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
The US Is Aging

Age and Sex Structure of the Population for the United States: 2012, 2030, and 2050

The World Is Aging

A. Less developed regions

B. More developed regions

United Nations, World Population Ageing 2013
## Prescription Drug Consumption (≥ 65 years)

<table>
<thead>
<tr>
<th>Year</th>
<th>Population, million</th>
<th>Population, %</th>
<th>Rx Consumption, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>35</td>
<td>12.4</td>
<td>25</td>
</tr>
<tr>
<td>2030</td>
<td>71</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td><strong>World</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2030</td>
<td>973</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>2050</td>
<td>-</td>
<td>20</td>
<td>-</td>
</tr>
</tbody>
</table>

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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).
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 bioavailability 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

- 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

Studies in Support of Special Populations: Geriatrics

- Arbitrary geriatric population $\geq 65$ years; important $\geq 75$ 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

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).
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.

Guidance on Geriatric Labeling

Guidance for Industry

Content and Format for Geriatric 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

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
Move “Geriatric Use” to Section 8.5

PLR = Physician Labeling Rule
ICH E7 Update

Guidance for Industry

**E7 Studies in Support of Special Populations: Geriatrics**

Questions and Answers

- 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.
The 2013 FDA Report to Congress

FDA Report

Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products
August 2013

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

https://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm
Older Adults in Clinical Trials
Age of Clinical Trial Participants

% ≥65 Years

Phase 1:
- 2% (2013)
- 3% (2014)
- 3% (2015)

Phase 2:
- 16% (2013)
- 23% (2014)
- 24% (2015)

Phase 3:
- 19% (2013)
- 31% (2014)
- 40% (2015)

Chen et al. J Womens Health (Larchmt) 2018 (modified)
% Older Adult in New Drug Trials 2013 – 2015

- Anesthesia/Analgesia (1) 22.3
- Anti-Infectives (7) 11.1
- Antivirals (8) 6.2
- Cardiovascular/Renal (10)† 45.3
- Dermatology (5) 7.4
- Gastroenterology/Inborn Errors (7) 9.6
- Medical Imaging (5) 45.3
- Metabolism/Endocrinology (12) 22.7
- Neurology (5) 11.4
- Oncology/Non-Oncology Hematology (28) 33.4
- Psychiatry (4) 0.2
- Pulmonary/Allergy/Rheumatology (9) 18.1
- Special Pathogens (1) 3.9

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 trials. Enrollement by age groups in trials for select oncology drugs approved between 2014 and 2017.

<table>
<thead>
<tr>
<th>Demographic subgroup</th>
<th>18–64 years</th>
<th>&gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (n = 5,914)*</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Colorectal (n = 5,009)</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>NSCLC (n = 3,952)*</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Prostate (n = 7,458)*</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>All cancers (n = 22,333)*</td>
<td>59%</td>
<td>41%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Demographic subgroup</th>
<th>Breast cancer (n = 833)</th>
<th>Colorectal cancer (n = 800)</th>
<th>NSCLC (n = 1,979)</th>
<th>All cancers (n = 3,612)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17–64 years</td>
<td>56</td>
<td>56</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>≥65 years</td>
<td>44</td>
<td>44</td>
<td>35</td>
<td>39</td>
</tr>
</tbody>
</table>

Regulatory Development in Other Regions

• Besides the ICH E7 and ICH E7 update
EMA’s Efforts to Care for Older Adults

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

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.

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 Guidelines on Developing Drug Products for Older Adults

- Food and Drug Administration: Human Factors and Medical Devices https://www.fda.gov/medicaldevices/medicaldevices/default.htm
高齢化の現状と将来

65+: 23.3% (2011)
65+: 39.9% (2060)
75+: 26.9%

* 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

Older Adults in Japanese Clinical Trials

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

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

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 (RA, NSCLC, Depression, AD)

RA

NSCLC

Depression

AD

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
Agenda & Speakers
Registration
Attendee Information & Directions
Contact

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.