Sarcopenia - a Regulatory Perspective

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The views expressed in this talk are those of the author, not of the FDA
Objective

• Describe several regulatory requirements as they relate to:
  – definition of an indication
  – current evidentiary standard for drug approval

• Highlight regulatory challenges to a sarcopenia indication:
  – definition of sarcopenia
  – relationship between definition and indication(s)
  – criteria for patient population selection
  – endpoint selection (Phase 2 and 3 in particular)
  – clinically meaningful benefit
• Indication
• Patient selection and clinical endpoints
• Registration clinical trials
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Sarcopenia and Related Indications

- No approved “sarcopenia” indication
- Several anabolic products have cachexia or cachexia-like indication(s);
  examples:
  - Oxandrin (1964): “adjunctive therapy to promote weight gain after weight loss […]”
  - Serostim (1996): “treatment of HIV patients with wasting or cachexia […]”
- Content of indications reflect disease understanding and scientific thinking at the time:
  - broader and less specific in the 60s
  - disease-specific in the 90s
- None defines a specific degree of muscle impairment, a qualitative or quantitative feature of muscle structure or function.
- Sarcopenia (indication) is new territory for the FDA
Indication – Regulatory Definition

• CFR 201.57(*Full prescribing information*):
  “This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.”

• Is sarcopenia a recognized disease or condition?
Is sarcopenia one indication?

• Age-related sarcopenia (geriatric syndrome)
• Disease-specific sarcopenia: reduction in muscle mass and muscle functioning in specific conditions (e.g. COPD, etc.)
• Disuse atrophy or improvement of physical function after orthopedic surgery or casting
Sarcopenia nomenclature

• Anatomic (low muscle mass) – sarcopenia

• Functional (low strength) – dynapenia

• Contextual (frailty) – sarcofrailty?
Sarcopenia vs. cachexia

**Sarcopenia**
- low muscle mass
- decreased strength
- chronic inflammation
- nutritional deficiencies

**Cachexia**
- low muscle mass
- decreased strength
- chronic inflammation
- nutritional deficiencies
Disease and Indication

• **Since the indication and definition of sarcopenia are closely related, there is a need for a clinically meaningful definition of disease**
  – not an artificial numerical concept that has minimal relevance for a practitioner
  – the indication has to result in labeling that is clear and useful for the practitioner
  – favors function over structure, improvement of everyday life activities over clinical research measurements and biomarkers
  – since sarcopenia is likely a continuum (from close to normal to extremely severe) there is a need for quantitative criteria for identifying patients with different degree of severity (different risk/benefit)

• **Without a generally accepted definition, the incidence, prevalence, and public health impact of sarcopenia cannot be assessed accurately**
Sarcopenia Indication

- If laboratory tests or physical performance/strength measurements are used to define the indication, ideally they should be widely available and easy to perform in a clinical setting.
- Examples:
  - Diabetes: fasting plasma glucose or oral glucose tolerance test, HbA1C
  - Obesity: BMI
  - Osteoporosis: DXA scan
  - Hypertension: blood pressure
Recognition of “sarcopenia” as a medical condition and an evidence-based disease definition are essential for a sarcopenia indication(s).
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At which point does the gradual decline in muscle mass and function due to chronological aging become a disease instead of a manifestation of normal aging?
“Prevention” vs. “Treatment” Indication

- very different indications
- different objective for clinical development
- different patient populations (healthier vs. sicker)
- may require different efficacy endpoints or different thresholds for the same endpoint
- different size of trials for efficacy (powered for different effects) regardless of safety considerations
- different risk/benefit decisions
- likely very different clinical development programs
“Prevention” vs. “Treatment” Indication

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- For prevention having accurate knowledge of the natural history of the disease is paramount
• Indication
• Patient selection and clinical endpoints
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Patient Selection

• Patient population selection will depend on disease definition which will impact:
  – type of indication(s) sought
  – specific quantitative criteria used for definition of the indication
  – age at enrollment
  – duration of intended treatment
Inclusion/exclusion criteria

• should reflect drug-specific safety concerns that may result from the preclinical program
• could be tailored to the stage of drug development
  – more restrictive in the Phase 2 program
  – broader in the Phase 3 program
• should differentiate between “sarcopenia” and cachexia, malnutrition, chronic conditions that result in muscle loss secondarily
• should ensure that weakness is related to muscle function rather than the overall health status
• may need to exclude co-morbid conditions and medications that may interfere with muscle strength and physical performance
Endpoint Selection

• **Endpoint selection will depend on disease definition**
• The endpoints should be consistent with the condition and meaningful for the indication(s) sought
• Pharmacodynamic endpoints in Phase 1-2 trials:
  – Drug-specific
    • IGF-1 for marker of GH function for GH, GHRH
  – General
    • Muscle strength/function
    • Functional performance
• Different drugs
  – may have different mechanisms of action
  – may require different endpoints/biomarkers
  – all need to confer in the end a clinically meaningful benefit
Endpoint Selection

• Functional endpoints are naturally more informative than structural endpoints
  – e.g. limitations of lean body mass (LBM)
    • may be an appropriate endpoint in Phase 2 trials along with a wide range of endpoints but only a secondary endpoint for phase 3 trials
    • improvements in LBM without clinically relevant functional improvements are not sufficient for an indication

• Across products a functional improvement should be not only statistically significant but **clinically relevant**

• How do sarcopenia endpoints relate to clinical outcomes (disease complications)?
  – decreased mobility
  – loss of autonomy
  – increased fracture rate
  – mortality
Clinical endpoints Phase 2-3

• List:
  – handgrip strength
  – gait speed
  – knee flexion/extension
  – short physical performance battery
  – stair climb
  – timed get-up-and-go test
  – appendicular body mass

• Which ones should be primary or secondary?
• Should be combination endpoints (e.g. co-primary endpoints)?
• Should a hierarchy of endpoints be used (algorithm that can be applied to clinical practice)?
Clinical endpoints Phase 2-3

- New endpoints need validation as do “old” endpoints when used in a new patient population or for a new indication
- Ideally should include measurements that can be widely applied in a clinical setting rather than a research setting
- Patient reported outcomes are anticipated to be important
Objective

• Indication
• Patient population and patient selection
• Clinical Endpoints
• Registration clinical trials
Level of evidence

• Phase 3 clinical trials must meet current evidentiary standard for approval: demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)

• Substantial evidence of benefit = adequate and well-controlled clinical studies (§314.126)

• Studies have to be designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation” (§314.126)
Phase 3 program – Trial Design Issues

- Randomized, controlled (placebo) design
  - Should resistance training and nutrition optimization be background intervention for pharmacological interventions?
  - Should clinical trials include a physical activity optimization treatment arm?
- Clear and meaningful definition of the patient population (will be reflected in the label!)
  - inclusion and exclusion criteria
  - baseline characteristics
- Will need to demonstrate a meaningful clinical benefit
What is a clinically meaningful benefit?

- **Clear benefits:**
  - Fracture risk reduction
  - Reduction in mortality
  - Improvement in mobility and everyday functions (i.e. reversion or improvement of loss of autonomy) and quality of life without additional harm

- **No clear benefit:**
  - Improvement in a structural endpoint (e.g. LBM) or a biomarker of drug activity without functional performance improvement
  - Improvement of unknown significance in a functional performance endpoint (unrelated to fracture risk, mortality, etc.)
Phase 3 Program - Safety

- Safety is anticipated to be at least as important as efficacy because patients targeted are frail, have limited functional reserve, major disease-specific and/or age-specific comorbidities
- Safety needs to individualized
  - ICH E1 recommendations for chronically used drugs are a good start but size of clinical program will depend on findings in the animal toxicology program, mechanism of action of each specific drug, findings in the phase 1-2 program
- Likely different safety questions
  - for an already marketed drug with relatively well known safety profile (e.g. GH, testosterone) vs. a new molecular entity
  - for drugs in a better characterized class (GH and GHRH analogs) vs. a new class of drugs
- Clinical programs reflect the size of the target population
- Risk of abuse: this class(ses) of drugs could have a substantial impact outside the patient population of interest