

MANUFACTURING SYSTEMS, METHODS, AND AI MODELS FOR REDUCING OUT OF SPECIFICATION (OOS) CAR T DRUG PRODUCTS

RELATED APPLICATIONS

5 The present application claims priority to U.S. provisional patent application serial number 63/602,289 filed November 22, 2023, U.S. provisional patent application serial number 63/602,359 filed November 22, 2023, U.S. provisional patent application serial number 63/602,356 filed November 22, 2023, U.S. provisional patent application serial number 63/606,827 filed December 6, 2023, and U.S. provisional patent application serial number 10 63/606,880 filed December 6, 2023, the entire contents of which are incorporated herein by reference and relied upon.

FIELD

15 The present application relates to improved samples for CAR T drug manufacturing, methods of manufacturing a CAR T drug product using the same, methods of optimizing manufacturing the CAR T drug product by reducing out of specification (OOS) CAR T drug products.

BACKGROUND

20 Medical treatment via drug products incorporating CAR T cells (also referred to herein as “CAR T drug therapy”) utilizes isolated T cells that have been genetically modified to enhance their specificity for a specific tumor associated antigen. These T cells are typically autologous, where the T cells are isolated from the patient to receive the CAR T drug therapy. This isolation involves collecting a patient’s blood and separating the lymphocytes from the blood through 25 apheresis. Genetic modification may involve the expression of a chimeric antigen receptor (CAR) or an exogenous T cell receptor to provide new antigen specificity onto the T cell. T cells expressing chimeric antigen receptors (such T cells referred to herein as “CAR T cells” or “CAR+ T cells”) can induce tumor immunoreactivity. B cell maturation antigen (BCMA) is a molecule expressed on the surface of mature B cells and malignant plasma cells and is a targeted molecule 30 in the treatment of cancer, for example, multiple myeloma. There is a need for not only better cancer therapies utilizing CAR T cells (in particular, CAR T cells specific for the BCMA tumor

associated antigen), but also for better way to determine whether a particular apheresis product can be successfully manufactured into a CAR T drug therapy that is suitable for treating a patient.

In order to generate a CAR T drug product for CAR T drug therapy, an apheresis sample typically undergoes a meticulous manufacturing process where T cells in the apheresis sample are activated, enriched, expanded and transduced to express CAR+. A large number of controllable and uncontrollable variables govern the manufacturing process and ultimately affect the attributes of the CAR T drug product. As CAR T drug products are expensive to produce and involve time and expertise, a defective CAR T drug product results in wastage of resources. Furthermore, production delays of a CAR T drug product needed by a patient can impact health outcomes. There is thus a desire and need to better predict attributes of a CAR T drug product and optimize the manufacturing process for the CAR T drug product.

In particular, CAR T drug products are typically held to high standards of quality, potency, and purity that are outlined in specifications to mitigate health risks and ensure the safety of patients. A CAR T drug product may be out of specification (OOS) if it fails to meet these standards. There is a desire and need for improved CAR T manufacturing systems and methods that predict, preempt, and reduce the likelihood of OOS CAR T drug products.

Various embodiments of the present disclosure address one or more of the above described shortcomings.

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SUMMARY

The present disclosure describes improved CAR T manufacturing systems and methods that predict, preempt, and reduce the likelihood of OOS CAR T drug products.

According to various embodiments, disclosed is a method for predicting whether a patient-specific CAR T drug product for a target patient would be out of specification (OOS), the method includes: receiving quantitative data for a set of OOS parameters, wherein the set of OOS parameters comprises OOS parameters selected from Table 1, wherein each OOS parameter belongs to one of a plurality of parameter types as outlined in Table 1; generating an input feature vector comprising the quantitative data for the set of OOS parameters; and applying, into a trained machine learning model, the input feature vector to generate an output feature vector predicting whether the patient-specific CAR T drug product would be OOS.

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In some aspects, which may be combined with any other aspects of the present disclosure, the OOS parameters as outlined in Table 1 are in order of significance to predicting whether the patient-specific CAR T drug product would be OOS, wherein OOS parameters with a higher significance are assigned a higher weight than other OOS parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.

In some aspects, which may be combined with any other aspects of the present disclosure, the set of OOS parameters includes a set of screening parameters selected from Table 1A, wherein Table 1A consists of screening parameters from Table 1.

In some aspects, which may be combined with any other aspects of the present disclosure, the screening parameters in Table 1A are arranged in order of significance to predicting whether the patient-specific CAR T drug product would be OOS, wherein screening parameters with a higher significance are assigned a higher weight than other screening parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.

In some aspects, which may be combined with any other aspects of the present disclosure, the set of OOS parameters includes a set of apheresis stage parameters selected from Table 1B, wherein Table 1B consists of apheresis stage parameters from Table 1.

In some aspects, which may be combined with any other aspects of the present disclosure, the apheresis stage parameters in Table 1B are arranged in order of significance to predicting whether the patient-specific CAR T drug product would be OOS using the trained machine learning model, wherein apheresis stage parameters with a higher significance are assigned a higher weight than other apheresis stage parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.

In some aspects, which may be combined with any other aspects of the present disclosure, the set of OOS parameters includes a set of manufacturing stage parameters selected from Table 1C, wherein Table 1C consists of manufacturing stage parameters from Table 1.

In some aspects, which may be combined with any other aspects of the present disclosure, the manufacturing stage parameters in Table 1C are arranged in order of significance to predicting whether the patient-specific CAR T drug product would be OOS using the trained machine learning model, wherein manufacturing stage parameters with a higher significance are assigned a

higher weight than other manufacturing stage parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.

In some aspects, which may be combined with any other aspects of the present disclosure, receiving quantitative data for the set of OOS parameters comprises receiving unstructured data
5 for the set OOS parameters. In some embodiments, the method further includes: vectorizing, by a feature extraction module of the computing device, the unstructured target data to the input feature vector.

In some aspects, which may be combined with any other aspects of the present disclosure, the trained machine learning model is trained using reference data from a plurality of reference
10 CAR T drug products manufactured from a plurality of reference patients, the plurality of reference CAR T drug products having known OOS outcomes.

In some aspects, which may be combined with any other aspects of the present disclosure, the method further includes: receiving, by the computing device, the reference data, wherein the reference data comprises a set of input feature parameters and the known OOS outcomes for each
15 of the plurality of reference CAR T drug products manufactured from the plurality of reference patients, wherein, for a given reference patient of the plurality of reference patients, the set of input feature parameters includes at least the set of OOS parameters; vectorizing, by a feature extraction module of the computing device, for each of the plurality of reference CAR T drug products manufactured from the plurality of reference patients, the set of input feature parameters and the
20 known OOS outcome to a reference input feature vector and a reference output feature vector, respectively, thereby generating a plurality of reference input feature vectors and a plurality of reference output feature vectors; associating, by a training module of the computing device, the plurality of reference input feature vectors to the plurality of reference output feature vectors in a machine learning model; and training, by the training module of the computing device, by
25 iteratively minimizing error to within a predetermined threshold, the machine learning model to generate the trained machine learning model, wherein the trained machine learning model includes a plurality of weights, each weight indicating a significance between an input feature parameter to an OOS outcome.

In some aspects, which may be combined with any other aspects of the present disclosure,
30 the set of input feature parameters are outlined in Appendix A.

In some aspects, which may be combined with any other aspects of the present disclosure, for each of the plurality of reference CAR T drug products manufactured from the respective plurality of reference patients, the set of input feature parameters comprises two or more of: a concentration of lactate or glucose in a T cell culture sample from a middle stage of a manufacturing process of the reference CAR T drug product; a concentration of lactate or glucose in the T cell culture sample from a late middle stage of the manufacturing process of the reference CAR T drug product; a multiplicity of infection (MOI) of a vector added to the T cell culture sample during an early middle stage of the manufacturing process of the reference CAR T drug product; a ratio of CD4⁺ T cells to CD8⁺ T cells in the T cell culture sample from an initial stage of the manufacturing process of the reference CAR T drug product; a concentration of viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the reference CAR T drug product; an average concentration of viable T cells per population from the early middle stage of the manufacturing process of the reference CAR T drug product; a percentage of cells that are viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the reference CAR T drug product; a count of viable T cell after sampling in the initial stage of the manufacturing process of the reference CAR T drug product; a volume of vector added to the T cell culture sample during the early middle stage of the manufacturing process of the reference CAR T drug product; whether the reference patient was refractory to pomalidomide treatment; a concentration of lymphocytes in the apheresis sample prior to the manufacturing process of the reference CAR T drug product; a sex of the reference patient; a number of seeded viable T cells at the initial stage of the manufacturing process of the reference CAR T drug product; a body mass index (BMI) of the reference patient; or a percentage of leukocytes that are monocytes in the apheresis sample prior to the manufacturing process of the reference CAR T drug product.

In some aspects, which may be combined with any other aspects of the present disclosure, the method further includes: determining that the patient-specific CAR T drug product would be OOS; and adjusting one or more manufacturing process parameters for manufacturing the CAR T drug product for the target patient.

In some aspects, which may be combined with any other aspects of the present disclosure, the method further includes: determining that the patient-specific CAR T drug product would not be OOS; and causing, based on the set of OOS parameters, manufacture of the CAR T drug product for the target patient.

In some aspects, which may be combined with any other aspects of the present disclosure, the two or more OOS parameters comprises two or more of: a concentration of lactate or glucose in a T cell culture sample from a middle stage of a manufacturing process of the CAR T drug product; a concentration of lactate or glucose in the T cell culture sample from a late middle stage of the manufacturing process of the CAR T drug product; a multiplicity of infection (MOI) of a vector added to the T cell culture sample during an early middle stage of the manufacturing process of the CAR T drug product; a ratio of CD4⁺ T cells to CD8⁺ T cells in the T cell culture sample from an initial stage of the manufacturing process of the CAR T drug product; a concentration of viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the CAR T drug product; an average concentration of viable T cells per population from the early middle stage of the manufacturing process of the CAR T drug product; a percentage of cells that are viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the CAR T drug product; a count of viable T cell after sampling in the initial stage of the manufacturing process of the CAR T drug product; a volume of vector added to the T cell culture sample during the early middle stage of the manufacturing process of the CAR T drug product; whether the target patient was refractory to pomalidomide treatment; a concentration of lymphocytes in the apheresis sample prior to the manufacturing process of the CAR T drug product; a sex of the target patient; a number of seeded viable T cells at the initial stage of the manufacturing process of the CAR T drug product; a body mass index (BMI) of the target patient; or a percentage of leukocytes that are monocytes in the apheresis sample prior to the manufacturing process of the CAR T drug product.

According to various embodiments, also disclosed is a method of treating cancer in a subject in need thereof, the method comprising administering a CAR T drug product produced by the methods of any aspect described herein to the subject, treating the cancer.

According to additional embodiments, disclosed are systems for predicting whether a patient-specific CAR T drug product for a target patient would be out of specification (OOS). The system comprises: a processor; and memory storing instructions that, when executed by the processor, cause the processor to perform a method described in any of the aspects disclosed in the present disclosure.

According to additional embodiments, disclosed are non-transitory computer-readable media. Each non-transitory computer-readable medium has stored thereon computer-readable

instructions executable to cause performance of operations comprising methods described in any of the aspects disclosed in the present disclosure.

According to some aspects, methods described in the present disclosure may be embedded in a computer-readable medium as computer program code comprising instructions that cause a processor to perform the steps of the methods.

Other aspects, features, and implementations will become apparent to those of ordinary skill in the art, upon reviewing the following description of specific, exemplary aspects in conjunction with the accompanying figures. While features may be discussed relative to certain aspects and figures below, various aspects may include one or more of the advantageous features discussed herein. In other words, while one or more aspects may be discussed as having certain advantageous features, one or more of such features may also be used in accordance with the various aspects. In similar fashion, while exemplary aspects may be discussed below as device, system, or method aspects, the exemplary aspects may be implemented in various devices, systems, and methods.

The foregoing has outlined, rather broadly, the features and technical advantages of examples according to the disclosure in order that the detailed description that follows may be better understood. Additional features and advantages will be described hereinafter. The conception and specific examples disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present disclosure. Such equivalent constructions do not depart from the scope of the appended claims. Characteristics of the concepts disclosed herein, both their organization and method of operation, together with associated advantages will be better understood from the following description when considered in connection with the accompanying figures. Each of the figures is provided for the purposes of illustration and description, and not as a definition of the limits of the claims.

While aspects and implementations are described in this application by illustration to some examples, those skilled in the art will understand that additional implementations and use cases may come about in many different arrangements and scenarios. Innovations described herein may be implemented across many differing platform types, devices, systems, shapes, sizes, and packaging arrangements. While some examples may or may not be specifically directed to use cases or applications, a wide assortment of applicability of described innovations may occur.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-1B are block diagrams illustrating an example process 100 for CAR T drug product manufacturing, according to non-limiting embodiments of the present disclosure.

FIG. 2 is a block diagram illustrating various stages of an example CAR T drug product manufacturing process 200 from which parameters are generated for predicting whether a CAR T drug product would be out-of-specification (OOS).

FIG. 3 is a block diagram illustrating an example computer network environment 300 for predicting whether a CAR T drug product would be OOS and optimizing the CAR T drug product based on the determination, according to non-limiting embodiments of the present disclosure.

FIG. 4 is a block diagram illustrating an example process 400 for predicting whether a CAR T drug product would be OOS and optimizing the CAR T drug product based on the determination, according to non-limiting embodiments of the present disclosure.

FIG. 5A is a graph showing an example decision tree modeling of parameter thresholds for predicting whether a CAR T drug product would be OOS, according to non-limiting embodiments of the present disclosure.

FIG. 5B is a block diagram showing an example process for the training of a decision tree model, according to non-limiting embodiments of the present disclosure.

FIG. 6A is a block diagram illustrating an example method 600 for predicting whether a patient-specific CAR T drug product for a target patient would be OOS, according to non-limiting embodiments of the present disclosure. Furthermore, FIGS. 6B-6D show tables of example parameters that the present disclosure describes as significant for their ability to predict whether the patient-specific CAR T drug product for the target patient would be OOS.

Like reference numbers and designations in the various drawings indicate like elements.

DETAILED DESCRIPTION

As previously discussed, CAR T drug products are typically held to high standards of quality, potency, and purity that are outlined in specifications to mitigate health risks and ensure the safety of patients. A CAR T drug product may be out of specification (OOS) if it fails to meet these standards.

Accordingly, the present disclosure describes improved CAR T manufacturing systems and methods that predict, preempt, and reduce the likelihood of OOS CAR T drug products. For example, the present disclosure provides, at least in part, embodiments for determining manufacturing outcomes for cellular therapies, including CAR T drug therapies (such as ciltacabtagene autoleucel DP). The disclosure relates, at least in part, to the discovery that certain characteristics (such as screening characteristics, pre-apheresis characteristics, apheresis characteristics, and/or manufacturing characteristics) can be determinative for manufacturing outcomes. In certain embodiments, patient factors can be associated with low-viability, low-dose, or other out of specification outcomes.

Data for such characteristics, referred to herein as parameters, may be obtained at various stages of the CAR T drug production process, the stages including but not limited to a screening stage of a patient, a pre-apheresis stage, an apheresis stage, and a manufacturing stage. Furthermore, each stage may include or may be segmented to one or more substages. For example, the manufacturing stage may include or may be segmented to an initial stage, an early middle stage, a middle stage, a late middle stage, and an advanced stage, where the aforementioned substages may be distinguishable from one another based on a time, a sequence, and/or an associated event. The present disclosure finds that various sets of parameters as having significance to predicting an outcome of a CAR T drug product produced in the CAR T drug production process. In at least one embodiment, a set of parameters obtained during the CAR T drug product manufacturing process may be used to predict whether a CAR T drug product would be OOS of the CAR T drug product to be produced using the production process. Furthermore, the predicted determination of whether the CAR T drug product would be OOS (hereinafter referred to as the "OOS outcome") may be used to optimize or improve the CAR T drug product manufacturing process, for example, by adjusting parameters of the CAR T drug product manufacturing process. For example, a computing device may receive quantitative data for a set of input parameters from one or more stages of the production process. The set of input parameters may include input parameters outlined in Appendix A. Each input parameter may belong to or may be classified as being one of a plurality of parameter types as outlined in Appendix A. The computing device may generate an input feature vector comprising the quantitative data for the set of input parameters. The input feature vector may be applied into a trained machine learning model to generate an output feature vector predicting the OOS outcome data (e.g., whether the CAR T

drug product would be OOS). The OOS outcome may be based on the assessment of whether one or more parameters of the CAR T drug product are in compliance with a specification for the CAR T drug product.

As used herein, a “a significance ... for predictability,” a “significance ... to predict,” or a
5 “significance ... to predicting,” such as when used in describing a significance of a parameter for predicting an OOS outcome of a CAR T drug product may refer to a quantified measurement of how well the parameter predicts the OOS outcome of the CAR T drug product . In some embodiments, a parameter’s significance to predicting an OOS outcome may be represented as a mathematical weight, whereby a parameter having a higher weight would predict the OOS
10 outcome better than a parameter having a lower weight. The weights of the various parameters in their significance to predicting a given OOS outcome may be determined or learned by training a machine learning model. Furthermore, a set of parameters may be ordered (e.g., ranked) based on their significance to predicting a given CAR T drug product OOS outcome, where a higher ordered parameter may predict the OOS outcome better than a lower ordered parameter.

As used herein, a “screening stage” may refer to a stage in the CAR T drug product
15 manufacturing process where patients are selected for the retrieval of biological samples for the CAR T drug product manufacturing process. During the screening stage, parameters pertaining to patient characteristics (e.g., demographic information of the patient, diagnostic information of the patient’s disease, previous treatment history received by the patient, refractory status of the patient,
20 etc.) may be obtained, such parameters may be referred to herein as “screening parameters.”

As used herein, a “pre-apheresis stage” may refer to a stage in the CAR T drug product
manufacturing process after the screening stage, where a biological sample from the patient may be lab tested to determine additional information about the patient in preparation for performing apheresis on the patient. During the pre-apheresis stage, parameters pertaining to such lab tests
25 may be obtained.

As used herein, an “apheresis stage” may refer to a stage in the CAR T drug product
manufacturing process after the screening stage (and, in some embodiments, after a pre-apheresis stage), but before a manufacturing stage, where a blood sample that includes T cells is isolated from a selected patient for use in a manufacturing facility to manufacture the CAR T drug product.
30 Parameters obtained from that isolated blood sample (referred to herein as apheresis sample) may be referred to as “apheresis stage parameters” or “apheresis parameters.”

As used herein, a “manufacturing stage” or “manufacturing process” may refer to a stage in the CAR T drug product manufacturing process after the apheresis stage, where the apheresis sample is further processed to manufacture the CAR T drug product. The processing includes genetically modifying T cells of the apheresis sample to produce chimeric antigen receptors (CAR). As used herein, the cell culture sample derived from the apheresis sample and used in various substages of the manufacturing stage, may be referred to as “T cell culture sample.” Parameters obtained from that T cell culture sample during the manufacturing stage or process may be referred to as “manufacturing stage parameters.”

Furthermore, it is contemplated that the manufacturing stage or process may include or may be segmented into various substages, including but not limited to an initial stage, an early middle stage, a middle stage, a late middle stage, and an advanced stage of the manufacturing stage or process.

As used herein, the “initial stage” of the manufacturing process may refer to the first substage of the manufacturing process after the apheresis stage and may be associated with the preparation of the T cell culture using the apheresis sample and the enrichment and activation of the T cells in the T cell culture. In some embodiments, the initial stage may include or may comprise day 0, day 1, day 2, or day 3 of the manufacturing process, a range or value defined by any two of the aforementioned days, for example, days 0-2 of the manufacturing process, preferably days 0-1 of the manufacturing process. In some embodiments, the initial stage may be further segmented into an early initial stage and a later initial stage. As used herein, the “early initial stage” of the manufacturing process may refer to the first substage of the manufacturing process after the apheresis stage and may be associated with the preparation of the T cell culture using the apheresis sample. In some embodiments, the early initial stage may comprise day 0 of the manufacturing process. As used herein, the “later initial stage” of the manufacturing process may refer to the first substage of the manufacturing process associated with the enrichment and activation of T cells in the T cell culture. In some embodiments, the later initial stage may include or may comprise day 1, day 2, or day 3 of the manufacturing process, or a range or value defined by any two of the aforementioned days, for example, days 1-3 of the manufacturing process, preferably day 1 of the manufacturing process.

As used herein, the “early middle stage” of the manufacturing process may refer to a substage of the manufacturing process associated with a stimulation and/or transduction of the of

the T cells in the T cell culture with CAR. In some embodiments, the early middle stage may include or may comprise day 2, day 3, day 4, or day 5 of the manufacturing process, or a range or a value defined by any two of the aforementioned days, for example, days 2-4 of the manufacturing process, preferably day 3 of the manufacturing process.

5 As used herein, the “middle stage” of the manufacturing process may refer to a substage of the manufacturing process associated with an expansion and growth monitoring of the T cell culture. In some embodiments, the middle stage may include or may comprise day 5, day 6, or day 7 of the manufacturing process, or a range or a value defined by any two of the aforementioned days, for example, day 6 of the manufacturing process.

10 As used herein, the “late middle stage” of the manufacturing process may refer to a substage of the manufacturing process associated with continued expansion and growth monitoring of the T Cell culture after the middle stage. In some embodiments, the late middle stage may include or may comprise day 7, day 8, day 9, or day 10 of the manufacturing process, or a range or a value defined by any two of the aforementioned days, for example, days 7-9 of the
15 manufacturing process, preferably day 8 of the manufacturing process.

 As used herein, an “advanced stage” of the manufacturing process may refer to a substage of the manufacturing process associated with the harvest and release of the final product (e.g., CAR+ T Cell drug) from the T cell culture. In some embodiments, the advanced stage may include or may comprise day 9, day 10, day 11, day 12, day 13, or day 14 of the manufacturing process,
20 or a range or a value defined by any two of the aforementioned days, for example, days 9-12 of the manufacturing process, days 10-12 of the manufacturing process, preferably day 10 of the manufacturing process.

I. Example Techniques for Parameter Acquisition

 In certain embodiments, parameter information used in methods disclosed herein is
25 collected from a patient. The parameter information can include screening stage characteristics (which include patient characteristics), pre-apheresis characteristics, apheresis characteristics, and manufacturing characteristics. The patient characteristics can include demographic information of the patient, diagnostic information of the patient’s disease, previous treatment history received by the patient, refractory status of the patient, or a combination thereof. The pre-apheresis
30 characteristics can include characteristics of a biological sample (such as a blood sample) obtained

from the patient. The pre-apheresis characteristics can include physical characteristics of the biological sample, measured protein levels, protein electrophoresis measurements (such as urine protein electrophoresis and/or serum protein electrophoresis), or a combination thereof. The apheresis characteristics can include measured characteristics of apheresis material obtained from the patient. The apheresis characteristics can include flow cytometry data obtained from apheresis material. The apheresis characteristics can include gene expression data. The apheresis characteristics can include sequencing data, including RNA sequencing data. The manufacturing characteristics can include the site of any of: the site of manufacturing a cellular therapy (including any cellular therapy disclosed herein), the site of the sample collection, the site of the cryopreservation of the sample, the site of a clinical study, and/or the site of processing of any of the materials. The manufacturing characteristics can include processing characteristics, post-thaw characteristics, post-wash characteristics, viability characteristics, or a combination thereof.

In certain embodiments, the parameter information comprises any parameter in screening stage 610. In certain embodiments, the parameter information comprises any parameter in pre-apheresis stage 620. In certain embodiments, the parameter information comprises any parameter in apheresis stage 630. In certain embodiments, the parameter information comprises any parameter in manufacturing stage 640.

II. Example Methodology for CAR T Drug Product Manufacturing Process

A. Screening Stage

In various embodiments, the CAR T drug product manufacturing process may begin with a screening stage where patients may be screened for various parameters (referred to herein as “screening stage parameters”). The screening stage parameters may help to select patients that are eligible for producing biological samples from which CAR T drug products are to be produced, as well as obtain other patient information useful for the efficacy of the CAR T drug product therapy. Thus, data for the screening stage parameters may be obtained. The screening stage parameters may include patient characteristics, for example, patient demographics (referred to herein as patient demographic parameters) and patient medical history (referred to herein as patient medical history parameters). In certain embodiments, the data is provided by an individual (e.g., the patient or medical service personnel) and/or extracted from networks of electronic health records (EHR), insurance claims, and census data. In some aspects, the categories for these networks may be

accessed, identified or implemented using EHR alone. In some embodiments, the screening stage parameters may also be based on social determinants of health, exposome, tumor registry, biosamples, genomic results, natural language processing, or patient-generated data. In certain embodiments, the data for the screening stage parameters may be obtained by a clinician and entered into a computing device. Screening stage parameters that are patient demographic parameters can include but is not limited to: age, sex, race, body mass index, ethnicity, and country of origin..

B. Biological Material Data

In certain embodiments, biological samples are collected from a patient, including any patient disclosed herein. The biological sample can be processed and assayed. The processing and/or assaying can be used to obtain one or more of the parameters disclosed herein, such as the pre-apheresis characteristics, the apheresis characteristics, and/or the manufacturing characteristics.

1. Sample Preparation

In certain embodiments, methods involve obtaining a sample from a subject. The methods of obtaining provided herein may include methods of biopsy such as fine needle aspiration, core needle biopsy, vacuum assisted biopsy, incisional biopsy, excisional biopsy, punch biopsy, shave biopsy or skin biopsy. In certain embodiments, the sample is a blood sample. In certain embodiments the sample is obtained from a biopsy. Alternatively, the sample may be obtained from any other source including but not limited to urine, sweat, hair follicle, buccal tissue, tears, menses, feces, or saliva. In certain embodiments of the current methods, any medical professional such as a doctor, nurse or medical technician may obtain a biological sample for testing. Yet further, the biological sample can be obtained without the assistance of a medical professional.

A sample may include but is not limited to, tissue, cells, or biological material from cells or derived from cells of a subject. The biological sample may be a heterogeneous or homogeneous population of cells or tissues. The biological sample may be obtained using any method known to the art that can provide a sample suitable for the analytical and/or manufacturing methods described herein.

The sample may be obtained by methods known in the art. In certain embodiments the samples are obtained by biopsy. In other embodiments the sample is obtained by phlebotomy, or any other methods known in the art. In some cases, the sample may be obtained, stored, or transported using components of a kit of the present methods. In some cases, multiple samples, such as multiple blood samples may be obtained for processing, assaying, and/or manufacturing by the methods described herein.

In some embodiments the biological sample may be obtained by a physician, nurse, or other medical professional such as a medical technician, endocrinologist, cytologist, phlebotomist, radiologist, or a pulmonologist. The medical professional may indicate the appropriate test or assay to perform on the sample. In certain embodiments a molecular profiling business may consult on which assays or tests are most appropriately indicated. In further embodiments of the current methods, the patient or subject may obtain a biological sample for testing without the assistance of a medical professional, such as obtaining a whole blood sample.

In other cases, the sample is obtained by an invasive procedure including but not limited to: biopsy, needle aspiration, endoscopy, or phlebotomy. The method of needle aspiration may further include fine needle aspiration, core needle biopsy, vacuum assisted biopsy, or large core biopsy. In some embodiments, multiple samples may be obtained by the methods herein to ensure a sufficient amount of biological material.

In some embodiments of the methods described herein, a medical professional need not be involved in the initial diagnosis or sample acquisition. An individual may alternatively obtain a sample through the use of an over the counter (OTC) kit. An OTC kit may contain a means for obtaining said sample as described herein, a means for storing said sample for inspection, and instructions for proper use of the kit. In some cases, molecular profiling services are included in the price for purchase of the kit. In other cases, the molecular profiling services are billed separately. A sample suitable for use by the molecular profiling business may be any material containing tissues, cells, nucleic acids, genes, gene fragments, expression products, gene expression products, or gene expression product fragments of an individual to be tested. Methods for determining sample suitability and/or adequacy are provided.

In some embodiments, the subject may be referred to a specialist such as an oncologist, surgeon, or endocrinologist. The specialist may likewise obtain a biological sample for testing or refer the individual to a testing center or laboratory for submission of the biological sample. In

some cases the medical professional may refer the subject to a testing center or laboratory for submission of the biological sample. In other cases, the subject may provide the sample. In some cases, a molecular profiling business may obtain the sample.

2. Material Characteristics

5 In certain embodiments, characteristics of biological material, such for example as a blood sample (which may comprise the pre-apheresis stage material), apheresis material, or manufactured cellular therapy material, are assayed. In certain embodiments, the characteristics comprise one or more of the pre-apheresis, apheresis, and/or manufacturing parameters disclosed herein. In certain embodiments, the characteristics are assayed by known protein assay methods, 10 such as protein electrophoresis. In certain embodiments, the characteristics are assayed by measuring specific proteins, such as for example specific antibodies, specific light chains, specific heavy chains, specific immunoglobins, and/or specific cellular markers. In certain embodiments the characteristics are assayed by measuring cell viability. Cell viability can be measured using known techniques, including by flow cytometry.

3. Flow Cytometry

In certain embodiments, flow cytometry data is collected. In certain embodiments, flow cytometry data is collected on apheresis stage material. In certain embodiments, flow cytometry data is collected on manufacturing stage material. Flow cytometry may be performed using standard techniques.

20 In certain embodiments, the biological material to be assayed by flow cytometry (including the apheresis stage materials and/or the manufacturing stage material) is prepared for flow cytometry, including by generating single cell suspensions. The prepared material can be contacted with one or more proteins capable of binding to selective cellular markers. In some embodiments, the selective cellular markers that indicate apheresis material will result in, or will likely result in, 25 an out of specification CAR T drug product. In some embodiments, the selective cellular markers comprise one or more markers disclosed herein, including any of the markers disclosed in the apheresis stage and/or manufacturing stage parameters. In some embodiments, the selective cellular markers comprise backbone markers (including viability markers), lineage markers, activation markers, differentiation markers, exhaustion markers, or a combination thereof. In some

embodiments, the selective cellular markers comprise CD14, CD19, CD16, CD56, HLA-DR, CD25, CD57, CCR7, CD45RA, CD45RO, CD95, CD127, CD27, CD28, CD57, KLRG1, CD39, CD244, CD160, CX3CR1, CD85j, Tim-3, NKG2A, CD90, CD126, PD-1, LAG-3, TIGIT, OX-40, CD103 KLRG1, CD80, GPR56, CD158, CD123, CD38-HITs, CD244, CD45, CD3, CD4, CD8, anti-ID, or some combination thereof. In certain aspects, the one or more proteins capable of binding to selective cellular markers are labeled with a fluorophore.

4. RNA Sequencing

Input data for the methods described herein, including for the pre-apheresis stage, apheresis stage, and/or manufacturing stage may comprise sequencing data, including but not limited to raw sequencing reads of RNA from subjects (e.g., patients), including raw sequencing reads from individual cells. In some aspects, RNA may be analyzed by sequencing. The RNA may be prepared for sequencing by any method known in the art, such as poly-A selection, cDNA synthesis, stranded or nonstranded library preparation, or a combination thereof. The RNA may be prepared for any type of RNA sequencing technique, including stranded specific RNA sequencing. In some aspects, sequencing may be performed to generate approximately 10M, 15M, 20M, 25M, 30M, 35M, 40M or more reads, including paired reads. The sequencing may be performed at a read length of approximately 50 bp, 55 bp, 60 bp, 65 bp, 70 bp, 75 bp, 80 bp, 85 bp, 90 bp, 95 bp, 100 bp, 105 bp, 110 bp, or longer. In some aspects, raw sequencing data may be converted to estimated read counts (RSEM), fragments per kilobase of transcript per million mapped reads (FPKM), and/or reads per kilobase of transcript per million mapped reads (RPKM).

In certain aspects, the RNA sequencing comprises single cell RNA sequencing (scRNA-Seq). In certain aspects, the RNA sequencing comprises a known sequencing technique including but not limited to any of the following:

CITE-Seq

CITE-Seq (Cellular Indexing of Transcriptomes and Epitopes by Sequencing) is a method for performing RNA sequencing along with gaining quantitative and qualitative information on surface proteins with available antibodies on a single cell level. It provides an additional layer of information for the same cell by combining both proteomics and transcriptomics data. For phenotyping, this method has been shown to be as accurate as flow cytometry (a gold standard) by the groups that developed it.

Drop-Seq

Drop-Seq analyzes mRNA transcripts from droplets of individual cells in a highly parallel fashion. This single-cell sequencing method uses a microfluidic device to compartmentalize droplets containing a single cell, lysis buffer, and a microbead covered with barcoded primers.

5 Each primer contains: 1) a 30 bp oligo(dT) sequence to bind mRNAs; 2) an 8 bp molecular index to identify each mRNA strand uniquely; 3) a 12 bp barcode unique to each cell and 4) a universal sequence identical across all beads. Following compartmentalization, cells in the droplets are lysed and the released mRNA hybridizes to the oligo(dT) tract of the primer beads. Next, all droplets are pooled and broken to release the beads within. After the beads are isolated, they are reverse-
10 transcribed with template switching. This generates the first cDNA strand with a PCR primer sequence in place of the universal sequence. cDNAs are PCR-amplified, and sequencing adapters are added using the Nextera XT Library Preparation Kit. The barcoded mRNA samples are ready for sequencing. This method is further described in Macosko, Evan Z., et al., Cell, 2015. 161(5): p. 1202-1214, which is herein incorporated by reference.

15 inDrop

inDrop is used for high-throughput single-cell labeling. This approach is similar to Drop-seq, but it uses hydrogel microspheres to introduce the oligonucleotides. Single cells from a cell suspension are isolated into droplets containing lysis buffer. After cell lysis, cell droplets are fused with a hydrogel microsphere containing cell-specific barcodes and another droplet with enzymes
20 for RT. Droplets from all the wells are pooled and subjected to isothermal reactions for RT. The barcodes anneal to poly(A)+ mRNAs and act as primers for reverse transcriptase. Now that each mRNA strand has cell-specific barcodes, the droplets are pooled and broken, and the cDNA is purified. The 3' ends of the cDNA strands are ligated to adapters, amplified, annealed to indexed primers, and amplified further before sequencing. This method is further described in Klein, Allon M., et al., Cell, 2015. 161(5): p. 1187-1201, which is herein incorporated by reference.
25

CEL-seq

CEL-Seq uses barcoding and pooling of RNA to overcome challenges from low input. In this method, each cell undergoes RT with a unique barcoded primer in its individual tube. After second-strand synthesis, cDNAs from all reaction tubes are pooled and PCR-amplified. Paired-
30 end deep sequencing of the PCR products allows for accurate detection of sequence information derived from both strands. This method, and related CEL-seq2 are further described in

Hashimshony, T., et al., Cell Reports, 2012. 2(3): p. 666-673 and Hashimshony, T., et al., Genome Biology, 2016. 17(1): p. 77, which are herein incorporated by reference.

Quartz-Seq

The Quartz-Seq method optimizes whole-transcript amplification (WTA) of single cells. In this method, an RT primer with a T7 promoter and PCR target is first added to the extracted mRNA. RT synthesizes first-strand cDNA, after which the RT primer is digested by exonuclease I. Next, a poly(A) tail is added to the 3' ends of first-strand cDNA, along with a poly(dT) primer containing a PCR target. After second-strand generation, a blocking primer is added to ensure PCR enrichment in sufficient quantity for sequencing. Deep sequencing allows for accurate, high-resolution representation of the whole transcriptome of a single cell.

MARS-Seq

MARS-Seq profiles the transcriptional dynamics of single cells in an automated and massively parallel workflow with high resolution. MARS-Seq can be used with in vivo samples containing a wide variety of different cell subpopulations. Single cells are first isolated into individual wells using FACS. Each cell is lysed, and the 3' ends of mRNAs are annealed to unique molecular identifiers containing a T7 promoter. The mRNA is reverse-transcribed to generate the first cDNA strand and treated with exonuclease I to remove leftover RT primers. Next, the cellular lysates are pooled together and converted to double-stranded cDNA. The DNA strands are transcribed to RNA and treated with DNase to remove leftover DNA templates in the mixture. The RNA strands are fragmented and annealed to sequencing adapters, followed by RT to generate barcoded cDNA libraries that are ready for sequencing.

CytoSeq

CytoSeq enables gene expression profiling of thousands of single cells. In this method, single cells are randomly deposited into wells. A combinatorial library of beads with specific capture probes is added to each well. After cell lysis, mRNAs hybridize to beads, which are pooled subsequently for RT, amplification, and sequencing. Deep sequencing provides accurate, high-coverage gene expression profiles of several single cells.

Hi-SCL

Hi-SCL generates transcriptome profiles for thousands of single cells using a custom microfluidics system, similar to Drop-Seq and inDrop. Single cells from cell suspension are isolated into droplets containing lysis buffer. After cell lysis, cell droplets are fused with a droplet

containing cell-specific barcodes and another droplet with enzymes for RT. The droplets from all the wells are pooled and subjected to isothermal reactions for RT. The barcodes anneal to poly(A)+ mRNAs and act as primers for reverse transcriptase. Now that each mRNA strand has cell-specific barcodes, the droplets are broken, and the cDNA is purified. The 3' ends of the cDNA strands are
5 ligated to adapters, amplified, annealed to indexed primers, and amplified further before sequencing.

Seq-Well

Single-cell RNA-seq can precisely resolve cellular states, but applying this method to low-input samples is challenging. Here, the inventors present Seq-Well, a portable, low-cost platform
10 for massively parallel single-cell RNA-seq. Barcoded mRNA capture beads and single cells are sealed in an array of subnanoliter wells using a semipermeable membrane, enabling efficient cell lysis and transcript capture. This method is further described in Gierahn et al., Nat Methods. 2017 Apr;14(4):395-398, which is herein incorporated by reference. This method is further described in Gierahn, T.M., et al., Nature Methods, 2017. 14: p. 395, which is herein incorporated by
15 reference.

Microwell-seq

Microwell-seq confines single cells and barcoded poly(dT) mRNA capture beads in a PDMS array of subnanoliter wells. Well dimensions are designed to accommodate only one bead. Cells are loaded by gravity with a rate of dual occupancy that can be tuned by adjusting the number
20 of cells and loaded and visualized prior to processing. This method is further described in Han, X., et al., Cell, 2018. 172(5): p.1091-1107.e17, which is herein incorporated by reference.

Nanogrid-seq

Nanogrid-seq is a nanogrid platform and microfluidic depositing system that enables imaging, selection, and sequencing of thousands of single cells or nuclei in parallel. This method
25 is further described in Gao, R., et al., Nature Communications, 2017. 8(1): p. 228, which is herein incorporated by reference.

sci-seq

Sci-seq refers to Single cell Combinatorial Indexed Sequencing (SCI-seq) that can be used as a means of simultaneously generating thousands of low-pass single cell libraries for somatic
30 copy number variant detection. This is further described in Vitak, S.A., et al., Nature Methods, 2017. 14: p. 302, which is herein incorporated by reference.

Direct-tagmentation

Enzymes called transposases randomly cut the DNA into short segments ("tags"). Adapters are added on either side of the cut points (ligation). Strands that fail to have adapters ligated are washed away. The adaptors may contain barcodes and/or primer binding sites for detection and amplification of the genomic sequences. This is further described in Zahn, H., et al., Nature Methods, 2017. 14: p. 167, which is herein incorporated by reference.

Sci-ATAC-seq

sci-ATAC-seq is a single-cell ATAC-seq protocol. This technique can be used to determine chromatin accessibility both between and within populations of single cells. Single-cell ATAC-Seq relies on combinatorial cellular indexing, and thus does not require the physical isolation of individual cells during library construction. The technique scales sublinearly in time and cost and can profile thousands of individual cells in a single experiment. This method is further described in Cusanovich, D.A., et al., Science, 2015. 348(6237): p. 910, which is herein incorporated by reference. A related method, nano-well scATAC-seq is described in Mezger, A., et al., High-throughput chromatin accessibility profiling at single-cell resolution, bioRxiv, 2018, which is incorporated by reference.

Other methods include 10x genomics RNA sequencing platform, described in Zheng, G.X.Y., et al., Nature Communications, 2017. 8: p. 14049; SMART-seq, described in Ramsköld, D., et al., Nature Biotechnology, 2012. 30: p. 777; SMART-seq2, described in Picelli, S., et al., Nature Protocols, 2014. 9: p. 171, which are all herein incorporated by reference in their entirety. It is contemplated that aspects in the disclosed references may be incorporated into aspects described in this disclosure.

5. Sequencing Methods

Massively parallel signature sequencing (MPSS).

The first of the next-generation sequencing technologies, massively parallel signature sequencing (or MPSS), was developed in the 1990s at Lynx Therapeutics. MPSS was a bead-based method that used a complex approach of adapter ligation followed by adapter decoding, reading the sequence in increments of four nucleotides. This method made it susceptible to sequence-specific bias or loss of specific sequences. Because the technology was so complex, MPSS was only performed 'in-house' by Lynx Therapeutics and no DNA sequencing machines were sold to

independent laboratories. Lynx Therapeutics merged with Solexa (later acquired by Illumina) in 2004, leading to the development of sequencing-by-synthesis, a simpler approach acquired from Manteia Predictive Medicine, which rendered MPSS obsolete. However, the essential properties of the MPSS output were typical of later "next-generation" data types, including hundreds of thousands of short DNA sequences. In the case of MPSS, these were typically used for sequencing cDNA for measurements of gene expression levels. Indeed, the powerful Illumina HiSeq2000, HiSeq2500 and MiSeq systems are based on MPSS.

Polony sequencing.

The Polony sequencing method, developed in the laboratory of George M. Church at Harvard, was among the first next-generation sequencing systems and was used to sequence a full genome in 2005. It combined an in vitro paired-tag library with emulsion PCR, an automated microscope, and ligation-based sequencing chemistry to sequence an E. coli genome at an accuracy of >99.9999% and a cost approximately 1/9 that of Sanger sequencing. The technology was licensed to Agencourt Biosciences, subsequently spun out into Agencourt Personal Genomics, and eventually incorporated into the Applied Biosystems SOLiD platform, which is now owned by Life Technologies.

454 pyrosequencing.

A parallelized version of pyrosequencing was developed by 454 Life Sciences, which has since been acquired by Roche Diagnostics. The method amplifies DNA inside water droplets in an oil solution (emulsion PCR), with each droplet containing a single DNA template attached to a single primer-coated bead that then forms a clonal colony. The sequencing machine contains many picoliter-volume wells each containing a single bead and sequencing enzymes. Pyrosequencing uses luciferase to generate light for detection of the individual nucleotides added to the nascent DNA, and the combined data are used to generate sequence read-outs. This technology provides intermediate read length and price per base compared to Sanger sequencing on one end and Solexa and SOLiD on the other.

Illumina (Solexa) sequencing.

Solexa, now part of Illumina, developed a sequencing method based on reversible dye-terminators technology, and engineered polymerases, that it developed internally. The terminated chemistry was developed internally at Solexa and the concept of the Solexa system was invented by Balasubramanian and Klennerman from Cambridge University's chemistry department. In

2004, Solexa acquired the company Manteia Predictive Medicine in order to gain a massively parallel sequencing technology based on "DNA Clusters", which involves the clonal amplification of DNA on a surface. The cluster technology was co-acquired with Lynx Therapeutics of California. Solexa Ltd. later merged with Lynx to form Solexa Inc.

5 In this method, DNA molecules and primers are first attached on a slide and amplified with polymerase so that local clonal DNA colonies, later coined "DNA clusters", are formed. To determine the sequence, four types of reversible terminator bases (RT-bases) are added and non-incorporated nucleotides are washed away. A camera takes images of the fluorescently labeled nucleotides, then the dye, along with the terminal 3' blocker, is chemically removed from the DNA,
10 allowing for the next cycle to begin. Unlike pyrosequencing, the DNA chains are extended one nucleotide at a time and image acquisition can be performed at a delayed moment, allowing for very large arrays of DNA colonies to be captured by sequential images taken from a single camera. Decoupling the enzymatic reaction and the image capture allows for optimal throughput and theoretically unlimited sequencing capacity. With an optimal configuration, the ultimately
15 reachable instrument throughput is thus dictated solely by the analog-to-digital conversion rate of the camera, multiplied by the number of cameras and divided by the number of pixels per DNA colony required for visualizing them optimally (approximately 10 pixels/colony). In 2012, with cameras operating at more than 10 MHz A/D conversion rates and available optics, fluidics and enzymatics, throughput can be multiples of 1 million nucleotides/second, corresponding roughly
20 to one human genome equivalent at 1x coverage per hour per instrument, and one human genome re-sequenced (at approx. 30x) per day per instrument (equipped with a single camera).

SOLiD sequencing.

Applied Biosystems' (now a Thermo Fisher Scientific brand) SOLiD technology employs sequencing by ligation. Here, a pool of all possible oligonucleotides of a fixed length are labeled
25 according to the sequenced position. Oligonucleotides are annealed and ligated; the preferential ligation by DNA ligase for matching sequences results in a signal informative of the nucleotide at that position. Before sequencing, the DNA is amplified by emulsion PCR. The resulting beads, each containing single copies of the same DNA molecule, are deposited on a glass slide. The result is sequences of quantities and lengths comparable to Illumina sequencing. This sequencing by
30 ligation method has been reported to have some issue sequencing palindromic sequences.

Ion Torrent semiconductor sequencing.

Ion Torrent Systems Inc. (now owned by Thermo Fisher Scientific) developed a system based on using standard sequencing chemistry, but with a novel, semiconductor based detection system. This method of sequencing is based on the detection of hydrogen ions that are released during the polymerization of DNA, as opposed to the optical methods used in other sequencing systems. A microwell containing a template DNA strand to be sequenced is flooded with a single type of nucleotide. If the introduced nucleotide is complementary to the leading template nucleotide it is incorporated into the growing complementary strand. This causes the release of a hydrogen ion that triggers a hypersensitive ion sensor, which indicates that a reaction has occurred. If homopolymer repeats are present in the template sequence multiple nucleotides will be incorporated in a single cycle. This leads to a corresponding number of released hydrogens and a proportionally higher electronic signal.

DNA nanoball sequencing.

DNA nanoball sequencing is a type of high throughput sequencing technology used to determine the entire genomic sequence of an organism. The company Complete Genomics uses this technology to sequence samples submitted by independent researchers. The method uses rolling circle replication to amplify small fragments of genomic DNA into DNA nanoballs. Unchained sequencing by ligation is then used to determine the nucleotide sequence. This method of DNA sequencing allows large numbers of DNA nanoballs to be sequenced per run and at low reagent costs compared to other next generation sequencing platforms. However, only short sequences of DNA are determined from each DNA nanoball which makes mapping the short reads to a reference genome difficult. This technology has been used for multiple genome sequencing projects.

Heliscope single molecule sequencing.

Heliscope sequencing is a method of single-molecule sequencing developed by Helicos Biosciences. It uses DNA fragments with added poly-A tail adapters which are attached to the flow cell surface. The next steps involve extension-based sequencing with cyclic washes of the flow cell with fluorescently labeled nucleotides (one nucleotide type at a time, as with the Sanger method). The reads are performed by the Heliscope sequencer. The reads are short, up to 55 bases per run, but recent improvements allow for more accurate reads of stretches of one type of nucleotides. This sequencing method and equipment were used to sequence the genome of the M13 bacteriophage.

Single molecule real time (SMRT) sequencing.

SMRT sequencing is based on the sequencing by synthesis approach. The DNA is synthesized in zero-mode wave-guides (ZMWs) – small well-like containers with the capturing tools located at the bottom of the well. The sequencing is performed with use of unmodified polymerase (attached to the ZMW bottom) and fluorescently labelled nucleotides flowing freely in the solution. The wells are constructed in a way that only the fluorescence occurring by the bottom of the well is detected. The fluorescent label is detached from the nucleotide at its incorporation into the DNA strand, leaving an unmodified DNA strand. According to Pacific Biosciences, the SMRT technology developer, this methodology allows detection of nucleotide modifications (such as cytosine methylation). This happens through the observation of polymerase kinetics. This approach allows reads of 20,000 nucleotides or more, with average read lengths of 5 kilobases.

C. Imaging

In certain embodiments, imaging data is also collected from the patient and used in the methods described herein. In certain embodiments, the imaging data can be determinative, alone or in combination with, manufacturing outcomes of cellular therapies described herein. Specific examples of derived contrast mechanisms using different types of imaging modalities, types of images, and characteristics include but are not limited to magnetic resonance imaging (MRI), computerized tomography (CT), positron emission tomography (PET), and photoacoustic tomography (PAT).

III. Example Methodology for CAR T Drug Product Manufacturing Process

Figure 1 is a flow diagram showing an example process 100 for CAR T drug product manufacturing according to example embodiments of the present disclosure. As will be described herein, various embodiments of the present disclosure describe systems and methods for optimizing OOS outcomes of the CAR T drug product produced based on parameters obtained at various stages of the CAR T drug product manufacturing process (such as but not limited to example process 100).

A. Screening Stage

In various embodiments, the CAR T drug product manufacturing process may begin with a screening stage where patients may be screened for various parameters (referred to herein as “screening stage parameters” or “screening parameters”) (block 110). The screening stage parameters may help to select patients 112 that are eligible for producing biological samples from which CAR T drug products are to be produced, as well as to obtain other patient information useful for the efficacy of the CAR T drug therapy. Thus, data for the screening stage parameters may be obtained (block 114). The screening stage parameters may include patient characteristics, for example, patient demographics (referred to herein as “patient demographic parameters”) and patient medical history (referred to herein as “patient medical history parameters” or “medical history parameters”). In certain embodiments, the data is provided by an individual (e.g., the patient or medical service personnel) and/or extracted from networks of electronic health records (EHR), insurance claims, and census data. In some aspects, the categories for these networks may be accessed, identified or implemented using EHR alone. In some embodiments, the screening stage parameters may also be based on social determinants of health, exposome, tumor registry, biosamples, genomic results, natural language processing, or patient-generated data. In certain embodiments, the data for the screening stage parameters may be obtained by a clinician and entered into a computing device. In some embodiments, patients selected at the screening stage may be patients having or having had a disease such as multiple myeloma (MM) or another cancer for which CAR T drug therapy is desired or indicated.

B. Pre-Apheresis Stage

In various embodiments, after the screening of a patient, the example process 100 for the CAR T drug product manufacturing process may include a pre-apheresis stage 120 in which one or more biological samples 122 are obtained from the screened patients 112 for lab testing. The characteristics of the biological sample 122 that are tested (e.g., at a lab) at the pre-apheresis stage 120 (referred to herein as “pre-apheresis stage parameters” or “pre-apheresis parameters”) may provide additional insights about patients from which a CAR T drug products is to be produced. The example process 100 may involve receiving data for these pre-apheresis parameters (block 124). In some embodiments, the additional insights may be used to further screen patients, prior to the apheresis stage 130 and the manufacturing stage 140 of the CAR T drug product

manufacturing process. In some aspects, the patient 112 may have or may have had a disease such as multiple myeloma (MM), for which CAR T drug therapy is desired. The biological sample 122 may be obtained from the patient based on techniques described herein.

5 In at least one embodiment (e.g., as shown in block 122) the biological sample may include a blood sample of the patient. In an example process, the lab testing for the pre-apheresis stage may include analyzing proteins from the blood sample from the patient. In some embodiments, electrophoresis may be performed on the blood sample to determine and/or detect various proteins and/or their characteristics. For example, electrophoresis and other techniques may be used to detect or measure characteristics (e.g., percentage, volume, concentrations, etc.) of albumin, alpha-
10 1 globulin, alpha-2 globulin, beta globulin, gamma globulin, monoclonal spike 1, or monoclonal spike 2 proteins in the blood sample (e.g., in the serum of the blood sample). In some embodiments, standard clinical lab testing assays are performed on the blood sample to determine total protein levels or to determine clinically relevant protein information. In some embodiments, blood urea nitrogen is measured in the blood sample. In some embodiments, electrophoresis and other
15 techniques may be used to determine a total M-protein in the serum or a total serum volume. In some embodiments, the blood sample may be further tested to determine characteristics of light chains, such as the absolute difference between involved and uninvolved free light chains (DFLC value), a measurement of the amount of lambda free light chains in the blood sample, a ratio of free kappa and free lambda light chain in the blood sample, or a measurement of the amount of
20 kappa free light chains in the blood sample.

Also or alternatively, as shown in block 124, the biological sample may include a urine sample of the patient. In an example process, the lab testing for the pre-apheresis stage may include analyzing proteins from a urine sample of the patient. In some embodiments, a protein electrophoresis may be performed on the urine sample to determine and/or detect various proteins
25 and/or their characteristics. For example, the amount of protein in urine over a 24 hour period (e.g., urinary 24 hour aliquot of protein) may be determined (e.g., via multiple urine samples of the patient over the 24 hour period). Furthermore, electrophoresis and other techniques may be used to detect or measure characteristics (e.g., percentage, volume, concentrations, etc.) of albumin, alpha-1 globulin, alpha-2 globulin, beta globulin, gamma globulin, and/or monoclonal spike 1 in
30 the urine sample. In some embodiments, the patient is assessed for proteinuria. In some embodiments, blood urea nitrogen are measured in the urine sample

In some embodiments, results from the lab testing at the apheresis stage may be used to determine disease or disease classifications, such as a multiple myeloma (MM) classification (e.g., MM classification 2).

After lab testing is performed using biological samples (e.g., urine sample, blood sample, etc.) for further screening and/or information gathering of the patient at the pre-apheresis stage, and data for pre-apheresis parameters are obtained via lab testing (block 124), the example methodology 100 of the CAR T drug product manufacturing process may proceed to an apheresis stage 130. Alternatively, in some embodiments, the CAR T drug product manufacturing process may proceed to the apheresis stage 130 after the screening stage 110.

10 C. Apheresis Stage

In various embodiments, after the screening stage 110 of a patient (and, in some embodiments, after the pre-apheresis stage 120), but before the manufacturing stage 140, the example methodology 100 of the CAR T drug product manufacturing process may include an apheresis stage 130. The example methodology at the apheresis stage 130 may include performing an apheresis procedure on a selected patient. The apheresis procedure may involve isolating a blood sample from the patient that includes T cells from the selected patient for use in a manufacturing facility to manufacture the CAR T drug product. In at least one embodiment, the apheresis may be performed by an apheresis device fluidly connected to the blood circulation of the patient, allowing blood from the patient to enter the apheresis device. The apheresis device may be configured to separate various components of the blood (e.g., plasma, red blood cells, white blood cells, and platelets). The apheresis device may be further configured to isolate a component of interest carrying T cells (e.g., white blood cells) from the rest of the patient blood to form the apheresis sample (block 132).

The example process 100 may include receiving data for various parameters from the isolated apheresis sample at the apheresis stage (the parameters referred to herein as “apheresis stage parameters” or “apheresis parameters”) (block 136). The data acquisition may rely on various techniques described herein, such as but not limited to flow cytometry, sequencing, electrophoresis and imaging (techniques represented via block 134). In some embodiments, apheresis stage parameters may include parameters describing the expression or the non-expression of cell surface markers (including any of those described herein e.g., cell surface proteins, cell surface receptors,

cell surface macromolecules, etc.), and such parameters may be specified herein as cell surface marker parameters. When such cell surface marker parameters are acquired during the apheresis stage, such parameters may be further specified as apheresis stage – cell surface marker parameters.

5 The example CAR T drug product manufacturing process 100 may involve obtaining data for the cell surface marker parameters through flow cytometry, sequencing, and/or electrophoresis techniques 134 described herein. In particular, such techniques may be used to detect the presence of the cell surface marker or determine one or more properties of the cell surface marker described by the cell surface marker parameter, such as but not limited to a percentage of cells in the apheresis
10 sample having an expression or non-expression of the cell surface marker, a concentration of the cells in the apheresis sample having an expression or a non-expression of the cell surface marker, a ratio between cells in the apheresis sample expressing a cell surface marker to cells in the apheresis sample expressing another cell surface marker, a count or a volume of cells in the apheresis sample expressing a cell surface marker, etc.

15 Example cell surface markers for which information is obtained at the apheresis stage may include but are not limited to the presence or absence of CD4, CD8, CD11b, CD14, CD16, CD33, CD62L, HLA, DRA1, DRA1, CD192, CAR, CD25, CD27, CD27, CD28, CD28, CD38, CD39, CD3, PD1, CD57, KLRG, CCR7, CD45RA, or a combination thereof. For example, the techniques described herein (e.g., flow cytometry) may detect the presence of or may determine one or more
20 properties of cells having a combination of the aforementioned cell surface markers, such as a percentage of cells that are CD25+, CAR-, CD4+ T cells in the apheresis sample.

 In some embodiments, apheresis stage parameters may include parameters describing various properties of the apheresis sample thus obtained using the apheresis process. As used herein, parameters describing properties of a sample (e.g., apheresis sample) obtained via a process
25 (e.g., apheresis parameters), and excluding cell surface marker parameters, may be referred to as “process parameters.” When such process parameters are obtained during the apheresis stage, such process parameters may be further specified herein as “apheresis stage – process parameters.” The example CAR T drug product manufacturing process 100 may involve obtaining data for these process parameters through flow cytometry, sequencing, and/or electrophoresis techniques
30 described herein. In particular, such process parameters may include a measurement of (e.g., a percentage of or a concentration of) one or more contents of the apheresis sample, such as but not

limited to lymphocytes, leukocytes, natural killer cells, stem natural killer cells, natural killer T cells, stem natural killer T cells, regulatory T cells, stem regulatory T cells, monocytes neutrophils, memory T cells, and/or stem memory T cells in the apheresis sample. In some embodiments, the process parameters may include measurements of one type of content in the apheresis sample relative to another type of content in the apheresis sample (e.g., a percentage of leukocytes that are monocytes in the apheresis sample).

D. Manufacturing Stage

In various embodiments, after the apheresis stage 130, the example methodology 100 of the CAR T drug product manufacturing process may include the manufacturing stage 140. At the manufacturing stage 140, the apheresis sample from the apheresis stage 130 may be further processed to manufacture the CAR T drug product. The processing can include one or more of: activating and enriching the T cells, genetically modifying the T cells to produce chimeric antigen receptors (CAR), and expanding and monitoring growth of CAR⁺ T cells. Furthermore, the manufacturing stage 140 can involve obtaining data for various parameters obtained from the cell culture sample derived from the apheresis sample and used in various substages of the manufacturing process (referred to herein as “T cell culture sample”). Such parameters obtained during any of the various substages of the manufacturing stage 140 may be referred to herein as “manufacturing stage parameters” or “manufacturing process parameters.” As shown in FIG. 1B, the manufacturing stage 140 may include or may be segmented into an initial stage 141, an early middle stage 152, a middle stage 158, a late middle stage 164, and an advanced stage 170 of the manufacturing process. In some embodiments, at various substages of the manufacturing process, the T cell culture sample may be incubated and various aspects of the incubation of the T cell culture (e.g., incubation time, incubation temperature, CO₂ saturation, etc.) may be measured. In some embodiments, at various substages of the manufacturing process, a measurement (e.g., a count, a volume, etc.) of seeded T cells in the T cell culture sample may be determined.

The manufacturing process 140 may begin with the initial stage 141, which may be further segmented into an early initial stage 142 and a late initial stage 148. In the example embodiment shown in FIG. 1, the initial stage may include days 0 and 1 of the manufacturing process (e.g., the early initial stage may occur on day 0 of the manufacturing process and the later initial stage may occur on day 1 of the manufacturing process). However, in some embodiments, the initial stage

may include or may comprise day 0, day 1, day 2, or day 3 of the manufacturing process, a range or value defined by any two of the aforementioned days, for example, day 0 and day 1 of the manufacturing process.

5 In at least one embodiment, at the early initial stage 142, the apheresis sample may be prepared for the manufacturing process by thawing the apheresis sample (e.g., from a frozen state after apheresis) and then washing the thawed sample (block 144). Furthermore, various characteristics of the T cells in the apheresis sample (e.g., viability, cell diameter, expression or non-expression of various cell surface markers, etc.) may be assessed after the thawing, and may be reassessed after the washing. For example, flow cytometry may be used to detect or measure a
10 property of cells expressing or not expressing the cell surface markers CD4, CD8, CD3, CD16, CD56, CD19, and/or CD 14 in the T cell culture sample. In some embodiments, compounds may be added to prepare the T cell culture sample for the manufacturing process, such as anticoagulants (e.g., ACD-A) and/or a DNase (e.g., Pulmozyme). In some embodiments, an in-line filtration may be performed to prepare the apheresis sample for the manufacturing process. In some
15 embodiments, T cells of the T cell culture sample may be arranged or distributed among bags (e.g., CultiLife bags) that may provide a provide a sterile, gas-permeable closed system for growing and transducing the T cell culture sample. In such embodiments, the number of cells per bags as well as the number of bags may be monitored throughout one or more substages of the manufacturing process. The example methodology 100 may further include adding a cell culture media, such as
20 a GMP media specialized for cultivation of T Cells (e.g., TexMACS) to form or maintain the T cell culture (block 146).

In at least one embodiment, at the late initial stage 148, T cells in the T cell culture sample may be activated and enriched for the remainder of the manufacturing process (block 150). In some embodiments, the activation may be performed by the addition of activation beads (e.g., T cell
25 TransAct beads) configured to activate and expand enriched T cell populations or resting T cells from the apheresis sample. In some embodiments, the example methodology may further involve detecting or assessing properties of clumps (e.g., the presence of clumps, the number of clumps, the size of one or more clumps, and the effects of mixing the T cell culture sample on the clumps) prior to and after the T cell activation within the T cell culture sample (block 151).

30 After the initial stage 141, the manufacturing process may proceed to the early middle stage 152, which may be associated with the stimulation and/or transduction of the of the T cells in the

T cell culture sample with a chimeric antigen receptor (CAR). In the example methodology shown in FIG. 1, the early middle stage may include day 3 of the manufacturing process. However, in some embodiments, the early middle stage may include or may comprise day 2, day 3, day 4, or day 5 of the manufacturing process, or a range or a value defined by any two of the aforementioned days, for example, days 2-4 of the manufacturing process, preferably day 3 of the manufacturing process. In some embodiments, the example methodology 100 at the early middle stage 152 may involve assessing T cell viability (e.g., a percentage of viable T cells, viable T cell count, a viable T cell concentration, a volume of T cells) in the T cell culture sample or within one or more bags holding the T cell culture sample (block 153). The example methodology may further involve mixing the T cell culture sample (block 154). In some embodiments, the example methodology may further involve detecting or assessing properties of clumps (e.g., the presence of, the number of size, effects of mixing, etc.) within the T cell culture sample before and after a mixing of the T cell culture sample. Furthermore, various properties of the T cells (e.g., pooled viability, pooled cell diameter, starting volume, etc.) may be assessed for the mixed T cell culture sample. In some embodiments, the example methodology at the early middle stage may involve performing sampling, seeding, and rapid expansion of T cells in the T cell culture sample (e.g., via gas permeable rapid expansion (G-Rex)), and measuring viability before and after these processes.

The example methodology at the early middle stage 152 may further include a transduction of the T cell culture sample to enable T cells to express CAR (block 156). In some embodiments, a vector (e.g., a lentivector) carrying the CAR expression gene may be added to the T cell culture sample or to one or more bags holding the T cell culture sample to enable the T cells to express CAR. Various parameters associated with the transduction process at the early middle stage may be measured (e.g., a lot number of the vector, a batch number of the vector, a lot number of the syringe used during the transduction, a vector type, a vector titer (IU/mL), a multiplicity of infection (MOI) of the target vector added to the T cell culture sample, a number of vector vials used in the transduction process, a vector hold time (min), an ambient hold time of the syringe during the transduction process, and/or a volume of vector added to a T cell culture sample).

After the early middle stage 152, the manufacturing process 140 may proceed to the middle stage 158, which may be associated with the expansion and growth monitoring of the T cell culture after the T cell culture has been transduced with CAR. In the example methodology shown in FIG. 1B, the middle stage 158 may include day 6 of the manufacturing process. However, in some

embodiments, the middle stage 158 may include or may comprise day 5, day 6, or day 7 of the manufacturing process, or a range or a value defined by any two of the aforementioned days, for example, day 6 of the manufacturing process 140. At the middle stage 158, the example methodology 100 may involve expanding the T cell culture containing the T cells that express
5 CAR (referred to herein as CAR+ T cells or CAR T cells) (block 160), and monitoring the growth of the T cell culture (block 162). In some embodiments, the expansion may be facilitated by the addition of interleukin-2 (IL-2) to drive T cell expansion and differentiation. In some embodiments, growth may be monitored by detecting the presence of and measuring a property (e.g., a concentration) of glucose or lactate in the T cell culture sample.

10 The manufacturing process 140 may further proceed to the later middle stage 164, which is associated with the continued expansion and growth monitoring of the T cell culture after the middle stage. For example, the T cell culture sample may continue to be expanded (block 166) via use of agents such as IL-2 and the growth may continue to be monitored (block 168) via measurements of concentrations of glucose or lactate in the T cell culture sample. As shown in
15 FIG. 1, the late middle stage 164 may include day 8 of the manufacturing process. However, in some embodiments, the late middle stage 164 may include or may comprise day 7, day 8, day 9, or day 10 of the manufacturing process, or a range or a value defined by any two of the aforementioned days, for example, days 7-9 of the manufacturing process, preferably day 8 of the manufacturing process.

20 After expansion and growth of CAR T cells in the middle and later middle stages, the manufacturing process 140 may proceed to the advanced stage 170, during which the final product (e.g., CAR+ T cell drug) is harvested and released from the T cell culture sample. As shown in FIG. 1B, the advanced stage 170 may include or may begin on day 10 of the manufacturing process 140. However, in some embodiments, the advanced stage 170 may include or may comprise day
25 9, day 10, day 11, day 12, day 13, or day 14 of the manufacturing process 140, or a range or a value defined by any two of the aforementioned days, for example, days 9-12 of the manufacturing process 140, days 10-12 of the manufacturing process 140, preferably day 10 of the manufacturing process 140. At the advanced stage 170, the example methodology 100 may include harvesting T cells from the T cell culture sample and washing the harvested T cells (block 172). In some
30 embodiments, measurements of various aspects of the harvested T cells (e.g., viable cell concentration, a total cell concentration, a percentage of viable cells, a volume, total and viable

cell counts, CAR⁺ expression, etc.) may be performed prior to and after the wash using techniques described herein (e.g., flow cytometry) (block 174). In some embodiments, growth of the T cells may be monitored by measuring concentrations of glucose or lactose in the harvested sample. Furthermore, the harvested T cells may be further inspected (e.g., for clumps or particulates) (block 5 176). CAR T cells from the harvested T cell sample may be released and formulated as a final product (block 178).

Throughout the manufacturing process 140, data for various parameters may be obtained (block 180), for example, through assessments, measurements, completion of steps, additions of reagents, etc. As will be discussed herein, the final product may be comply with, or fail to satisfy 10 a regulatory specification for the CAR T drug product. Such determination (OOS outcome) can be predicted based on the data for parameters obtained throughout the CAR T drug product manufacturing process.

IV. Example Parameters Obtained From Stages Of An Example CAR T Drug Production Process

15 FIG. 2 is a block diagram illustrating various stages of an example CAR T drug product manufacturing process from which parameters are generated for predicting the CAR T drug product OOS outcome. As previously discussed in the foregoing description, CAR T drug product manufacturing may include, for example, a screening stage 210, a pre-apheresis stage 220, an apheresis stage 230, and a manufacturing stage 240. Each stage of the CAR T drug production 20 process may be characterized by various parameters that affect or are otherwise predictive of whether a CAR T drug product would be OOS 252 based on the CAR T manufacturing process. The OOS outcome 252 may be based on a stored or accessible specification 259. In some embodiments, the OOS outcome 252 of the determination of whether the CAR T drug product is predicted to be out of specification (OOS) may be based on the failure to satisfy (e.g., to a 25 predetermined threshold) one or more specifications for attributes of the CAR T drug product (e.g., dose, viability, VCN, CAR, etc.).

As previously discussed, at the screening stage 210, patients may be screened and/or selected from which biological samples may be obtained to manufacture patient-specific CAR T drug products. However, the demographics of the patient as well as the medical history of the 30 patient may affect the OOS outcome of the CAR T drug product to be produced. Thus, the screening stage may be characterized by various parameters (referred to herein as “screening

parameters” 212), including those pertaining to patient demographics (referred to herein as “patient demographic parameters” 214) and patient medical history (referred to herein as “patient medical history parameter type”). In particular, the present disclosure describes various screening parameters 212 that were found to have a predictive quality on the OOS outcome of the CAR T drug product.

Examples of patient demographic parameters 214 from the screening stage that were found to have that predictive quality include but are not limited to: age, sex, race, body mass index, ethnicity, and country of origin.

Examples of patient medical history parameters 216 from the screening stage that were found to have that predictive quality include but are not limited to: a time since initial diagnosis (e.g., of a disease for which the CAR T drug product therapy is intended to treat), a measurable disease type (e.g., of the disease the CAR T drug product therapy is intended to treat), an oncology performance status score at baseline of an oncology condition (e.g., an Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline), a left ventricular ejection fraction (%), a baseline tumor burden category, a baseline number of extramedullary plasmacytomas, a baseline presence of evaluable bone marrow assessment, a baseline International Staging System (ISS) stage, a baseline type of myeloma, a baseline bone marrow percent plasma cells aspirate, a baseline bone marrow percent plasma cells, a baseline bone marrow percent plasma cells aspirate category, a baseline bone marrow percent plasma cells category, prior alkylating agents used (e.g., in a prior treatment of the patient), a prior allogeneic transplantation in the patient, a prior use of anthracyclines in the patient, a number of times of prior autologous transplantation in the patient, a prior autologous transplantation in the patient, a prior use of bortezomib in the patient, a prior cancer-related surgery/procedure for the patient, a prior use of carfilzomib in the patient, a prior use of anti-CD38 antibodies in the patient, a prior use of daratumumab in the patient, a prior use of dexamethasone in the patient, a prior use of elotuzumab in the patient, a prior use of an immunomodulatory drug (IMiD) in the patient, a prior use of isatuximab in the patient, a prior use of ixazomib in the patient, a prior use of lenalidomide in the patient, a number of prior therapy lines experienced by the patient, a prior use of oprozomib in the patient, a prior use of panobinostat in the patient, a prior primary immunodeficiency (PI) in the patient, a prior use of pomalidomide in the patient, a prior use of prednisone in the patient, a prior use of radiotherapy on the patient, a prior use of corticosteroids in the patient, a prior use of mezagitamab (e.g., TAK-079) in the

patient, a prior use of thalidomide in the patient, a prior transplantation performed on the patient, a refractory status of the patient, whether a patient was refractory to a treatment based on Penta, whether a patient was refractory to a treatment based on an alkylating agent, whether a patient was refractory to a treatment based on bortezomib, whether a patient was refractory to a treatment based on carfilzomib, whether a patient was refractory to a treatment based on anti-CD38 Antibody only, whether a patient was refractory to a treatment based on daratumumab, whether a patient was refractory to a treatment based on elotuzumab, whether a patient was refractory to a treatment based on IMiD only, whether a patient was refractory to a treatment based on isatuximab, whether a patient was refractory to a treatment based on ixazomib, whether a patient was refractory to a treatment based on lenalidomide, whether a patient was refractory to a treatment based on a last therapy line, whether a patient was refractory to a treatment based on panobinostat, whether a patient was refractory to a treatment based on pomalidomide, whether a patient was refractory to a treatment based on any prior therapy, whether a patient was refractory to a treatment based on mezagitamab (e.g., TAK-079), whether a patient was refractory to a treatment based on thalidomide, whether a patient was refractory to a treatment based on any anti-CD38 antibody, whether a patient was refractory to a treatment based on any IMiD, whether a patient was refractory to a treatment based on any primary immunodeficiency (PI).

Furthermore, at the pre-apheresis stage 220 of the CAR T drug production process, biological samples of a patient (e.g., urine samples, blood samples, etc.) may be lab tested for various characteristics to determine additional information about and provide additional screening of the patient. The lab tests however may be used to measure or otherwise provide data for various parameters of the biological sample (referred to herein as “pre-apheresis parameters” 222). In particular, the present disclosure describes that various parameters at the pre-apheresis stage that were found to have a predictive quality on the OOS outcome of the CAR T drug product. Examples of such pre-apheresis parameters 222 may include but are not limited to: a total volume of the biological sample obtained, a urine protein electrophoresis collection criteria, a serum protein electrophoresis collection criteria, whether a urine protein electrophoresis sample was received, an absolute difference between involved and uninvolved serum free light chains (DFLC value) in the biological sample, a multiple myeloma (MM) classification of the patient (e.g., MM-2 classification), an elapsed date and/or time associated with the pre-apheresis lab tests, a measurement of total protein (e.g., in the urine sample or in the blood sample of the patient) , a

urinary 24 hour aliquot of protein, a urinary 24 hour aliquot of protein indicative of myeloma, a detection or a measurement of lambda free light chains in the biological sample, a ratio of free kappa light chains to free lambda light chains in the biological sample, a measurement (e.g., a percent volume) of albumin in the biological sample, a measurement (e.g., a percent volume) of alpha 2 globulin in the biological sample, a measurement (e.g., a percent volume) of alpha 2 globulin in the biological sample, a measurement (e.g., a percent volume) of beta globulin in the biological sample, a measurement (e.g., a percent volume) of gamma globulin in the biological sample, a measurement (e.g., a percent volume) of monoclonal spike 1 in the biological sample, a measurement (e.g., a percent volume) of monoclonal spike 2 in the biological sample, a measurement based on an immunofixation impression test for myeloma using serum protein electrophoresis, a total or cumulative amount M-Protein in the biological sample, a serum volume of the biological sample.

Even further, at the apheresis stage 230 of the CAR T drug production process, post-apheresis samples may be tested for various parameters using a flow cytometer and other devices. Such parameters may be associated with the presence, absence, and/or a measurement of various components within the apheresis sample produced by the apheresis process (referred to herein as “apheresis stage - process parameters” 236); the presence, absence, and/or a measurement of cell surface markers (the parameters referred to herein as “cell surface marker parameters” 634). In particular, the present disclosure describes that various parameters at the apheresis stage were found to have a predictive quality on the OOS outcome of the CAR T drug product.

Examples of such parameters from the apheresis stage 230 (referred to herein as “apheresis stage parameters” 232, and which may include but are not limited to cell surface marker parameters 234, and/or process parameters 236 that were found to be predictive of the OOS outcome of the CAR T drug product include but are not limited: a ratio of CD4+ T Cells to CD8+ T Cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CAR-, CD4+ terminally differentiated effector memory T cells (TEMRA) in the apheresis sample; a percentage of lymphocytes that are CAR- natural killer (NK) T Cells in the apheresis sample; a percentage of lymphocytes that are CAR- NK cells in the apheresis sample; a concentration of CAR- Regulatory T cells in the apheresis sample; a percentage of lymphocytes that are CAR- T cells in the apheresis sample; a percentage of regulatory T (Treg) cells that are CAR- Treg cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CAR-, CD4+ Treg cells in the apheresis sample; a

percentage of CAR- T cells that are CAR- Treg cells in the apheresis sample; a percentage of leukocytes that are CAR- monocytes in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CAR-, naive CD4+ T cells in the apheresis sample; a percentage of leukocytes that are CAR- neutrophils in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CAR-,
5 CD4 Stem Memory T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CAR-, CD4 T Central Memory Cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CAR-, CD4+ Effector Memory T cells in the apheresis sample; a percentage of CAR- T Cells that are CAR-, CD4+ T Cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CAR-, CD8 Central Memory T cells in the apheresis sample; a percentage of CAR-, CD8+
10 T cells that are CAR-, CD8+ Effector Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ Stem Memory T cells; a percentage of CAR- T cells that are CAR-, CD8+ T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ TEMRA in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ naive T cells in the apheresis sample; a percentage of CAR- T Cells that are CAR-, double
15 negative T cells in the apheresis sample; a percentage of CAR- T Cells that are CAR-, double positive T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CD25+, CAR-, CD4+ T cells in the apheresis sample; a percentage of CAR-CD8+ T cells that are CD25+, CAR-, CD8+ T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, naive, CD4+ T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are
20 CD27+, CAR-, CD4+ Central Memory T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, CD4+ Effector Memory T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, CD4+ Stem Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ Central Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CD27+,
25 CAR-, CD8+ Effector Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ Stem Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ naive T cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CD27-, CAR-, CD4+ Effector Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CD27-, CAR-, CD8+ Effector
30 Memory T cells in the apheresis sample; a percentage of CAR-, CD8+ T Cells that are CD27-, CAR-, CD8+ TEMRA in the apheresis sample; a percentage of CAR-, CD4+ T Cells that are

CD28+, CAR-, CD4+ T cells; a percentage of CAR-, CD8+ T cells that are CD28+, CAR-, CD8+ T cells in the apheresis sample; a concentration of CD3+, CAR-, CD4+, CD8- T cells in the apheresis sample; a concentration of CD3+, CAR-, CD4-, CD8+ T cells in the apheresis sample; a percentage of CD3+ T cells that are CD3+, CAR- T cells in the apheresis sample; a concentration of CD3+, CAR- T cells in the apheresis sample; a percentage of CAR- Treg cells that are CD38+, CAR- Treg cells in the apheresis sample; a percentage of CAR-, CD4+ T cells that are CD38+, CAR-, CD4+ T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are CD38+, CAR-, CD8+ T cells in the apheresis sample; a percentage of CAR- Treg cells that are CD38+, CD39+, CAR- Treg cells in the apheresis sample; a percentage of CAR- Treg cells that are CD38-, CD39-, CAR- Treg cells in the apheresis sample; a percentage of CAR- Treg cells that are CD39+, CAR- Treg cells in the apheresis sample; a concentration of lymphocytes in the apheresis sample; a percentage of leukocytes that are monocytes in the apheresis sample; a percentage of lymphocytes that are NK T Cells in the apheresis sample; a percentage of lymphocytes that are NK Cells in the apheresis sample; a percentage of leukocytes that are neutrophils in the apheresis sample; a percentage of CAR-, CD4+ T cells that are PD1+, CAR-, CD4+ T cells in the apheresis sample; a percentage of CAR-, CD8+ T cells that are PD1+, CAR-, CD8+ T cells in the apheresis sample; a percentage of lymphocytes that are T cells in the apheresis sample; a percentage of CD4+ T cells that are CD4+ Treg cells in the apheresis sample; a percentage of T cells that are Treg cells in the apheresis sample.

The present disclosure also describes that sites at the apheresis stage, at which testing proved to have a predictive effect on the OOS outcome of the CAR T drug product include but are not limited to a manufacturing site, a clinical site, a cryopreservation site, a clinical study, and the process.

Furthermore, as previously discussed, at the manufacturing stage 240 of the CAR T drug production process, the selected post apheresis samples may be prepared to become CAR T drug products. The CAR T drug products may be provided in a final container. In some embodiments, the manufacturing stage 240 may be divided into a plurality of sub-stages. For example, the substages may include an early initial stage, a late initial stage, and early middle stage, a middle stage, a late middle stage, and an advanced stage closer to and/or including the release of the final product. Manufacturing stage parameters may be obtained from assessments of cell culture samples at any of these substages. In some embodiments, the parameters may indicate a detection

of a cell surface marker or a measurement of cells expressing such cell surface markers in one or more substages of the manufacturing process; such parameters may be referred to herein as manufacturing stage cell surface marker parameters 644. In some embodiments, a manufacturing stage parameter may describe a characteristic of a process performed in one or more substages of the manufacturing process and/or may describe contents of a cell culture sample in one or more substages of the manufacturing process; such parameters may be referred to herein as manufacturing stage process parameters 246.

In some embodiments, the manufacturing stage and substages may affect whether a CAR T drug product would be OOS based on various parameters measured of the working products and/or samples (e.g., T cell culture samples, T cell culture populations, etc.) at various points of the manufacturing stage and/or substages.

The present disclosure notes that various manufacturing stage parameters 242 were found to be predictive of the OOS outcome of the CAR T drug product. In particular, the present disclosure notes that manufacturing stage parameters 242 found in substages closer to the final product were more predictive of the OOS outcome of the CAR T drug product (e.g., parameters obtained from early middle, middle, late middle, or advanced stages were more predictive than manufacturing stage parameters obtained during the early initial or late initial stage of the manufacturing process).

Examples of such manufacturing stage parameters 242 found to be predictive that are obtained from the T cell culture sample at the early initial stage of the manufacturing process include but are not limited to: a duration of thawing; a concentration of viable T cells (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection or undergoing negative selection etc.); a percentage of cells that are viable T cells (e.g., post thaw and/or post wash, rounded or unrounded, in T cell culture samples undergoing positive selection or undergoing negative selection, etc.); a T cell diameter (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection or undergoing negative selection); an apheresis volume; a volume of an anticoagulant (e.g., ACD-A) added to the T cell culture sample (e.g., post thaw); a viable T cell count before sampling (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection or undergoing negative selection); a sample volume (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection or undergoing negative selection); a viable T cell count after sampling (e.g., post thaw and/or post wash, in T cell culture

samples undergoing positive selection or undergoing negative selection); whether a DNase (e.g., Pulmozyme) was added to the T cell culture sample (e.g., post thaw); whether an anticoagulant (e.g., ACD-A) was added to the T cell culture sample (e.g., post thaw); whether an in-line filtration of the T cell culture sample occurred (e.g., post thaw); a percentage of cells that are CD4+ T Cells (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection); a percentage of cells that are CD8+ T cells (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection); a ratio of CD4+ T cells to CD8+ T cells in the T cell culture sample (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection); a percentage of cells that are viable CD3+ T cells (e.g., post that and/or post wash, in T cell culture samples undergoing positive selection); a percentage of cells that are CD3+ T cells (e.g., post that and/or post wash, in T cell culture samples undergoing positive selection); a percentage of cells that are CD16+ and/or CD56+ T cells (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection); a percentage of cells that are CD19+ T cells (e.g., post that and/or post wash, in T cell culture samples undergoing positive selection); a percentage of cells that are CD14+ T cells (e.g., post thaw and/or post wash, in T cell culture samples undergoing positive selection, etc.); a volume of the T cell culture sample (e.g., post wash); a volume of clump removal from the T cell culture sample (e.g., post wash); a total incubation time for labeling CD4+ T cells and CD8+ T cells; a total enrichment time for labeling CD4+ T cells and CD8+ T cells; a number of cycles of running the T cell culture sample through a cell processing platform (e.g., Prodigy); whether or not CD4+ beads and/or CD8+ beads were manually drained; the time spent between thawing and a run through a cell processing platform (e.g., Prodigy) for the T cell culture sample, a time spent in a run through a cell processing platform (e.g., Prodigy) for the T cell culture sample, a concentration of viable T cells that were positively selected (e.g., post wash); a percentage of viable T cells that were positively selected (e.g., post wash); a number of viable T cells per bag; a number of T cell culture bags; a number of viable T cells for recovery; a volume of T cells added to a bag for culturing; a volume of culture media (e.g., TexMACS) added to a bag for culturing; a volume of T cells seeded in a bag; a densitue of viable T Cells in a bag; an actual number of number of viable T cells seeded; and a post selection hold time.

Examples of manufacturing process parameters 242 found to be predictive that can be obtained from assessments of the T cell culture sample at the late initial stage of the manufacturing process may include but are not limited to: an incubation time for the T cell culture sample at the

initial stage; whether there are any pre-activation clumps in the T cell culture sample; a number of pre-activation clumps (e.g., before massage); a mitigation effect of a massage on the pre-activation clumps; a volume of activation beads (e.g., Transact Beads) added to a bag of the T cell culture sample, a volume of T cell culture sample that is seeded in a bag; whether there are post-activation clumps; a number of post-activation clumps before a massage; a size of post-activation clumps before a massage; and a mitigation effect of a massage on the post-activation clumps.

Examples of manufacturing process parameters 242 found to be predictive that can be obtained from assessments of the T cell culture sample at the early middle stage of the manufacturing process may include but are not limited to: an incubation time for the T cell culture sample at the early middle stage (e.g., days 1-3 of the manufacturing process), a concentration of viable T Cells in a bag of the T cell culture sample, a percentage of cells that are viable T cells in a bag of the T cell culture sample; a volume of T cells in a bag of the T cell culture sample; a number of cells that are viable T cells in a bag of the T cell culture sample; whether there are any clumps in the T cell culture samples (e.g., pre-mixing or post-mixing); a number of clumps in the T cell culture samples (e.g., pre-mixing or post-mixing); a size of one or more clumps (e.g., pre-mixing or post-mixing); an effectiveness of mixing the clumps in a T cell culture sample; an average concentration of viable T Cells per population of the T cell culture samples; an average percentage of viable T Cells per population of the T cell culture samples; an average cell diameter of viable T cells per population of the T cell culture samples; a starting volume of the T cell culture samples; a number of viable T cells before sampling; a sample volume of the T cell culture; a number of viable T cells after sampling; a number of viable T cells available for seeding in the T cell culture; a number of gas permeable rapid expansion (G-Rex) to seed, a number of viable T cells per G-Rex; a volume of T cell culture sample transferred from a bag to G-Rex; a volume of T cells Seeded in G-Rex A; a vector lot of the vector used in the transduction of the T cell culture sample; a vector batch number of the vector used in the transduction of the T cell culture sample; a syringe lot of the syringe used for the transduction of the T cell culture sample; a vector type of the vector used in the transduction of the T cell culture sample; a vector titer of the vector used in the transduction of T cell culture sample; a target vector multiplicity of infection (MOI) of the vector used in the transduction of the T cell culture sample; a target number of vector vials for vectors used in the transduction of the T cell culture sample; a number of vector vials used for the transduction of the T cell culture sample; a vector hold time associated with the transduction of

the T cell culture sample; a syringe ambient hold time for the syringe used in the transduction of the T cell culture sample; a volume of the vector added to a G-Rex; an incubation time of a G-Rex; a number of target viable T cells for vesicular stomatitis virus glycoprotein (VSV-g) sampling; a volume of VSV-g sampling; a concentration of viable T cells in the VSV-g sample; an actual
5 number of viable T cells in the VSV-g sample; a number of pellets generated; a percent loss of T cells, and a number of viable T cells for expansion after VSV-g sampling.

Examples of manufacturing process parameters 242 found to be predictive that can be obtained from assessments of the T cell culture sample at the middle stage of the manufacturing process may include but are not limited to: an incubation temperature (e.g., in and out of an incubator); an incubation CO₂ saturation (e.g., in and out of an incubator); a total incubation time
10 (e.g., from days 3-6 of the manufacturing process); whether a batch of IL-2 was added to the T cell culture sample, a protein content of IL-2 was added to the T cell culture sample; an activity of IL-2, a volume of IL-2 added to a G-Rex of the T cell culture sample; a concentration of lactate or glucose in the T cell culture sample; and a concentration of lactate or glucose in a G-Rex of the T
15 cell culture sample.

Examples of manufacturing process parameters 242 found to be predictive that can be obtained from assessments of the T cell culture sample at the late middle stage of the manufacturing process may include but are not limited to: an incubation temperature (e.g., in and out of an incubator); an incubation CO₂ saturation (e.g., in and out of an incubator); a total
20 incubation time (e.g., from days 6-8 of the manufacturing process); whether a batch of IL-2 was added to the T cell culture sample; a protein content of IL-2 was added to the T cell culture sample; an activity of IL-2; a volume of IL-2 added to a G-Rex of the T cell culture sample; a concentration of lactate or glucose in the T cell culture sample; and a concentration of lactate or glucose in a G-Rex of the T cell culture sample.

Examples of manufacturing process parameters 242 found to be predictive that can be obtained from assessments of the T cell culture sample at the advanced stage of the manufacturing process may include but are not limited to: an incubation temperature (e.g., in and out of an incubator); an incubation CO₂ saturation (e.g., in and out of an incubator); a total incubation time
25 (e.g., from days 8-10 of the manufacturing process); a total expansion or incubation time for the T cell culture sample (e.g., from days 3-10 of the manufacturing process); a concentration of viable
30 CAR⁺ T cells in a harvested sample of the T cell culture (e.g., pre-wash and post wash); a

concentration of T cells in a harvested sample of the T cell culture (e.g., pre-wash and post wash); a percentage of cells that are viable CAR+ T cells in a harvested sample of the T cell culture (e.g., pre-wash and post wash); a volume of the harvested sample of the T cell culture (e.g., pre-wash and post wash); a number of viable CAR+ T cells in the harvested sample of the T cell culture (e.g., pre-wash and/or post wash, before sampling and after sampling); a number of T cells in the harvested sample of the T cell culture (e.g., pre-wash and/or post wash, before sampling and/or after sampling); a concentration of glucose or lactate in the harvested sample of the T cell culture; an incubation temperature for flow cytometry (e.g., in and out of the incubator); an incubation CO2 saturation for flow cytometry (e.g., in and out of the incubator); a harvest and sampling processing time; a time for the completion of the flow cytometry of the harvested sample; a percentage of cells that are CAR+ T cells in the harvested sample of the T cell culture (e.g., pre-wash and/or post wash); a post-wash dose of CAR+ T cells in the harvested sample of the T cell culture; a number of viable target CAR+ T Cells per dose; a number of viable CAR+ T cells per dose; a concentration of a target formulation of viable CAR+ T Cells; a number of bags for the harvested sample of the T cell culture; a volume of CAR+ T cells per bag in the harvested sample of the T cell culture; a volume of CAR+ T cells used for the formulation of the final product; a volume of CS5 used for the formulation of the final product; a result of a particulate inspection of a bag of the harvested sample; a presence of a clump in the bag of the harvested sample; the time spent for the formulation of the final product; the contact time for CS5; a concentration of CS5 viable CAR+ T cells in the final formulation; a percentage of CS5 viable CAR+ T cells in the final formulation; an average concentration of CS5 viable CAR+ T cells in the final formulations; an average percentage of CS5 viable CAR+ T cells in the final formulations; a percent dosing accuracy associated with the final formulation; a volume of the final product per bag of the final formulation; an appearance of color in the final product; an appearance of a primary container in the final product; a BacT/Alert rapid sterility (or other measurement of the sterility of the final product); a concentration of an endotoxin in the final product; a mycoplasma in the final product; a final product replication competent lentivirus (RCL); a result of the VSV-g sampling in the early middle stage of the manufacturing process; a result of the VSV-g sampling in the advanced stage of the manufacturing process; a provirus vector copy number (e.g., copies/transduced cell); a percentage of cells that are viable CAR+ T cells in the final product (e.g., post-thaw); a percentage of cells that are viable CD3+ T cells in the final product; a provirus transduction efficiency (vector

copies/cell); a percentage of cells that are CD19+ T cells in the final product; a percentage of cells that are NK CD3-, CD16+, CD56+ T cells in the final product; a percentage of cells that are CD3+ T cells in the final product; a CAR of T cells in the final product; a concentration of viable T cells in the final product; a count of viable T cells in the final product; a dose based on a number viable CAR+ T cells per mass; a dose based on a number of viable CAR+ T Cells (cells); a percentage of cells that are CAR+ T cells in the final product; a presence of or a measurement of interferon (IFN) gamma in the final product; a processing time associated with one or more substages of the manufacturing process; a time from a flow completion to a removal of PFB; a processing time associated with CRF; a step yield (%) of the total viable T cells based on a cell processing platform (e.g., Prodigy); a step yield (%) of viable CD3+ T Cells of the T cell culture sample based on a cell processing platform (e.g., Prodigy); a culture bag step recovery (%) (i.e., a percentage of T cells recovered after activation from the T cell culture sample at the early middle stage of the manufacturing process relative to the T cells in the apheresis sample at the early initial stage of the manufacturing process); a LOVO Step Yield (%); a percentage of a pre-formulated bulk used for the formulation of the final product; a percentage of a recovery dose (e.g., from formulation to post thaw); a percentage recovery total viable concentration (target to post thaw); a percentage of a recovery dose (e.g., from target to post thaw); a population doubling time (PDT) for the T cell culture sample measured between the early middle stage and the advanced stage of the manufacturing process; a cumulative population doubling level (cPDL) for the T cell culture sample measured between the early middle stage and the advanced stage of the manufacturing process; a number of final bags used for the final product; an actual dose of CAR+ T cells per unit mass of the final product; a calculated dose of CAR+ T cells per unit mass of the final product; whether or not clumps were present at the late initial stage or the early middle stage of the manufacturing process; whether or not the manufacturing process was completed; whether or not the manufacturing and release testing was completed; whether or not the final product is OOS; a type of non-conformance of the final product with a specification; an OOS Type; an OOS/termination Comment; whether the final product is controllable (e.g., an OOS or termination of the final product is due to known reasons) or uncontrollable (e.g., an OOS or termination of the final product is due to unknown reasons); whether or not a batch of the final product was released to a patient; whether a release of a batch of the final product to a patient was an exceptional release (e.g., when a final product is found to be OOS but a batch is still considered safe to be released to

the patient); whether a released batch of the final product was infused by the patient; whether a batch was terminated during manufacturing; a shift or time category in which the final product is completed (e.g., first time category, a second time category, etc.); a total number of data points (e.g., features per column) in a batch associated with the final product; a visual inspection result
5 of the final product.

In some embodiments, manufacturing stage parameters 242 may include but are not limited to: a percentage of cells that are CAR+ T cells in the final product; a percentage of cells that a viable T cells in the final product (e.g., post thaw); a weight of a subject (e.g., a patient); a determination of whether a VCN is OOS (“VCN OOS”); and a determination of whether a CAR
10 is OOS (“CAR OOS”).

The aforementioned parameters (e.g., aforementioned examples of screening parameters 212, pre-apheresis parameters 222, apheresis parameters 230, and manufacturing process parameters 242) were found to be predictive of the OOS outcome of the CAR T drug product based on the training of machine learning models, as will be described in relation to FIG. 4. As such,
15 data for at least a subset of the aforementioned examples of parameters may be obtained at the respective stages and sent to one or more computing devices, such as computing device(s) 310 as will be discussed further below. At the computing device, the data may be structured (e.g., vectorized) and applied to one or more trained machine learning models 280 as one or more input feature vectors 282. The trained machine learning models 280 may then output an output feature
20 vector 284, that may indicate an the OOS outcome of the CAR T drug product 252 (e.g., a binary truth (“1”) indicating compliance with a specification and the absence of OOS indication, a binary false (“0”) indicating OOS). Furthermore, as will be discussed in relation to FIG. 4, if the OOS outcome is known, then data for the aforementioned examples of parameters may be obtained from the various stages of the CAR T drug product manufacturing process along with data for the known
25 drug quality OOS outcome. Such data, referred to as reference data or training data, may be used to form input feature vectors and output feature vectors, respectively, for training a machine learning model. The input feature vectors and output feature vectors thus formed may be referred to herein as “reference input feature vectors” and “reference output feature vectors,” to indicate their formation from reference data. The trained machine learning models 280 may then be used
30 to predict the OOS outcome of the CAR T drug product where the OOS outcome is not known based on parameters obtained from various stages of the CAR T drug product manufacturing

process. In some embodiments, as will be described in relation to FIG. 4, the predicted CAR T drug product OOS outcome may be used to adjust one or more of the manufacturing process parameters, for example to optimize, or otherwise correct deficiencies associated with, the CAR T drug product OOS outcome.

- 5 For simplicity, parameters obtained for the purpose of predicting an OOS outcome of a CAR T drug product may be referred to as “OOS parameters.”

V. Example Systems And Network Environment

FIG. 3 is a block diagram illustrating an example computer network environment 300 for predicting an OOS outcome for a CAR T drug product and optimizing the manufacturing of the
10 CAR-T drug product based on the OOS outcome, according to non-limiting embodiments of the present disclosure.

The computer network environment 300 may include one or more computing devices 310, one or more clinical data systems that store records of CAR T drug therapies (clinical data systems 340), one or more analytical systems 350, a bioreactor system 370, and one or more electronic
15 health record (EHR) systems 330. Each of the systems of network environment 300 may communicate with one or more of the remaining systems via a communication network 780.

The one or more computing devices 310 may be used to train and apply machine learning models to predict one or more CAR-T drug OOS outcomes (e.g., corresponding to various attributes of the CAR T drug product and whether each attribute complies with a specification). The one or
20 more computing devices may comprise a general computing device or a special purpose computing device (e.g., with hardware configured to facilitate numerous iterative processes comprising large data sets). For simplicity, computing device 310 as used herein may refer to any one of or a subset of the one or more computing devices 310. In some aspects, while one computing device or one set of computing devices of the one or more computing devices 310 may be configured to train the
25 machine learning models, another or another set of computing devices of the one or more computing devices 310 may be configured to apply the machine learning model to patient-specific data for a target patient. In another aspects, the training and application may be performed by the same computing device or same set of computing devices. In some embodiments, the one or more computing devices may include a computing device that optimizes manufacturing process
30 parameters for the production of CAR T drug products based on the outputs of the application of

the machine learning model after patient-specific data for a target patient is applied to the machine learning model.

In some embodiments, an example computing device of the one or more computing devices 310 may comprise one or more of the components shown for the one or more computing devices 310, such as one or more processors 312, memory 314, a linking engine 316 a network interface 324, a feature extraction module 318, a training module 320, an application module 322, a user interface 326, or an optimization module 328. The one or more processors 312 may comprise any one or more types of digital circuit configured to perform operations on a data stream, including functions described in the present disclosure. In some aspects, the one or more processors 312 may include special purpose processors such as a natural language processor, an image processor, etc. Also or alternatively, the one or more processors 312 may include a high performance processor having functionalities (e.g., processor speed, core count, etc.) configured to read and execute on large data sets (e.g., millions of base pairs of gene sequences). Also or alternatively, the one or more processors 312 may comprise a general purpose processor. The memory 314 may comprise any type of long term, short term, volatile, nonvolatile, or other memory and is not to be limited to any particular type of memory or number of memories, or type of media upon which memory is stored. The memory 314 may store instructions that, when executed by the processor 312, can cause the one or more computing devices 302 to perform one or more methods discussed herein. The network interface 324 (e.g., a wired interface (e.g., electrical, RF (via coax), optical interface (via fiber)), a wireless interface, a modem, etc.) may allow the computing device 310 to communicate with other systems over the communication network 380.

The linking engine 316 may comprise a software, program, module, and/or plug-in that, when executed by a processor, such as but not limited to the one or more processors 312, causes data received from disparate sources (e.g., electronic health records systems 330, clinical data systems 340, sample analytical systems 350, bioreactor system 370) to be linked or otherwise associated together. The data may comprise reference data (e.g., for a plurality of reference patients from which CAR T drug products were produced with known OOS outcomes) for training machine learning models as well as target data (e.g., for a target patient from which CAR T drug product is to be produced and for which a prediction of an OOS outcome of the CAR T drug product is desired). The linkage or association may be based on, for example, the data pertaining to a patient (e.g., a reference patient or a target patient) or a specific CAR T drug product manufacturing

process. In some aspects, the linking engine 316 may rely on metadata within the received data to form the linkage or association.

The feature extraction module 318 may comprise a software, program, module, and/or plug-in that, when executed by a processor, such as but not limited to the one or more processors 312, causes the processor to generate features that can be arranged in a feature vector from raw data in a format supported by machine learning models. The features may comprise a structured and/or a quantifiable data representing a characteristic. The raw dataset may include but are not limited to a natural language text, an image data, an RNA sequence, a DNA sequence, or a proteomic sequence. In some embodiments, the feature extraction module 318 may be used to vectorize (e.g., generate in a s quantified data) unstructured data from a dataset to a feature vector (e.g., input feature vectors, output feature vectors, reference input feature vectors, reference output feature vectors, etc.). In some aspects, the feature extraction module 318 may rely on special purpose processors (e.g., natural language processor, image processor, high performance processor for gene sequencing, etc.) to extract features from raw data.

The training module 320 may comprise a software, program, module, and/or plug-in that, when executed by a processor, such as but not limited to the one or more processors 312, causes the processor to train a machine learning model using, for example, a training data set (e.g., for supervised learning). In some aspects, the training module 320 may be used to associate input feature vectors (e.g., reference input feature vectors) to output feature vectors (e.g., reference output feature vectors). The input feature vectors and output feature vectors may be generated by the feature extraction module 318, or may be formed based on features extracted by the feature extraction module 318 from raw datasets. As used herein, a reference input feature vector or a reference output feature vector may refer, respectively, to an input feature vector and an output feature vector specifically generated from a training dataset for the purpose of training a machine learning model. The training dataset may comprise raw data concerning a plurality of patients (referred to herein as reference patients), OOS outcomes for CAR T drug products generated from the reference patients, as well as process parameters associated with the production of such CAR T drug products. Furthermore, the training module 320 may associate the reference input feature vector to the reference output feature vector along a machine learning model. For example, for a neural network, the training module may input the reference input feature vectors along an input layer and the reference output feature vectors along the output layer, with the input layer and output

layers separated by a predetermined number of hidden layers. The training of the machine learning model may involve performing iterative processes to determine a relation between the input feature vector and the output feature vector. The relation may be represented as a set of weights to apply to parameters represented by the input feature vectors, that indicate the capability of a specific parameter to predict the output feature vector.

The application module 322 may comprise a software, program, module, and/or plug-in that, when executed by a processor, such as but not limited to the one or more processors 312, causes the processor to apply an input feature vector a trained machine learning model to generate an output feature vector. For example, the application module 322 may be used to apply the trained machine learning model to generate an output feature vector predicting values for a set of output parameters corresponding to one or more manufacturing qualities of a CAR-T drug intended to be manufactured. The input feature vector may correspond to quantitative data for parameters of a patient for which CAR-T drug OOS outcomes are desired to be known or predicted (the patient referred to herein as a “target patient”).

The user interface 326 may include, for example, a graphical user interface, an input output module, keyboard or keypad, mouse, a display, and other functionalities that allow the entry of data as well as the output of data.

The optimization module 328 may comprise a software, program, module, and/or plug-in that, when executed by a processor, such as but not limited to the one or more processors 312, causes the processor to identify or recommend an optimization of one or more manufacturing processing parameters for a CAR T drug product based on a CAR T drug product OOS outcome prediction. In some aspects, based on the identification of the optimization, the computing device 310 may cause implementation of the optimization, for example, by transmitting commands to the appropriate device in control of the manufacturing process parameters over communication network 380 (e.g., bioreactor system 370).

In some embodiments, the network environment 300 may include one or more electronic health record systems 330, which may that facilitate the import of patient-specific data and the storage of patient-specific electronic health records (EHR) in a database (e.g., patient health record database 332). In some aspects, the electronic health records systems 330 may further include an encryption module 336. The encryption unit 339 may comprise an application, program, software, code, or plug-in to implement a method to encrypt and decrypt electronic protected health

information. The encryption and decryption protocols implemented by the encryption unit 239 may be pursuant to regulations (e.g., HIPAA). For example, the computing device 310 may establish communications with the electronic health record systems (e.g., via the communication network and network interfaces). The electronic health record systems 330 may further include a network interface 334 that, like network interface 334, allows the electronic health record systems 330 to communicate with or receive communications from other systems and devices of network environment 300 over communication network 380. For example, the computing device 310 may then receive patient-specific health data from the patient health record database 332 of the electronic health record systems 330, and extract various feature parameters from the patient-specific health data, such as parameters belonging to the patient demographic parameter type and patient medical history parameter type. Such parameters may be incorporated into feature vectors for the training and application of machine learning models to predict an OOS outcome for a CAR T drug product and optimize the CAR T drug product based on the OOS outcome.

The network environment 300 may include a clinical data system 340 that stores records of CAR T drug therapies (e.g., known OOS outcomes for manufactured CAR T drug products, and parameters at various stages of producing the CAR T drug products). The clinical data system 340 may comprise an electronic data management system for storing and accessing clinical data, for example, as it pertains to parameters affecting the manufacturing of CAR-T drugs and the OOS outcomes of respective CAR T drug products. The clinical data may be in compliance with applicable regulatory requirements. Such clinical data concerning the production and OOS outcomes of CAR T drug products and the parameters affecting said CAR T drug products may be stored in a database (e.g., CAR T database 342). In some aspects, the clinical data system 340 may include a query engine 348, which may comprise a software, program, module, and/or plug-in allowing a user (e.g., of the computing device 310) to search for clinical data from the stored patient-specific EDC data, and receive query results (e.g., answers to questions, search results, location of a specific clinical data or file, etc.). Furthermore, patient-specific and other sensitive information pertaining to the clinical data may be deidentified and/or encrypted (e.g., via an encryption module 346). In some aspects, the encryption module 346 may be used to decrypt or otherwise link various parameters concerning a CAR T drug product manufacturing, as stored in the CAR T database, to patient-specific parameters (e.g., patient demographic parameter type or patient medical history parameter type), as retrievable from the patient health record database 332.

A network interface 344, like network interface 324, can allow the clinical data system 340 to communicate with or receive communications from other systems and devices of network environment 300 over communication network 380. For example, the computing device 310 may facilitate the linking of parameters obtained from the CAR T database 342 with parameters from the patient health record database 332 via network interfaces 324, 344, and 334.

The network environment 300 may further include one or more sample analytical systems 350. The sample analytical systems 350 may comprise or refer to systems, devices, and instruments used to receive data pertinent to the manufacturing of a CAR-T drug based on an analysis of biological samples (e.g., apheresis samples) of a target patient. For example, samples from the target patient's apheresis starting material may be obtained and then analyzed under the one or more sample analytical systems 350 for cellular characterization (e.g., single-cell RNA sequencing [scRNA-seq], cellular indexing of transcriptomes and epitopes sequencing [CITE-seq], and flow cytometry). In some embodiments, the sample analytical systems 350 may generate (e.g., after obtaining measurements from a biological sample of a target patient via various modalities) data from which parameters pertaining to CD Markers, transcriptomic markers, patient lab results, and cellular components can be obtained. For example, the sample analytical systems 350 may include but are not limited to a flow cytometer system 354 (e.g., for obtaining data pertaining to CD markers and cellular components), a single cell sequencing system 3756 (e.g., for obtaining transcriptomic markers), and lab instruments (e.g., for obtaining patient lab results, apheresis markers, etc.). In some embodiments, data to be obtained from such analytical systems 350 may be requested, viewed, filtered, and/or associated via one or more user interfaces 352. In some embodiments, the sample analytical systems 350 may further include one or more network interfaces 358 that, like network interface 324, allow the sample analytical systems 350 to communicate with or receive communications from other systems and devices of network environment 300 over communication network 380. For example, the computing device 310 may receive data pertinent to the manufacturing of a CAR-T drug based on an analysis of biological samples of a target patient, and extract various feature parameters from the this data, such as parameters belonging to the apheresis stage cell surface marker parameters 234, pre-apheresis parameters 622, apheresis stage process parameters 236, manufacturing stage cell surface marker parameters 244, and manufacturing stage process parameters 246. Such parameters may be

incorporated into feature vectors for the training and application of machine learning models to predict and optimize CAR T drug product OOS outcomes.

In some embodiments, the network environment 300 may include a bioreactor system 370. The bioreactor system 370 may comprise a device (e.g., a vessel) or a system that supports an environment for the manufacturing of CAR T drug products, with functionalities to adjust various manufacturing process parameters 374 (e.g., manufacturing process parameters 242) via a user interface 372. For example, the bioreactor system 370 may comprise an active biological environment for the culturation of CAR T cell samples having desirable parameters from stages of the CAR T drug production process prior to the manufacturing stage (e.g., screening stage, apheresis stage, etc.). However, as selected CAR T cell samples are cultured and undergo other manufacturing processes, various parameters may be adjusted at the manufacturing stage (manufacturing process parameters). Example of such manufacturing process parameters include but are not limited to those shown in Appendix A. In some embodiments, the bioreactor system 370 may further include a network interface 376 that, like network interface 324, can allow the bioreactor system 370 to communicate with or receive communications from other systems and devices of network environment 300 over communication network 380. For example, the computing device 310 may receive manufacturing process parameters currently being used to manufacture a batch or a set of CAR T drug products to predict an OOS outcome for the CAR T drug product. Furthermore, based on the prediction, the computing device 310 may transmit signals to the bioreactor system 370 to alter or adjust manufacturing process parameters to achieve a better outcome for the CAR T drug product OOS outcome.

VI. Training And Application Of Machine Learning Models To Predict CAR-T Drug Product OOS outcomes

FIG. 4 is a block diagram illustrating an example process 400 for predicting and optimizing CAR T drug OOS outcomes, according to non-limiting embodiments of the present disclosure. As illustrated, process 400 includes a number of enumerated steps, but aspects of process 400 may include additional steps before, after, and in between the enumerated steps. In some embodiments, one or more of the enumerated steps may be omitted or performed in a different order. Process 400, which may comprise a training phase 400A and an application phase 400B, may be performed by one or more computing devices (e.g., such as but not limited to computing device 310). For example, process 400 may be performed by one or more processors (such as, but not limited to,

one or more processor 312) based on computer-executable or machine readable instructions stored in a memory (such as, but not limited to, memory 314) of the one or more computing device. In some aspects, the training phase 400A may be performed by a computing device separate or distinct from the computing device performing the application phase 400B, for example, to
5 conserve computer resources and/or bandwidth.

In various embodiments, the training phase 400A may involve receiving reference data from reference CAR-T drugs manufactured from reference patients (block 402). The reference data may correspond to at least a subset of the aforementioned parameters from various stages of a production process for a CAR T drug product (e.g., screening parameters 212 from screening
10 stage 210, pre-apheresis parameters 222 from pre-apheresis stage 220, apheresis parameters 2632 from apheresis stage 230, and manufacturing stage parameters 242 from manufacturing stage 240), and data for an OOS outcome of the CAR T drug product that is produced from the CAR T drug product manufacturing process. As previously discussed, an OOS outcome for the CAR T drug product may relate to whether the CAR T drug product complies with requirements and/or
15 recommendations of a specification for CAR T drug products. In some embodiments, an OOS outcome may be based on one or more assessments corresponding to a comparison of the data for one or more corresponding attributes of the CAR T drug product with one or more respective recommendations and/or requirements for the one or more corresponding attributes.

Machine learning models that are trained in training phase 400A may be specifically
20 trained to predict an OOS outcome of a CAR T drug product (e.g., whether the CAR T drug product formed from the production process would be out of specification (OOS)). In some aspects, the reference data may be unstructured and a processor (e.g., a natural language processor, image processor, a special purpose gene sequencing processor, etc.) may process, translate, decrypt,
25 decipher, and/or quantify the unstructured data into a format that can be vectorized.

The machine learning model trained in training phase 400A (which may then be applied in application phase 400B) may itself be comprised of any number of machine learning models and/or algorithms. For example, the machine learning models may include, but are not limited to, at least one of a decision tree, a deep learning model, a neural network, a linear discriminant analysis
30 model, a quadratic discriminant analysis model, a support vector machine, a random forest algorithm, a nearest neighbor algorithm (e.g., a k-Nearest Neighbors algorithm), a combined

discriminant analysis model, a k-means clustering algorithm, an unsupervised model, a multivariable regression model, a penalized multivariable regression model, or another type of model. In various embodiments, the machine learning model may comprise any number of or combination of the models or algorithms described above.

5 In some embodiments, the reference data may be received from disparate sources, such as other computing systems, for example, electronic health record systems 330, clinical data management systems 340, sample analytical systems 350, or bioreactor system 370 of network environment, or databases and/or repositories, for example, the patient health record database 332 or clinical database for CAR T drug therapy (“CAR T database” 342). In some aspects, received
10 reference data may be linked together appropriately, for example, as corresponding to a reference patient, or a reference CAR T drug product manufactured from the reference patient (e.g., using a biological sample from the reference patient). The linkages may be formed using, for example, linking engine 316 of computing device 310.

 At block 404, the computing device may vectorize the reference data to generate reference
15 input feature vectors and reference output feature vectors. In some embodiments, each reference input feature vector may be associated with a respective reference patient from which a CAR T drug product is manufactured (e.g., using a biological sample from the reference patient), and each reference output feature vector may indicate whether a CAR T drug product manufactured from the respective reference patient would be OOS. Thus, each reference input feature vector may be
20 paired with a respective reference output feature vector. In some aspects, the vectorization may involve the feature extraction module 318 of computing device 310 compressing unstructured data received in block 402 such that disparate inputs for a given parameter may be aggregated as a composite input for that parameter. The vectorization may result in a reference input feature vector comprising composite data inputs for each of a plurality of input parameters. In some aspects, the
25 plurality of input parameters may comprise at least a subset of the input parameters shown in Appendix A. In some embodiments, redundant or unnecessary parameters may be removed, for example, for dimensionality reduction of the reference input feature vector. The dimensionality reduction may enhance the speed of the machine learning model being trained or may be used to overcome issues of overfitting.

30 At block 406, the computing device may associate the reference input feature vectors with reference output feature vectors on a machine learning model. For example, for each pair of

reference input feature vector (representing input parameters for a respective CAR T drug production process from a respective reference patient) and reference output feature vector (representing whether a CAR T drug product would be OOS of the respective CAR T drug product that is produced), the input feature vector may be inputted within the machine learning model with
5 randomized or initialized weights and/or biases for each input parameter represented by the reference input feature vector. The machine learning model may be structured to allow the weights to be iteratively adjusted through an error minimization process as the relation between the reference input feature vector and the respective reference output feature vector is determined. For example, for a neural network, the input feature vector may be aligned along an input layer of the
10 neural network, whereas the output feature vector may be aligned along an output layer separated from the input layer by one or more hidden layers. Each layer may comprise one or more nodes that may involve an activation function. The aforementioned weights may be assigned to the various nodes of input layer.

At block 408, the computing device may train the machine learning model to iteratively
15 minimize error within a predetermined threshold. For example, the training module 320 of computing device 310 may train the machine learning model by iteratively minimizing errors in determining a relation between parameters represented by the reference input feature vector and the reference output feature vector. The relation may be represented by the set of weights assigned to the parameters represented by the input feature vector. The initial set of weights for the
20 parameters of the input feature vector may be tested for how correctly the set of weights indicating the significance of various parameters in their ability to predict the OOS outcome of the CAR T drug product represented by the reference output feature vector. Each prediction may be a quantitative and/or binary data that is compared to the known OOS outcome. If the difference does not fall below a predetermined threshold or tolerance, an iterative process occurs involving a new
25 set of weights for the parameters. The training involves determining a correct set of weights for the input parameters of the input feature vector. Each weight may indicate a significance of a parameter associated with the weight in the parameter's ability to predict whether the CAR T drug product would be OOS (e.g., represented by the output feature vector).

At block 410, the computing device may output the trained machine learning model
30 comprising the finalized set of weights indicating a relation between the input parameters and the output feature vector indicating whether the reference CAR T drug product would be OOS. For

example, the trained machine learning model may be stored in a memory (e.g., memory 314 of computing device 310) or may otherwise be accessible to the computing device that performed the training or to another computing device. Also or alternatively, the trained machine learning model may be stored in a local or remote server that may be accessed by a computing device
5 performing the application phase 400B.

In various embodiments, the application phase 400B may involve a computing device having a processor (e.g., computing device 310 having memory 314) receiving unstructured target data for a target patient from which the CAR T drug is intended to be produced (block 412). The target patient may be distinguishable from a reference patient as the target patient is an intended
10 recipient of a CAR T drug product that is optimized or for which unknown data for OOS outcomes are otherwise predicted using the systems and methods presented herein. As used herein, the reference patient may refer to a patient for whom the OOS outcome of the CAR T drug product obtained using the reference patient may already be known. Thus, reference patients, the production process for CAR T drug products produced from the reference patients, as well as the
15 OOS outcomes for the CAR T drug products may be applicable for the training phase 400A, whereas the target patient, as well as the production process for a CAR T drug product to be produced from the target patient, as well as OOS outcome to be predicted of the CAR T drug product to be manufactured or undergoing manufacturing, may be applicable for the application phase 400B.

In some embodiments, the target data may correspond to at least a subset of the aforementioned parameters from various stages of a production process for a CAR T drug product (e.g., screening parameters 212 from screening stage 210, pre-apheresis parameters 222 from pre-apheresis stage 220, flow cytometry and site testing parameters 232 from flow cytometry and site testing stage 230, and manufacturing parameters 242 from manufacturing stage 244) for which an
20 OOS outcome is unknown or desired to be predicted. In some embodiments, the subset of the aforementioned parameters may comprise those parameters that the present disclosure describes as having significant predictive value for the OOS outcome desired to be predicted. For example, as will be discussed herein, the present disclosure describes, for the CAR T drug product OOS outcomes (e.g., for various attributes), key parameters found to have significant predictive value
25 for determining data for the CAR T drug product OOS outcome (e.g., for any given attribute).
30

As used herein data for a parameter received for predicting a CAR T drug product OOS outcome for a target patient may be referred to as target data to differentiate from data for a parameter received for a reference patient for the training of a machine learning model. The latter data being received for training may be referred to herein as reference data.

5 In some aspects, the target data may be unstructured and a processor (e.g., a natural language processor, image processor, a special purpose gene sequencing processor, etc.) may process, translate, decrypt, decipher, and/or quantify the unstructured data into a format that can be vectorized.

10 In some embodiments, the target data may be received from disparate sources, such as other computing systems, for example, electronic health record systems 330, clinical data management systems 340, sample analytical systems 350, or bioreactor system 370 of network environment, or databases and/or repositories, for example, the patient health record database 732 or clinical database for CAR T cell therapy (“CAR T database” 342). In some aspects, received target data may be linked together appropriately, for example, as corresponding to a target patient, 15 or to various stages of a production process for a CAR T drug product to be produced using the target patient (e.g., using a biological sample from the target patient). The linkages may be formed using, for example, linking engine 316 of computing device 310.

At block 414, the computing device may vectorize the target data to generate an input feature vector. In some aspects, the vectorization may involve the feature extraction module 318 20 of computing device 310 compressing unstructured data received in block 412 such that disparate inputs for a given parameter may be aggregated as a composite input for that parameter. The vectorization may result in an input feature vector comprising composite data inputs for each of a plurality of input parameters. In some aspects, the plurality of input parameters may comprise at least a subset of the input parameters shown in Appendix A. For example, the subset may comprise 25 of parameters that the present disclosure has found to be particularly predictive for the CAR T drug product OOS outcome that is desired to be predicted, as will be discussed in relation to subsequent Figures. In some embodiments, redundant or unnecessary parameters may be removed, for example, for dimensionality reduction of the reference input feature vector. The dimensionality reduction may enhance the speed of the machine learning model being trained or may be used to 30 overcome issues of overfitting.

At block 416, the computing device may apply the input feature vector to the trained machine learning model (e.g., from block 410) to generate an output feature vector predicting whether a CAR T drug product would be OOS. As previously discussed, the trained machine learning model may have a stored set of weights that indicate the capability for each of a plurality of parameters towards predicting the OOS outcome of the CAR T drug product. The plurality of parameters may include, comprise, and/or correspond to the parameters represented by the input feature vector. Thus, the input feature vector may be associated with the set of weights in the trained machine learning model to generate the output feature vector predicting whether a CAR T drug product would be OOS.

At block 418, the computing device may assess whether the the OOS outcome is a prediction that the CAR T drug product is OOS. As discussed herein, regulators have set up specifications or quality criteria for performing quality control of manufactured drugs such as CAR T drug products. A manufactured drug or batch thereof, may meet such quality control criteria—i.e., the drug may be “in specification”—or it may fail to meet such drug product criteria—i.e., the drug may be “out of specification (OOS).” Furthermore, such criteria may include individual criterion or subset of criteria for various attributes of the CAR T drug product. The specification for which the assessment may be performed may be stored in memory 314 of computing device 310, and may be periodically updated (e.g., based on updates to the specification).

At block 420, if the OOS outcome is that the CAR T drug product fails to satisfy the specification (i.e., if the drug is predicted to be out of specification (OOS)), the computing device may adjust or alter one or more manufacturing process parameters associated with the production of the CAR T drug product. For example, the computing device may output (e.g., via user interface 326), an indication that the predicted data for the OOS outcome is out of specification, and prompt the user (e.g., a manufacturer of the CAR T drug product, the target patient, a medical professional associated with the target patient, etc.) to alter or adjust the one or more manufacturing process parameters. Examples of manufacturing process parameters include those described under “Manufacturing Process Parameters” in Appendix A. Also or alternatively, the computing device may automatically cause a device or apparatus performing the manufacturing to adjust the manufacturing process parameters. For example, computing device 310 may transmit a signal to the bioreactor system 370 via communication network 380 to alter or adjust one or more manufacturing process parameters. In some aspects, the process of altering or adjusting

manufacturing process parameters may be performed using programs, software, or logic stored in the optimization module 328 of the computing device 310. For example, the deficiency in a parameters leading to the OOS outcome may be relied on by the optimization module 328 to search for a manufacturing process parameter that would mitigate the deficiency. In some embodiments, after altering the one or more manufacturing process parameters, or generating a recommendation for the altering, the computing device may repeat one or more steps of application phase 400B, using a revised input feature vector based on the one or more altered manufacturing process parameters. Furthermore, the application phase may be repeated until the OOS outcome results in the satisfaction the specification (i.e., it is in-specification and therefore not OOS).

At block 422, if the predicted OOS outcome is that the CAR T drug product satisfies the specification, the computing device may cause the manufacture of the CAR-T drug product based on the current set of manufacturing process parameters. For example, computing device 310 may display (e.g., via user interface 326) the prediction that the CAR T drug product that is being produced would meet the specification. Also or alternatively, the computing device may transmit signals causing a device configured to manufacture the CAR T drug product (e.g., bioreactor system 370) to proceed with the manufacture.

VII. An Exemplary Machine Learning Model That May Be Used in Embodiments Described Herein:

In some embodiments, an example machine learning model that is trained (e.g., based on a reference dataset) and applied to predict the OOS outcome of the CAR T drug product may comprise a decision tree. For example, a decision tree such as a classification decision tree may be used for the prediction of CAR T drug product OOS outcomes characterized by binary outcomes (e.g., whether or not the produced CAR T drug product will be out-of-specification (OOS), etc.). In another example, a decision tree such as a regression decision tree may be used for the prediction of CAR T drug product OOS outcomes characterized by continuous values (e.g., a probability of the CAR T drug product being OOS, etc.). The reference to a decision tree in FIGS. 5A-5B and their accompanying description is merely for demonstration purposes of an example machine learning model used in the embodiments, and does not in any way restrict the machine learning model used in the embodiments to a decision tree. For example, other machine learning models may also or alternatively be implemented in the embodiments described herein. Such machine learning models may include but are not limited to a parametric model, a nonparametric model, a

deep learning model, a neural network, a linear discriminant analysis model, a quadratic discriminant analysis model, a support vector machine, a random forest algorithm, a nearest neighbor algorithm, a combined discriminant analysis model, a k-means clustering algorithm, a supervised model, an unsupervised model, logistic regression model, a multivariable regression model, a penalized multivariable regression model, or another type of model.

FIG. 5A is a graph showing an example decision tree modeling of parameter thresholds for predicting a CAR T drug product OOS outcome, according to non-limiting embodiments of the present disclosure. In this example, each datapoint (indicated as one of a circle or a star) is based on the values of two input parameters. As previous discussed, such input parameters may be two parameters selected from any of the aforementioned examples of screening parameters 212, pre-apheresis parameters 222, apheresis parameters 230, and manufacturing process parameters 242. Thus, the two parameters shown in FIG. 5A as parameters A and B may comprise, for example, a percentage of post thaw viable CAR+ T cells in the final product and a concentration of CAR+ T cells in the final product, respectively. A given datapoint may represent an input feature vector comprising respective values for parameter A and parameter B (representing two input features, respectively). The given datapoint may also be associated with an output feature vector, which may comprise an OOS outcome of the CAR T drug product – i.e., Outcome 1 (shown as a circle) or Outcome 2 (shown as a star). A decision tree model may be used to determine a threshold 532 for values of parameter A for which datapoints that satisfy the threshold 532 are likely to be associated with a given outcome. For example, as shown in FIG. 5A, datapoints having a value for parameter A that is below threshold 532 tend to be associated with Outcome 2, whereas datapoints having a value for parameter A above threshold 532 tend to be associated with Outcome 1. The decision tree model may also be used to determine a threshold 534 for values of parameter B, for which datapoints that satisfy the threshold 534 are likely to be associated with a given outcome. For example, as shown in FIG. 5A, datapoints having a value for parameter B that is below threshold 534 tend to be associated with Outcome 2, whereas datapoints having a value for parameter B above threshold 534 tend to be associated with Outcome 1. In some embodiments, the thresholds can be adjusted to increase precision. For example, thresholds 532 and 534 may be adjusted to a threshold range for each of parameter A and parameter B value, respectively. The combined threshold ranges are thus shown as box 536. As shown in FIG. 5A, the datapoints within box 836 more precisely predict a specific OOS outcome for the CAR T drug product - e.g.,

outcome 2 – based on the values of the input features of the datapoints (i.e., values for parameters A and B) falling within the threshold ranges specified by box 536.

Although FIG. 5A shows two input parameters, and an OOS outcome comprising two discrete outcomes, it is contemplated (based on the embodiments described herein) that there may be a large plurality of input parameters being used to train machine learning models such as the decision tree model to predict a CAR T drug product quality OOS outcome. Although the example shown in FIG. 5A uses two input parameters for purposes of demonstration, it is contemplated that the use of the large plurality of input feature parameters, such as those in the embodiments described herein, may not be depictable via graphs such as FIG. 5A. In some aspects, the training and application of models based on the large plurality of input parameters may rely on computing devices with processors equipped to process large datasets characterized by a large plurality of dimensions for the respective input parameters. Furthermore, it is contemplated (based on the embodiments described herein) that the OOS outcome may not necessarily be characterized by two outcomes. For example, the CAR T drug product quality OOS outcome may be characterized by continuous or semicontinuous outcomes (e.g., to signify probabilities of being OOS).

FIG. 5B is a block diagram showing an example process for the training of a decision tree model, such as but not limited to the example shown in FIG. 5A, to predict a CAR T drug product OOS outcome. In at least one embodiment, the training of the decision tree model may be performed by a computing device having a processor configured to perform one or more of the following steps (e.g., such as but not limited to the computing device 310 having the processor 312). The training may involve a dataset comprising a plurality of datapoints (e.g., such as but not limited to reference data received in block 402 of training phase 400A of FIG. 4). For example, each datapoint may be a set of values for various input feature parameters obtained in the development of a CAR T drug product, with one or more values indicating a known OOS outcome for the CAR T drug product. For each input feature parameter being used (e.g., parameter A, parameter B of FIG. 5A), the computing device may determine an initial candidate threshold to split the datapoints (block 540). In some aspects, the candidate threshold may be a randomized value. In some aspects, the candidate threshold may be based on statistical characteristics of the various datapoints (e.g., the max, min, or average values for the input feature parameter). The candidate threshold may then be assessed to determine how well it splits the datapoints based on their known outcome (block 542). For example, for outputs characterized by two discrete

outcomes, a number of datapoints belonging to a certain outcome (e.g., Outcome 1) can be calculated for each side of the threshold. A measure of performance for the candidate threshold may be based on the maximization of datapoints associated with a given outcome on one side of the threshold, and a minimization of datapoints associated with the given outcome on the other side of the threshold.

The aforementioned steps of identifying a candidate threshold for a given input parameter and assessing how well it splits the datapoints based on the known outcomes can be iterated until a convergence is reached, i.e., a candidate threshold is found to best split the datapoints based on their outcomes (e.g., as compared to other candidate thresholds) (block 544). This convergence may be determined via an error minimization approach, where the ability for a given candidate threshold to split the datapoints based on their outcome is assessed and errors in doing so is measured. A convergence may be reached when the error is minimized to a preset tolerance level. Also or alternatively, a convergence may be reached when a candidate threshold is found to split the datapoints based on their outcomes to a significantly better degree compared to previously tested candidate thresholds. Thus, in some embodiments, optimizing the candidate threshold may involve a determination whether the distribution of the datapoints on either sides of the candidate threshold is better than the previously best candidate. Once the best candidate threshold is found, the candidate threshold may be identified or designated to be the threshold for the input parameter (block 546). The aforementioned process may be repeated for the other input feature parameters until thresholds for all input parameters are determined (block 548). Furthermore, the determined thresholds for each of the plurality of input feature parameters may thus function as weights or relations for predicting the CAR T drug product OOS outcome. The determined thresholds may thus be stored as part of the trained decision learning model output for use in predicting the CAR T drug product OOS outcome (block 550).

VIII. Predicting Whether A Patient-Specific CAR T Drug Product For A Target Patient Would Be Out Of Specification (OOS)

FIG. 6A is a block diagram illustrating an example method 600 for predicting whether a patient-specific CAR T drug product for a target patient would be out of specification (OOS), according to non-limiting embodiments of the present disclosure. Furthermore, FIGS. 6B-6D show tables of example parameters that the present disclosure describes as significant for their ability to predict whether the patient-specific CAR T drug product for the target patient would be

OOS. Method 600, which may be performed by one or more computing devices (e.g., such as but not limited to one or more computing device(s) 310). For example, method 600 may be performed by one or more processors (such as, but not limited to, one or more processors 312) based on computer-executable or machine readable instructions stored in a memory (such as, but not limited to, memory 314) of the one or more computing device. As illustrated, method 600 includes a number of enumerated steps, but aspects of method 600 may include additional steps before, after, and in between the enumerated steps. In some embodiments, one or more of the enumerated steps may be omitted or performed in a different order.

In various embodiments, the method 600 may comprise receiving quantitative data for a set of OOS parameters (block 602). The set of OOS parameters may comprise OOS parameters selected from Table 1, which is shown in FIG. 6B. Each OOS parameter belongs to one of a plurality of parameter types as outlined in Table 1 (shown in FIG. 6B).

In some embodiments, the OOS parameters as outlined in Table 1 may be in order of significance to predicting whether the patient-specific CAR T drug product for the target patient would be OOS (i.e., starting with the highest significance at the top and ending with the lowest significance at the bottom). OOS parameters with a higher significance may be assigned a higher weight than other OOS parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product for the target patient would be OOS.

In some embodiments, the set of OOS parameters may comprise a subset of parameters listed in Appendix A. For example, in at least one embodiment, the set of OOS parameters may include one or more of the following parameters: a concentration of lactate or glucose in the T cell culture sample from the middle stage of the manufacturing process; a concentration of lactate or glucose in the T cell culture sample from the late middle stage of the manufacturing process; a multiplicity of infection (MOI) of a vector added to the T cell culture sample during the early middle stage of the manufacturing process; a ratio of CD4⁺ T cells to CD8⁺ T cells in the T cell culture sample from the initial stage of the manufacturing process; a concentration (cells /mL) of viable T cells in the T cell culture sample from the initial stage of the manufacturing process; an average concentration of viable T cells per population from the early middle stage of the manufacturing process; a percentage of cells that are viable T cells in the T cell culture sample from the initial stage of the manufacturing process; a viable T Cell count after sampling in the initial stage of the manufacturing process; a volume of vector added to the T cell culture sample

during the early middle stage of the manufacturing process; whether a patient was refractory to pomalidomide treatment; a concentration of lymphocytes in the apheresis sample prior to the manufacturing process; a sex of the patient; a number of seeded viable T cells at the initial stage of the manufacturing process; a body mass index (BMI) of the patient; and a percentage of
5 leukocytes that are monocytes in the apheresis sample prior to the manufacturing process. In one embodiment, the foregoing list of parameters, as written, is arranged in order of significance to predict whether the patient-specific CAR T drug product for the target patient would be OOS using the trained machine learning model (i.e., starting with the highest significance at the top and ending with the lowest significance at the bottom). Thus, parameters with a higher significance may be
10 assigned a higher weight than other parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product for the target patient would be OOS (e.g., as discussed in subsequent steps).

In some embodiments, the set of OOS parameters includes a set of screening parameters selected from Table 1A (shown in FIG. 6C). Furthermore, the screening parameters in Table 1A
15 (shown in FIG. 6C) may be in order of significance to predicting whether the patient-specific CAR T drug product for the target patient would be OOS (i.e., starting with the highest significance at the top and ending with the lowest significance at the bottom). Screening parameters with a higher significance may be assigned a higher weight than other screening parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product for
20 the target patient would be OOS.

In some embodiments, the set of OOS parameters includes a set of apheresis stage parameters as outlined in Table 1B (shown in FIG. 6C). Furthermore, the apheresis stage parameters in Table 1B may be arranged in order of significance to predicting whether the patient-specific CAR T drug product for the target patient would be OOS using the trained machine
25 learning model (i.e., starting with the highest significance at the top and ending with the lowest significance at the bottom). For example, apheresis stage parameters with a higher significance may be assigned a higher weight than other apheresis stage parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product for the target patient would be OOS.

30 In some embodiments, the set of OOS parameters includes a set of manufacturing stage parameters selected from Table 1C (shown in FIG. 6D). Furthermore, the manufacturing stage

parameters in Table 1C may be arranged in order of significance to predicting whether the patient-specific CAR T drug product for the target patient would be OOS using the trained machine learning model (i.e., starting with the highest significance at the top and ending with the lowest significance at the bottom). Manufacturing stage parameters with a higher significance may be assigned a higher weight than other manufacturing stage parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product for the target patient would be OOS.

10 In various embodiments, the method 600 for predicting OOS outcome in the patient-specific CAR T drug product for the target patient may further comprise generating an input feature vector comprising the quantitative data for the set of OOS parameters (block 604).

In various embodiment, the method 600 may further comprise applying, into a trained machine learning model, the input feature vector to generate an output feature vector predicting whether the patient-specific CAR T drug product for the target patient would be OOS (block 606).

15 In some embodiments, receiving quantitative data for the set of OOS parameters comprises receiving unstructured data for the set OOS parameters. Method 600 may further comprise vectorizing (e.g., by the feature extraction module 318 of the computing device 310), the unstructured target data to the input feature vector.

In some embodiments, the trained machine learning model may be trained using reference data from a plurality of reference CAR-T drug products manufactured from a plurality of reference patients, where the plurality of reference CAR T drug products may have known OOS outcomes (e.g., whether the manufactured CAR T drug product is in specification or OOS). Furthermore, method 600 may further comprise receiving (e.g., by a computing device 310), the reference data, which may comprise a set of input feature parameters and the known OOS outcome in the patient-specific CAR T drug product for each of the plurality of reference CAR-T drug products manufactured from the plurality of reference patients. Moreover, for a given reference patient of the plurality of reference patients, the set of input feature parameters may include at least the set of OOS parameters. In some aspects, the method 600 may further comprise vectorizing (e.g., by the feature extraction module 318 of the computing device 310), for each of the plurality of reference CAR-T drug products manufactured from the plurality of reference patients, the set of input feature parameters and the known OOS outcome in the patient-specific CAR T drug product to a reference input feature vector and a reference output feature vector, respectively, thereby

generating a plurality of reference input feature vectors and a plurality of reference output feature vectors. In some aspects, method 600 may further comprise associating (e.g., by the training module 320 of the computing device 310) the plurality of reference input feature vectors to the plurality of reference output feature vectors in a machine learning model. Furthermore, method 5 600 may further comprise training (e.g., by the training module 320 of the computing device 310), by iteratively minimizing error to within a predetermined threshold, the machine learning model to generate the trained machine learning model. As previously discussed, the trained machine learning model includes a plurality of weights. Each weight may indicate a significance of an input feature parameter to predicting whether the patient-specific CAR T drug product for the target 10 patient would be OOS. In some embodiments, the set of input feature parameters are drawn from those outlined in Appendix A.

In various embodiments, method 600 may further comprise determining whether the CAR T drug product is predicted to be OOS (block 608). If OOS, the method 600 may further comprise altering or adjusting one or more manufacturing process parameters for manufacturing the CAR T 15 drug product for the target patient (block 610). For example, the adjusted one or more manufacturing process parameters may be output (e.g., as recommendations via user interface 326 of the computing device 310). Also or alternatively, the adjusted one or more manufacturing process parameters may be implemented in the production process of the CAR T drug product. In some embodiments, for example, where the patient-specific CAR T drug product for the target 20 patient is predicted to not be OOS (e.g., the patient-specific CAR T drug product is in-specification), method 600 may further comprise causing manufacture of the CAR T drug product (block 612). In some aspects, the manufacturing may be based on the current set of manufacturing process parameters. In some embodiments, causing the manufacture may involve the computing device displaying (e.g., via a user interface such as user interface 326) the prediction that the CAR 25 T drug product that is being produced would be in-specification. Also or alternatively, the computing device may transmit signals causing a device configured to manufacture the CAR T drug product (e.g., bioreactor system 370) to proceed with the manufacture.

Those of skill in the art would further appreciate that the various illustrative logical blocks, 30 modules, circuits, and algorithm steps described in connection with the disclosure herein may be implemented as electronic hardware, computer software, or combinations of both. Skilled artisans

will also readily recognize that the order or combination of components, methods, or interactions that are described herein are merely examples and that the components, methods, or interactions of the various aspects of the present disclosure may be combined or performed in ways other than those illustrated and described herein.

5 The operations of a method or algorithm disclosed herein may be implemented in a processor-executable software module which may reside on a computer-readable medium and commercially made available as a computer program product as software. Computer-readable media includes both computer storage media and communication media including any medium that may be enabled to transfer a computer program from one place to another. A storage media
10 may be any available media that may be accessed by a computer. By way of example, and not limitation, such computer-readable media may include random-access memory (RAM), read-only memory (ROM), electrically erasable programmable read-only memory (EEPROM), CD-ROM or other optical disk storage, magnetic disk storage or other magnetic storage devices, or any other medium that may be used to store desired program code in the form of instructions or data
15 structures and that may be accessed by a computer. Also, any connection may be properly termed a computer-readable medium. Disk and disc, as used herein, includes compact disc (CD), laser disc, optical disc, digital versatile disc (DVD), floppy disk, and Blu-ray disc wherein disks usually reproduce data magnetically and discs reproduce data optically with lasers. Combinations of the above should also be included within the scope of computer-readable media.

20 Various modifications to the implementations described in this disclosure may be readily apparent to those skilled in the art, and the generic principles defined herein may be applied to some other implementations without departing from the spirit or scope of this disclosure. Thus, the claims are not intended to be limited to the implementations shown herein but are to be accorded the widest scope consistent with this disclosure, the principles and the novel features
25 disclosed herein.

 Certain features that are described in this specification in the context of separate implementations also may be implemented in combination in a single implementation. Conversely, various features that are described in the context of a single implementation also may be implemented in multiple implementations separately or in any suitable subcombination. Moreover,
30 although features may be described above as acting in certain combinations and even initially claimed as such, one or more features from a claimed combination may in some cases be excised

from the combination, and the claimed combination may be directed to a subcombination or variation of a subcombination.

Similarly, while operations are depicted in the drawings in a particular order, this should not be understood as requiring that such operations be performed in the particular order shown, or in sequential order, or that all illustrated operations be performed to achieve desirable results. Further, the drawings may schematically depict one or more example processes in the form of a flow diagram. However, other operations that are not depicted may be incorporated in the example processes that are schematically illustrated. For example, one or more additional operations may be performed before, after, simultaneously, or between any of the illustrated operations. In certain circumstances, multitasking and parallel processing may be advantageous. Moreover, the separation of various system components in the implementations described above should not be understood as requiring such separation in all implementations, and it should be understood that the described program components and systems may generally be integrated together in a single software product or packaged into multiple software products. Additionally, some other implementations are within the scope of the following claims. In some cases, the actions recited in the claims may be performed in a different order and still achieve desirable results.

As used herein, including in the claims, the term “or,” when used in a list of two or more items, means that any one of the listed items may be employed by itself, or any combination of two or more of the listed items may be employed. For example, if a composition is described as containing components A, B, or C, the composition may contain A alone; B alone; C alone; A and B in combination; A and C in combination; B and C in combination; or A, B, and C in combination. Also, as used herein, including in the claims, “or” as used in a list of items prefaced by “at least one of” indicates a disjunctive list such that, for example, a list of “at least one of A, B, or C” means A or B or C or AB or AC or BC or ABC (that is A and B and C) or any of these in any combination thereof.

The previous description of the disclosure is provided to enable any person skilled in the art to make or use the disclosure. Various modifications to the disclosure will be readily apparent to those skilled in the art, and the generic principles defined herein may be applied to other variations without departing from the spirit or scope of the disclosure. Thus, the disclosure is not intended to be limited to the examples and designs described herein but is to be accorded the widest scope consistent with the principles and novel features disclosed herein.

Appendix A

<u>Screening Stage Parameters</u>		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Screening Stage, Patient Demographic	Age	Age
Screening Stage, Patient Demographic	Sex	Sex
Screening Stage, Patient Demographic	Race	Race
Screening Stage, Patient Demographic	Body mass index	Body mass index
Screening Stage, Patient Demographic	Ethnic	Ethnicity
Screening Stage, Patient Demographic	Country	Country
Screening Stage, Patient Medical History	Time Since Initial Diagnosis (years)	Time since initial diagnosis
Screening Stage, Patient Medical History	Measurable Disease Type	Measurable disease type
Screening Stage, Patient Medical History	ECOG Perf Status Score at Baseline	An oncology performance status score at baseline
Screening Stage, Patient Medical History	Left Ventricular Ejection Fraction (%)	Left Ventricular Ejection Fraction (%)
Screening Stage, Patient Medical History	Baseline Tumor Burden Category	Baseline Tumor Burden Category
Screening Stage, Patient Medical History	Baseline Number of Extramedullary Plasmacytomas	Baseline Number of Extramedullary Plasmacytomas
Screening Stage, Patient Medical History	Baseline Presence of Evaluable Bone Marrow Assessment	Baseline Presence of Evaluable Bone Marrow Assessment
Screening Stage, Patient Medical History	Baseline ISS Stage	Baseline International Staging System (ISS) stage
Screening Stage, Patient Medical History	Baseline Type of Myeloma	Baseline Type of Myeloma

Screening Patient History	Stage, Medical	Baseline Bone Marrow Percent Plasma Cells Aspirate	Baseline Bone Marrow Percent Plasma Cells Aspirate
Screening Patient History	Stage, Medical	Baseline Bone Marrow Percent Plasma Cells	Baseline Bone Marrow Percent Plasma Cells
Screening Patient History	Stage, Medical	Baseline Bone Marrow Percent Plasma Cells Aspirate Category	Baseline Bone Marrow Percent Plasma Cells Aspirate Category
Screening Patient History	Stage, Medical	Baseline Bone Marrow Percent Plasma Cells Category	Baseline Bone Marrow Percent Plasma Cells Category
Screening Patient History	Stage, Medical	Prior Alkylating Agents	Prior use of alkylating agents on patient
Screening Patient History	Stage, Medical	Prior Allogeneic Transplantation	Prior use of allogeneic transplantation on patient
Screening Patient History	Stage, Medical	Prior Anthracyclines	Prior use of anthracyclines on patient
Screening Patient History	Stage, Medical	Times of Pr. Autologous Transplantation	Times of Pr. Autologous Transplantation on patient
Screening Patient History	Stage, Medical	Prior Autologous Transplantation	Prior use of autologous transplantation on patient
Screening Patient History	Stage, Medical	Prior Bortezomib	Prior use of Bortezomib on patient
Screening Patient History	Stage, Medical	Prior Cancer-related Surgery/Procedure	Prior cancer-related surgery/procedure performed on patient
Screening Patient History	Stage, Medical	Prior Carfilzomib	Prior use of Carfilzomib on patient
Screening Patient History	Stage, Medical	Prior Anti-CD38 Antibodies	Prior use of Anti-CD38 Antibodies on patient
Screening Patient History	Stage, Medical	Prior Daratumumab	Prior use of Daratumumab on patient
Screening Patient History	Stage, Medical	Prior Dexamethasone	Prior use of Dexamethasone on patient

Screening Patient History	Stage, Medical	Prior Elotuzumab	Prior use of Elotuzumab on patient
Screening Patient History	Stage, Medical	Prior IMiD	Prior use of IMiD on patient
Screening Patient History	Stage, Medical	Prior Isatuximab	Prior use of Isatuximab on patient
Screening Patient History	Stage, Medical	Prior Ixazomib	Prior use of Ixazomib on patient
Screening Patient History	Stage, Medical	Prior Lenalidomide	Prior use of Lenalidomide on patient
Screening Patient History	Stage, Medical	Number of Prior Therapy Lines	Number of Prior Therapy Lines
Screening Patient History	Stage, Medical	Prior Oprozomib	Prior use of Oprozomib on patient
Screening Patient History	Stage, Medical	Prior Panobinostat	Prior use of Panobinostat on patient
Screening Patient History	Stage, Medical	Prior PI	Prior use of PI on patient
Screening Patient History	Stage, Medical	Prior Pomalidomide	Prior use of Pomalidomide on patient
Screening Patient History	Stage, Medical	Prior Prednison	Prior use of Prednison on patient
Screening Patient History	Stage, Medical	Prior Radiotherapy	Prior use of Radiotherapy on patient
Screening Patient History	Stage, Medical	Prior Corticosteroids	Prior use of Corticosteroids on patient
Screening Patient History	Stage, Medical	Prior TAK-079	Prior use of mezagitamab (e.g., TAK-079) on patient
Screening Patient History	Stage, Medical	Prior Thalidomide	Prior use of thalidomide on patient

Screening Patient History	Stage, Medical	Prior Transplantation	Prior use of transplantation on patient
Screening Patient History	Stage, Medical	Refractory Status	A refractory status of patient
Screening Patient History	Stage, Medical	Refractory Status Penta	Whether patient was refractory to Penta
Screening Patient History	Stage, Medical	Refractory Status Alkylating Agent	Whether patient was refractory to Alkylating Agent
Screening Patient History	Stage, Medical	Refractory Status Bortezomib	Whether patient was refractory to Bortezomib
Screening Patient History	Stage, Medical	Refractory Status Carfilzomib	Whether patient was refractory to Carfilzomib
Screening Patient History	Stage, Medical	Refractory Status Anti-CD38 Antibody Only	Whether patient was refractory to Anti-CD38 Antibody Only
Screening Patient History	Stage, Medical	Refractory Status Daratumumab	Whether patient was refractory to Daratumumab
Screening Patient History	Stage, Medical	Refractory Status Elotuzumab	Whether patient was refractory to Elotuzumab
Screening Patient History	Stage, Medical	Refractory Status IMiD Only	Whether patient was refractory to IMiD Only
Screening Patient History	Stage, Medical	Refractory Status Isatuximab	Whether patient was refractory to Isatuximab
Screening Patient History	Stage, Medical	Refractory Status Ixazomib	Whether patient was refractory to Ixazomib
Screening Patient History	Stage, Medical	Refractory Status Lenalidomide	Whether patient was refractory to Lenalidomide
Screening Patient History	Stage, Medical	Refractory Status Last Line	Whether patient was refractory to Last Line
Screening Patient History	Stage, Medical	Refractory Status Panobinostat	Whether patient was refractory to Panobinostat

Screening Patient History	Stage, Medical	Refractory Status Pomalidomide	Whether patient was refractory to Pomalidomide
Screening Patient History	Stage, Medical	Refractory Status to Any Prior Therapy	Whether patient was refractory to Any Prior Therapy
Screening Patient History	Stage, Medical	Refractory Status TAK-079	Whether patient was refractory to mezagitamab (e.g., TAK-079)
Screening Patient History	Stage, Medical	Refractory Status Thalidomide	Whether patient was refractory to Thalidomide
Screening Patient History	Stage, Medical	Refractory Status Any Anti-CD38 Antibody	Whether patient was refractory to Any Anti-CD38 Antibody
Screening Patient History	Stage, Medical	Refractory Status Any IMiD	Whether patient was refractory to Any IMiD
Screening Patient History	Stage, Medical	Refractory Status Any PI	Whether patient was refractory to Any PI

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Pre-Apheresis Parameters		
Parameter Type and Subtype	Parameter Name	Parameter Description
Pre-Apheresis Stage	Total Volume	A total volume of the biological sample obtained
Pre-Apheresis Stage	UPEP Collection Criteria-PS	A urine protein electrophoresis (UPEP) collection criteria
Pre-Apheresis Stage	SPEP Container Received Y/N	Whether or not a serum protein electrophoresis (SPEP) container was received
Pre-Apheresis Stage	UPEP Sample Received Y/N	Whether or not urine protein electrophoresis (UPEP) sample was received
Pre-Apheresis Stage	ABSOLUTE DFLC VALUE	an absolute difference between involved and uninvolved serum free light chains (DFLC value) in the biological sample
Pre-Apheresis Stage	MM Classification 2	a multiple myeloma (MM) classification of the patient
Pre-Apheresis Stage	Elapsed Date & Time	An elapsed date and/or time associated with the pre-apheresis lab test
Pre-Apheresis Stage	Total Protein	A volume of the total protein in the pre-apheresis biological sample of the patient
Pre-Apheresis Stage	U.24hr Aliq T. Protein	a urinary 24 hour aliquot of protein

Pre-Apheresis Stage	Myeloma UPE 24hr T. Protein	a urinary 24 hour aliquot of protein indicative of myeloma
Pre-Apheresis Stage	Lambda Free Light Chain-CL-QT	a detection or a measurement of lambda free light chains in the pre-apheresis biological sample
Pre-Apheresis Stage	Free Kappa/Free Lambda RatioQT	a ratio of free kappa light chains to free lambda light chains in the pre-apheresis biological sample
Pre-Apheresis Stage	Myeloma SPE-Albumin(%)-CL	a percent volume of albumin in a serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Alpha 1(%)-CL	a percent volume of Alpha-1 globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Alpha 2(%)-CL	a percent volume of alpha 2 globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Beta(%)-CL	a percent volume of beta globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Gamma(%)-CL	a percent volume of gamma globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-M-spike 1(%)-CL	a percent volume of monoclonal spike 1 in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-M-spike 2(%)-CL	a percent volume of monoclonal spike 2 in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Albumin-CL	a measurement of albumin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Alpha 1-CL	a measurement of Alpha-1 globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Alpha 2-CL	a measurement of alpha 2 globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Beta-CL	a measurement of beta globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE-Gamma-CL	a measurement of gamma globulin in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE, M-spike Qty 1-CL	a measurement of monoclonal spike Qty 1 in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE, M-spike Qty 2-CL	a measurement of monoclonal spike Qty 2 in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE, M-spike Reg.1-CL	a measurement of monoclonal spike Reg. 1 in the serum protein electrophoresis sample
Pre-Apheresis Stage	Myeloma SPE, M-spike Reg.2-CL	a measurement of monoclonal spike Reg. 2 in the serum protein electrophoresis sample
Pre-Apheresis Stage	MyeloSPE Immunofix.Impress1-CL	a first immunifixation impression test score for myeloma using serum protein electrophoresis
Pre-Apheresis Stage	MyeloSPE Immunofix.Impress2-CL	a second immunifixation impression test score for myeloma using serum protein electrophoresis

Pre-Apheresis Stage	Total M-Protein, Serum-CL	total M protein in a serum sample
Pre-Apheresis Stage	MyeloUPE Immunofix.Impress1-CL	a first immunifixation impression test score for myeloma using urinary protein electrophoresis
Pre-Apheresis Stage	MyeloUPE Immunofix.Impress2-CL	a second immunifixation impression test score for myeloma using urinary protein electrophoresis
Pre-Apheresis Stage	Myeloma UPE-Albumin (%) -CL	a percent volume of albumin in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE-Alpha1 glob(%) -CL	a percent volume of Alpha-1 globulin in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE-Alpha2 glob(%) -CL	a percent volume of alpha 2 globulin in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE-Beta glob(%) -CL	a percent volume of beta globulin in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE-Gamma glob(%) -CL	a percent volume of gamma globulin in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE-M-spike 1(%) -CL	a percent volume of monoclonal spike 1 in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE, M-spikeQty 2-CLQT	a measurement of monoclonal spike Qty 2 in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE, M-spikeQty 3-CLQT	a measurement of monoclonal spike Qty 3 in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Myeloma UPE, M-spikeReg.1-CLQT	a measurement of monoclonal spike Reg. 1 in a urinary protein electrophoresis sample
Pre-Apheresis Stage	Kappa Free Light Chain-CLQT	a measurement of free kappa light chains in the pre-apheresis biological sample

Apheresis Stage Parameters		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Apheresis Stage, Cell Surface Marker Parameter	T cells CD4/CD8 Ratio	a ratio of CD4+ T Cells to CD8+ T Cells in the apheresis sample
Apheresis Stage, Cell Surface Marker Parameter	CAR- CD4+ TEMRA CAR-CD4+T cells Percent	a percentage of CAR-, CD4+ T cells that are CAR-, CD4+ terminally differentiated effector memory T cells (TEMRA) in the apheresis sample
Apheresis Stage, Cell Surface	CAR- NK T cells Lymphocytes Percent	a percentage of lymphocytes that are CAR- natural killer (NK) T Cells in the apheresis sample

Marker Parameter		
Apheresis Stage, Cell Surface Marker Parameter	CAR- NK cells Lymphocytes Percent	a percentage of lymphocytes that are CAR- NK cells in the apheresis sample
Apheresis Stage, Cell Surface Marker Parameter	CAR- Regulatory T cells Concentration	a percentage of lymphocytes that are CAR- NK cells in the apheresis sample
Apheresis Stage, Cell Surface Marker Parameter	CAR- T cells Lymphocytes Percent	a percentage of lymphocytes that are CAR- T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR- Treg cells Treg cells Percent	a percentage of regulatory T (Treg) cells that are CAR- Treg cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR- Treg CAR-CD4+T cells Percent	a percentage of CAR-, CD4+ T cells that are CAR-, CD4+ Treg cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR- Treg CAR-T cells Percent	a percentage of CAR- T cells that are CAR- Treg cells in the aphereisis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR- monocytes Leukocytes Percent	a percentage of leukocytes that are CAR- monocytes in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR- naive CD4+ T cells CAR-CD4+ T cells Percent	a percentage of CAR-, CD4+ T cells that are CAR-, naive CD4+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR- neutrophils Leukocytes Percent	a percentage of leukocytes that are CAR- neutrophils in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-CD4 Stem Memory T cell CAR-CD4+Tcell Percent	a percentage of CAR-, CD4+ T cells that are CAR-, CD4 Stem Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD4 T Central Memory CAR-, CD4+T cells Percent	a percentage of CAR-, CD4+ T cells that are CAR-, CD4 T Central Memory Cells in the apheresis sample;

Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD4+ Eff Mem Tcell CAR-, CD4+ T cells Percent	a percentage of CAR-, CD4+ T cells that are CAR-, CD4+ Effector Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD4+ T cells CAR- T cells Percent	a percentage of CAR- T Cells that are CAR-, CD4+ T Cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD8 Cen Mem T cell CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are CAR-, CD8 Central Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD8 Eff Mem T cell CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ Effector Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD8 Stem Mem Tcells CAR-, CD8+ Tcells Percent	a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ Stem Memory T cells;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD8+ T cells CAR- T cells Percent	a percentage of CAR- T cells that are CAR-, CD8+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD8+ TEMRA CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ TEMRA in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, CD8+ naive T cells CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are CAR-, CD8+ naive T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, Double Negative T cells CAR-, T cells Percent	a percentage of CAR- T Cells that are CAR-, double negative T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CAR-, Double Positive T cells CAR- T cells Percent	a percentage of CAR- T Cells that are CAR-, double positive T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD25+, CAR-, CD4+ T cells CAR-, CD4+ T cells Percent	a percentage of CAR-, CD4+ T cells that are CD25+, CAR-, CD4+ T cells in the apheresis sample;

Apheresis Stage, Cell Surface Marker Parameter	CD25+, CAR-, CD8+ T cells CAR-, CD8+ T cells Percent	a percentage of CAR-CD8+ T cells that are CD25+, CAR-, CD8+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR- naive CD4+ Tcell CAR-, CD4+Tcell Percent	a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, naive, CD4+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD4+ Cen Mem Tcel CAR- CD4+Tcell Percent	a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, CD4+ Central Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD4+ Eff Mem Tcel CAR-, CD4+ T cell Percent	a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, CD4+ Effector Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD4+ Stem Mem Tcel CAR-, CD4+ Tcell Percent	a percentage of CAR-, CD4+ T cells that are CD27+, CAR-, CD4+ Stem Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD8+ Cen Mem Tcel CAR-, CD8+ Tcell Percent	a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ Central Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD8+, Eff Mem Tcel CAR-, CD8+ T cell Percent	a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ Effector Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD8+ Stem Mem Tcel CAR-, CD8+ Tcell Percent	a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ Stem Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27+, CAR-, CD8+ naive Tcell CAR-, CD8+, Tcell Percent	a percentage of CAR-, CD8+ T cells that are CD27+, CAR-, CD8+ naive T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27-, CAR-, CD4+ Eff Mem Tcel CAR-, CD4+, Tcell Percent	a percentage of CAR-, CD4+ T cells that are CD27-, CAR-, CD4+ Effector Memory T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD27-, CAR-, CD8+ Eff Mem Tcel CAR-, CD8+, Tcell Percent	a percentage of CAR-, CD8+ T cells that are CD27-, CAR-, CD8+ Effector Memory T cells in the apheresis sample;

Apheresis Stage, Cell Surface Marker Parameter	CD27-, CAR-, CD8+ TEMRA CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T Cells that are CD27-, CAR-, CD8+ TEMRA in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD28+, CAR-, CD4+ T cells CAR-, CD4+ T cells Percent	a percentage of CAR-, CD4+ T Cells that are CD28+, CAR-, CD4+ T cells;
Apheresis Stage, Cell Surface Marker Parameter	CD28+, CAR-, CD8+ T cells CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are CD28+, CAR-, CD8+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD3+, CAR-, CD4+, CD8- T cells Concentration	a concentration of CD3+, CAR-, CD4+, CD8- T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD3+, CAR-, CD4-, CD8+ T cells Concentration	a concentration of CD3+, CAR-, CD4-, CD8+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD3+, CAR- CD3+ Percent	a percentage of CD3+ T cells that are CD3+, CAR- T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD3+, CAR- Concentration	a concentration of CD3+, CAR- T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD38+, CAR- Treg CAR- Treg Percent	a percentage of CAR- Treg cells that are CD38+, CAR- Treg cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD38+, CAR-, CD4+ T cells CAR-, CD4+ T cells Percent	a percentage of CAR-, CD4+ T cells that are CD38+, CAR-, CD4+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD38+, CAR-, CD8+ T cells CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are CD38+, CAR-, CD8+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD38+, CD39+, CAR- Treg CAR- Treg Percent	a percentage of CAR- Treg cells that are CD38+, CD39+, CAR- Treg cells in the apheresis sample;

Apheresis Stage, Cell Surface Marker Parameter	CD38-, CD39-, CAR- Treg CAR-Treg Percent	a percentage of CAR- Treg cells that are CD38-, CD39-, CAR- Treg cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	CD39+, CAR- Treg CAR- Treg Percent	a percentage of CAR- Treg cells that are CD39+ CAR- Treg cells in the apheresis sample;
Apheresis Stage, Process Parameter	Lymphocytes Concentration	a concentration of lymphocytes in the apheresis sample;
Apheresis Stage, Process Parameter	Monocytes Leukocytes Percent	a percentage of leukocytes that are monocytes in the apheresis sample;
Apheresis Stage, Process Parameter	NK cells Lymphocytes Percent	a percentage of lymphocytes that are NK T Cells in the apheresis sample;
Apheresis Stage, Process Parameter	NK cells Lymphocytes Percent	a percentage of lymphocytes that are NK Cells in the apheresis sample;
Apheresis Stage, Process Parameter	Neutrophils Leukocytes Percent	a percentage of leukocytes that are neutrophils in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	PD1+, CAR-, CD4+ T cells CAR-, CD4+ T cells Percent	a percentage of CAR-, CD4+ T cells that are PD1+, CAR-, CD4+ T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	PD1+, CAR-, CD8+ T cells CAR-, CD8+ T cells Percent	a percentage of CAR-, CD8+ T cells that are PD1+, CAR-, CD8+ T cells in the apheresis sample;
Apheresis Stage, Process Parameter	T cells Lymphocytes Percent	a percentage of lymphocytes that are T cells in the apheresis sample;
Apheresis Stage, Cell Surface Marker Parameter	Treg CD4+ T cells Percent	a percentage of CD4+ T cells that are CD4+ Treg cells in the apheresis sample;
Apheresis Stage, Process Parameter	Treg T cells Percent	a percentage of T cells that are Treg cells in the apheresis sample
Apheresis Stage, Process Parameter	Manufacturing Site	Quality of manufacturing site

Apheresis Stage, Process Parameter	Clinical Site	Quality of Clinical Site
Apheresis Stage, Process Parameter	Cryopreservation Site	Quality of Cryopreservation Site
Apheresis Stage, Process Parameter	Clinical Study	Quality of Clinical Study
Apheresis Stage, Process Parameter	Process	Quality of Process

<u>Manufacturing Stage Parameters Obtained During Early Initial Stage</u>		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Thaw Duration - Initial Stage	a duration of thawing of the apheresis sample performed at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post Thaw Viable Cell Concentration - Initial Stage	a concentration of viable T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Thaw Viability (%) - Initial Stage	a percentage of cells that are viable T cells in the T cell culture sample after thawing at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Thaw Viability (%) Unrounded - Initial Stage	an unrounded percentage of cells that are viable T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Thaw Cell Diameter - Initial Stage	a T cell diameter in the T cell culture samples after thawing at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Apheresis Volume - Initial Stage	a volume of the apheresis sample at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume ACD-A Added Post Thaw - Initial Stage	a volume of an anticoagulant (e.g., ACD-A) added to the T cell culture sample after thawing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Thaw Viable Cell Count before sampling - Initial Stage	a viable T cell count of the T cell culture sample after thawing but before sampling in the initial stage of the manufacturing process

Manufacturing Stage, Process Parameter	Post Thaw Sample Volume - Initial Stage	a sample volume of T cell culture sample after thawing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Thaw Viable Cell Count after sampling - Initial Stage	a viable T cell count in the T cell culture sample after thawing and after sampling in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Pulmozyme Added After Thaw? - Initial Stage	whether a DNase (e.g., Pulmozyme) was added to the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	ACD-A Added After Thaw?	whether an anticoagulant (e.g., ACD-A) was added to the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	In-line Filtration After Thaw? - Initial Stage	whether an in-line filtration of the T cell culture sample occurred after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD4+ (%) - Initial Stage	a percentage of cells that are CD4+ T Cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD8+ (%) - Initial Stage	a percentage of cells that are CD8+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD4:CD8 - Initial Stage	a ratio of CD4+ T cells to CD8+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD3+ Viability (%) - Initial Stage	a percentage of cells that are viable CD3+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD3+ (%) - Initial Stage	a percentage of cells that are CD3+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD16/56+ (%) - Initial Stage	a percentage of cells that are CD16+ and/or CD56+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD19+ (%) - Initial Stage	a percentage of cells that are CD19+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Thaw CD14+ (%) - Initial Stage	a percentage of cells that are CD14+ T cells in the T cell culture sample after thawing in the initial stage of the manufacturing process;

Manufacturing Stage, Process Parameter	Post Wash Viable Cell Concentration - Initial Stage	a concentration of viable T cells in the T cell culture sample after washing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash Viability (%) - Initial Stage	a percentage of cells that are viable T cells in the T cell culture sample after washing at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash Volume - Initial Stage	a volume of the T cell culture sample after washing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash Clump Removal Volume - Initial Stage	a volume of clump removal from the T cell culture sample after washing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash Viable Cell Count before Sampling - Initial Stage	a viable T cell count of the T cell culture sample after washing but before sampling in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash Sample Volume - Initial Stage	a sample volume of T cell culture sample after washing in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash Viable Cell Count After Sampling - Initial Stage	a viable T cell count in the T cell culture sample after washing and after sampling in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	CD4/CD8 Labeling Incubation Total Time - Initial Stage	a total incubation time for labeling CD4+ T cells and CD8+ T cells in the T cell culture sample at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	CD4/CD8 Enrichment Total Time - Initial Stage	a total enrichment time for labeling CD4+ T cells and CD8+ T cells in the T cell culture sample at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Number of Prodigy Cycles - Initial Stage	a number of prodigy cycles at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	CD4/CD8 Beads Manually Drained? - Initial Stage	whether or not CD4+ beads and/or CD8+ beads were manually drained from the T cell culture sample at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post thaw hold time (thaw to Prodigy start) - Initial Stage	the time spent between thawing and the prodigy run in the T cell culture sample at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Prodigy Run Time - Initial Stage	a time spent in the prodigy run for the T cell culture sample at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post Wash POS Viable Cell Concentration - Initial Stage	a concentration of viable T cells, in T cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process

Manufacturing Stage, Process Parameter	Post Wash POS Viability (%) - Initial Stage	a percentage of cells that are viable T cells, in T cell culture samples undergoing positive selection, after washing, at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash POS Viability (%) Unrounded - Initial Stage	an unrounded percentage of cells that are viable T cells, in T cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash POS Cell Diameter (µm) - Initial Stage	a T cell diameter, in T cell culture samples undergoing positive selection, after washing, at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash POS Volume - Initial Stage	a volume of the T Cell culture samples undergoing positive selection, after washing, at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post Wash POS Viable Cell Count before sampling (cells) - Initial Stage	a viable T cell count of the T Cell culture samples undergoing positive selection, after washing but before sampling, in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash POS Sample Volume - Initial Stage	a sample volume of T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash POS Viable Cell Count after Sampling (cells)	a viable T cell count in the T Cell culture samples undergoing positive selection, after washing and after sampling, in the initial stage of the manufacturing process
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD4+ (%) - Initial Stage	a percentage of cells that are CD4+ T Cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD8+ (%) - Initial Stage	a percentage of cells that are CD8+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD4:CD8 (CALC) - Initial Stage	a ratio of CD4+ T cells to CD8+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD3+ Viability (%) - Initial Stage	a percentage of cells that are viable CD3+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;

Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD3+ (%) - Initial Stage	a percentage of cells that are CD3+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD16/56+ (%) - Initial Stage	a percentage of cells that are CD16+ and/or CD56+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD19+ (%) - Initial Stage	a percentage of cells that are CD19+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Cell Surface Marker Parameter	Post Wash POS CD14+ (%) - Initial Stage	a percentage of cells that are CD14+ T cells in the T Cell culture samples undergoing positive selection, after washing, in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post Wash NEG Viable Cell Concentration - Initial Stage	a concentration of viable T cells, in T cell culture samples undergoing negative selection, after washing, in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash NEG Viability (%) - Initial Stage	a percentage of cells that are viable T cells, in T cell culture samples undergoing negative selection, after washing, at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post Wash NEG Volume - Initial Stage	a volume of the T Cell culture samples undergoing negative selection, after washing, at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post Wash NEG Viable Cell Count - Initial Stage	a viable T cell count of the T Cell culture samples undergoing negative selection, after washing, in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Viable Cells/bag - Initial Stage	a number of viable T cells per bag for T cell culturing, in the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	# of Culture Bags - Initial Stage	a number of bags for T cell culturing, in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Viable Cells for Recovery - Initial Stage	a number of viable T cells for recovery in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume Cells Added to Culture Bag A - Initial Stage	a volume of T cells added to a bag A for T cell culturing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume Cells Added to Culture Bag B - Initial Stage	a volume of T cells added to a bag B for T cell culturing in the initial stage of the manufacturing process;

Manufacturing Stage, Process Parameter	Volume IL-2 Added to Bag A - Initial Stage	a volume of interleukin-2 added to a bag A for T cell culturing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume IL-2 Added to Bag B - Initial Stage	a volume of interleukin-2 added to a bag B for T cell culturing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume TexMACS Added to Bag A - Initial Stage	a volume of culture media (e.g., TexMACS) added to bag A for T cell culturing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume TexMACS Added to Bag B - Initial Stage	a volume of culture media (e.g., TexMACS) added to bag B for T cell culturing in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Volume Seeded Bag A - Early Initial Stage	a volume of T cells seeded in bag A for T cell culturing in the early initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Volume Seeded Bag B - Early Initial Stage	a volume of T cells seeded in bag B for T cell culturing in the early initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Viable Cell Density Bag A - Initial Stage	a density of viable T Cells in bag A in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Viable Cell Density Bag B - Initial Stage	a density of viable T Cells in bag B in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Actual Total Viable Cells Seeded (cells) - Initial Stage	an actual number of number of viable T cells seeded in the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post Selection Hold Time - Initial Stage	A post selection hold time in the initial stage of the manufacturing process;
<u>Manufacturing Stage Parameters Obtained During Late Initial Stage</u>		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Total Incubation Time - Initial Stage	an incubation time for the T cell culture sample at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Pre-Activation Clumps: Y/N?	whether there are any pre-activation clumps in the T cell culture sample at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Pre-Activation Clumps: # of Clumps before massage - Initial Stage	a number of pre-activation clumps in the T cell culture sample before massaging the clumps at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Pre-Activation Clumps: Size of Clumps before massage - Initial Stage	a size of one or more pre-activation clumps in the T cell culture sample before massaging the clumps at the initial stage of the manufacturing process

Manufacturing Stage, Process Parameter	Pre-Activation Clump Post Massage Mitigation Effect - Initial Stage	a mitigation effect of the massage on the pre-activation clumps in the T cell culture sample at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume Transact Beads added to Bag A - Initial Stage	a volume of activation beads (e.g., Transact Beads) added to bag A of the T cell culture sample at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume Transact Beads added to Bag B - Initial Stage	a volume of activation beads (e.g., Transact Beads) added to bag B of the T cell culture sample at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Volume Seeded in Bag A - Late Initial Stage	a volume of T cell culture sample that is seeded in bag A at the late initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Volume Seeded Bag B - Late Initial Stage	a volume of T cell culture sample that is seeded in bag B at the late initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post-Activation Clumps: Y/N? - Initial Stage	whether there are post-activation clumps in the T cell culture sample at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post-Activation Clumps: # of Clumps before massage - Initial Stage	a number of post-activation clumps in the T cell culture sample before massaging the clumps at the initial stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post-Activation Clumps: Size of Clumps before massage - Initial Stage	a size of one or more post-activation clumps in the T cell culture sample before massaging the clumps at the initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Post-Activation Clump Post Massage Mitigation Effect - Initial Stage	a mitigation effect of the massage on the post-activation clumps in the T cell culture sample at the initial stage of the manufacturing process

Manufacturing Stage Parameters Obtained During Early Middle Stage

<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Total Incubation Time - Late Initial and Early Middle Stage	an incubation time for the T cell culture sample from the late initial through the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Bag A Viable Cell Concentration - Early Middle Stage	a concentration of viable T Cells in bag A of the T cell culture sample in the early middle stage of the manufacturing process

Manufacturing Stage, Process Parameter	Bag A Viability (%)	a percentage of cells that are viable T cells in bag A of the T cell culture sample in the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Bag A Volume - Early Middle Stage	a volume of bag A of the T cell culture sample in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Bag A Viable Cell Count - Early Middle Stage	a number of cells that are viable T cells in bag A of the T cell culture sample in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Bag B Viable Cell Concentration - Early Middle Stage	a concentration of viable T Cells in bag B of the T cell culture sample in the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Bag B Viability (%) - Early Middle Stage	a percentage of cells that are viable T cells in bag B of the T cell culture sample in the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Bag B Volume - Early Middle Stage	a volume of bag B of the T cell culture sample in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Bag B Viable Cell Count - Early Middle Stage	a number of cells that are viable T cells in bag B of the T cell culture sample in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Pre-Mixing Clumps: Y/N? - Early Middle Stage	whether there are any clumps in the T cell culture samples, pre-mixing, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Pre-Mixing Clumps: # of Clumps - Early Middle Stage	a number of clumps in the T cell culture samples, pre-mixing, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Pre-Mixing Clumps: Size of Clumps - Early Middle Stage	a size of one or more clumps in the T cell culture samples, pre-mixing, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post-Mixing Clumps: Y/N? - Early Middle Stage	whether there are any clumps in the T cell culture samples, post-mixing, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post-Mixing Clumps: # of Clumps - Early Middle Stage	a number of clumps in the T cell culture samples, post-mixing, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post-Mixing Clumps: Size of Clumps - Early Middle Stage	a size of one or more clumps in the T cell culture samples, post-mixing, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post-Mixing Clumps: Effectiveness of Mixing - Early Middle Stage	an effectiveness of mixing on the clumps in the T cell culture sample in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Post-Mixing Massage: Clumps - Early Middle Stage	an effectiveness of massaging the clumps on the T cell culture sample in the early middle stage of the manufacturing process;

Manufacturing Stage, Process Parameter	Average of Pooled Viable Cell Concentration - Early Middle Stage	an average concentration of viable T Cells per population of the T cell culture samples in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Average of Pooled Viability (%) - Early Middle Stage	an average percentage of viable T Cells per population of the T cell culture samples in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Average Pooled Cell Diameter - Early Middle Stage	an average cell diameter of viable T cells per population of the T cell culture samples in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Starting Volume - Early Middle Stage	a starting volume of the T cell culture samples in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Viable Cells before sampling - Early Middle Stage	a number of viable T cells before sampling in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Sample Volume - Early Middle Stage	a sample volume of the T cell culture; a number of viable T cells after sampling in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Viable Cells after Sampling - Early Middle Stage	a number of viable T cells in the T cell culture, after sampling, in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Viable Cells Available for Seeding G-Rex - Early Middle Stage	a number of viable T cells available for seeding in the T cell culture in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Number of G-Rex to seed - Early Middle Stage	a number of gas permeable rapid expansion (G-Rex) to seed in the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Viable Cell Number per G-Rex - Early Middle Stage	a number of viable T cells per G-Rex;
Manufacturing Stage, Process Parameter	Volume From Bag A to G-Rex A - Early Middle Stage	a volume of T cell culture sample transferred from a bag for T cell culturing (bag A) to a medium for gas permeable rapid expansion (G-Rex A) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume From Bag A to G-Rex B - Early Middle Stage	a volume of T cell culture sample transferred from a bag for T cell culturing (bag A) to a medium for gas permeable rapid expansion (G-Rex B) at the early middle stage of the manufacturing process;

Manufacturing Stage, Process Parameter	Volume From Bag B to G-Rex A - Early Middle Stage	a volume of T cell culture sample transferred from a bag for T cell culturing (bag B) to a medium for gas permeable rapid expansion (G-Rex A) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume From Bag B to G-Rex B - Early Middle Stage	a volume of T cell culture sample transferred from a bag for T cell culturing (bag B) to a medium for gas permeable rapid expansion (G-Rex B) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Volume Cells Seeded in G-Rex A - Early Middle Stage	a volume of T cells Seeded in a medium for gas permeable rapid expansion (G-Rex A) during the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Volume Cells Seeded in G-Rex B - Early Middle Stage	a volume of T cells Seeded in a medium for gas permeable rapid expansion (G-Rex B) during the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Volume Cells Seeded in G-Rex C - Early Middle Stage	a volume of T cells Seeded in a medium for gas permeable rapid expansion (G-Rex C) during the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Total Volume Cells Seeded in G-Rex D - Early Middle Stage	a volume of T cells Seeded in a medium for gas permeable rapid expansion (G-Rex D) during the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Vector Lot	a vector lot of the vector used in the transduction of the T cell culture sample
Manufacturing Stage, Process Parameter	Vector Batch Number	a vector batch number of the vector used in the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Syringe Lot	a syringe lot of the syringe used for the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Vector Type	a vector type of the vector used in the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Vector Titer (IU/mL)	a vector titer of the vector used in the transduction of T cell culture sample;
Manufacturing Stage, Process Parameter	Target Vector MOI	a target vector multiplicity of infection (MOI) of the vector used in the transduction of the T cell culture sample;

Manufacturing Stage, Process Parameter	Target Number of Vector Vials	a target number of vector vials for vectors used in the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Number of Vector Vials Used	a number of vector vials used for the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Vector hold time (min)	a vector hold time associated with the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Syringe Ambient Hold Duration - Early Middle Stage	a syringe ambient hold time for the syringe used in the transduction of the T cell culture sample;
Manufacturing Stage, Process Parameter	Volume Vector Added to G-Rex A	a volume of the vector added to a T cell culture sample (e.g., G-Rex A) at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume Vector Added to G-Rex B	a volume of the vector added to a T cell culture sample (e.g., G-Rex B) at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume Vector Added to G-Rex C	a volume of the vector added to a T cell culture sample (e.g., G-Rex C) at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume Vector Added to G-Rex D	a volume of the vector added to a T cell culture sample (e.g., G-Rex D) at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Amount of Time G-Rex A in Incubator - Early Middle Stage	an incubation time of a T cell culture sample (e.g., G-Rex A) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Amount of Time G-Rex B in Incubator - Early Middle Stage	an incubation time of a T cell culture sample (e.g., G-Rex B) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Amount of Time G-Rex C in Incubator - Early Middle Stage	an incubation time of a T cell culture sample (e.g., G-Rex C) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Amount of Time G-Rex D in Incubator - Early Middle Stage	an incubation time of a T cell culture sample (e.g., G-Rex D) at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Target Viable Cells for VSV-g Sampling - Early Middle Stage	a number of target viable T cells for vesicular stomatitis virus glycoprotein (VSV-g) sampling at the early middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume of VSV-g Sampling - Early Middle Stage	a volume of VSV-g sampling from the T cell culture sample at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Viable Cell Concentration of VSV-	a concentration of viable T cells in the VSV-g sample at the early middle stage of the manufacturing process

	g Sample - Early Middle Stage	
Manufacturing Stage, Process Parameter	Actual Viable Cells in VSV-g Sample (cells)	an actual number of viable T cells in the VSV-g sample at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Number of Pellets Generated	a number of pellets generated at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Percent Loss (%) - Early Middle Stage	a percent loss of T cells from the T cell culture sample at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Viable Cells for Expansion after VSVg Sampling (cells)	a number of viable T cells for expansion after VSVg sampling at the early middle stage of the manufacturing process

<u>Manufacturing Stage Parameters Obtained During Middle Stage</u>		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Incubator Out Temperature - Middle Stage	an incubation temperature for the T cell culture sample going out of the incubator in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Incubator Out CO2 Saturation (%) - Middle Stage	a percentage of incubation CO2 saturation for the T cell culture sample going out of the incubator in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Incubation Time - Early Middle Stage through Middle Stage	a total incubation time for the T cell culture sample from the early middle stage to the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	IL-2 Batch - Middle Stage	whether a batch of IL-2 was added to the T cell culture sample in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	IL-2 Protein Content (µg/vial) - Middle Stage	an amount per vial of IL-2 protein content added to the T cell culture sample in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Activity of IL-2 (IU/mg) - Middle Stage	an activity of IL-2 in the T cell culture sample in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume IL-2 Added to G-Rex A - Middle Stage	a volume of IL-2 added to G-Rex A of the T cell culture sample in the middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume IL-2 Added to G-Rex B - Middle Stage	a volume of IL-2 added to G-Rex B of the T cell culture sample in the middle stage of the manufacturing process;

Manufacturing Stage, Process Parameter	Glucose G-Rex A - Middle Stage	a concentration of glucose in the T cell culture sample (e.g., in G-Rex A holding the T cell culture sample) in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Glucose G-Rex B - Middle Stage	a concentration of glucose in the T cell culture sample (e.g., in G-Rex B holding the T cell culture sample) in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Lactate G-Rex A - Middle Stage	a concentration of lactate in the T cell culture sample (e.g., in G-Rex A holding the T cell culture sample) in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Lactate G-Rex B - Middle Stage	a concentration of lactate in the T cell culture sample (e.g., in G-Rex B holding the T cell culture sample) in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Incubator In Temperature - Middle Stage	an incubation temperature for the T cell culture sample going into the incubator in the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Incubator In CO2 Saturation (%)	a percentage of incubation CO2 saturation for the T cell culture sample going into the incubator in the middle stage of the manufacturing process

<u>Manufacturing Stage Parameters Obtained During Late Middle Stage</u>		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Incubator Out Temperature - Late Middle Stage	an incubation temperature for the T cell culture sample going out of the incubator in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Incubator Out CO2 Saturation (%) - Late Middle Stage	a percentage of incubation CO2 saturation for the T cell culture sample going out of the incubator in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Incubation Time - Middle Stage through Late Middle Stage	a total incubation time for the T cell culture sample from the early middle stage to the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	IL-2 Batch - Late Middle Stage	whether a batch of IL-2 was added to the T cell culture sample in the late middle stage of the manufacturing process

Manufacturing Stage, Process Parameter	IL-2 Protein Content - Late Middle Stage	an amount per vial of IL-2 protein content added to the T cell culture sample in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Activity of IL-2- Late Middle Stage	an activity of IL-2 in the T cell culture sample in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume IL-2 Added to G-Rex A - Late Middle Stage	a volume of IL-2 added to G-Rex A of the T cell culture sample in the late middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Volume IL-2 Added to G-Rex B (mL)	a volume of IL-2 added to G-Rex B of the T cell culture sample in the late middle stage of the manufacturing process;
Manufacturing Stage, Process Parameter	Glucose G-Rex A - Late Middle Stage	a concentration of glucose in the T cell culture sample (e.g., in G-Rex A holding the T cell culture sample) in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Glucose G-Rex B - Late Middle Stage	a concentration of glucose in the T cell culture sample (e.g., in G-Rex B holding the T cell culture sample) in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Lactate G-Rex A- Late Middle Stage	a concentration of lactate in the T cell culture sample (e.g., in G-Rex A holding the T cell culture sample) in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Lactate G-Rex B - Late Middle Stage	a concentration of lactate in the T cell culture sample (e.g., in G-Rex B holding the T cell culture sample) in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Incubator In Temperature - Late Middle Stage	an incubation temperature for the T cell culture sample going into the incubator in the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Incubator In CO2 Saturation (%) - Late Middle Stage	a percentage of incubation CO2 saturation for the T cell culture sample going into the incubator in the late middle stage of the manufacturing process

Manufacturing Stage Parameters Obtained During Advanced Stage

<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Incubator Out Temperature - Advanced Stage	an incubation temperature for the T cell culture sample going out of the incubator in the advanced stage of the manufacturing process

Manufacturing Stage, Process Parameter	Incubator Out CO2 Saturation (%) - Advanced Stage	a percentage of incubation CO2 saturation for the T cell culture sample going out of the incubator in the advanced of the manufacturing process
Manufacturing Stage, Process Parameter	Total Incubation Time - Late Middle Stage to Advanced Stage	a total incubation time for the T cell culture sample from the late middle stage to the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Expansion Incubation Time- Late Middle Stage through Advanced Stage	a total expansion incubation time for the T cell culture sample from the late middle stage to the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Viable Cell Concentration - Advanced Stage	a concentration of viable T cells in a harvested sample of the T cell culture, pre wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Total Cell Concentration - Advanced Stage	a concentration of T cells in a harvested T cell culture sample, pre wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Cell Viability (%) - Advanced Stage	a percentage of cells that are viable CAR+ T cells in a harvested T cell culture sample, pre wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Volume - Advanced Stage	a volume of the harvested T cell culture sample, pre wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Viable Cells (MBR) - Advanced Stage	a number of viable CAR+ T cells in the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Viable Cell Count before sampling - Advanced Stage	a number of T cells in the harvested T cell culture sample, pre-wash and before sampling, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Sample Volume - Advanced Stage	a volume of a sample of the harvested T cell culture, pre wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Viable Cell Count after Sampling - Advanced Stage	a count of viable T cells in the harvested T cell culture sample, pre wash and after sampling, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Total Cell Count before Sampling - Advanced Stage	a count of total T cells in the harvested T cell culture sample, pre wash and before sampling, in the advanced stage of the manufacturing process

Manufacturing Stage, Process Parameter	Harvest Pre-Wash Total Cell Count after Sampling - Advanced Stage	a count of total T cells in the harvested T cell culture sample, pre wash and after sampling, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Glucose - Advanced Stage	a concentration of glucose in the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Lactate - Advanced Stage	a concentration of lactate in the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Flow Cytometry Incubator In Temperature - Advanced Stage	an incubation temperature for flow cytometry for the T cell culture going into the incubator in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Flow Cytometry Incubator In CO2 Saturation (%) - Advanced Stage	an incubation CO2 saturation for flow cytometry for the T cell culture going into the incubator in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest and Sampling Processing Time - Advanced Stage	a harvest and sampling processing time in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Flow Cytometry Incubator Out Temperature - Advanced Stage	an incubation temperature for flow cytometry for the T cell culture going out of the incubator in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Flow Cytometry Incubator Out CO2 Saturation (%) - Advanced Stage	an incubation CO2 saturation for flow cytometry for the T cell culture going out of the incubator in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Time for Completion of Flow Cytometry - Advanced Stage	a time for the completion of the flow cytometry of the harvested sample in the advanced stage of the manufacturing process
Manufacturing Stage, cell surface marker parameter	Harvest Pre-Wash Flow CAR+ Expression (%) - Advanced Stage	a percentage of cells that are CAR+ T cells in the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Concentration A - Advanced Stage	a concentration of viable T cells in a harvested T cell culture sample A, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viability A (%) - Advanced Stage	a percentage of cells that are viable T cells in a harvested T cell culture sample A, post wash, in the advanced stage of the manufacturing process

Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Concentration B - Advanced Stage	a concentration of viable T cells in a harvested T cell culture sample B, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viability B (%) - Advanced Stage	a percentage of cells that are viable T cells in a harvested T cell culture sample B, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Concentration C - Advanced Stage	a concentration of cells that are viable T cells in a harvested T cell culture sample C, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viability C (%) - Advanced Stage	a percentage of cells that are viable T cells in a harvested T cell culture sample C, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Concentration Average - Advanced Stage	an average concentration of viable T cells in the harvested T cell culture sample, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viability Average (%) - Advanced Stage	an average percentage of cells that are viable T cells in the harvested T cell culture samples, post-wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Volume - Advanced Stage	a volume of the harvested T cell culture sample, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Count - Advanced Stage	a count of viable T cells in the harvested T cell culture sample, post wash, in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Count after sampling - Advanced Stage	a count of viable T cells in the harvested T cell culture sample, post wash and after sampling, in the advanced stage of the manufacturing process
Manufacturing Stage, Cell Surface Marker Parameter	Harvest Post Wash Viable CAR+ Cell Count before sampling - Advanced Stage	a count of viable CAR+ T cells in the harvested T cell culture sample, post wash and before sampling, in the advanced stage of the manufacturing process
Manufacturing Stage, Cell Surface Marker Parameter	Harvest Post Wash Viable CAR+ Cell Count after sampling - Advanced Stage	a count of viable CAR+ T cells in the harvested T cell culture sample, post wash and after sampling, in the advanced stage of the manufacturing process

Manufacturing Stage, Process Parameter	Post Wash Dose - Advanced Stage	a post-wash dose of CAR+ T cells in the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Cell Surface Marker Parameter	Target CAR+ Viable Cells per dose - Advanced Stage	a number of viable target CAR+ T Cells per dose in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Total Viable Cells per Dose - Advanced Stage	a number of viable CAR+ T cells per dose;
Manufacturing Stage, Process Parameter	Target Formulation Viable Cell Concentration - Advanced Stage	a concentration of a target formulation of Viable CAR+ T Cells;
Manufacturing Stage, Process Parameter	Number of Bags - Advanced Stage	a number of bags for the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume per Bag - Advanced Stage	a volume of CAR+ T cells per bag in the harvested T cell culture sample in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Volume of Cells Used for Formulation - Advanced Stage	a volume of CAR+ T cells used for the formulation of the final product;
Manufacturing Stage, Process Parameter	Volume CS5 Used for Formulation - Advanced Stage	a volume of CS5 used for the formulation of the final product;
Manufacturing Stage, Process Parameter	Particulate Inspection Bag 1 - Advanced Stage	a result of a particulate inspection of bag 1 of the harvested sample;
Manufacturing Stage, Process Parameter	Clump Present Bag 1 - Advanced Stage	a presence of a clump in bag 1 of the harvested sample;
Manufacturing Stage, Process Parameter	Visual Particulate Inspection Bag 2 - Advanced Stage	a result of a particulate inspection of bag 2 of the harvested sample;
Manufacturing Stage, Process Parameter	Clump Present Bag 2 - Advanced Stage	a presence of a clump in bag 2 of the harvested sample;

<u>Additional Manufacturing Process Parameters Obtained During and After Advanced Stage</u>		
<u>Parameter Type and Subtype</u>	<u>Parameter Name</u>	<u>Parameter Description</u>
Manufacturing Stage, Process Parameter	Total Time for Formulation	A total time for the formulation of the final product

Manufacturing Stage, Process Parameter	Total CS5 Contact Time	A total contact time for the T cell sample with a cryopreservation media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viable Cell Concentration A	a concentration of viable T cells in final formulation A in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viability A (%)	a percentage of cells that are viable T cells in final formulation A in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viable Cell Concentration B	a concentration of viable T cells in final formulation B in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viability B (%)	a percentage of cells that are viable T cells in final formulation B in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viable Cell Concentration C	a concentration of viable T cells in final formulation C in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viability C (%)	a percentage of cells that are viable T cells in final formulation C in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viable Cell Concentration Average	an average concentration of viable T cells in the final formulations in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Final Formulation CS5 Viability Average (%)	an average percentage of cells that are viable T cells in the final formulations in cryopreserved media (e.g., CS5)
Manufacturing Stage, Process Parameter	Dosing Accuracy (%)	a percent dosing accuracy in the final product
Manufacturing Stage, Process Parameter	FP Volume per bag	A volume per bag of the final product
Manufacturing Stage, Process Parameter	Appearance of Color	An appearance of color in the final product
Manufacturing Stage, Process Parameter	Appearance of Primary Container	An appearance of the primary container of the final product
Manufacturing Stage, Process Parameter	BacT/Alert Rapid Sterility	BacT/Alert Rapid Sterility of the final product
Manufacturing Stage, Process Parameter	Endotoxin (EU/mL)	A concentration of endotoxin in the final product

Manufacturing Stage, Process Parameter	Mycoplasma	A presence of mycoplasma in the final product
Manufacturing Stage, Process Parameter	FP Replication Competent Lentivirus (RCL)	A presence of Replication Competent Lentivirus (RCL) in the final product
Manufacturing Stage, Process Parameter	VSVg Result - Early Middle Stage	A result of VSVg sampling on the T cell culture sample at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	VSVg Result - Advanced Stage	A result of VSVg sampling on the T cell culture sample at the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Provirus Vector Copy Number (copies/transduced cell)	Provirus Vector Copy Number (copies/transduced cell)
Manufacturing Stage, Process Parameter	FP Post-Thaw Viability (%)	A percentage of cells that are viable T cells in the final product post-thaw
Manufacturing Stage, Process Parameter	FP Flow CD3+ Viability (%)	A percentage of cells that are viable CD3+ T cells in the final product
Manufacturing Stage, Process Parameter	Provirus Transduction Efficiency (vector copies/cell)	Provirus Transduction Efficiency (vector copies/cell) in the final product
Manufacturing Stage, Process Parameter	FP Flow CD19+ (%)	A percentage of cells that are CD19+ T cells in the final product
Manufacturing Stage, Process Parameter	FP Flow CD3-, CD16+, CD56+ NK cells (%)	A percentage of cells that are CD3-, CD16+, CD56+, CD56+ NK cells in the final product
Manufacturing Stage, Process Parameter	FP Flow CD3+ (%)	A percentage of cells that are CD3+ cells in the final product
Manufacturing Stage, Process Parameter	FP Flow CAR	A CAR expression of the T cells in the final product
Manufacturing Stage, Process Parameter	Viable Cell Concentration	A concentration of viable T cells in the final product
Manufacturing Stage, Process Parameter	Total Viable Cell Count (TNC) (cells)	Total viable T cell count in the final product
Manufacturing Stage, Process Parameter	Dose (CAR+ viable cells/kg)	A dose based on a number of viable CAR+ T cells per unit mass

Manufacturing Stage, Process Parameter	Dose: Number of CAR+ Viable T Cells (cells)	A dose based on a number of viable CAR+ T cells in the final product
Manufacturing Stage, Process Parameter	FP Flow CAR+ (%)	A percentage of cells that are CAR+ T cells in the final product
Manufacturing Stage, Process Parameter	IFN Gamma	A presence of interferon gamma in the final product
Manufacturing Stage, Process Parameter	Processing Time (aph thaw to inc in) - Early Initial Stage	A processing time between thawing of the aphereis sample to incubation initiation at the early initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Processing Time (inc out to inc in) - Late Initial Stage	A processing time for the T cell culture sample between incubation initiation and initiation completion at the late initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	Processing Time (inc out to inc in) - Early Middle Stage	A processing time for the T cell culture sample between incubation initiation and initiation completion at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Time from Inc out to post transduction inc in - Early Middle Stage	A time spent by the T cell culture sample between incubation completion to an incubation initiation after transduction at the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Processing Time (inc out to inc in) - Middle Stage	A processing time for the T cell culture sample between incubation initiation and initiation completion at the middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Processing Time (inc out to inc in) - Late Middle Stage	A processing time for the T cell culture sample between incubation initiation and initiation completion at the late middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Time from flow completion to PFB removed - Advanced Stage	A processing time for the T cell culture sample between completion of flow cytometry to the removal of PFB at the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Processing Time (inc out to dp sent to CRF) - Advanced Stage	A processing time for the T cell culture sample between incubation completion to the T cell culture sample being sent to a controlled rate freezer (CRF) at the advanced stage of the manufacturing process

Manufacturing Stage, Process Parameter	Prodigy Total Viable Cell Step Yield (%)	A step yield (%) of total viable T cells based on a cell processing platform (e.g., Prodigy)
Manufacturing Stage, Process Parameter	Prodigy Total Viable CD3+ Cell Step Yield (%)	A step yield (%) of total viable CD3+ T cells based on a cell processing platform (e.g., Prodigy)
Manufacturing Stage, Process Parameter	Culture Bag Step Recovery (%)	A percentage of T cells recovered after activation from the T cell culture sample at the early middle stage of the manufacturing process relative to the T cells in the apheresis sample at the early initial stage of the manufacturing process
Manufacturing Stage, Process Parameter	LOVO Step Yield (%)	A step yield (%) based on a cell processing platform (e.g., LOVO)
Manufacturing Stage, Process Parameter	% Pre-formulated bulk used for formulation (%)	A percentage of pre-formulated bulk used for formulation of the final product
Manufacturing Stage, Process Parameter	% Recovery Dose (formulation to post thaw)	% recovery dose of the final product from its formulation to post thaw
Manufacturing Stage, Process Parameter	% Recovery Total Viable Concentration (target to post thaw)	% Recovery Total Viable Concentration of the final product from the target to post thaw
Manufacturing Stage, Process Parameter	% Recovery Dose (target to post thaw)	% Recovery dose of final product from target to post thaw
Manufacturing Stage, Process Parameter	PDT (D3 to D10)	A population doubling time (PDT) for the T cell culture sample measured between the early middle stage and the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	cPDL (D3 to D10)	A cumulative population doubling level (cPDL) for the T cell culture sample measured between the early middle stage and the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Pre-Wash Viable Cell Count Per G-Rex (cells)	A number of harvested pre-wash viable T cells per G-Rex in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable Cell Count Per G-Rex (cells)	A number of harvested post-wash viable T cells per G-Rex in the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Harvest Post Wash Viable CAR+ Cell Count Per G-Rex (cells)	A number of harvested post-wash viable CAR+ T cells per G-Rex in the advanced stage of the manufacturing process

Manufacturing Stage, Process Parameter	Potential number of 70mL final bags based on 1 G-Rex (bags)	A potential number of 70mL final bags based on 1 G-Rex
Manufacturing Stage, Process Parameter	Actual Dose of CAR+ T cells/kg	An actual dose of CAR+ T cells per unit mass of the final product
Manufacturing Stage, Process Parameter	Calculated Dose of CAR+ T cells/kg	A calculated dose of CAR+ T cells per unit mass of the final product
Manufacturing Stage, Process Parameter	Clumping Present on D1 or D3?	Whether any clumping was present in the T cell culture sample during the late initial stage or the early middle stage of the manufacturing process
Manufacturing Stage, Process Parameter	Manufacturing Completed?	Whether the manufacturing process has been completed
Manufacturing Stage, Process Parameter	Manufacturing and Release Testing Completed? (Y/N)	Whether manufacturing and release testing of the final product has been completed
Manufacturing Stage, Process Parameter	OOS? (Y/N)	Whether the final product is out of specification
Manufacturing Stage, Process Parameter	Non-Conformance Type	A broad categorization of a manufacturing failure based on OOS or Termination
Manufacturing Stage, Process Parameter	OOS Type	A reason category for the final product being out of specification
Manufacturing Stage, Process Parameter	OOS/Termination Comment	OOS/Termination Comment
Manufacturing Stage, Process Parameter	Controllable/Uncontrollable	Whether a reason for failure in the first manufacturing attempt was deemed controllable or uncontrollable
Manufacturing Stage, Process Parameter	Batch Released to Patient (Y/N)	A flag indicating if the manufactured batch was released to the patient for infusion.
Manufacturing Stage, Process Parameter	Exceptional Release?	When an OOS occurs but the batch is still considered safe to be released to the patient. If certain exceptional release criteria is met, then the batch is released to the patient. This flag indicates if the particular batch was released under exceptional release formulation.

Manufacturing Stage, Process Parameter	Infused? (Y/N)	Field marks if the batch was released and further infused for the patient.
Manufacturing Stage, Process Parameter	Batch terminated during manufacturing? (Y/N)	Batch terminated during manufacturing? (Y/N)
Manufacturing Stage, Process Parameter	Shift (1st/2nd)	A time category when the final product was completed
Manufacturing Stage, Process Parameter	Total number of data points	A total number of features per column in a batch associated with the final product
Manufacturing Stage, Process Parameter	Particulates Observed on Day 10?	Whether any particulates were observed in the T cell culture sample during the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	Clumps Observed on Day 10?	Whether any clumps were observed in the T cell culture sample during the advanced stage of the manufacturing process
Manufacturing Stage, Process Parameter	FP Visual Inspection Result	A result of a visual inspection in the final product

What is claimed is:

1. A method for predicting whether a patient-specific CAR T drug product for a target patient would be out of specification (OOS), the method comprising:

receiving quantitative data for a set of OOS parameters, wherein the set of OOS parameters comprises two or more OOS parameters selected from Table 1, wherein each OOS parameter belongs to one of a plurality of parameter types as outlined in Table 1;

generating an input feature vector comprising the quantitative data for the set of OOS parameters; and

applying, into a trained machine learning model, the input feature vector to generate an output feature vector predicting whether the patient-specific CAR T drug product would be OOS.

2. The method of claim 1, wherein the OOS parameters as outlined in Table 1 are in order of significance to predicting whether the patient-specific CAR T drug product would be OOS, wherein OOS parameters with a higher significance are assigned a higher weight than other OOS parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.

3. The method of claim 1 or 2, wherein the set of OOS parameters includes a set of screening parameters selected from Table 1A, wherein Table 1A consists of screening parameters from Table 1.

4. The method of claim 3, wherein the screening parameters in Table 1A are arranged in order of significance to predicting whether the patient-specific CAR T drug product would be OOS, wherein screening parameters with a higher significance are assigned a higher weight than other screening parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.

5. The method of any one of the preceding claims, wherein the set of OOS parameters includes a set of apheresis stage parameters selected from Table 1B, wherein Table 1B consists of apheresis stage parameters from Table 1.

6. The method of claim 5, wherein the apheresis stage parameters in Table 1B are arranged in order of significance to predicting whether the patient-specific CAR T drug product would be OOS using the trained machine learning model, wherein apheresis stage parameters with a higher significance are assigned a higher weight than other apheresis stage parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.
7. The method of any one of the preceding claims, wherein the set of OOS parameters includes a set of manufacturing stage parameters selected from Table 1C, wherein Table 1C consists of manufacturing stage parameters from Table 1.
8. The method of claim 7, wherein the manufacturing stage parameters in Table 1C are arranged in order of significance to predicting whether the patient-specific CAR T drug product would be OOS using the trained machine learning model, wherein manufacturing stage parameters with a higher significance are assigned a higher weight than other manufacturing stage parameters when using the trained machine learning model to predict whether the patient-specific CAR T drug product would be OOS.
9. The method of any one of the preceding claims, wherein receiving quantitative data for the set of OOS parameters comprises receiving unstructured data for the set OOS parameters, the method further comprising:
 - vectorizing, by a feature extraction module of the computing device, the unstructured target data to the input feature vector.
10. The method of any one of the preceding claims, wherein the trained machine learning model is trained using reference data from a plurality of reference CAR T drug products manufactured from a plurality of reference patients, the plurality of reference CAR T drug products having known OOS outcomes.
11. The method of claim 10, further comprising:
 - receiving, by the computing device, the reference data, wherein the reference data comprises a set of input feature parameters and the known OOS outcomes for each of the plurality of reference CAR T drug products manufactured from the plurality of reference patients,

wherein, for a given reference patient of the plurality of reference patients, the set of input feature parameters includes at least the set of OOS parameters;

vectorizing, by a feature extraction module of the computing device, for each of the plurality of reference CAR T drug products manufactured from the plurality of reference patients, the set of input feature parameters and the known OOS outcome to a reference input feature vector and a reference output feature vector, respectively, thereby generating a plurality of reference input feature vectors and a plurality of reference output feature vectors;

associating, by a training module of the computing device, the plurality of reference input feature vectors to the plurality of reference output feature vectors in a machine learning model; and

training, by the training module of the computing device, by iteratively minimizing error to within a predetermined threshold, the machine learning model to generate the trained machine learning model, wherein the trained machine learning model includes a plurality of weights, each weight indicating a significance between an input feature parameter to an OOS outcome.

12. The method of claim 11, wherein the set of input feature parameters are outlined in Appendix A.

13. The method of claim 11 or 12, wherein, for each of the plurality of reference CAR T drug products manufactured from the respective plurality of reference patients, the set of input feature parameters comprises two or more of:

a concentration of lactate or glucose in a T cell culture sample from a middle stage of a manufacturing process of the reference CAR T drug product;

a concentration of lactate or glucose in the T cell culture sample from a late middle stage of the manufacturing process of the reference CAR T drug product;

a multiplicity of infection (MOI) of a vector added to the T cell culture sample during an early middle stage of the manufacturing process of the reference CAR T drug product;

a ratio of CD4⁺ T cells to CD8⁺ T cells in the T cell culture sample from an initial stage of the manufacturing process of the reference CAR T drug product;

a concentration of viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the reference CAR T drug product;

an average concentration of viable T cells per population from the early middle stage of the manufacturing process of the reference CAR T drug product;

a percentage of cells that are viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the reference CAR T drug product;

a count of viable T cell after sampling in the initial stage of the manufacturing process of the reference CAR T drug product;

a volume of vector added to the T cell culture sample during the early middle stage of the manufacturing process of the reference CAR T drug product;

whether the reference patient was refractory to pomalidomide treatment;

a concentration of lymphocytes in the apheresis sample prior to the manufacturing process of the reference CAR T drug product;

a sex of the reference patient;

a number of seeded viable T cells at the initial stage of the manufacturing process of the reference CAR T drug product;

a body mass index (BMI) of the reference patient; or

a percentage of leukocytes that are monocytes in the apheresis sample prior to the manufacturing process of the reference CAR T drug product.

14. The method of any one of the preceding claims, further comprising:
determining that the patient-specific CAR T drug product would be OOS; and
adjusting one or more manufacturing process parameters for manufacturing the CAR T drug product for the target patient.

15. The method of any one of the preceding claims, further comprising:
determining that the patient-specific CAR T drug product would not be OOS; and
causing, based on the set of OOS parameters, manufacture of the CAR T drug product for the target patient.

16. The method of any one of the preceding claims, wherein the two or more OOS parameters comprises two or more of:

a concentration of lactate or glucose in a T cell culture sample from a middle stage of a manufacturing process of the CAR T drug product;

a concentration of lactate or glucose in the T cell culture sample from a late middle stage of the manufacturing process of the CAR T drug product;

a multiplicity of infection (MOI) of a vector added to the T cell culture sample during an early middle stage of the manufacturing process of the CAR T drug product;

a ratio of CD4+ T cells to CD8+ T cells in the T cell culture sample from an initial stage of the manufacturing process of the CAR T drug product;

a concentration of viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the CAR T drug product;

an average concentration of viable T cells per population from the early middle stage of the manufacturing process of the CAR T drug product;

a percentage of cells that are viable T cells in the T cell culture sample from the initial stage of the manufacturing process of the CAR T drug product;

a count of viable T cell after sampling in the initial stage of the manufacturing process of the CAR T drug product;

a volume of vector added to the T cell culture sample during the early middle stage of the manufacturing process of the CAR T drug product;

whether the target patient was refractory to pomalidomide treatment;

a concentration of lymphocytes in the apheresis sample prior to the manufacturing process of the CAR T drug product;

a sex of the target patient;

a number of seeded viable T cells at the initial stage of the manufacturing process of the CAR T drug product;

a body mass index (BMI) of the target patient; or

a percentage of leukocytes that are monocytes in the apheresis sample prior to the manufacturing process of the CAR T drug product.

17. A system for predicting whether a patient-specific CAR T drug product for a target patient would be out of specification (OOS), the system comprising:

a memory storing processor-readable code; and

one or more processors coupled to the memory, the one or more processors being configured to execute the processor-readable code to cause the one or more processors to perform a method of any one of the preceding claims.

18. A non-transitory computer-readable medium storing computer instructions for predicting whether a patient-specific CAR T drug product for a target patient would be out of specification (OOS), the computer instructions comprising a method of any one of claims 1-16.