The Industry's Views on "Older" Old Patients

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Outline

- Introduction
- EFPIA Survey: Overview of collected answers addressing representation of "older" old patients in the clinical development programmes
- Evolving our Future Together

Introduction

- **"Older"old patients** (subjects aged 80+) are **generally excluded** from pre-authorisation Clinical Trials of development programs from which they might potentially benefit,

because they are **frail**

- The resulting **lack of knowledge** on the effects of drugs in this population leads to increased drug adverse events when they are nonetheless prescribed in 'real life'.

Frailty – an area of unmet needs

- **= Increased vulnerability to stress**

  Accumulation of deficits & resulting decreased physiological reserve of multiple, interacting physiological systems

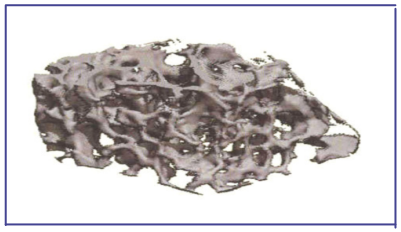
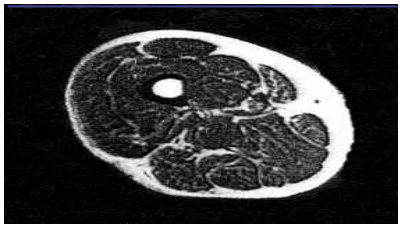
- **→ Increased incidence of adverse outcomes**
  - Falls & Fractures
  - Delirium
  - Hospitalizations & Institutionalization
  - Disability & Death
  - Greater use of health care services

- **Prevalence in the EU (SHARE)**
  - Age 50-64 : Pre-frailty: 37.4% , Frailty: 4.1%
  - Age 65+ : Pre-frailty: 42.3% , Frailty: 17.0%

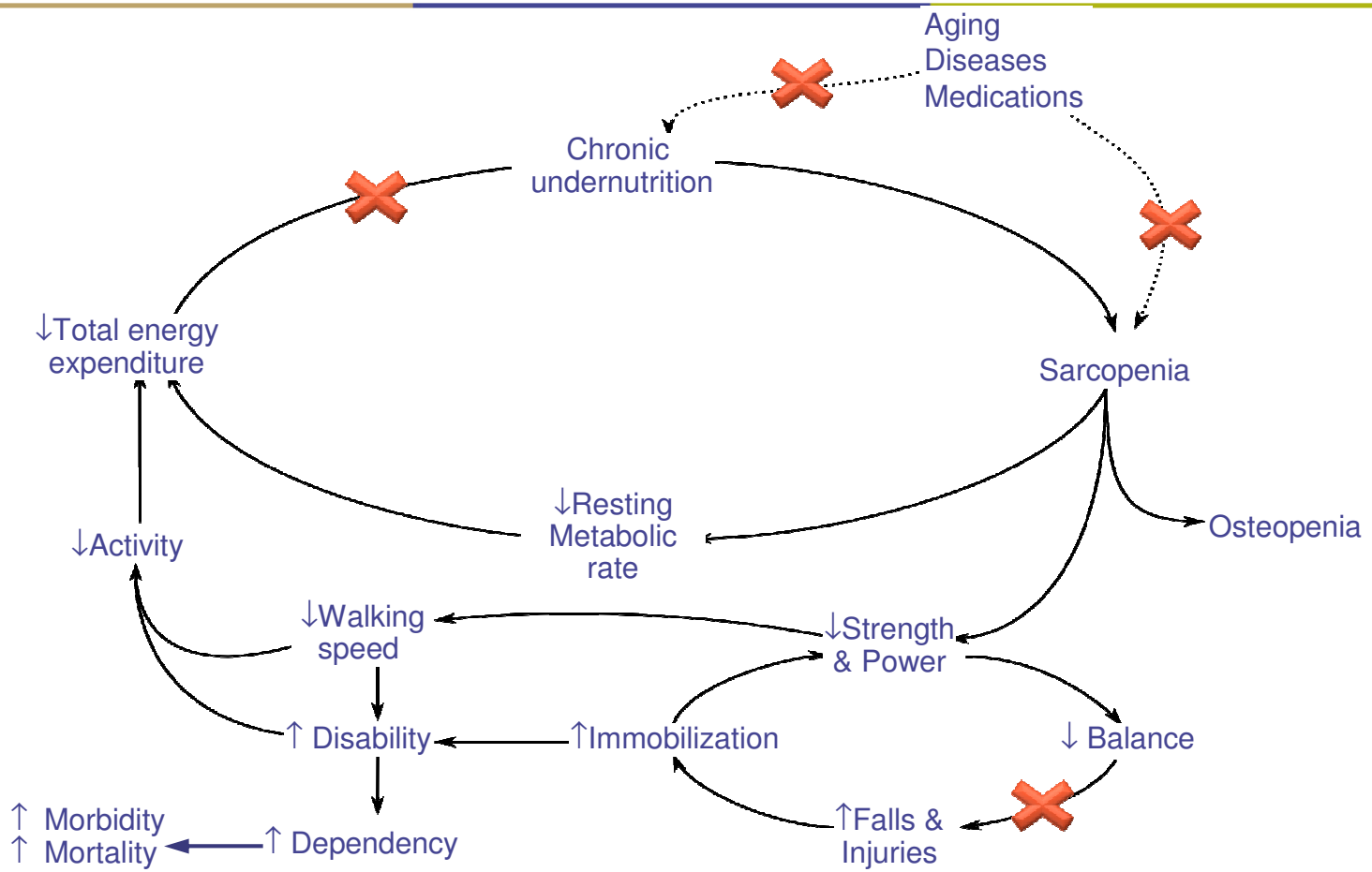
- **A potentially reversible condition**
  - Recovery to relatively fittest state common at younger ages
  - Chance of complete recovery declines with age

Outcome	Hazard Ratio
Incident Fall	1.29
Worsening Mobility	1.50
Worsening ADL Disability	1.98
Hospitalizations	1.29
Death	2.24

Estimated yearly cost of Sarcopenia

Osteoporotic fractures	Sarcopenia
	
$16.3 billion	$18.5 billion

The Frailty Cycle – Physical Phenotype



Modified from Fried LP et al. J of Gerontol 56:M146;2001

Overall, are there **specific aspects, beyond ICH E7** content and scope, that should be considered to more consistently evaluate the benefits and risks of a new medicine in the older population?

- Guidance with regard to “very elderly” would be **helpful**.
- Consideration should be given to **methodologies** to evaluate how a medicine intended to treat a specific organ/condition, contributes to the **overall function** of the patient.
- Clinical trial patient population **should be representative** of the population who will be prescribed the drug
- **Withdrawal effects** and **compliance** are important to keep in mind.
- Considering increased requirements to conduct post-authorisation efficacy and safety studies within the older patients population. Certain **specific adverse events** should be specifically investigated : e.g. effects on cognitive function, urinary incontinence or retention, weight loss, sarcopenia, effects on balance and falls

Comments from the Survey : Are Clinical trials in **frail older patients** realistic? How to generate data in this group?

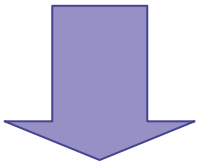
- **It is very important to have a well accepted operational definition of frailty** and predictive biomarkers related to disease occurrence are important to identify and to be validated in this type of population.
- **Frailty** should not be confused with **'calendar age'**
- We lack an accepted **definition of frailty.**
  - Comment from HTA perspective: from a PRO standpoint, the distinction between
    - deficiency (pathophysiology),
    - disability (function), and
    - handicap (adaptation to environment)
  - is a very useful distinction when developing and validating PROs for clinical trials

Conclusions

- Pre-authorisation CTs need to include “Older” Old patients, taking into account their **specific characteristics** :
  - by systematically evaluating their **frailty status** (using a suitable instrument),
  - by identifying **multi-morbidity clusters**.
  - Safety assessment should also record specific **geriatric syndromes**, which might occur during the study.
- Only the systematic study of outcomes specific to this population will enable improvement of the Benefit/Risk of interventions needed in this population.
- **Categorical classification** of diseases is no longer sufficient to handle the complex therapeutic needs of the “Older” Old patients.
- Adequate **regulatory appraisal** and **guidance** is necessary to help the Industry in pursuing innovative programs that aim to fulfil specific unmet medical needs of geriatric population, including the “Older Old”

SANOFI Ageing TSU Vision

- **Deliver to the world-wide aging population a series of important pharmaceutical products in integrated solutions that:**
  - Extends the period of “healthy aging” to reduce the incidence and duration of living with severe medical conditions and disability
  - Increases Independence/Autonomy to reduce caretaker burden and incidence and duration of institutionalization



Benefit to Individuals and Society

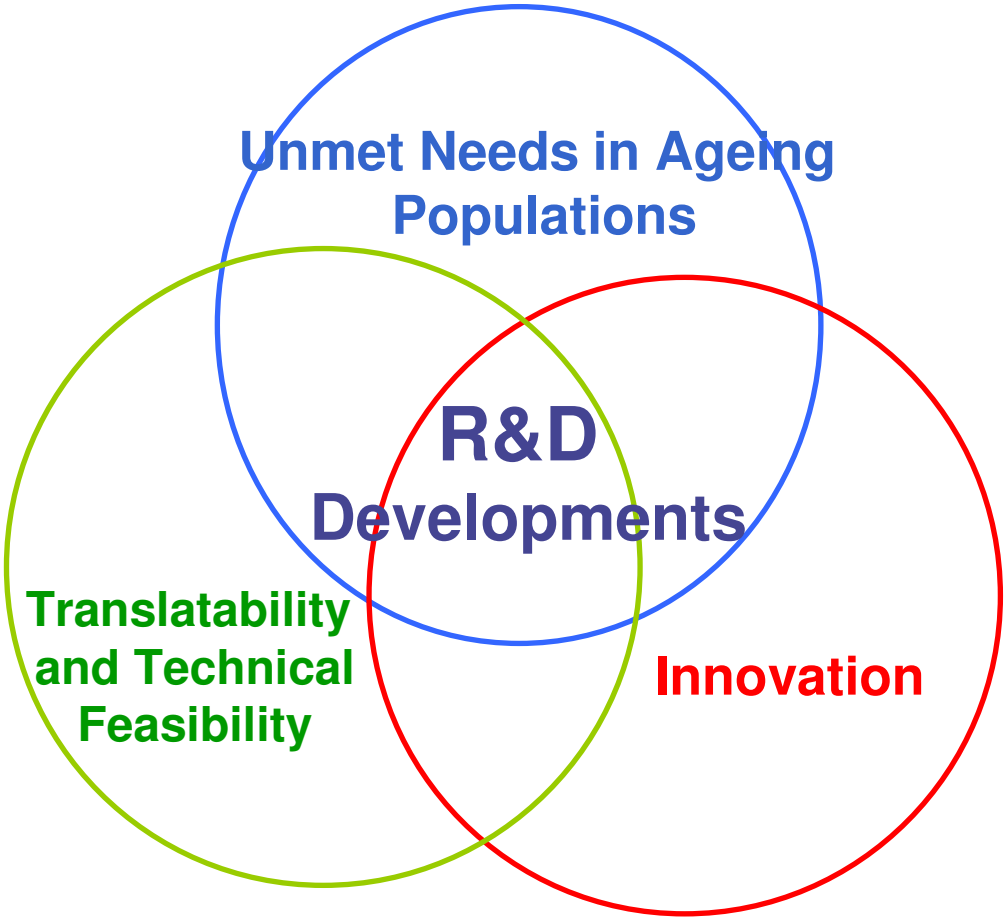
Conclusions:
New objectives for the pharmaceutical industry

- Shift from the old paradigm of a product–centred innovation to

  a patient-centred innovation aimed to:

  - **Fulfil the complex therapeutic needs of the geriatric population.**
  - **Deal with specific geriatric medical conditions.**
  - **Prevent and slow chronic diseases complications and loss of autonomy.**

Ageing TSU R&D Strategy in 2011



Evolving our Future Together

- Categorical classification of diseases is no longer sufficient to handle the complex therapeutic needs of the “older old” patient.
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The EFPIA Temporary Working Group is recommending to establish a **collaborative regulatory Think-Tank** to establish a **consensus** on adapted methodologies, including **the operational definition of Frailty** and the endorsement of good **geriatric functional outcomes**

The Industry's Views on Geriatric Medicines

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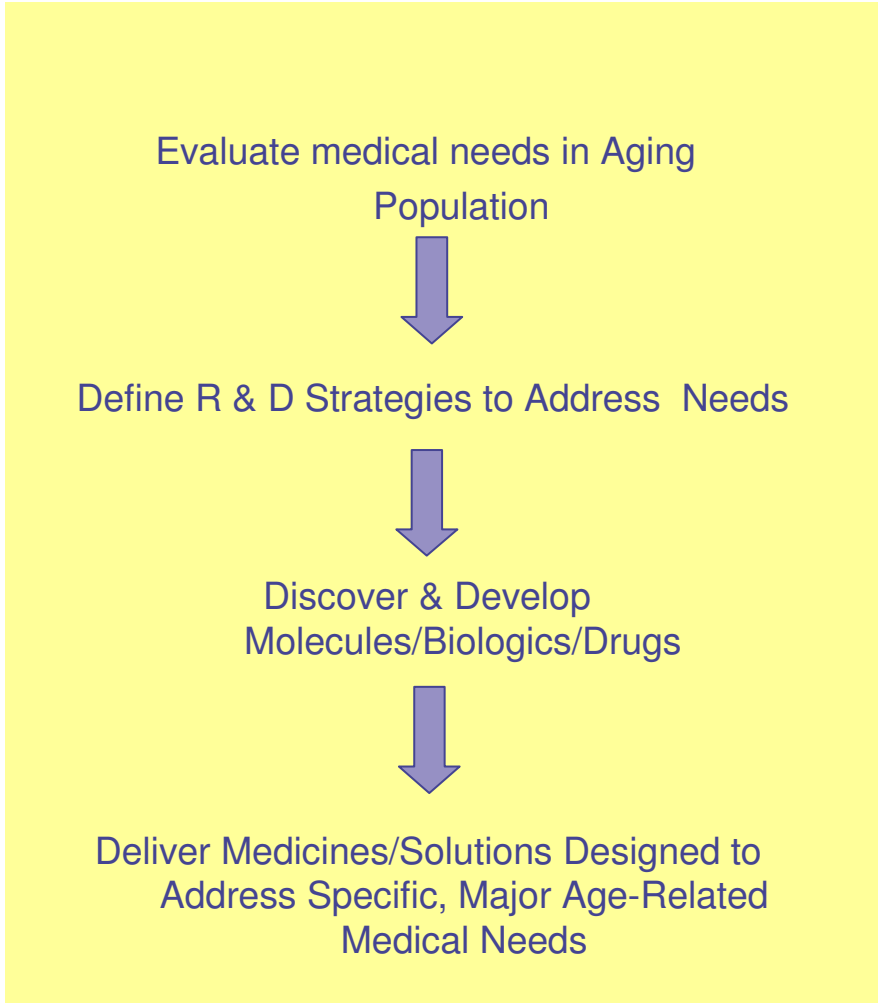
TSU Aging R&D Concept



Healthy Aging

- Preventive approaches using existing active ingredients (i.e. synthetic drug substance already on the market or well known natural or food ingredient)
  - **Ability to proceed directly to large, simple clinical trials to demonstrate preventive actions**
- Strategies being explored
  - **Natural mitochondrial function modulator with robust pharmacologic rationale and evidence to prevent:**
    - **Frailty from pre-frailty**
    - **Dementia from MCI**
  - **Polypills for cardiovascular prevention**