-associated intravascular volume contraction and symptomatic hypotension in geriatric patients *[see Warnings and Precautions (5.1)]*.

The recommended dosage of DRUG-X in geriatric patients is lower than younger adult patients *[see Dosage and Administration (2.2)]*.

Include exposure data ...

Summarize Specific PK¹ or PD¹ Studies: *Geriatric Use Subsection*²



If specific PK or PD studies have been carried out in geriatric patients they must be:

- Summarized in the *Geriatric Use* subsection (see example)
- Described in detail in the CLINICAL PHARMACOLOGY section.

8.5 Geriatric Use

... Geriatric patients had higher plasma drugozide AUC compared to younger adult patients, and the plasma drugozide AUC observed in geriatric patients increases the risk of DRUG X-related adverse reactions [see *Warnings and Precautions (5.x)* and *Clinical Pharmacology (12.3)*]. Therefore, the recommended dosage of DRUG X in geriatric patients is lower than in younger adult patients [see *Dosage and Administration (2.x)*].

¹ Pharmacokinetic = PK; pharmacodynamic = PD; ² 21 CFR 201.57(c)(9)(v)(C)(1).

Dedicated Studies in Geriatric Patients



- Consider summarizing dedicated geriatric studies in *Geriatric Use* subsection
- Details of adequate and well-controlled dedicated geriatric studies must be included in CLINICAL STUDIES section¹

¹ See 21 CFR 201.57(c)(15) the guidance for industry: *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006)

Geriatric Use Information in Other Sections of Labeling

(Drug is Approved for Use in Adult Patients, Including Geriatric Patients)



Geriatric Use Information in Other Sections of Labeling (1 of 3)



- **DOSAGE AND ADMINISTRATION:** must include recommended dosage in geriatric patients if different than younger adult patients¹

- **WARNINGS AND PRECAUTIONS:**
 - Must include clinically significant adverse reactions or risks unique to geriatric patients²
 - Should generally include clinically significant adverse reactions or risks that occur at a greater severity or frequency than in younger adult patients

Geriatric Use Information in Other Sections of Labeling (2 of 3)



- **ADVERSE REACTIONS:** Should include *details* of geriatric adverse reactions (AR) if there are:
 - Differences in the frequency, severity, or type of AR compared to younger adult patients, or
 - AR that are unique to geriatric patients

- **CLINICAL PHARMACOLOGY:**
 - Must include detailed descriptions of PK and/or PD study data if such studies were carried out in geriatric patients¹
 - Should include relevant pharmacogenomic study data, data obtained from population analyses, and dose response information.

Geriatric Use Information in Other Sections of Labeling (3 of 3)

- **CLINICAL STUDIES:** Should include detailed descriptions of studies that provide substantial evidence of effectiveness for use in geriatric patients

Omitting, Revising, and/or Updating Geriatric Use Information: *Geriatric Use Subsection*



Omission of or Alteration of Required Statement(s) in the *Geriatric Use* Subsection¹

- Applicants may propose omission or alteration of required statement(s) in the *Geriatric Use* subsection:
 - Must provide a rationale for an omission or an alternative statement
- FDA may permit omission of statement(s) or an alternative appropriate and accurate statement if no required statement is appropriate or relevant

Omit Statements in the *Geriatric Use* Subsection That Discuss Age-Related Morbidity Not Related to the Drug



Omit following statement:

“There is a greater incidence of infections in the elderly population in general.”

Updating Geriatric Use Information in Labeling



- Labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading¹
- When revising existing information in the labeling, evaluate labeling content to ensure that it accurately reflects current knowledge about the use of the drug in geriatric patients *for all approved indications*

Future Topics: Geriatric Use Information in Labeling

Situations when it is not clear when there are sufficient data to determine if there are differences in responses between geriatric and younger adults





Prescription Drug Labeling Resources



FDA's *Prescription Drug Labeling Resources* website provides over 150 labeling resources for the Prescribing Information, FDA-approved patient labeling, and/or carton and container labeling for human prescription drugs, including biological products (including over 50 guidances with labeling content) - see [Overview of Website](#).

Highlights of Prescribing Information: Format Sample

<p>HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.</p> <p>PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol Initial U.S. Approval: YYYY</p>	
<p>WARNING: TITLE OF WARNING See full prescribing information for complete boxed warning.</p> <ul style="list-style-type: none"> Text (4) Text (5.x) 	
<p>-----RECENT MAJOR CHANGES----- Section Title, Subsection Title (x.x) M/YYYY Section Title, Subsection Title (x.x) M/YYYY</p>	
<p>-----INDICATIONS AND USAGE----- PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)</p> <p><u>Limitations of Use</u> Text (1)</p>	
<p>-----DOSAGE AND ADMINISTRATION----- <ul style="list-style-type: none"> Text (2.x) Text (2.x) </p>	
<p>-----DOSAGE FORMS AND STRENGTHS----- Dosage form(s); strength(s) (3)</p>	
<p>-----CONTRAINDICATIONS----- <ul style="list-style-type: none"> Text (4) Text (4) </p>	
<p>-----WARNINGS AND PRECAUTIONS----- <ul style="list-style-type: none"> Text (5.x) Text (5.x) </p>	
<p>-----ADVERSE REACTIONS----- Most common adverse reactions (incidence > x%) are text (6.x)</p> <p>To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.</p>	
<p>-----DRUG INTERACTIONS----- <ul style="list-style-type: none"> Text (7.x) Text (7.x) </p>	
<p>-----USE IN SPECIFIC POPULATIONS----- <ul style="list-style-type: none"> Text (8.x) Text (8.x) </p>	
<p>See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling Q&A and Medication Guide.</p> <p style="text-align: right;">Revised: M/YYYY</p>	

Prescription Drug Labeling Resources

Webpage (1 of 2)¹



- Prescribing Information (PI) Requirements and Rules
- PI Guidances
- Presentations
 - Sections of the PI
 - Broad Labeling Content
- Safety-Related Labeling Resources
- PLLR Resources
- Sample Templates and Format Tools for PI
- Established Pharmacologic Class Resources

Prescription Drug Labeling Resources

Webpage (2 of 2)¹



- Product-Specific Labeling Resources
 - Generic Drugs
 - Biological Products
- Product Quality-Related Labeling Resources
- Resources for Other Labeling Types
 - Patient Labeling
 - Carton and Container Labeling
- SPL Resources
- Labeling-Related Databases

Questions for Audience



Parts 3 and 4: Challenge Question #1



Which of the following is **true** about geriatric exposure data in the *Geriatric Use* subsection?

1. Must always provide percentage of patients ≥ 65 years of age and older and percentage of patients ≥ 75 years of age and older
2. FDA recommends providing the number and percentage of geriatric patients
3. Alternative age cutoff points may be permitted
4. Should provide exposure data for each disease rather than pooling data from all diseases
5. Items #2 and #3

Parts 3 and 4: Challenge Question #2



Which of the following should **NOT** be included in the *Geriatric Use* subsection?

1. Specific risks or safety concerns associated with the use of the drug in geriatric patients
2. Specific monitoring in geriatric patients
3. A summary of PK studies in geriatric patients
4. Current knowledge about the use of the drug in geriatric patients for all approved indications
5. All of the above should be included in the *Geriatric Use* subsection



Questions: cdersbia@fda.gov