April 20, 2021

Peter Choi
Sidley Austin LLP
1501 K Street, NW
Washington, DC 20005

Re: Docket No. FDA-2020-P-1416

Dear Mr. Choi:

This letter responds to the citizen petition (Petition), which the Food and Drug Administration (FDA or the Agency) received on May 20, 2020. The Petition, submitted on behalf of Cell2in Inc. (Petitioner), requests that FDA update one or more of certain guidance documents to "identify real-time glutathione monitoring methods as an acceptable means of measuring potency for purposes of submitting a Biologics License Application (BLA) for cell-based therapies, including stem cell therapies, under Section 351 of the Public Health Service Act (PHS Act)." Your Petition explains that the Petitioner has been developing a version of a reversible and real-time glutathione (GSH) monitoring assay (i.e., "fluorescent real-time thiol tracer" or "FreSHtracer"), and the Petition includes data obtained using FreSHtracer intended "to demonstrate that GSH assays can be used to measure cells' antioxidant capacity, functionality, stemness, and consequently, potency."

We have carefully considered the information submitted in your Petition and other relevant information available to the Agency. For the reasons stated below, your Petition is denied.

I. BACKGROUND

All biological products regulated under section 351 of the PHS Act must meet prescribed requirements of safety, purity and potency for BLA approval (21 CFR 601.2). For cellular therapy products regulated under section 351 of the PHS Act, conformance testing (21 CFR 601.20(a)) and control of the manufacturing process (21 CFR 601.20(c)) are required to comply with FDA's Current Good Manufacturing Practice (CGMP) For Finished Pharmaceuticals regulations (21 CFR Parts 210 and 211) as well as applicable biologics regulations in 21 CFR Part 600. "No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product," (21 CFR 610.1), which include tests for potency, sterility, purity, and identity (21 CFR Part 610, Subpart B).

Potency is defined as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of

the product in the manner intended, to effect a given result." (21 CFR 600.3(s)). FDA requires potency testing for licensed biological products, as provided in 21 CFR 610.10:

> Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency [in 21 CFR 600.3(s)].

For investigational cellular therapy products, although it may not be possible to meet all of the requirements related to potency testing for licensed biological products, the sponsor must submit data to assure the identity, quality, purity and strength (21 CFR 312.23(a)(7)(i)) as well as stability (21 CFR 312.23(a)(7)(ii)) of products used during all phases of clinical study. The amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available (21 CFR 312.23(a)(7)(i)).

II. RESPONSE TO PETITION

The Petition specifically requests that FDA update any or all of the following guidance documents to identify real-time GSH monitoring assays as an acceptable means of measuring potency for the purposes of a BLA for cellular therapy products, including stem cell therapies:

- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (April 2008) (CMC Information for Human Somatic Cell Therapy INDs Guidance);
- Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (January 2011) (Potency Tests for CGT Products Guidance); and
- Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System (March 2014) (Cord Blood Licensure Guidance).

In describing the grounds for this request, the Petition argues that the Agency should encourage use of GSH monitoring assays as potency assays for cellular therapy products in general; it also includes arguments specific to the use of GSH monitoring assays as potency assays for "HPC, Cord Blood Products" [1] that are the subject of the Cord Blood Licensure Guidance. We address these arguments below.

[1] As used in the Cord Blood Licensure Guidance and in this response, the term "HPC, Cord Blood" refers to "the final drug product (cryopreserved or thawed) of minimally manipulated hematopoietic stem/progenitor cells from placental/umbilical cord blood, sourced from an unrelated allogeneic cord blood donor and intended for hematopoietic and immunologic reconstitution."

A. Use of GSH Monitoring Assays to Measure Potency for All Cellular Therapy Products

In support of your request that FDA update any or all of the above-listed guidance documents, you argue that real-time GSH monitoring assays "meet FDA's requirements for potency assays for cell therapy products." The Petition further states that while GSH assays are non-biological analytical assays, FDA guidance indicates that such assays "can be used in conjunction with an already existing bioassay or in circumstances where development of a suitable bioassay for a cellular therapy is not possible."[2] In addition, you assert that GSH monitoring assays "use intracellular GSH concentration as a surrogate measurement of cells' antioxidant capacity and the stem cells' biological activity,"[3] consistent with FDA's Potency Tests for CGT Products Guidance, which states that characterization data from non-biological assays "may be used to demonstrate potency if the surrogate measurement(s) can be substantiated by correlation to a relevant product-specific biological activity(s)."

As an initial matter, with respect to your argument that real-time GSH monitoring assays "meet FDA's requirements for potency assays for cell therapy products," we believe the Petition confuses the recommendations in the referenced guidance documents with statutory and regulatory requirements regarding potency of biological products regulated under section 351 of the PHS Act.[4] Further, as stated in the Potency Tests for CGT Products Guidance:

> "FDA regulations allow for considerable flexibility in determining the appropriate measurement(s) of potency for each product. Potency is determined based on individual product attributes; therefore, the adequacy of potency tests is evaluated on a case-by-case basis."[5]

Indeed, the Petition states the following (p. 12), underscoring this point:

> "Because potency assays are designed specifically for each product, the Agency has long maintained its position of allowing sponsors considerable freedom to design and choose potency assays that would fulfill the Agency's requirements."

Whether a GSH monitoring assay would be adequate to meet potency testing requirements is therefore something that would be evaluated on a product-specific basis. For example, when CBER considers potency in the context of licensing cellular therapy

[2] Petition, p. 14.
[3] Petition, p. 15.
[4] Similarly, we note that your Petition states "Cell2in believes that real-time GSH monitoring assays can also meet, or will be able to meet with further development and validation, the additional requirements for potency assays outlined in the Potency Tests for CGT Products Guidance . . . ." (Petition, p. 15.) While the Potency Tests for GCT Products Guidance summarizes FDA regulatory requirements related to potency assays and includes recommendations for potency measurement and design and validation of potency assays, it does not establish any new or additional requirements.
[5] For a more detailed summary of the regulatory requirements for potency of licensed biological products, see section II.A & B of the Potency Tests for CGT Products Guidance.

products, it evaluates, among other things, whether the specific potency tests have been validated as suitable for use with each product.

Regardless of whether GSH monitoring assays would ultimately be adequate to measure potency in support of a specific IND or BLA for a cellular therapy product, FDA does not agree that updating its guidance documents to recommend use of these assays for all cellular therapy products is warranted at this time. The Potency Tests for CGT Products Guidance does not recommend any specific potency assays for cellular therapy products. Similarly, the CMC Information for Human Somatic Cell Therapy INDs Guidance also does not recommend specific potency assays for cellular therapy products. Instead, these guidance documents provide more general recommendations to help clarify the potency information that could support an IND or BLA for cellular and gene therapy products and the types of information that sponsors of human somatic cell therapies should submit in the CMC section of an IND. In addition, there are numerous potency assays in development for cellular therapy products. It is, accordingly, not feasible or appropriate at this time to mention all the specific types of assays that might be adequate to use as potency assays to support an IND or BLA for all cellular therapy products. We also believe it is inappropriate at this time to recommend use of a GSH monitoring assay as a potency assay for all cellular therapy products, including stem cell therapies, given the product-specific nature of potency measurements, the wide variety of cellular therapy products and stem cell therapies in development, and the complexity of these products, including, in many cases, a complex and/or not fully characterized mechanism of action.

B. Use of GSH Monitoring Assays to Measure Potency for HPC, Cord Blood Products

The Petition further argues that there is precedent for Agency guidance documents to identify specific assays for potency. Specifically, the Petition notes that the Cord Blood Licensure Guidance identifies three assays that may satisfy requirements for purity and potency for HPC, Cord Blood Products: total nucleated cell count, viable nucleated cells, and viable CD34+ cells."[6]

FDA acknowledges that the Cord Blood Licensure Guidance lists total nucleated cells (TNC), viable nucleated cells, and viable CD34+ cells as recommended tests to provide purity and potency information on HPC, Cord Blood Products.[7] However, these tests are included in the Cord Blood Licensure Guidance as recommendations for manufacturers that wish to rely on data submitted to the docket for the guidance and data in Docket Number FDA-1997-N-0010 (Legacy Docket Number 97N-0497) to support their BLAs. Specifically, Table A of the Cord Blood Licensure Guidance, provides the description

[6] Petition, p. 3, 13.

[7] The guidance applies only to HPC, Cord Blood Products that are "manipulated minimally" and "intended for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment." Cord Blood Licensure Guidance, p. 4.

and characteristics of the cord blood and HPC, Cord Blood (i.e., tests performed and the results) used to obtain the clinical data submitted to FDA in Docket Number FDA-1997-N-0010 (Legacy Docket Number 97N-0497), which demonstrate the safety, purity, and potency of HPC, Cord Blood. Because GSH monitoring assays were not part of the characterization for the cord blood and HPC, Cord Blood used to obtain the substantial clinical evidence submitted in Docket Number FDA-1997-N-0010, it would not be appropriate to include GSH monitoring assays as part of the recommended tests in Table A or in other sections of the guidance describing recommended tests for product potency.

The Petition also argues that there is "much controversy" as to whether tests for TNC, viable nucleated cells, and viable CD34+ cells adequately measure HPC, Cord Blood Product potency and that these three tests do not provide accurate quantification of the active stem cells. In addition, the Petition asserts that "there is a need for a potency assay that reflects how stem cell therapies work[,]" given the "shortcomings" of these three tests and another commonly used potency test, the colony-forming unit (CFU) assay.[8] The Petition appears to suggest that GSH monitoring assays should be recommended in the Cord Blood Licensure Guidance because they address this need and have advantages over these other assays.

The potency tests recommended in the Cord Blood Licensure Guidance represent the minimum measurements of potency recommended for HPC, Cord Blood Products based on the clinical data submitted to FDA in Docket Number FDA-1997-N-0010 (Legacy Docket Number 97N-0497), and FDA encourages additional measurements of potency. The guidance makes clear that manufacturers are not limited to the three types of potency testing recommended in the guidance or required to use them. For example, the guidance states that "other purity and potency assays may be considered under the BLA."[9] However, as noted above, there are numerous potency assays in development for cellular therapy products, including cord blood products, and it is not feasible or appropriate to mention all potential assays in the Cord Blood Licensure Guidance at this time.

In summary, FDA encourages development and application of new, improved technologies for characterizing the biological products that we license, and a BLA sponsor may choose to use a GSH monitoring assay such as the FreSHtracer to measure potency (likely as part of an assay matrix[10]) for a cellular therapy product, if the assay complies with applicable biologic and CGMP regulations; however, we do not believe it is necessary or appropriate to specifically mention real-time GSH monitoring assays in the referenced guidance documents at this time.

[8] Petition, p. 15-16.
[9] Cord Blood Licensure Guidance, p. 10 and p. 11, Table A, footnote 3.
[10] As noted in the Potency Tests for CGT Products Guidance (p. 8), in many cases, a single biological or analytical assay may not provide an adequate measure of potency.

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely yours,

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