Innovative Genomics Institute

November 13, 2023

Attn: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Therapeutic Products

Re: Docket No. FDA-2023-D-2436

Re: Docket No. FDA-2023-D-2436 – Draft Guidance on Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products.

To whom it may concern,

The Innovative Genomics Institute (IGI), a public, academic research institute formed through a partnership between the University of California, Berkeley and the University of California, San Francisco, below submits comments to issuance of the Draft Guidance on Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products by the U.S. Food and Drug Administration. We thank the FDA for preparing this important draft guidance and hope the agency finds our suggestions helpful. We are available to address any questions should they arise.

On behalf of the Innovative Genomics Institute,

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We would like to thank the following contributors for their expertise evaluating the draft guidance and adding valuable insights based on their experiences:

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The draft guidance clearly lays out the need to have in place a manufacturing process that can be translated to the commercial setting without the need to cross significant comparability bridges. For a number of reasons outlined below, this is a particularly challenging demand of academic developers and manufacturing centers and may have significant unintended consequences. As currently presented, we understand that the comparability requirements are expected to be followed by all developers equally, without considering implementation challenges in the academic setting, where much of the early-phase preclinical and clinical work is performed. While we recognize that the agency aims to avoid situations where novel products are generated in a way that is not conducive to scaling up or out upfront, early-

stage academic investigations are critical to generate essential proof-of-principle data in humans. There should be a pathway for investigational products to provide evidence of safety (and efficacy) in Phase I trials without inevitably failing due to comparability challenges in later stages of development.

Key challenges for academic manufacturing:

1. As cGMP requirements are phase-appropriate, so should the guidance for manufacturing changes and comparability. We are concerned that the draft guidance presents a *de facto* expectation of "full GMP" (i.e., in compliance with 21 CFR Part 211) for Phase I studies. This is not feasible in the academic manufacturing setting, and, per the draft guidance, a transfer from Phase-I-appropriate GMP to full GMP may face insurmountable comparability barriers. Importantly, a 2020 analysis found that 50% of all gene therapy clinical trials (all of which were in Phase I or II) were funded exclusively by academia or NIH, suggesting that a substantial number of products would be affected by such stringent comparability requirements. Notably, all Phase III trials were performed by industry, but only about 25% of either Phase I or II trials.[1] Without a clear differentiation between requirements for early- and late-stage development, we are concerned that this guidance, if finalized in its current form, will stymie innovation, prevent development of therapies for ultra-rare disorders, and exacerbate affordability and access challenges. Therefore, we ask that the agency differentiate between earlier and later stages of development and establish more detailed phase-appropriate guidance on this subject to support all types of developers, not just established industry players. We believe that existing affordability and access challenges for cell and gene therapies (CGTs) can only be addressed by a diverse ecosystem of players, which includes academic, startup, and nonprofit developers.

2. CGT products exclusively developed and administered in the academic setting may not overcome comparability barriers. In the event that a comparability study becomes necessary in the academic setting, e.g., due to the need to change the source of a critical raw material or a change in manufacturing facility, investigational products that are exclusively manufactured and administered in the academic hospital setting may no longer reach patients, despite evidence of safety and efficacy. This is a particular issue for treatments for ultra-rare diseases that are unlikely to garner commercial interest. We therefore urge FDA to be especially flexible and support comparability assessments for such INDs.

3. A locked-in manufacturing process would require much earlier industry involvement. In practice, to be able to 'lock in' the manufacturing process prior to advancing to clinic (e.g., in lines 132-134, the agency recommends any extensive manufacturing changes to be introduced prior to clinical studies), technology transfer from academia to industry would have to be completed prior to any first-in-human studies. However, a biotech or pharmaceutical company with adequate manufacturing capacity may view an investigational CGT product without clinical data as too risky, potentially precluding the therapy from moving into the clinic or beyond Phase I studies, ultimately decreasing the number of approved products. Some have interpreted this section to be exclusively referring to a pivotal trial – we ask that the agency clarify this. Nonetheless, for rare diseases with small patient population sizes, there may not be traditional separation of trials into

[1] Kassir et al. Sponsorship and Funding for Gene Therapy Trials in the United States. *JAMA. 2020;323(9):890–891. doi:10.1001/jama.2019.22214*

Phases I, II, and III and a single Phase I/II trial may be used to provide evidence of safety and effectiveness in support of a BLA. The alternative – for academic centers to have advanced manufacturing capabilities (compliant with full cGMP) and mature quality control systems in place – is an unrealistic expectation.

Ensuring that academic trials can investigate and transfer novel products to the commercial setting *after* clinical evidence of safety (and possibly efficacy) have been collected, without facing insurmountable comparability barriers, is central to continued innovation and patient treatment.

4. Risk management systems and analytic assays. Academic manufacturing facilities typically do not have the capabilities (or funding) to develop, qualify, and validate a wide range of analytic assays in anticipation of a thorough comparability assessment. Academic centers also often do not have the capacity to implement failure mode and effects analyses or other risk management strategies. In early stages of development, academic manufacturers may not evaluate certain CQAs and, thus, would not have established analytic assays for these quality attributes. Therefore, in the event a comparability assessment is needed in the academic setting, these limitations may preclude continued product development. Lines 412-417 and 426-451 acknowledge the complexities of CGT products and their risk assessments and highlight that gaps in knowledge necessitate more extensive comparability studies. Ultimately, these limitations make it challenging to submit a detailed study design to the agency, as specified in V.B.
   We ask FDA to consider these limitations and update the guidance to align the need for risk management systems and analytic assays for products to the feasibility thereof in early stages of development. Accordingly, comparability assessments between pre-change products manufactured in academic settings and post-change products manufactured by industry should be adjusted based on the knowledge about a product that can reasonably be generated in the academic setting.

5. Lack of clarity regarding minor manufacturing changes and expectations for comparability studies. While the draft guidance specifies that transferring a process to a new manufacturing facility is considered a major change (lines 419-422), it would be helpful if an updated guidance included examples of minor manufacturing changes – and the expectations for comparability evaluations, if any – as well as additional examples of major manufacturing changes. Lines 297-299 outline that manufacturing changes that could affect product quality must be reported to FDA. We ask FDA to further clarify what types of changes, if any, are *not* expected to affect product quality. For example:
   a. Is a change of material to a higher grade considered a change that would not affect product quality and would therefore not have to be reported to FDA?
   b. Is a change in a cryopreservation parameter, e.g., from using 5% DMSO to 10% DMSO, considered a minor change?
   c. Is a small change in the process, e.g., a wash buffer changes from 3% to 5% human serum albumin, considered a minor change?
   d. If the manufacturer of a reagent changes, but the stated activity of both the previous and new reagent is the same, and the biological/chemical composition similar (i.e., as far as can be gleaned without insight into proprietary information), would changing reagent manufacturer be considered a minor change?

Additional comments and specific requests for clarification:

1. Request for additional examples of CMC changes that require new IND submissions. We appreciate that the agency highlights several examples of CMC changes that would constitute new INDs (IV.A.). We would appreciate understanding whether the following scenarios would also require new IND submissions:
    a. Is a small change in the nucleotide sequence of a transgene that does not affect the potency or safety of the gene therapy considered a new product? For example, a wildtype hemoglobin sequence vs. anti-sickling (HbA-T87Q) variant?
    b. Line 286 indicates changing a target gene for genome editing constitutes a new IND. Does a change in guide RNA sequence targeting the same gene for the same disease also constitute a new product?
    c. To what extent are changes in non-viral delivery methods considered CMC changes requiring new IND submissions? For example, does a change in a lipid nanoparticle's composition that does not alter the target tissue specificity constitute such a change?

2. With reference to lines 366-371, where the agency outlines that significant benefits in effectiveness and/or safety may be interpreted as products being incomparable, we ask for additional clarification to understand under what circumstance, if any, a manufacturing change that improves a product's safety and/or effectiveness (without adverse effects) can be implemented without the post-change product being considered a different product. This would greatly support improved patient care and avoid the need to submit a new IND for a similar, yet improved, product.

3. The draft guidance highlights the importance of retaining samples from all lots in order to be able to perform potency assays in future comparability assessments (lines 604-613). We ask that the agency clarify its expectations in cases where samples from initial lots might be compromised due to prolonged storage (or are otherwise not representative of the lots when initially used in investigations).

To summarize, we urge the FDA to consider the importance of academic and other not-for-profit developers in advancing innovative cell and gene therapies and to design phase-appropriate guidance relating to manufacturing changes and comparability assessments that does not stymie innovation or complicate patient access. We thank the agency for its diligent work on this issue and are available to answer any questions.
