

What is claimed is:

1. A computer-implemented method of determining criticality of a product quality attribute (PQA) of an antibody after multiple administrations of the antibody to a subject, comprising:

(a) predicting an *in vivo* serum concentration of ~~an~~the antibody with a ~~post-translational modification of interest~~PQA after a single administration of the antibody, comprising by:

_____ (i) predicting a percentage of the antibody with the ~~post-translational modification of interest~~PQA using an *in vivo* rate constant determined for the ~~post-translational modification~~; and

~~multiplying the predicted percentage of the antibody with the post-translational modification of interest by a total *in vivo* concentration of the antibody to determine the concentration of the antibody with the post-translational modification of interest ($C_{PTM}(t) = C(t) \cdot P(t)$), where $C_{PTM}(t)$ is the serum concentration of the antibody with the post-translational modification of interest; $C(t)$ is the serum concentration of the antibody; and $P(t)$ is the percentage of the post-translational modification of interest).~~

2. _____ The method of claim 1PQA, wherein ~~the~~an *in vivo* rate constant ~~for the post-translational modification~~ is determined by quantitating a percentage of the ~~post-translational modification of interest~~PQA as a function of time and fitting the quantitated percentage of the ~~post-translational modification of interest~~PQA to the equation $P_{PTM}(t) = 1 - (1 - P_0) \cdot e^{-k_{PTM}t}$, where $P_{PTM}(t)$ is the proportion of the ~~post-translational modification~~PQA as a function of time; P_0 is an initial percentage post-translational modification; and k_{PTM} is the ~~post-translational modification~~PQA rate constant; and

3. _____ (ii) multiplying the predicted percentage of the antibody with the PQA by a total *in vivo* concentration of the antibody to determine the concentration of the antibody with the PQA and thereby producing a single-administration model;

(b) repeating step (a) at least once and thereby producing one or more additional single-administration models;

(c) superimposing the single-administration models of steps (a) and (b) and thereby producing a multiple-administration model; and

(d) using the multiple-administration model to determine the criticality of the PQA, wherein the PQA includes a post-translational modification of interest.

2. The method of claim 1-~~or 2~~, further comprising determining the exposure of the subject to the antibody with the post-translational modification of interest-

~~4. The method of claim 3, wherein determining the exposure of the subject to the antibody with the post-translational modification of interest, wherein determining an exposure of the subject to the antibody with the post-translational modification of interest~~ comprises determining the area under the curve (AUC) of the concentration ~~($C_{PTM}(t)$)~~ of the antibody with the post-translational modification of interest.

53. The method of any one of claims 1-4 or 2, wherein the serum concentration of the antibody is described by a two-compartment pharmacokinetic model equation as $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$, where A and B are hybrid coefficients when α and β are hybrid first order constants, respectively.

~~6. The method of any one of claims 1-5, further comprising predicting the *in vivo* serum concentration of the antibody with the post-translational modification of interest after multiple administrations of the antibody.~~

~~7. The method of claim 6, wherein predicting the *in vivo* serum concentration of the antibody with the post-translational modification of interest after multiple administrations of the antibody comprises superimposing multiple single administration models, wherein the serum concentration of the antibody at each administration is described individually by a two-compartment pharmacokinetic model equation as $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$, where A and B are hybrid coefficients when α and β are hybrid first order constants, respectively.~~

84. The method of any one of claims 1-73, wherein the antibody comprises a recombinant therapeutic monoclonal antibody.

~~95.~~ The method of any one of claims 1-~~84~~, wherein the ~~post-translational modification comprises a product quality attribute that~~PQA can impact drug stability, safety, and/or efficacy.

~~406.~~ The method of any one of claims 1-~~95~~, wherein the method ~~predictively monitors~~is used to predict or monitor the post-translational modification profile of a monoclonal antibody.

~~447.~~ The method of any one of claims 1-~~40~~, ~~wherein the method further comprises creating a predictive model of the in vivo progression of post-translational modifications and a subject's exposure to product quality attributes.~~

~~42.~~ ~~The method of any one of claims 1-416,~~ wherein the post-translational modification comprises one or more of deamidation, oxidation, glycation, disulfide formation, N-terminal pyroglutamate formation, C-terminal lysine removal, and high mannose glycosylation.

~~438.~~ The method of any one of claims 1-~~427~~, further comprising modeling a correlation between ~~PK~~pharmacokinetic concentration and proportion of post-translational modification variants.

~~449.~~ The method of any one of claims 1-~~438~~, further comprising quantitatively assessing and predicting the subject exposure to a representative post-translational modification in ~~both~~either a single- and dose regimen or a multiple-dose regimensregimen.

~~4510.~~ The method of any one of claims 1-~~439~~, further comprising predicting ~~the~~a maximum and a minimum post-translational modification ~~levels~~level observed in ~~the~~a multiple-dose ~~regimensregimen~~.

~~46-11.~~ The method of any one of claims 1-~~4510~~, further comprising, ~~administering the antibody to the subject.~~

~~47.~~ ~~The method of any one of claims 1-46, wherein the antibody is a mAb.~~

~~18. The method of any one of claims 1-17, further comprising, determining the-a~~
total *in vivo* concentration of the antibody in the subject.

~~19. A method for~~ 12. The method of any one of claims 1-11, further comprising
predicting ~~exposure of a subject to a variant of a recombinant therapeutic monoclonal~~pre-dose
in vivo concentration of an antibody ~~following administration to~~with the subject, comprising:
identifying ~~a rate constant for a~~ post-translational modification (PTM) ~~process that~~
~~causes formation of the variant;~~of interest.

~~calculating a predicted proportion of the variant as a function of time;~~
~~calculating a predicted serum concentration of the variant in the subject as a function~~
~~of time based on the predicted proportion of the variant; and~~
~~predicting exposure of the subject to the variant following administration of the~~
~~antibody based on the predicted serum concentration of the variant.~~

~~20. The method of claim 19, wherein calculating the predicted proportion of the~~
~~variant as a function of time is performed via the following equation:~~

$$P_{PTM}(t) = 1 - (1 - P_0) \cdot e^{-k_{PTM} t}$$

~~wherein $P_{PTM}(t)$ is the proportion of the variant as a function of time, P_0 is the initial~~
~~level of the variant at the time of administration, k_{PTM} is the rate constant for the PTM process,~~
~~and t is time.~~

~~21. The method of claim 19 or 20, wherein calculating the predicted serum~~
~~concentration of the variant in the subject as a function of time is performed via the following~~
~~equation:~~

$$C_{PTM}(t) = C(t) \cdot P_{PTM}(t)$$

~~wherein $C_{PTM}(t)$ is the serum concentration of the variant, $C(t)$ is the serum~~
~~concentration of the antibody, and $P_{PTM}(t)$ is the proportion of the variant at time t .~~

~~22. A method for predicting exposure of a subject to a variant of a recombinant~~
~~therapeutic monoclonal antibody following administration of multiple doses of the antibody to the~~
~~subject, comprising:~~

~~performing the method of any one of claim 19-21;~~

~~calculating the predicted proportion of the variant prior to and after each subsequent dose of the antibody based on a dosing interval;~~

~~calculating the predicted serum concentration of the variant in the subject based on the predicted proportion of the variant at each dosing interval; and~~

~~predicting exposure of the subject to the variant over the course of two or more doses of the antibody based on the predicted serum concentration of the variant.~~

~~23-13. The method of any one of claims 19-22, wherein the post translational modification comprises one or more of deamidation, oxidation, glycation, disulfide formation, N-terminal pyroglutamate formation, C-terminal lysine removal, and high mannose glycosylation.~~

~~24. The method of any one of claims 19-23 1-12, further comprising, administering the antibody to the subject.~~

~~25. The method of any one of claims 18-24, wherein the antibody is a mAb.~~

~~26. The method of any one of claims 18-25, further comprising, determining the a total- predicting a post-dose *in vivo* concentration of the antibody in the subject. an antibody with the post-translational modification of interest.~~