Organogenesis inc.
Advancing Healing

150 Dan Road • Canton, MA 02021 • www.organogenesis.com • 1-888-HEAL-2DAY

August 17, 2017

Tejashri Purohit-Sheth, M.D.
Director
Division of Clinical Evaluation and
Pharmacology/Toxicology
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

RE: STN, BL125400/81; Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen (GINTUIT)
RESPONSE TO PREA NON-COMPLIANCE
DEFERRAL EXTENSION REQUESTED

Dear Dr. Purohit-Sheth,

By letter dated June 29, 2017, you advised us of FDA's determination that, Organogenesis, Inc. has failed to meet a postmarketing requirement ("PMR") of the Pediatric Research Equity Act (PREA) identified in the Agency's approval letter of March 9, 2012 for Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen (BLA 125400), which has been given the trade name GINTUIT™. This letter provides the reason(s) for the delayed pediatric assessment and a date by which we expect to submit the assessment.

As the Agency is aware, GINTUIT has been indefinitely withdrawn from the market (for reasons (b) (4) Accordingly, pediatric use is not reasonably anticipated at this time. The information that you requested is set forth below, along with a request for an extension of the deferral previously granted for the required pediatric assessment. We believe that the unique circumstances surrounding this request warrant the granting of the requested extension.

A. Background

The Pediatric Research Equity Act (PREA) of 2003 requires all NDAs and BLAs for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment, generally based on required pediatric clinical studies, of the safety and effectiveness of the product (and at what doses) in all relevant pediatric populations, unless FDA waives or defers the requirement in accordance with statutory criteria for doing so. 21 U.S.C. § 355c. In enacting PREA, Congress intended to address the fact that "80 percent of drugs on the market were not tested for use in children-yet, doctors were prescribing these drugs to our children" and "to ensure that drugs for children are tested for safety and efficacy and that

they are labeled properly."[1] As one sponsor of the legislation explained, "our bill would help make certain that children are no longer a therapeutic afterthought by ensuring that all new drugs are studied for pediatric use *at the time a drug comes to market*. This would put children on a level playing field with adults for the first time."[2]

On March 9, 2012, FDA approved the above-referenced BLA for use of GINTUIT as a topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. The approval letter included a deferred requirement, imposed under PREA, that Organogenesis study the use of the product for treatment of mucogingival disorders in patients ages 12 to 18 and submit the final study report to FDA by March 31, 2017. As described below in greater detail, shortly thereafter, Organogenesis was (b) (4) (b) (4) to withdraw GINTUIT from the market while the Company was still in the early stages of launching the product. Organogenesis promptly informed FDA of the development and advised that, because the Company was (b) (4) (b) (4) it would not be possible to carry out the pediatric study specified in FDA's approval letter. The Company did not submit a request for extension of the study deferral because it had, at that time, no reasonable expectation of being able to conduct the deferred study on any concrete timeline. Organogenesis brought the situation to FDA's attention multiple times thereafter and requested that FDA suspend the Company's post-marketing commitments for Gintuit (b) (4) including the Pediatric Study requirement.[3] Organogenesis also asked FDA to place GINTUIT on CBER's Discontinued List of Biologics, which FDA confirmed it had done by letter dated September 22, 2015.[4] At no time did FDA advise the Company, in response, that its request was insufficient and that it would be necessary, instead, to request a deferral extension in order to avoid a determination of non-compliance.

B. Reason for Delayed Pediatric Assessment

As the Agency should be aware from our prior correspondence, soon after GINTUIT was approved, (b) (4)

(b) (4)

[1] Remarks of Congressman Michael Dewine (R-OH), for himself, Congresswoman Hillary Clinton (D-NY), Congressman Judd Gregg (R-NH), Congressman Chris Dodd (D-CT) and Congressman Ted Kennedy (D-MA), 149 Cong. Rec. S3883-01, 149 Cong. Rec. S3883-01, S3897, 2003 WL 1237652, 39, 41 (March 18, 2003).

[2] *Id.*

[3] *See e.g.,* Organogenesis Inc., Annual Report for Gintuit™ (Allogeneic Keratinocytes and Fibroblasts in Bovine Collagen) BL: 125400, covering the period March 9, 2013 through March 8, 2014, § 1.13.12 Status of Postmarketing Study Commitments.

[4] Letter from Raj Puri, M.D., Ph.D., Director, Division of Cellular and Gene Therapies, to Mr. Patrick Bilbo, dated September 22, 2015.

(b) (4)

(b) (4)

(b) (4) In its May 2014 Annual Report to the GINTUIT BLA, Organogenesis expressly advised FDA that it had suspended all activities related to the pediatric study and that no subjects had ever been enrolled in the study and no sites had received investigational product or enrolled any subjects. In its cover letter to the Annual Report, the Company reiterated (b) (4) (b) (4) the cessation of (b) (4) activities related to commercializing GINTUIT.[7] Accordingly, the Company requested that FDA suspend all postmarketing commitments including the pediatric study. The Company has reiterated to FDA several times over the intervening two years that it is not conducting the pediatric study because the product is not currently being marketed.[8] CBER has not objected nor affirmatively advised Organogenesis of an expectation that pediatric studies would be conducted for GINTUIT prior to such time as the Company resumes marketing it.

(b) (4)

C. Deferral Request and Expected Timing for Submission of Pediatric Assessment

Section 505B of the Federal Food, Drug, and Cosmetic Act ("FDCA") provides that FDA may defer submission of some or all assessments required under the Pediatric Research Equity Act until a specified date after approval of the drug or issuance of the license for a biological product if there is an "appropriate reason for deferral." 21 U.S.C. § 355c(a)(3)(A)(i)(III). Having granted such a deferral, FDA may grant an extension of the deferral if there continues to be an appropriate reason to do so, provided that the applicant submits a new timeline for completion of the studies. 21 U.S.C. § 355c(a)(3)(B)(i). Organogenesis believes that the circumstances described above constitute an appropriate, reasonable and fair rationale for extending the pediatric deferral.

---

[6] *See* Letter from Geoff MacKay, then-President and Chief Executive Officer of Organogensis to then-Commissioner Margaret Hamburg. A copy of this letter was provided the same day to Dr. Karen Midthun, then CBER Director.

[7] *See* Letter from Patrick Bilbo, Vice President, Regulatory and Government Relations at Organogenesis, Inc. to Celia Witten, M.D., Ph.D., Director, Office of Cellular, Tissue and Gene Therapy, CBER, dated May 15, 2014, accompanying the Annual Report to BL 125400.

[8] *See e.g.,* Letter from Patrick Bilbo, Senior Vice President, Regulatory, Government Affairs and Administration at Organogenesis, Inc. to Raj Puri M.D., Ph.D., dated November 24, 2015.

(b) (4)

It is therefore not possible at this time to initiate the requested requested pediatric assessment. In (b) (4) the Company is nevertheless optimistic that it will be in a position do so in the future. We propose, therefore, the following deferred timeline for the requested pediatric study of the use of GINTUIT to treat mucogingival disorders in patients ages 12 to 18:

Study Completion Date:	April 1, 2024, or 45 months after Organogenesis notifies CBER, as instructed by FDA's September 22, 2015 letter to the Company, that it plans to resume marketing of the product,[9] whichever is earlier.
Final Report Submission:	October 1, 2024, or 51 months after the study completion date calculated as described above, whichever is earlier.

We note that while an original request for deferral of a pediatric study requirement must include evidence that the study is being conducted or will be conducted with due diligence and at the earliest possible time, 21 U.S.C. § 355c(a)(3)(A)(ii)(III), a request for a deferral extension is not expressly required to contain such information. 21 U.S.C. § 355c(a)(3)(B). Organogenesis invested *substantial* time and financial resources in obtaining approval to market GINTUIT and is committed to returning the product to the market, in full compliance with regulatory requirements, when it becomes feasible to do so. Organogenesis therefore fully intends to meet its post-approval obligations and commits that it will conduct the pediatric study specified in the GINTUIT approval letter with due diligence, as promptly as possible following renewal of marketing of the product or such earlier time as may be feasible in light of a change in the circumstances described herein.

The proposed time line represents Organogenesis's good faith effort to anticipate the future business and regulatory environment for tissue-engineered wound-healing products subject to premarket approval requirements. The Company acknowledges, however, that some uncertainty exists with respect to when, if at all, it will become possible to commercialize GINTUIT, a situation that was not anticipated when PREA was enacted. PREA provides that FDA may waive a pediatric study requirement where necessary studies are impossible or highly impractical, and also provides that FDA may defer a pediatric study requirement to a specified future date where there is an appropriate reason to do so. A gap in the statute exists, however, for the circumstance where studies that are *currently* impossible or highly impractical may become feasible in the future but a timeline for completion of those studies cannot be specified. More specifically, the statute simply does not contemplate the circumstance that, through no fault of the applicant, it becomes

[9] See Letter from Raj Puri, M.D., Ph.D., Director, Division of Cellular and Gene Therapies, to Mr. Patrick Bilbo, dated September 22, 2015, confirming that GINTUIT had been placed on the Discontinued Products list and instructing that "If [the Company] plan[s] to resume marketing Gintuit™ at any time in the future, please notify the Office of Cellular, Tissue and Gene Therapies (OCTGT)."

impossible following approval for a drug or biological product to be commercialized even for adult patients, negating any reasonable likelihood that it could or would be used in pediatric patients. Nevertheless, it is clear from the legislative history cited above that it is not the intent of the statute to require a company that secures an approval of a product to conduct a pediatric assessment if that product that is not being marketed and there is accordingly no danger that the product will be used in pediatric patients without adequate clinical data to support such use. Under those circumstances, a permanent waiver of the requirement would appear to be appropriate but for the possibility, as exists here, that commercialization of the product could become feasible in the future, making future pediatric use foreseeable. In such a case, we believe that a substantial deferral of the pediatric study requirement is reasonable and appropriate.

We trust that, in light of the unique circumstances surrounding the status of GINTUIT and the absence of any expectation that it will be used in pediatric populations unless the product is reintroduced into commerce, the Agency will grant this request and defer the deadline for submission of the pediatric study report until the requested date.

D. Publication of FDA's Non-Compliance Letter and Organogenesis's Response

Your letter notes that, in accordance with FDASIA, FDA will post this letter and our response on the Agency's website, redacting any trade secrets and confidential commercial information, 6o calendar days from the date of FDA's letter. We note that FDASIA provides that no non-compliance letter shall be issued if a request for an extension is pending, 21 U.S.C. § 355c(d), and we understood from our telephone conversation with you that neither your June 29, 2017 letter nor our response will be posted on the Agency's website while our request for an extended deferral is pending or thereafter if our request is granted. Nevertheless, in the event that this letter becomes subject to public disclosure, we hereby advise you that we consider all information herein related to the Company's (b) (4) to be confidential commercial information, as well as all information related to prior communications between the Company and FDA related to (b) (4) or the status of the Company's pediatric studies, to be trade secret and/or confidential commercial information. We request that you redact that information prior to making our letter public. We are attaching hereto a version of this letter appropriately redacted for public disclosure, which we consent to only in the event, and to the extent, that disclosure is mandated by law. In the event that FDA determines that any information that we have designated as trade secret or confidential commercial information should be disclosed, we request that you notify us in advance and provide us with an opportunity to object.

E. Conclusion

As explained above, Organogenesis has been compelled, by factors beyond its control, and (b) (4) to withdraw GINTUIT indefinitely from the market. The product is (b) (4) according, pediatric use is not reasonably anticipated at this time. However, Organogenesis believes strongly in the therapeutic value of the product, the development and approval of which required the investment of significant effort and

resources, and the Company intends to re-launch the product, and initiate the required pediatric study, as soon as feasible. In view of GINTUIT's unique circumstances, we trust that FDA will determine that the requested extension is appropriate.

Sincerely,

/s/

Patrick R. Bilbo
Chief Operating Officer