Sarcopenia: Regulatory Questions

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The views expressed in this talk are those of the author, and do not necessarily reflect the views of the Food and Drug Administration.
Overview

• What FDA does, and how it relates to a proposed sarcopenia indication
• What FDA has been telling sponsors so far
• Why a good definition is important
• Challenges regarding indication
• Challenges regarding endpoints
• Challenges regarding measurement methods
• Other trial design challenges and concerns
• Some of FDA’s biggest remaining questions
What Does the FDA Do?

- The FDA’s main job with respect to drugs and biologic medicines is to make sure that the labeling of the product is accurate in regard to efficacy and safety information.
- By “labeling”, we mainly mean the Full Prescribing Information, which is a multipage document containing sections on the indication; dosage and administration; contraindications, warnings and adverse reactions; drug interactions; clinical studies; and several other topics.
- Development programs for drugs need to give the Agency the information it needs to ensure the Full Prescribing Information is complete and accurate.
- The indication for a drug is driven by the disease definition, by the types of patients who were studied in clinical trials, and by the endpoints that were measured. For a proposed indication related to sarcopenia, these areas, and others, present regulatory challenges to the FDA.
What FDA Has Been Telling Sponsors Before this Conference

Agency aware of increasing interest in developing drugs to treat disorders associated with decreased muscle mass, often accompanied by decreased muscle strength and/or decreased muscle performance.
What FDA Has Been Telling Sponsors Before this Conference (cont)

Consensus does not appear to exist in the medical literature, and in academia in general, regarding:

- How to define the specific disorder
- Which potential trial endpoints would be most clinically meaningful
- Which measurement methods for endpoints are best-validated
What FDA Has Been Telling Sponsors Before this Conference (cont)

• Agency expects that additional research and academic consensus conference discussions will lend more clarity to key issues over the coming years

• At present, FDA cannot endorse any specific definition, endpoint or measurement method over another
What FDA Has Been Telling Sponsors Before this Conference (cont)

• Sponsors who wish to pursue development programs related to these conditions during this evolutionary stage of consensus development should design trials that measure multiple parameters of muscle strength and muscle performance.

• Choice of endpoints should be guided by assessment of the medical literature for measures that seem to be likely candidates in future consensus conferences.

• Emphasis on endpoints that appear to be predictive of important clinical outcomes, particularly survival, and which can be reproducibly measured using validated methods.
Demonstration of a consistently positive effect on a clinically meaningful primary endpoint, and on multiple secondary endpoints that appear predictive of important clinical outcomes, seems the best approach for sponsors who choose to pursue indications in this area at this time.
A Good Definition is Important

• Definition → trial patient selection → indication
• The definition of the condition drives the patient selection for clinical trials.
• The indication for a drug is based on the patient population that has been studied.
• The limitations of use of a drug are related, in part, to the limitations of the information that can be obtained from the studied patient population.
• Not everyone who has relatively low muscle mass has a clinical problem.
A Good Definition is Important (cont)

In the end, will have to conform to CFR 201.57, i.e. will need to satisfactorily define sarcopenia as:

- “a recognized disease or condition”, or
- “a manifestation of a recognized disease or condition”, or
- “symptom(s) associated with a recognized disease or condition”
A Good Definition is Important (cont)

• Definition (and the subsequent indication) cannot be an artificial numerical concept that is not supported by evidence of clinical meaningfulness.

• For example, one can’t arbitrarily define the disease as a muscle mass in the 10th percentile or below.

• If the definition includes measure(s) of strength or performance, methods should be widely available in a clinical setting.

• The definition needs to facilitate the main job of the FDA, which is to make sure there is clear, accurate prescribing information, starting with a clear, usefully worded indication.
Definition: What if a Component of the Definition Isn’t Really Important?

- The word “sarcopenia” means “too little muscle”, implying that muscle mass is an important part of the definition.
- Prior to this conference, the debate about definitions has revolved around inclusion of components of muscle mass (or lean body mass), strength and/or performance.
- However, what if only one or two of these components is predictive of important clinical outcomes, such as mortality, fracture, hospitalization, etc.? That is, what if increasing muscle mass doesn’t improve clinically meaningful outcomes, but increasing strength does? What if patients have improvement in important outcomes, even though their muscle mass doesn’t increase?
- If mass ends up “not mattering”, or mattering much less than strength or performance, is “sarcopenia” really the disorder that warrants treatment, or is the true disorder something different, such as lack of strength (perhaps dynapenia) or poor muscular performance (perhaps frailty)?
- Might need to see some large trials that target all three aspects in order to answer this question.
Indication(s):
Additional Challenges

• Short-term vs long-term use? Different regulatory requirements (e.g. carcinogenicity studies for drugs intended for chronic use)

• Prevention vs treatment? A higher bar for demonstration of safety for a prevention indication. If a drug recipient is not yet “sick”, the benefit:risk equation changes.
Endpoint Challenges

- Is the endpoint clinically meaningful?
- If the endpoint is not survival, does the endpoint have other independent clinical meaningfulness?
- Is it an endpoint or a surrogate?
- If it’s a surrogate, how well-established is the predictive value of the surrogate for a clinically important outcome? How can one eventually demonstrate efficacy definitively?
- What amount of change in the endpoint is clinically meaningful?
- If it’s a patient-reported outcome, can it provide key supportive evidence of efficacy?
- If it’s a patient-reported outcome, has it been adequately validated?
Endpoint Challenges (cont)

• Does there appear to be agreement in the academic community about what the most clinically meaningful endpoint(s) are?
• If studying sarcopenia in a particular patient population, e.g. patients with cancer or a chronic illness, does the drug convey any benefit for the underlying illness?
• Will efficacy for a single endpoint be adequate in trials of the first candidate drugs? Will efficacy for a single endpoint ever be adequate, given the somewhat generalized nature of the condition being treated?
Measurement Method Challenges

• Methods must be reproducible and validated.
• Methods that are available in a research setting might not be practical in a doctor’s office.
• If doctors’ offices don’t have the measurement tools used in the clinical trials, how will doctors know their patient is getting better?
• If a drug is studied with methods that can’t easily be used clinically, it will be hard to write prescribing information that tells clinicians how to use the drug.
Trial Design: Other Challenges

• In general, the larger the potential population for a drug, the larger the safety database should be. If the proposed indication is such that it could include a large segment of the population, registration trials may need to be large.

• The populations for whom the drugs are targeted might have high cardiovascular risk. The drugs might be administered chronically, perhaps for years. Will the development programs need to be structured (and have adequate statistical power) to permit a meta-analysis of major adverse cardiovascular events?
Ethical Concern

- The FDA review must document that informed consent was obtained.
- The population (often the frail elderly) to be studied for sarcopenia may present challenges to documentation of fully informed consent. May be vulnerable population, both physically and cognitively.
- Study design and execution will need to address this concern.
Additional Concern: Risk of Abuse

Anticipate potential for abuse for purposes of:

- Body-building
- “Fountain of youth”/ anti-aging in the absence of debility

Some agents may be classified as controlled substances.
Some of FDA’s Biggest Remaining Questions

• Is sarcopenia clearly a “medically recognized disease or condition”, as specified in the Code of Federal Regulations?
• Is there consensus in academia for the definition of sarcopenia?
• What kinds of patients should be enrolled in clinical trials for sarcopenia?
• What endpoints are clinically meaningful?
• If surrogate endpoints are proposed, which ones best predict clinically meaningful outcomes?
• How many primary and secondary endpoints need to be measured to provide adequate information for assessment of efficacy and safety?
• How large will the target population be, and how large will clinical trials need to be to adequately assess safety?