Companion Article to Regulatory Primer for Longevity Biotech Companies (including applicants for XPRIZE Healthspan and ARPA-H PROSPR)

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This is a companion article to the Kitalys Institute's Targeting Healthy Longevity 2025 virtual Session 3: Regulatory Primer for Longevity Biotech Companies (including applicants for XPRIZE Healthspan and ARPA-H PROSPR), held on July 18, 2025 and described and linked to the recording here: https://www.linkedin.com/pulse/regulatory-primer-longbio-companies-including-applicants-thomas-seoh-ptrze/.

The Need for a Clear Regulatory Pathway

Longevity biotech companies are doing amazing work, seeking to develop and translate cutting-edge understanding of the biology of aging to prevent or reverse age-related chronic diseases and conditions. However, in order to remain relevant, they need to demonstrate efficacy for increasing healthspan and safety of their molecules in human clinical trials.

It has long been recognized that the lack of a clear regulatory pathway for longevity medicines was a structural barrier to the emergence of a trillion dollar longevity industry.

The industry's responses have included (i) a "stepping stone" strategy of initially targeting a specific disease, then generating additional data to add indications over time (see, e.g., Keytruda and GLP-1 drugs); (ii) proposing composite baskets of diseases to delay the emergence of the first disease among the basket (such as in the long-discussed but not-yet-conducted TAME – Targeting Aging with Metformin – trial); (iii) targeting individual or related diseases with a clinical trial endpoint that could be seen as a proxy for longevity (such as the PROTECTOR 1 Phase 3 trial of resTOR Bio, which failed to meet its endpoint); and (iv) seeking reversal/rejuvenation endpoints, that, if met in the context of a disease, could be easily assessed by the current regulatory framework.

XPRIZE Healthspan and ARPA-H PROSPR Require Clinical Data

Ambitious challenges such as XPRIZE Healthspan (https://www.xprize.org/prizes/healthspan) and ARPA-H PROSPR (https://arpa-h.gov/explore-funding/programs/prospr) stretch the limits of the existing regulatory framework. In the case of XPRIZE Healthspan, competitors are expected to develop therapeutic treatments that significantly extend healthy lifespan (by 10 or 20 years) by restoring muscle, cognitive, and immune function in individuals aged 65-80, within a treatment period of one year. In the case of ARPA-H PROSPR, contract parties are expected to work on extension of healthspan of Americans by 20 years or more through the development of an Intrinsic Capacity composite score measurable at home that predicts long-term health outcomes based on physiological and biochemical measures, or the development of repurposed or new drugs that increase healthspan.

Whether to compete for the prize or complete a contract, clinical data will be needed, and clinical investigation will require approval of and supervision by the FDA or another regulatory agency where the trial(s) will be conducted. The competition and the contracts draw innovators who may not necessarily be drug developers with extensive regulatory experience, thus the purpose of the Regulatory Primer webinar.

Investigational New Drug Application (IND) under the FDA

In the US, a developer needs to submit an IND to the FDA and receive a 'clear to proceed' determination in order to commence clinical investigation. The IND requires detailed data and/or plans pertaining to (i) Chemistry, Manufacturing and Controls (CMC), (ii) Non-Clinical; and (iii) Clinical matters.

CMC

CMC information for a drug needs to cover drug substance characterization, impurity identification/characterization, formulation and manufacturing process information, assay development, and significant stability information for both the drug substance (API) and drug product in final dosage form to support initial and later-stage clinical development. There are analogous requirements for a biologic, or an advanced therapy such as cell or gene therapy.

Non-clinical

IND-enabling non-clinical typically requires data from studies following Good Laboratory Practice (GLP) covering general toxicology (dosed over the same duration as targeted for the early clinical studies); safety pharmacology (trying to define the dose-response relationship of behavioral, respiratory, cardiovascular and other adverse effects); genetic toxicology (in vitro and in vivo tests for genetic mutation); repeat dose toxicology (establishing, e.g., the no-observed-effect level (NOEL), no-observed-adverse-effect level (NOAEL), maximum tolerable dose (MTD), and the target organs of toxicity; non-clinical proof-of-concept pharmacodynamic studies *in vitro* and in animals to demonstrate the potential clinical benefits; and estimates of the human dose range.

Clinical

The IND will also require an early clinical development plan including the protocol(s) for the opening clinical studies, such as Phase 1 Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies in healthy humans. XPRIZE Healthspan competitors and ARPA-H PROSPR contract parties will need more than clinical safety data, so they will want to discuss Phase 2 initial efficacy studies with the FDA (which presumably will be needed to compete for the prize or complete the contract.

Some Considerations for XPRIZE Healthspan and ARPA-H PROSPR Competitors

Regulatory requirements must be met in order to generate clinical data for the prize or a contract, but an FDA NDA or BLA is not required, nor particularly plausible within the time frame of the prize or contract. Thus, an applicant to XPRIZE Healthspan or an ARPA-H PROSPR contract has to take a short term and a longer term view of regulatory considerations: how to get into the clinic and generate human data that will be competitive for the prize or responsive to the contract, in the short term; and how to leverage such data while reducing the need to re-do such trials to the extent possible for an NDA or BLA a number of years from now.

- ***What initial indication should be targeted? This will also determine which FDA Division will be involved.***

In the case of XPRIZE Healthspan, an FDA review division for a therapeutic area is not currently equipped to look at multiple primary endpoints in therapeutic areas as disparate as cognitive decline, frailty and decline in immune resilience. Thus, a competitor must choose the initial target indication, and primary endpoint(s) in that indication, as well as secondary and exploratory endpoints in that and in other indications, and other data, that can be presented as evidence of satisfying the prize requirements.

Likewise in the case of ARPA-H PROSPR, Intrinsic Capacity (the objective of Technical Area 1), and repurposed and novel drugs (the objective of Technical Areas 2 and 3, respectively), must target increasing healthspan, which involves preventing, delaying or reducing the risk of or reversing multiple chronic diseases.

- ***What will be the primary, secondary, and exploratory endpoints, to ensure that the product is being developed within the existing regulatory framework, yet enough data is generated to be in competition for the prize or responsive to the contract?***

The geroscience field has been intensely looking for reliable biomarkers of aging. While a number of intriguing candidates have been proposed and are being investigated, no aging biomarker has been accepted by FDA as a surrogate marker or a registrable endpoint. Thus, there will be a bit of 'double book-keeping' – the clinical trials for regulatory purposes will seek to hit endpoints that are either already validated, or negotiated with and accepted, by the FDA, while the developer will seek to hit those measures and results that it believes the prize jury or ARPA-H is looking for. Competitors and contractors must thus manage two sets of goals simultaneously, one for the FDA, and one for the prize or the contract.

- ***Should the IND be commercial or Investigator-Initiated?***

While the technical requirements of a corporate IND and an Investigator Initiated (e.g. an academic) IND are in theory identical, in practice, the FDA is to a point more flexible and supportive of the latter. Thinking in the short term, a developer might be able to get into the clinic faster, cheaper and with less data under an Investigator-Initiated IND. But thinking in the long term, commercialization will require a corporate IND, and while clinical data generated under an Investigator-Initiated IND may certainly be accepted by the FDA as supportive, they may not be substitutes for the clinical data FDA may require under a corporate IND.

- ***Should the clinical trial(s) be conducted in the US, or ex-US?***

While most US drug development is based on clinical trials conducted in the US under an IND, there are certain jurisdictions where it can be advantageous (easier, faster, less expensive) to start clinical trials (e.g. Australia, Japan for stem cells), and US NDAs/BLAs can certainly include data generated from countries ex-US, provided FDA feels it can rely on the adequacy of regulatory controls.

XPRIZE Healthspan explicitly bills itself as a global competition, and some international applicants have indicated their intention to generate at least initial clinical data ex-US. Presumably, the jurisdiction where the clinical data is generated will be considered as part of the quality of the entry.

It is conceptually possible to generate clinical data in countries with less rigorous regulatory requirements that are destinations of medical tourism. While this may be a way to obtain preliminary clinical proof of concept, our assumption is that clinical data generated in the US, or a jurisdiction with a comparable regulation of drug development, will be an indispensable part of the winning dossier for XPRIZE Healthspan, or a contract deliverable for ARPA-H PROSPR.

In contrast, ARPA-H emphasizes that it is funding innovations to improve the health of Americans, and is seeking to create a network of clinical sites reasonably accessible to most Americans. Thus, clinical development will likely have to be conducted in the US under an IND.

- ***What are special regulatory considerations of combination approaches?***

Solutions proposed by competitors and contractors are often combination approaches, e.g., one or more compounds, devices, supplements, lifestyle modifications, medical treatment protocols, etc. Regulatory science requires rigorous showings of individual additive or synergistic contributions of product components, which are not requirements of the prize or contract. Even a winning solution may not be easily registrable in all its parts as a regulated drug or device, and developers will have to be strategic and resourceful in their long game to develop an approvable regulated product based on component data that the FDA will assess.

Conclusion

Products pursued by XPRIZE Healthspan competitors and ARPA-H PROSPR contractors will need to meet regulatory requirements in order to generate necessary clinical data. But competitors and contractors need to approach their development programs with both a short term and a long term perspective, to satisfy regulatory requirements for clinical trials, generate the range of data necessary to be competitive or responsive for the prize or contract, and maximize the usability of the data for ultimate regulatory approval. And, at present, the first regulatory approvals will be pursuant to a 'stepping stone' strategy of collecting sufficient evidence to gain approval disease by disease, for diseases recognized by regulatory science.

It is worth noting that there are efforts underway to enable and facilitate regulatory review of drugs, devices and supplements that target healthspan, such as the Kitalys Institute's THRIVE Act,* that should be of interest to all longevity biotech companies.

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* The draft THRIVE Act proposes an optional regulatory pathway for healthspan products (those that can prevent, delay, reduce the risk of or reverse chronic diseases of aging), with three tiers of escalating evidentiary requirements, and a period of market exclusivity per tier, to incentivize the generation of clinical evidence for extending healthspan. Tier 3 is analogous to full FDA approval, Tier 2 somewhat analogous to Accelerated Approval, and Tier 1 would afford qualifying products earlier access to the market than under current regulations, in order to generate increasingly rigorous clinical data on the capitalization of a commercial-stage company. THRIVE v.2.0, responding to feedback from various stakeholders, is now available at www.kitalys.org.

About Kinexum and the Kitalys Institute

Kinexum is a regulatory, clinical, product and corporate development strategic advisory firm (www.kinexum.com). Since 2017, Kinexum, and later its not-for-profit Kitalys Institute (www.kitalys.org), have organized the *Targeting Healthy Longevity* (previously called *Targeting Metabesity*) conference, convening leaders of NIH, FDA, Congress, the UK Parliament, geroscience and chronic disease research, industry and capital markets in furtherance of the Kitalys mission to accelerate the translation of science into public health to prevent chronic diseases and extend healthy longevity for all. Over 200 conference sessions are posted on Kitalys's YouTube channel at www.healthy-longevity.org. Kitalys has advised XPRIZE Healthspan and ARPA-H PROSPR on strategic regulatory matters, and Kinexum represents a number of longevity biotech companies, including semi-finalists in XPRIZE Healthspan.