THE WAY FORWARD

Robert J. Temple, M.D.
Deputy Center Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration
March 17, 2021

The Way Forward: Potential Solutions

What do we need and what can the FDA do?

- What can we require? (Laws and regulations), and
- What can we urge/suggest? (Guidance, case-by-case recommendations)

with respect to

1) inclusion of the elderly, and

2) analysis of elderly subgroup results for assessment of safety, effectiveness, and PK/PD?

What Do We Want?

1) As you will hear from Dr. Madabushi,, we need PK information in the older population as a starting point, a need emphasized in guidance since the 1980's, and not difficult to obtain. It should not require a large population and we know what to measure, in contrast to identifying PD/effectiveness differences, where we are not nearly as clear about what we need (but we are learning) and where larger populations are needed in most cases to identify differences.

2) Enough (and how much is that?) actual clinical exposure to look for age-related differences in both safety and effectiveness, including the impact of:

Other illnesses

Other drugs (polypharmacy)

3) We particularly need more elderly exposure (and the elderly therefore should not be excluded based on age or concomitant illness/treatment) for drugs that

Have sedative properties

Have effects on blood pressure (lowering)

Are used to treat illnesses that are prominent in the elderly

First, consider regulation and potential requirements regarding both need for inclusion and requirements for analysis of elderly subgroups. Of course, a requirement for analyses can have implications for inclusion/participation (you can’t analyze data you do not have).

Required Analyses

CFR314.50(d)(5)(v) and (vi)

This section of the regulations was added in 1998 and might SEEM to be solely about data analyses, and indeed the text says clearly and repeatedly that it was NOT changing the amount of data needed. It says:

"The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modification of dose or dose interval for specific subgroups"

" The safety data shall be presented by gender, age , and racial subgroups (and, when appropriate, other subpopulations, such as people with renal failure or disease severity)"

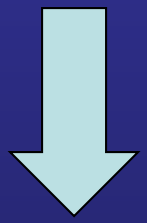
On face, these are analytic requirements, not inclusion requirements, BUT if those analyses are important enough to be included in a regulation, and if the drug labeling covers use in both genders, all races, and the elderly, it seems quite within the scope of the rule to REQUIRE enough patients in those groups to allow a reasonable analysis. We have not specifically said that, but it is suggested by another part of the 1998 rules change (the IND rules) and by the preamble

The 1998 rule also changed the IND regulations at 21CFR312.33 to require that annual reports tabulate patients who had entered trials by age, gender, and race. The reason given for this was “to alert sponsors as early as possible to potential demographic deficiencies that could lead to avoidable deficiencies (later) in the NDA submission.” That language, it seems to me, represents a clear indication that lack of participation by subgroups could be an NDA deficiency, probably a safety deficiency, as 21CFR314.125 [Refusal to Approve an Application] gives as one reason for refusal [314.125(b)(4)]

> “insufficient information about the drug to determine whether it is safe for use under the conditions prescribed, requested, or suggested in its proposed labeling”. The law in 505(d) similarly refers to adequate tests by all methods reasonably applicable to [assess safety under the prescribed conditions]

Inadequate Safety Information

- This language strongly indicates that lack of important information in a subgroup with potentially distinct responses, such as the elderly, could be a safety deficiency leading to a refusal to approve a drug.



- Include older populations, and
- Do not exclude older patients for concomitant illness and concomitant therapy.

Guidance on Subpopulation Inclusion

- In 1983 (draft) and 1989 (final), FDA published the “Guideline for the Study of Drugs Likely to Be Used in the Elderly.”
- There was also a 1994 ICH Elderly Guideline and a 1993 MaPP for FDA reviewers stating that they should not start their review of an NDA unless demographic subset data analyses were done or readily available.
- Guidance on the evaluation of subgroups was critical. As I noted before, the regulations demanded analysis of these groups and strongly suggested that they should be included,
- BUT what should you do with those data?

1989 Guidance: Guidance for the study of Drugs Likely to be Used in The Elderly

- 1) Early PK
  - The guidance focuses initially on a critical point: age-related differences CAN arise from PK or PD differences
  - The FIRST thing to do (it is easiest and fastest and is needed to interpret PD and clinical measures).
  - They are known to occur (recognized for decades)

- They are more frequent (at the time, but probably still true) than documented PD differences
- They relate to age-associated conditions like renal impairment, CHF, or multiple drug therapies.

1989 Guidance

- 2) PD in special cases, such as drugs with CNS effects (sedative/hypnotics, and others)
- Dr. Slattum, in a 2007 paper, reviewed documented PD differences in older adults, and found that: The most frequent differences were in responses to CNS-active drugs. There were some differences in CV responses, but there were not too many others.
- No doubt there are others and the data base is surely growing.

Multiple Actions are Usual, Rarely Expected

- 3) Include:
  - Patients in studies should reflect the ultimate user population. It is OK to exclude people who could not participate (do what was required) or who might be at risk from the drug, but phase 3 trials should NOT exclude based on age alone or based on concomitant illness of treatment.

- We will surely learn more about differential responses as we become better at including the older patients.