MEMORANDUM **Department of Health and Human Services**
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: March 22, 2021

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And

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Subject: DSCSA Exemption Request, submitted July 27, 2020 from Celgene Corporation (Celgene) for ABECMA® (idecabtagene vicleucel), suspension for intravenous infusion (BLA STN 125736/0)

Action due date: 3/26/2021.

I. Background:

A. Product Description: The following information was excerpted from the Highlights section of Celgene's proposed prescribing information (PI) that was submitted in BLA STN 125736/0, dated July 27, 2020, describes the intended use, dosage and administration, and supply of ABECMA (idecabtagene vicleucel). (see Appendix 1 for complete proposed PI).

INDICATIONS AND USAGE

ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

- Do NOT use a leukodepleting filter (2.2).
- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before infusion of ABECMA (2.2).
- Confirm the patient's identity prior to infusion (2.2).
- Premedicate with acetaminophen and an H_1-antihistamine (2.2).
- Avoid prophylactic use of dexamethasone or other systemic corticosteroids (2.2).
- Confirm availability of tocilizumab prior to infusion (2.2, 5.1).
- The target dose is 450 x 10^6 CAR-positive T cells within a range of (b) (4) × 10^6 CAR-positive T cells (2.1).
- Administer ABECMA at a REMS-certified healthcare facility (2.2, 5.1, 5.2, 5.3).

DOSAGE FORMS AND STRENGTHS

A single dose of ABECMA contains a cell suspension of (b) (4) x 10^6 chimeric antigen receptor (CAR)-positive T cells in one or more infusion bags (3).

HOW SUPPLIED

ABECMA is supplied in one or more infusion bag(s) (see below) containing a frozen suspension of genetically modified autologous T cells in 5% DMSO concentration.

Each infusion bag of ABECMA is individually packed in a metal cassette. ABECMA is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry vapor shipper. An RFI Certificate is affixed inside the shipper.

- 50 mL infusion bag and metal cassette (NDC 59572-515-01)
- 250 mL infusion bag and metal cassette (NDC 59572-515-02)
- 500 mL infusion bag and metal cassette (NDC 59572-515-03)

Match the identity of the patient with the patient identifiers on the cassette(s) and infusion bag(s) upon receipt.

Store ABECMA frozen in the vapor phase of liquid nitrogen (less than or equal to minus 130°C).

Thaw ABECMA prior to infusion *[see Dosage and Administration (2.2)]*.

II. Celgene requests an exemption from certain requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Drug Supply Chain Security Act (DSCSA)

As part of its July 27, 2020 original BLA submission, Celgene included a formal letter requesting exemptions from certain sections of the DSCSA. Specifically, Celgene is seeking exemptions from the following section 582 requirements, as amended by the DSCSA, for

transactions of ABECMA (see Celene's DSCSA Exemption request letter in Appendix 2 for complete details and Appendix 3 for mock-ups of proposed carton and cassette case labels):

1) Section 582 (a)(9), (b)(2) – Product Identifier requirements

2) Section 582 (b)(1)(A, B, C) – Manufacturer Product Tracing requirements in a single document

3) Section 582 (b)(4)(C, D, E) – Requests for Verification, Electronic database, Saleable Returned Product requirements

4) SEC. 203. ENHANCED DRUG DISTRIBUTION SECURITY – Section 582 (g) – All requirements set forth as defined under the Drug Supply Chain Security Act.

Section 582 of the FD&C Act, as established by the DSCSA, establishes several requirements to facilitate the tracing, identification, and verification of prescription drugs through the pharmaceutical distribution supply chain. The DSCSA (Title II of Public Law 113-54) was signed into law on November 27, 2013 and added section 582 to the FD&C Act. Specifically, this section established product tracing, product identifier, authorized trading partner and verification requirements for manufacturers, wholesale distributors, repackagers and dispensers to facilitate the tracing of a product through the pharmaceutical distribution supply chain. Failure to comply with the requirements of section 582 is a prohibited act under section 301(t) of the FD&C Act (21 U.S.C. 331(t)).

Section 582(a)(9): Product identifiers: With respect to any requirement relating to product identifiers under this subchapter, Section 582(a)(9) requires that (A) unless the Secretary allows, through guidance, the use of other technologies for data instead of or in addition to the technologies described in clauses (i) and (ii), the applicable data- (i) shall be included in a 2-dimensional data matrix barcode when affixed to, or imprinted upon, a package; and (ii) shall be included in a linear or 2-dimensional data matrix barcode when affixed to, or imprinted upon, a homogeneous case; and (B) verification of the product identifier may occur by using human-readable or machine-readable methods.

Section 582(b)(1): Beginning not later than January 1, 2015, section 582(b)(1)(A) requires a manufacturer (i) prior to, or at the time of, each transaction in which such manufacturer transfers ownership of a product, provide the subsequent owner with transaction history[1], transaction

[1] Under section 581(25) the term transaction history means a statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.

information[2], and a transaction statement[3], in a single document in an paper or electronic format; (ii) capture the transaction information (including lot level information), transaction history, and transaction statement for each transaction and maintain such information, history, and statement for not less than 6 years after the date of the transaction. Under section 582(b)(1)(B) (Requests for Information), upon a request by the Secretary or other appropriate Federal or State official, in the event of a recall or for the purpose of investigating a suspect product or an illegitimate product, a manufacturer shall, not later than 1 business day, and not to exceed 48 hours, after receiving the request, or in other such reasonable time as determined by the Secretary, based on the circumstances of the request, provide the applicable transaction information, transaction history, and transaction statement for the product. And section 582(b)(1)(C) (Electronic Format), requires in general, (i) beginning not later than 4 years after the date of enactment of the Drug Supply Chain Security Act, except as provided under clause (ii)[4], a manufacturer shall provide the transaction information, transaction history, and transaction statement required under subparagraph (A)(i) in electronic format.

Section 582(b)(2)(A): Section 582(b)(2)(A) requires that manufacturers affix or imprint to each package and homogenous case of product intended to be introduced in a transaction into commerce a product identifier[5] that is encoded with the product's standardized numerical identifier,[6] lot number, and expiration date. Under the statute, manufacturers are required to

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[2] Under section 581(26) the term transaction information means (A) the proprietary or established name or names of the product;(B) the strength and dosage form of the product; (C) the National Drug Code number of the product; (D) the container size; (E) the number of containers; (F) the lot number of the product; (G) the date of the transaction; (H) the date of the shipment, if more than 24 hours after the date of the transaction;

(I) the business name and address of the person from whom ownership is being transferred; and (J) the business name and address of the person to whom ownership is being transferred.

[3] Under section 581(27), the transaction statement is a statement, in paper or electronic form, that the entity transferring ownership in a transaction- (A) is authorized as required under the Drug Supply Chain Security Act;

(B) received the product from a person that is authorized as required under the Drug Supply Chain Security Act;

(C) received transaction information and a transaction statement from the prior owner of the product, as required

under section 582; (D) did not knowingly ship a suspect or illegitimate product; (E) had systems and processes in place to comply with verification requirements under section 582; (F) did not knowingly provide false transaction information; and (G) did not knowingly alter the transaction history.

[4] Under section 582(b)(1)(C)(ii), there is an exception that a manufacturer may continue to provide the transaction information, transaction history, and transaction statement required under subparagraph (A)(i) in a paper format to a licensed health care practitioner authorized to prescribe medication under State law or other licensed individual under the supervision or direction of such a practitioner who dispenses product in the usual course of professional practice.

[5] Under section 581(14) of the FD&C Act the term product identifier means a standardized graphic that includes, in both human-readable form and on a machine-readable data carrier that conforms to the standards developed by a widely recognized international standards development organization, the standardized numerical identifier, lot number, and expiration date of the product.

[6] *Standard numerical identifier* is defined in section 581(20) of the FD&C Act as a set of numbers or characters used to uniquely

begin affixing or imprinting a product identifier to each package and homogenous case of a product intended to be introduced in a transaction into commerce no later than November 27, 2017.

FDA Compliance Policy: In September, 2018, FDA published a final guidance regarding its compliance policy whereby FDA does not intend to take action against manufacturers who do not, prior to November 27, 2018, affix or imprint a product identifier to each package and homogenous case of product as required by section 582(b)(2)(A) of the FD&C Act.[7] At the same time, FDA also issued a final guidance to help trading partners understand their compliance obligations under section 582 for packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582.[8]

Section 582(b)(4): Section 582(b)(4)(A)-(F) requires manufacturers to comply with certain verification-related activities. Specifically, section 582(b)(4) requires, among other things, that, beginning not later than January 1, 2015, a manufacturer shall have systems in place to enable the manufacturer to comply with the following requirements: (A) SUSPECT PRODUCT: (i) In general, upon making a determination that a product in the possession or control of the manufacturer is a suspect product, or upon receiving a request for verification from the Secretary that has made a determination that a product within the possession or control of a manufacturer is a suspect product, a manufacturer shall (I) quarantine such product within the possession or control of the manufacturer from product intended for distribution until such product is cleared or dispositioned, and (II) promptly conduct an investigation in coordination with trading partners, as applicable, to determine whether the product is an illegitimate product, which shall include validating any applicable transaction history and transaction information in the possession of the manufacturer and otherwise investigating to determine whether the product is an illegitimate product, and, beginning 4 years after the date of enactment of the Drug Supply Chain Security Act, verifying the product at the package level, including the standardized numerical identifier.

Relevant text of Section 528(g): Enhanced Drug Distribution Security: Section 528(g) requires, in part, that (1) In general.--On the date that is 10 years after the date of enactment of the Drug Supply Chain Security Act, the following interoperable, electronic tracing of product at the package level requirements shall go into effect: (A) The transaction information and the

identify each package or homogenous case that is composed of the National Drug Code that corresponds to the specific product (including the particular package configuration) combined with a unique alphanumeric serial number of up to 20 characters.

[7] See Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy, Guidance for Industry, September, 2018, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM565272.pdf. This compliance policy has now ended.

[8] See Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier, Guidance for Industry, September 2018, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM586509.pdf

transaction statements as required under this section shall be exchanged in a secure, interoperable, electronic manner in accordance with the standards established under the guidance issued pursuant to paragraphs (3) and (4) of subsection (h), including any revision of such guidance issued in accordance with paragraph (5) of such subsection. (B) The transaction information required under this section shall include the product identifier at the package level for each package included in the transaction.(C) Systems and processes for verification of product at the package level, including the standardized numerical identifier, shall be required in accordance with the standards established under the guidance issued pursuant to subsection (a)(2) and the guidances issued pursuant to paragraphs (2), (3), and (4) of subsection (h), including any revision of such guidances issued in accordance with paragraph (5) of such subsection, which may include the use of aggregation and inference as necessary. (see Appendix 4 for complete text of Section 528(g)).

III. OCBQ Review

The below section describing Celgene's Chain of Custody (COI) for ABECMA have been excerpted from Celgene's facilities and equipment COI submission, included in BLA. 125736/0, dated July 27, 2020 (See Appendix 5 for Celgene's complete COI submission):

Celgene delivers Chain of Identity (COI) and Chain of Custody (COC) for autologous products by means of a global standard that define physical and procedural controls, and electronic computer systems: Global Patient Services (GPS), Enterprise Resource Planning (ERP), Manufacturing Execution System (MES), and Laboratory Information Management System (LIMS).

The COI and COC controls are in place from patient enrollment through production, storage, testing, release, and distribution to ensure the identity of each patient's cellular material is tracked. Specifically, these controls ensure patient cellular material, including test samples, is not accidentally exchanged with cellular material from another patient, and control is maintained over the location and access to patient cellular material. Throughout the manufacturing process, COI is checked and verified before subsequent processing. As COI checks are performed, COC information is recorded allowing the tracking and tracing of all parties handling the product. When a patient is scheduled for treatment, a unique identification number, JOIN, is assigned by the GPS system to the patient's treatment. The JOIN, a 10-character pseudo-random data element consisting of four alphanumeric characters, a hyphen, and 5 alphanumeric characters, is the primary data element for COI and is contained within all collection, in-process and final drug product labels. The JOIN is associated with the patient's first name, last name, and date of birth (patient identifiers).

The manufacturing orders created each have order numbers containing the JOIN of the incoming leukapheresis material and produce output material with "Lot Numbers" containing the JOIN of the incoming leukapheresis material, enabling electronic COI tracking and control. The "Lot Number" (which contains the JOIN) represents the leukapheresis material lot number, the manufacturing batch number, and the drug product lot number. The MES generates COI labels prior to manufacturing, and the COI labels are scanned throughout manufacturing.

Final product labels, which include the patient identifiers (First Name, Last Name, DOB), are issued by Quality Assurance. Prior to shipment, a final electronic COI verification is performed on the COI barcode on the final drug product, which is scanned into the MES during the packaging process. The packaging process can only continue if there is a match between the MES order number and the scanned value of the drug product COI barcode.

Documentation approving the drug product for infusion (release for infusion certificate) accompanies the product during shipment to treatment sites and includes the JOIN and all patient identifiers. Before initiating infusion of drug product, treatment sites are instructed to verify the JOIN and patient's identity against the drug product label and the release for infusion documentation.

Celgene also submitted a complete process validation document (see Appendix 6) that also describes its comprehensive chain of identity (COI) control strategy, that makes use of electronic systems, risk assessment, and procedural controls, has been established to ensure in-process material, idecel product, and QC sample COI is maintained across all operations of a patient treatment from leukapheresis collection to administration.

In summary, Celgene explained in its cover letter that product-specific identifiers (Lot # + Bag ID and NDC number in both human and machine readable formats) and patient-specific identifiers (Name, Date of Birth, DIN/Aph ID, JOIN in human readable format) are provided on the primary container (drug product cryopreservation bag) and secondary container (cassette) labels to allow for adequate traceability of the product and security of the supply chain. Of note, they also explained that there are no wholesalers, repackagers, or dispensers involved in the handling of the product as defined in Section 582 of the FD&C Act. Celgene also acknowledged that this traceability approach utilizes both human-readable form and machine-readable data carrier (2D data matrix) on the product label but does not conform to the standards developed by a widely recognized international standards development organization as defined by Section 582 of the FD&C Act. Also included on the label will be: storage conditions, the expiration date, as well as other information (see Appendix 3).

III. OCBQ's CONCLUSION AND RECOMMENDATIONS

In determining whether to grant these exemptions, OCBQ evaluated Celgene's detailed request and has also taken into consideration that ABECMA is intended to treat multiple myeloma, a serious and fatal disease that, despite advances in treatment, remains largely incurable. Ide-cel is a novel anti-myeloma therapy with a different mechanism of action than currently approved drugs evaluated in a population with substantial unmet medical need. Celgene received orphan designation for ABECMA (see Appendix 7, CBER Filing Notification).

Celgene's request sufficiently describes the supply chain processes for ABECMA as highly controlled, pre-defined, secure, and closed, with tracking procedures that are also adequate to maintain a secure and limited supply chain across all operations of a patient treatment from leukapheresis collection to administration. Celgene's COI documentation also describes a system that does not rely on wholesale distributors. Based on the information provided, we have not identified potential risks associated with granting the following three of four exemption

requests from Celgene:

1) Section 582 (a)(9), (b)(2) – Product Identifier requirements

2) Section 582 (b)(1)(A, B, C) – Manufacturer Product Tracing requirements in a single document

3) Section 582 (b)(4)(C, D, E) – Requests for Verification, Electronic database, Saleable Returned Product requirements

We believe the supply chain and COI for ABECMA is adequately secure and is appropriate to facilitate access to this product for an essential public health function. Additionally, Celegene's carton and cassette labels for ABECMA include certain human-readable elements (NDC number, lot number, and expiration date) required by the DSCSA's requirements for the product identifier, even though all four elements that are required under the DSCSA are not in the machine-readable, 2-dimensional data matrix barcode format that the DSCSA mandates. Specifically, the 2D matrix barcode on these labels does not contain the requisite expiration date and unique serial number.

Given the proposed unique, critical public health indication of ABECMA, and Celgene's rigorous and meticulous product tracking, tracing and security measures, we have determined that exemptions from the above noted section 582 requirements are appropriate, and as such, we believe that granting these exemptions is appropriate to maintain public health.

Regarding Celgene's fourth DSCSA exemption request from all requirements under Section 528(g), OCBQ believes that it is premature to grant this request at this time because this section of the DSCSA, by statute, is not expected to be implemented until November 27, 2023. CBER intends to complete biennial reviews of every DSCSA exemption request granted to trading partners involved with specific CBER-regulated products (see below for more details). For ABECMA, CBER intends to include its review of Celgene's exemption request from the requirements of Section 528(g) at the time of the most appropriate biennial review. For example, if such a biennial review finds it appropriate to maintain CBER's granted exemptions to Celgene's three requests described above and below, OCBQ believes that such extensions may also support granting the requested exemption from the requirements in Section 528(g), when they go into effect.

In summary, OCBQ recommends that CBER grant Celgene exemptions from the following section 582 requirements for transactions of ABECMA, if/when approved:

- The product tracing requirements under section 582(b)(1)
- The product identifier requirement under section 582(a)(9) and 582(b)(2).
- The verification-related requirements that manufacturers are obligated to comply with under section 582(b)(4).

OCBQ recommends that CBER deny Celgene's exemption request from Section 582 (g) requirements for transactions of ABECMA at this time.

As discussed above, there are no wholesale distributors involved in the pre-defined, uni-directional and closed supply chain for ABECMA. Therefore, at this time, exemptions from the requirements of section 582(c)(1), (c)(2), and (c)(4)[9] are not warranted and we note were not requested by Celgene.

We disagree that there are no dispensers in Celgene's described COI plan because the term, as described under the DSCSA, states "or any other person authorized by law to dispense or administer prescription drugs" (see footnote 10 for complete definition). However, we also note that, as of October 2020, the requirement at 582(d)(2) for dispenser(s)[10, 11] does not become effective until November 27, 2023[12, 13]. Therefore, although an exemption from the requirements of section 582(d)(2) may be appropriate in this situation (e.g., at each treatment site that directly receives and subsequently administers ABECMA to the specifically intended patient), such an exemption is premature, and, therefore, not warranted at this time.

The exemptions granted herein are only valid for transactions of Celgene's ABECMA (pending approval of BLA 125736/0[14]). These exemptions do not extend to any other transactions. In

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[9] See sections "582(c) Wholesale Distributor Requirements.-"(1) product tracing, (2) product identifier, and (4) verification" for extensive description and complete details of these requirements.

[10] Under section 581(3), the term 'dispenser' (A) means a retail pharmacy, h ospital pharmacy, a group of chain pharmacies under common ownership and control that do not act as a wholesale distributor, or any other person authorized by law to dispense or administer prescription drugs, and the affiliated warehouses or distribution centers of such entities under common ownership and control that do not act as a wholesale distributor; and '(B) does not include a person who dispenses only products to be used in animals in accordance with section 512(a)(5).

[11] We note that, under section 582(d)(5), the requirements of section 582(d)(1) and (d)(4) do not apply to licensed health care practitioners authorized to prescribe or administer medication under State law or other licensed individuals under the supervision or direction of such practitioners who dispense or administer product in the usual course of professional practice.

[12] See section "582(d) Dispenser Requirements.- (2) product identifier" for extensive description and complete details of these requirements.

[13] See FDA's final guidance, entitled Wholesale Distributor Verification Requirement for Saleable Returned Drug Product and Dispenser Verification Requirements When Investigating a Suspect or Illegitimate Product—Compliance Policies, dated October 2020, for current recommendations regarding the enforcement of the DSCSA requirements for wholesale distributor verification of saleable returned products and dispenser verification of the product identifier for suspect and illegitimate product. Under this guidance, FDA also does not intend to take action against dispensers who do not, prior to November 27, 2023, verify the product identifier for suspect or illegitimate product in the dispenser's possession or control. This provides dispensers three additional years to comply with this requirement.

[14] As noted above, the action due date for this BLA is March 27, 2021. OCBQ notes that, as summarized in FDA's minutes for the mid-cycle meeting that occurred on November 19, 2020, inspections of the (b) (4) facility (FEI: (b) (4)) and the Celgene Corporation facility (FEI: 3004991673; Summit, NJ, USA) are required before the application can be approved. FDA must assess the ability of these facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel we may be unable to conduct inspections of the (b) (4) facility and the Celgene Corporation facility prior to the User Fee Date. FDA will continue to monitor the public health situation as well as travel restrictions. FDA is actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other
Factors (see Appendix 8 for complete minutes).

such cases, all applicable requirements of section 582 must be met. Additionally, the exemptions granted by this letter are valid until further notice from FDA. Pursuant to section 582(a)(3) of the FD&C Act, FDA has issued guidance on waivers, exceptions and exemptions from section 582 requirements that includes a process for the biennial review and renewal of exemptions; FDA intends to apply the review and renewal process to these exemptions