

PHARMACEUTICAL PRODUCT AND METHOD OF ANALYSING LIGHT EXPOSURE OF A PHARMACEUTICAL PRODUCT

Background

[0001] This patent is directed to a pharmaceutical product, and, in particular, to a pharmaceutical product with photosensitive properties, including a photosensitive device that defines the product in part and methods of using the photosensitive device in conjunction with the pharmaceutical product.

[0002] It has been recognized that when proteins are exposed to visible and ultraviolet (UV) radiation, the proteins may degrade. See, for example, Bruce Kerwin and Richard Remmele, *Protect from light: Photodegradation and protein biologics* in *Journal of Pharmaceutical Sciences*, vol. 96, June 2007, pp. 1468-80. This degradation may be both chemical and physical, in the forms of photo-induced oxidation, covalent aggregation, and deamidation of Asn residues. While relatively little is known about how this light exposure affects biopharmaceuticals, the authors suggest that it is foreseeable that photolysis of proteins in biopharmaceuticals could produce changes in the conformation leading to aggregation, with small concentrations of aggregates acting as nucleating centers leading to visible particulates. Other problems may include changes to the immunogenic potential of the protein or reduction in bioactivity.

[0003] As noted by Kerwin and Remmele, products may be exposed to visible and UV light sources during manufacturing, storage, and/or transportation, as well as during use in clinics and other healthcare facilities. During manufacturing, for example, the products may be exposed to light sources during fill and finish operations, visual inspections, and packaging. During use, the products may be exposed when removed from the protective packaging in which they are stored prior to delivery, and may be exposed even at the time of delivery when diluted into solutions in clear IV bags as may occur when the product is delivered intravenously.

[0004] The solutions proposed by Kerwin and Remmele, as well as others, address the photodecompositions indirectly through packaging or directly through the use of excipients or inert atmospheric packaging. As to the former solution, it relies upon the creation of a barrier to block incoming light. As noted by the authors, such a solution necessarily relies on identifying all possible regions of the container where

the product may be exposed to light (e.g., at an inspection window), and establishing barriers to exposure at each such region. As to the latter solution, while existing publications suggest promise for the use of excipients and inert atmospheric packaging, the literature is limited and the possibility for unintended consequences exists.

[0005] As set forth in more detail below, the present disclosure sets forth a pharmaceutical product embodying advantageous alternatives to the conventional devices discussed above.

Summary

[0006] In an aspect of the present disclosure, a pharmaceutical product includes a container having an exterior surface and an interior chamber, an active ingredient disposed in the interior chamber, the active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y, and a layer of photosensitive material disposed on the exterior surface of the container and exposed to environmental conditions contemporaneous with the active ingredient being disposed in the interior chamber. The photosensitive material is reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the active ingredient.

[0007] In another aspect of the present disclosure, a pharmaceutical product includes a container having an interior chamber, the container constructed from a material that is photo-resistive, and a layer of photosensitive material disposed in the interior chamber of the container. The photosensitive material is reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in a photosensitive property of an active ingredient.

[0008] In a further aspect of the present disclosure, a pharmaceutical product includes a container having an exterior surface and an interior chamber, an active ingredient disposed in the interior chamber, the active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y, and a label having a first

region affixed to the exterior surface of the container with a layer of photosensitive material applied thereto and a second region removably attached to the exterior surface of the container with a layer of the photosensitive material applied thereto, the first and second regions exposed to environmental conditions contemporaneous with the active ingredient being disposed in the interior chamber. The photosensitive material is reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the active ingredient.

[0009] In a still further aspect of the present disclosure, a method of confirming correct handling of photo-sensitive material includes applying a layer of photosensitive material to an exterior surface of a container having an active ingredient disposed therein, the active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y and the photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the active ingredient. The method also includes delivering the container to a recipient, collecting the container from the recipient, examining the layer of photosensitive to determine if the photosensitive material has experienced the property change, and identifying the container as mishandled if the photosensitive materials has experienced the property change.

[0010] In yet another aspect of the present disclosure, a method of analyzing light exposure of a pharmaceutical product includes identifying a path for the pharmaceutical product within a facility comprising at least one space through which the pharmaceutical product passes, the pharmaceutical product comprising an active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y, and disposing at least one photosensitive device along the path, the at least one photosensitive device comprising a layer of photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range

between X and Y. The method also includes reading the at least one photosensitive device after being disposed along the path for evidence of the property change to the photosensitive material of the photosensitive device, and changing the path for the pharmaceutical product through the facility if the property change occurs to the photosensitive material of the photosensitive device.

Brief Description of the Drawings

[0011] It is believed that the disclosure will be more fully understood from the following description taken in conjunction with the accompanying drawings. Some of the figures may have been simplified by the omission of selected elements for the purpose of more clearly showing other elements. Such omissions of elements in some figures are not necessarily indicative of the presence or absence of particular elements in any of the exemplary embodiments, except as may be explicitly delineated in the corresponding written description. None of the drawings are necessarily to scale.

[0012] Fig. 1 is a perspective view of a pharmaceutical product according to the present disclosure having a container with a layer of photosensitive material disposed on an exterior surface of the container;

[0013] Fig. 2 is a perspective view of another pharmaceutical product according to the present disclosure having a container with a layer of photosensitive material disposed on an exterior surface of the container;

[0014] Fig. 3 is a graph illustrating the color change of a layer of photosensitive material, as registered using a colorimeter, with increasing UV exposure;

[0015] Fig. 4 is a graph illustrating the color change of a layer of photosensitive material, as registered using a colorimeter, with increasing visible light exposure;

[0016] Fig. 5 is a graph illustrating one measure of the degradation of a protein exposed to visible light;

[0017] Fig. 6 is a graph illustrating a measure of the degradation (% increase in high molecular weight species) of a monoclonal antibody polypeptide exposed to visible light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0018] Fig. 7 is a graph illustrating a measure of the degradation (yellow index) of a monoclonal antibody polypeptide exposed to visible light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0019] Fig. 8 is a graph illustrating a measure of the degradation (increase in basic peak for Cation Exchange-HPLC) of a monoclonal antibody polypeptide exposed to visible light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0020] Fig. 9 is a graph illustrating a measure of the degradation (increase in acidic peak for Cation Exchange-HPLC) of a monoclonal antibody polypeptide exposed to visible light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0021] Fig. 10 is a graph illustrating a measure of the degradation (absorption change) of a small molecule exposed to UV light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0022] Fig. 11 is a graph illustrating a measure of the degradation (yellow index) of a small molecule exposed to UV light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0023] Fig. 12 is a graph illustrating a measure of the degradation (% increase high molecular weight species) of a monoclonal antibody polypeptide exposed to UV light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0024] Fig. 13 is a graph illustrating a measure of the degradation (% increase low molecular weight species) of a monoclonal antibody polypeptide exposed to UV light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0025] Fig. 14 is a graph illustrating a measure of the degradation (yellow index) of an amino acid exposed to UV light, with reference to a color change of an associated layer of photosensitive material, as registered using a colorimeter;

[0026] Fig. 15 is a graph illustrating the color change of a layer of photosensitive material, as registered using a colorimeter, with increasing visible light exposure over a range of temperatures;

[0027] Fig. 16 is a perspective view of an alternative to the pharmaceutical product of Fig. 1;

[0028] Fig. 17 is a perspective view of a pharmaceutical product including an alternative label to that illustrated in Fig. 1, with a photo-resistive cover;

[0029] Fig. 18 is a perspective view of a pharmaceutical product including an alternative label to that illustrated in Fig. 1, with first and second detachable regions;

[0030] Fig. 19 is a perspective of a system including a product including the label of Fig. 18 and a syringe;

[0031] Fig. 20 is a perspective view of a pharmaceutical product including an alternative label to that illustrated in Fig. 1, with first and second detachable regions and a cover over the second region;

[0032] Fig. 21 is a perspective of a system including a product including the label of Fig. 20 and a syringe;

[0033] Fig. 22 is a perspective view of a pharmaceutical product including a primary label similar to that illustrated in Fig. 1, and a secondary label for determining changes in temperature in a first state;

[0034] Fig. 23 is the product of Fig. 22, with the secondary label in a second state wherein the label has changed at least one characteristic to highlight that the product has been exposed to high temperatures;

[0035] Fig. 24 is a perspective view of another pharmaceutical product according to the present disclosure having a container with a layer of photosensitive material disposed within the container;

[0036] Fig. 25 is a graph of illustrating the color change of a layer of photosensitive material disposed within a container as illustrated in Fig. 23, as registered using a colorimeter, with increasing UV light exposure for a range of materials used in the fabrication of the container;

[0037] Fig. 26 is a schematic diagram of a manufacturing plant layout wherein phototracking units according to the present disclosure have been disposed along a path, P, along which the pharmaceutical product passes within the manufacturing plant;

[0038] Fig. 27 is a graph illustrating changes in color of different sensitivities (in increasing order of sensitivity: "sen1", "sen2", "sen3", "sen4", "sen5") of photosensitive material that may be used in the products, systems and methods disclosed herein, with increasing UV exposure;

[0039] Fig. 28 is a graph illustrating the color change of a layer of photosensitive material, as registered using a colorimeter, stored at 4°C compared with a control;

[0040] Fig. 29 is a graph illustrating the color change of a layer of photosensitive material, as registered using a colorimeter, stored at 25°C compared with a control; and

[0041] Fig. 30 is a graph illustrating the color change of a layer of photosensitive material disposed inside and outside containers for a range of materials used in the fabrication of the container.

Detailed Description of Various Embodiments

[0042] Although the following text sets forth a detailed description of different embodiments of the invention, it should be understood that the legal scope of the invention is defined by the words of the claims set forth at the end of this patent. The detailed description is to be construed as exemplary only and does not describe every possible embodiment of the invention because describing every possible embodiment would be impractical, if not impossible. Numerous alternative embodiments could be implemented, using either current technology or technology developed after the filing date of this patent, which would still fall within the scope of the claims defining the invention.

[0043] It should also be understood that, unless a term is expressly defined in this patent using the sentence “As used herein, the term ‘_____’ is hereby defined to mean...” or a similar sentence, there is no intent to limit the meaning of that term, either expressly or by implication, beyond its plain or ordinary meaning, and such term should not be interpreted to be limited in scope based on any statement made in any section of this patent (other than the language of the claims). To the extent that any term recited in the claims at the end of this patent is referred to in this patent in a manner consistent with a single meaning, that is done for sake of clarity only so as to not confuse the reader, and it is not intended that such claim term be limited, by implication or otherwise, to that single meaning. Finally, unless a claim element is defined by reciting the word “means” and a function without the recital of any structure, it is not intended that the scope of any claim element be interpreted based on the application of 35 U.S.C. §112, sixth paragraph.

[0044] As disclosed herein, a pharmaceutical product includes a container having an exterior surface and an interior chamber, which interior chamber may be defined by an interior surface. A material, such as a polypeptide, may be disposed within the interior chamber, which material may be photosensitive and may experience

degradation with exposure to light over a particular range of wavelengths. A layer of photosensitive material may be disposed either on the exterior surface of the container or in the interior chamber, and may be exposed to environmental conditions contemporaneous with the polypeptide being disposed in the interior chamber, according to certain embodiments. According to other embodiments, the exposure of the layer of photosensitive material to environmental conditions may be delayed. The photosensitive layer may be reactive to light of a particular wavelength so as to experience a property change at a threshold of cumulative exposure, which property change of the photosensitive layer may be related to the change in the photosensitive property of the polypeptide or other material. As one example, the property change of the material defining the photosensitive layer can be a color change that is “colorimetrically detectable” (i.e., a color change that is detectable visually or by the use of colorimetric instrumentation).

[0045] As one example of such a product, a pharmaceutical product 100 is illustrated in Fig. 1 that includes a container 110 having an exterior surface 112 and an interior chamber 114, which chamber 114 may be defined by an interior surface 116. The exterior surface 112 and the interior surface 116 may be defined by a wall 118 made of a single layer, or the surfaces 112, 116 may be defined by different layers of a multi-layered structure, for example.

[0046] According to the illustrated exemplary embodiment of Fig. 1, the container 110 may be a glass vial having an open end 120 and a closed end 122, with the open end 120 including an opening formed at the end of a neck region 126 of reduced cross-section defined by a rim, which opening may be closed off by a rubber stopper held in place with a metal crimp ring or seal. While an exemplary embodiment of the container 110 has been illustrated in Fig. 1, the present disclosure is not limited to the illustrated embodiment. For example, the container 110 may be made of polymeric materials, such as polycarbonate, polypropylene or Teflon, instead of glass. Moreover, the container 110 may be larger or smaller than the illustrated example, and have a different shape than that illustrated in Fig. 1. For example, the container 110 may be a larger container used for storage and transportation, such as a carboy (see Fig. 2), or a smaller container used for a single-dose treatment, such as a single-dose vial similar in structure but smaller in size than the container illustrated in

Fig. 1. The container also may have a non-rigid shape, such as in the form of a plastic bag, for example.

[0047] As noted above, the pharmaceutical product 100 may also include a material disposed within the interior chamber 114 of the container 110. In general terms, the material disposed in the chamber 114 typically refers to (and thus includes) active ingredients, such as polypeptides, amino acids, and/or small molecules, and/or may also refer to (and thus include) an inactive ingredient or excipient in addition to the polypeptides, amino acids and/or small molecules. Active ingredients may also include viruses, which viruses may contain cDNA or RNA encoded by glycoproteins and lipid layers. The one or more active ingredients can be therapeutically active ingredients, stabilizing agents (e.g., amino acids), or diagnostic reagents, or a combination of therapeutic molecules, stabilizing agents, and/or diagnostic reagents. In particular, the material disposed within the interior chamber 114 may be a material that has sensitivity to light. When the material is exposed to light, the light may change the characteristics of the material in the container. In certain cases, exposure to light may cause the material to degrade, and be less useful or cease to be useful for its intended purpose.

[0048] As one non-limiting example, the material disposed in the interior chamber 114 of the container 110 may be a polypeptide. More particularly, the polypeptide may be suspended in an aqueous medium, and may be fluid (a liquid state) or frozen (a solid state). The polypeptide may have, for example, a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y. According to other embodiments, it may be desirable to monitor light exposure even when no relationship has been previously established between change or degradation of the polypeptide or other material and light exposure.

[0049] In this regard, it should be noted that polypeptide and protein are used interchangeably herein and include a molecular chain of two or more amino acids linked covalently through peptide bonds. The terms do not refer to a specific length of the product. Thus, peptides and oligopeptides are included within the definition of polypeptide. The terms include post-translational modifications of the polypeptide, for example, glycosylations, acetylations, biotinylations, 4-pentynoylations, PEGylations, phosphorylations and the like. In addition, protein fragments, analogs,

mutated or variant proteins, fusion proteins and the like are included within the meaning of polypeptide. The terms also include molecules in which one or more amino acid analogs or non-canonical or unnatural amino acids are included as can be expressed recombinantly using known protein engineering techniques.

[0050] Non-limiting examples of materials that may be disposed in the interior chamber 114 may include darbepoetin alfa (such as Aranesp®), epoetin alfa (such as Epogen®), anakinra (Kineret®), pegfilgrastim (such as Neulasta®), denosumab (such as Prolia® or XGEVA™) and filgrastim (such as Neupogen®). Aranesp®, Epogen®, Kineret®, Neulasta®, Prolia®, XGEVA™ and Neupogen® are manufactured by Amgen Inc. of Thousand Oaks, California. In addition, products such as etanercept (such as Enbrel®), adalimumab (such as Humira®), infliximab (such as Remicade®), certolizumab pegol (such as Cimzia®), golimumab (such as Simponi®), abatacept (such as Orencia®), tocilizumab (such as Actemra®), panitumumab (such as Vectibix®), cetuximab (such as Erbitux®), trastuzumab (such as Herceptin®), bevacizumab (such as Avastin®), pegylated epoetin beta (such as Mircera®), peginesatide (such as Hematide™) and rituximab (such as Rituxan®) may be disposed in the interior chamber 114. Still further non-limiting examples include epoetin beta, epoetin zeta, epoetin theta, mogamulizumab, omalizumab (such as Xolair®), brodalumab, secukinumab, nimotuzumab, and ixekizumab.

[0051] In fact, the material disposed in the interior chamber 114 may include proteins with amino acid sequences identical to or substantially similar to all or part of one of the following proteins: a flt3 ligand (as described in International Application WO 94/28391, incorporated herein by reference), a CD40 ligand (as described in US Patent No. 6,087,329, incorporated herein by reference), erythropoietin, thrombopoietin, calcitonin, leptin, IL-2, angiopoietin-2 (as described by Maisonpierre et al. (1997), Science 277(5322): 55-60, incorporated herein by reference), Fas ligand, ligand for receptor activator of NF-kappa B (RANKL, as described in International Application WO 01/36637, incorporated herein by reference), tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL, as described in International Application WO 97/01633, incorporated herein by reference), thymic stroma-derived lymphopoietin, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor (GM-CSF, as described in Australian Patent No. 588819, incorporated herein by reference), mast cell growth factor, stem cell growth factor

(described in e.g. US Patent No. 6,204,363, incorporated herein by reference), epidermal growth factor, keratinocyte growth factor, megakaryocyte growth and development factor, RANTES, human fibrinogen-like 2 protein (FGL2; NCBI accession no. NM_00682; Rüegg and Pytela (1995), *Gene* 160: 257-62) growth hormone, insulin, insulinotropin, insulin-like growth factors, parathyroid hormone, interferons including α interferons, γ interferon, and consensus interferons (such as those described in US Patent Nos. 4,695,623 and 4,897,471, both of which are incorporated herein by reference), nerve growth factor, brain-derived neurotrophic factor, synaptotagmin-like proteins (SLP 1-5), neurotrophin-3, glucagon, interleukins 1 through 18, colony stimulating factors, lymphotoxin- β , tumor necrosis factor (TNF), leukemia inhibitory factor, oncostatin M, and various ligands for cell surface molecules ELK and Hek (such as the ligands for eph-related kinases or LERKS). Other descriptions of proteins may be found in, for example, *Human Cytokines: Handbook for Basic and Clinical Research*, Vol. II (Aggarwal and Gutterman, eds. Blackwell Sciences, Cambridge, MA, 1998); *Growth Factors: A Practical Approach* (McKay and Leigh, eds., Oxford University Press Inc., New York, 1993); and *The Cytokine Handbook* (A.W. Thompson, ed., Academic Press, San Diego, CA, 1991), all of which are incorporated herein by reference.

[0052] Other exemplary proteins may include proteins comprising all or part of the amino acid sequence of a receptor for any of the above-mentioned proteins, an antagonist to such a receptor or any of the above-mentioned proteins, and/or proteins substantially similar to such receptors or antagonists. These receptors and antagonists include: both forms of tumor necrosis factor receptor (TNFR, referred to as p55 and p75, as described in US Patent No. 5,395,760 and US Patent No. 5,610,279, both of which are incorporated herein by reference), Interleukin-1 (IL 1) receptors (types I and II; described in EP Patent No. 0 460 846, US Patent No. 4,968,607, and US Patent No. 5,767,064, all of which are incorporated herein by reference), IL-1 receptor antagonists (such as those described in US Patent No. 6,337,072, incorporated herein by reference), IL-1 antagonists or inhibitors (such as those described in US Patent Nos. 5,981,713, 6,096,728, and 5,075,222, all of which are incorporated herein by reference) IL-2 receptors, IL-4 receptors (as described in EP Patent No. 0 367 566 and US Patent No. 5,856,296, both of which are incorporated by reference), IL-15 receptors, IL-17 receptors, IL-18 receptors, Fc receptors,

granulocyte-macrophage colony stimulating factor receptor, granulocyte colony stimulating factor receptor, receptors for oncostatin-M and leukemia inhibitory factor, receptor activator of NF-kappa B (RANK, described in WO 01/36637 and US Patent No. 6,271,349, both of which are incorporated by reference), osteoprotegerin (described in e.g. US. Patent No. 6,015,938, incorporated by reference), receptors for TRAIL (including TRAIL receptors 1, 2, 3, and 4), and receptors that comprise death domains, such as Fas or Apoptosis-Inducing Receptor (AIR).

[0053] Still further exemplary proteins may include proteins comprising all or part of the amino acid sequences of differentiation antigens (referred to as CD proteins) or their ligands or proteins substantially similar to either of these. Such antigens are disclosed in Leukocyte Typing VI (Proceedings of the VIth International Workshop and Conference, Kishimoto, Kikutani et al., eds., Kobe, Japan, 1996, which is incorporated by reference). Similar CD proteins are disclosed in subsequent workshops. Examples of such antigens include CD22, CD27, CD30, CD39, CD40, and ligands thereto (CD27 ligand, CD30 ligand, etc.). Several of the CD antigens are members of the TNF receptor family, which also includes 41BB and OX40. The ligands are often members of the TNF family, as are 41BB ligand and OX40 ligand.

[0054] In addition, enzymatically active proteins or their ligands may be included as part of the product 100. Examples include proteins with all or part of one of the following proteins or their ligands or a protein substantially similar to one of these: metalloproteinase-disintegrin family members, various kinases, glucocerebrosidase, superoxide dismutase, tissue plasminogen activator, Factor VIII, Factor IX, apolipoprotein E, apolipoprotein A-I, globins, an IL-2 antagonist, alpha-1 antitrypsin, TNF-alpha Converting Enzyme, ligands for any of the above-mentioned enzymes, and numerous other enzymes and their ligands.

[0055] Still further, the product 100 may include antibodies or portions thereof. The term "antibody" includes reference to both glycosylated and non-glycosylated immunoglobulins of any isotype or subclass or to an antigen-binding region thereof that competes with the intact antibody for specific binding, unless otherwise specified, including human, humanized, chimeric, multi-specific, monoclonal, polyclonal, and oligomers or antigen binding fragments thereof. Antibodies can be any class of immunoglobulin. Also included are proteins having an antigen binding fragment or region such as Fab, Fab', F(ab')₂, Fv, diabodies, Fd, dAb, maxibodies, single chain

antibody molecules, complementarity determining region (CDR) fragments, scFv, diabodies, triabodies, tetrabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to a target polypeptide. The term “antibody” is inclusive of, but not limited to, those that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from a host cell transfected to express the antibody.

[0056] Thus, the antibodies may include human antibodies, or portions thereof, as well as chimeric or humanized antibodies. Chimeric antibodies include human constant antibody immunoglobulin domains coupled to one or more murine variable antibody immunoglobulin domain, fragments thereof, or substantially similar proteins. Humanized antibodies include variable regions comprising framework portions of human origin and CDR portion from a non-human source. The 100 product may also include conjugates of an antibody and a cytotoxic or luminescent substance. Such substances include: maytansine derivatives (such as DM1); enterotoxins (such as a Staphylococcal enterotoxin); iodine isotopes (such as iodine-125); technium isotopes (such as Tc-99m); cyanine fluorochromes (such as Cy5.5.18); and ribosome-inactivating proteins (such as bouganin, gelonin, or saporin-S6). The product 100 may further include chimeric proteins selected *in vitro* to bind to a specific target protein and modify its activity such as those described in International Applications WO 01/83525 and WO 00/24782, both of which are incorporated by reference.

[0057] Other examples of antibodies, *in vitro*-selected chimeric proteins, or antibody/cytotoxin or antibody/luminophore conjugates may include those that recognize any one or a combination of proteins including, but not limited to, the above-mentioned proteins and/or the following antigens: CD2, CD3, CD4, CD8, CD11a, CD14, CD18, CD20, CD22, CD23, CD25, CD33, CD40, CD44, CD52, CD80 (B7.1), CD86 (B7.2), CD147, IL-1 α , IL-1 β , IL-2, IL-3, IL-7, IL-4, IL-5, IL-8, IL-10, IL-2 receptor, IL-4 receptor, IL-6 receptor, IL-13 receptor, IL-18 receptor subunits, FGL2, PDGF- β and analogs thereof (such as those described in US Patent Nos. 5,272,064 and 5,149,792), VEGF, TGF, TGF- β 2, TGF- β 1, EGF receptor (including those described in US Patent No. 6,235,883 B1, incorporated by reference) VEGF receptor, hepatocyte growth factor, osteoprotegerin ligand, interferon gamma, B lymphocyte stimulator (BlyS, also known as BAFF, THANK, TALL-1, and

zTNF4; see Do and Chen-Kiang (2002), Cytokine Growth Factor Rev. 13(1): 19-25), C5 complement, IgE, tumor antigen CA125, tumor antigen MUC1, PEM antigen, LCG (which is a gene product that is expressed in association with lung cancer), HER-2, a tumor-associated glycoprotein TAG-72, the SK-1 antigen, tumor-associated epitopes that are present in elevated levels in the sera of patients with colon and/or pancreatic cancer, cancer-associated epitopes or proteins expressed on breast, colon, squamous cell, prostate, pancreatic, lung, and/or kidney cancer cells and/or on melanoma, glioma, or neuroblastoma cells, the necrotic core of a tumor, integrin alpha 4 beta 7, the integrin VLA-4, B2 integrins, TRAIL receptors 1, 2, 3, and 4, RANK, RANK ligand, TNF- α , the adhesion molecule VAP-1, epithelial cell adhesion molecule (EpCAM), intercellular adhesion molecule 3 (ICAM-3), leukointegrin adhesin, the platelet glycoprotein gp IIb/IIIa, cardiac myosin heavy chain, parathyroid hormone, rNAPc2 (which is an inhibitor of factor VIIa-tissue factor), MHC I, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), tumor necrosis factor (TNF), CTLA-4 (which is a cytotoxic T lymphocyte-associated antigen), Fc- γ -1 receptor, HLA-DR 10 beta, HLA-DR antigen, L-selectin, Respiratory Syncytial Virus, human immunodeficiency virus (HIV), hepatitis B virus (HBV), Streptococcus mutans, and Staphylococcus aureus.

[0058] Specific examples of known antibodies include, but are not limited to, adalimumab, bevacizumab, infliximab, abciximab, alemtuzumab, bapineuzumab, basiliximab, belimumab, briakinumab, canakinumab, certolizumab pegol, cetuximab, conatumumab, denosumab, eculizumab, gemtuzumab ozogamicin, golimumab, ibritumomab tiuxetan, labetuzumab, mapatumumab, matuzumab, mepolizumab, mogamulizumab, motavizumab, muromonab-CD3, natalizumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, pemtumomab, pertuzumab, ranibizumab, rituximab, rovelizumab, tocilizumab, tositumomab, trastuzumab, ustekinumab, zalutumumab, and zanolimumab.

[0059] The product 100 may include an anti-idiotypic antibody or a substantially similar protein, including anti-idiotypic antibodies against: an antibody targeted to the tumor antigen gp72; an antibody against the ganglioside GD3; an antibody against the ganglioside GD2; or antibodies substantially similar to these.

[0060] The product 100 may include recombinant fusion proteins including any of the above-mentioned proteins. For example, recombinant fusion proteins including

one of the above-mentioned proteins plus a multimerization domain, such as a leucine zipper, a coiled coil, an Fc portion of an antibody, or a substantially similar protein, can be produced using the methods of the invention. See e.g. WO94/10308; Lovejoy et al. (1993), Science 259:1288-1293; Harbury et al. (1993), Science 262:1401-05; Harbury et al. (1994), Nature 371:80-83; Håkansson et al.(1999), Structure 7:255-64, all of which are incorporated by reference. Specifically included among such recombinant fusion proteins are proteins in which a portion of TNFR or RANK is fused to an Fc portion of an antibody etanercept (a p75 TNFR:Fc), and belatacept (CTLA4:Fc). TNFR:Fc comprises the Fc portion of an antibody fused to an extracellular domain of TNFR, which includes amino acid sequences substantially similar to amino acids 1-163, 1-185, or 1-235 of Figure 2A of US Patent No. 5,395,760, which is incorporated by reference. RANK:Fc is described in International Application WO 01/36637, which is incorporated by reference.

[0061] In addition, the pharmaceutical product 100 illustrated in Fig. 1 includes a layer 140 of photosensitive material disposed on the exterior surface 112 of the container 110. The photosensitive material may be reactive to light having a wavelength within the range between X and Y so as to experience a property change. According to certain embodiments, the color of the material may change, from yellow to green for example. A non-limiting example of a photosensitive material that may be used in the layer 140 is available from UV Process Supply, Inc. of Chicago, Illinois under the UV FastCheck™ brand.

[0062] Along these lines, Fig. 3 illustrates a graph prepared relative to a photosensitive material that experiences a change in color (as exhibited by a change a colorimeter reading) with increasing UV exposure, the UV exposure occurring with a peak wavelength of about 350 to 370 nm and over a range of wavelengths about 315 to 400 nm (UVA). Similarly, Fig. 4 illustrates a graph prepared relative to a photosensitive material that experiences a change in color (as exhibited by a change in a colorimeter reading) with increasing visible light exposure, the visible light exposure occurring with a range of wavelengths from 401 to 750 nm. These measurements were and similar measurements may be determined using a colorimeter, such as the HunterLab UltraScan PRO colorimeter available from Hunter Associates Laboratory Inc. of Reston, Virginia, while a color reflection

spectrodensitometer, such as the X-rite Model 530 available from X-rite Inc. of Grand Rapids, Michigan, may be used according to other embodiments.

[0063] It will be recognized that the threshold of cumulative exposure to light received within the range between X and Y related to the property (e.g., color) change of the material in photosensitive layer 140 may be related to the change in the photosensitive property of the polypeptide or other material or substance disposed in the container 110. For example, the change in the photosensitive property of the polypeptide may be measured quantitatively using separation techniques such as chromatography, for example. In particular, size-exclusion (SEC), cation-exchange (CEX) and hydrophobic-interaction (HIC) chromatography may be used to correlate light exposure to product degradations. Fig. 5 shows the relationship between readings generated using HIC with an exemplary polypeptide exposed to visible light, with increasing HIC readings reflecting an increase in inactive species of the polypeptide with increased light exposure. Given these results and the known performance of the material in the photosensitive layer 140, illustrated for example in Fig. 4, a correlation may be defined between the colorimeter readings and the HIC readings over a range of light exposures such that a particular colorimeter reading may be associated with a particular degree of inactivation or degradation of the polypeptide represented.

[0064] In further support of these correlations, the graphs of Figs. 6-14 directly illustrate the relationship between (i) various measures of the degradation of monoclonal antibody polypeptides (as an example of a polypeptide), of quinine monohydrochloride dihydrate (as an example of a small molecule), or of tryptophan (as an example of an amino acid) with increasing visible light or UV light exposure and (ii) colorimeter readings of the color change of an associated layer of photosensitive material. Without attempting to limit the discussion of the degradation reflected in the results of this testing to a particular mechanism, it is noted that degradation may be both chemical and physical, and may be, for example, in the form of photo-induced oxidation, covalent aggregation, and/or deamidation of Asn residues. In particular, Figs. 6-9, 12 and 13 relate to experiments performed with a monoclonal antibody, while Figs. 10 and 11 relate to experiments performed with quinine monohydrochloride dihydrate (2% solution) and Fig. 14 relates to experiments performed with tryptophan (1 mM aqueous solution). Moreover, Figs. 6-

9 relate to experiments performed using visible light, while Figs. 10-14 relate to experiments performed using UV light. These experiments were conducted with light having a range of wavelengths between 190 to 1100 nm, with the UV exposure occurring with a peak wavelength of about 350 to 370 nm and principally over a range of wavelengths from about 315 to 400 nm (UVA) and the visible light exposure occurring principally over a range of wavelengths from about 401 to 750 nm.

[0065] In regard to these experiments, all were performed at room temperature (25°C) and 40% relative humidity. A 3 cc glass vial was filled with a sample of monoclonal antibody (“mAb”), quinine monohydrochloride dihydrate (“quinine”), or tryptophan and the vial was capped. A layer of photosensitive material was then applied to the outside wall of an empty 3 cc glass vial. Three different sensitivities of photosensitive material were used in these experiments, as reflected in the graphs of Figs. 6-14, with the material associated with “sen1” having the lowest light sensitivity and the material associated with “sen3” having the highest light sensitivity, the materials being commonly available from UV Process Supply Inc. of Chicago, Illinois as CON-TROL-CURE® UV Fastcheck™ Strips, part # N010-002. The three sensitivities (“sen1”, “sen2”, and “sen3”) are the same as the three similarly named sensitivities (“sen1”, “sen2” and “sen3”) found in Fig. 27, discussed below. The filled vial and the empty vial were exposed to the same light source (a cool white light with a 10 klux intensity setting or a UV light with a 30 W/m² intensity setting).

[0066] In all experiments, the color of the layer of photosensitive material was measured using an X-Rite spectodensitometer (manufactured by X-Rite of Grand Rapids, Michigan), which device is exemplary of the types of color-measuring equipment that may be used in such an experimental set-up. The various measurements related to the degradation of the monoclonal antibody or quinine sample were generated using appropriate techniques. For example, Size Exclusion-HPLC was used to determine the measurements relating to % increase in high molecular weight or low molecular weight species (Figs. 6, 12, 13), while Cation Exchange-HPLC was used to determine the measurements relating to changes in basic and acidic peak (Figs. 8, 9). In this regard, a high molecular weight species is typically in the form of aggregates that may lead to immunogenic reactions or adverse events upon administration, while a low molecular weight species is typically in the form of degradants. A Ultrascan® PRO spectrophotometer (manufactured by Hunter

Associates Labs., Inc. of Reston, Virginia) was used to determine the measurements relating to the yellow index (Figs. 7, 11, 14). It will be recognized that reference to the yellow index refers to a single value calculated from spectrophotometric data to describe the change in color of a test sample from clear or white toward yellow, which value is commonly associated with general product degradation and is chiefly used to quantify this degradation, with the calculation being described, for example, in the application note on Yellowness Indices provided by Hunter Associates Laboratory Inc. of Reston, Virginia, vol. 8, no. 15 (2008), which application note is incorporated by reference herein in its entirety. A Beckman Coulter spectrophotometer was used to measure the light absorbance at 400 nm (Fig. 10).

[0067] In each of the graphs of Figs. 6-14, it will be recognized that the color change in the photosensitive material increases with increasing light exposure. Similarly, the measure of the degradation of the sample also increases with increasing light exposure. That is an increase in high or low molecular weight species is reflective of degradation of the mAb polypeptide (Figs. 6, 12, 13), as would be an increase in the acidic or basic peak produced using Cation Exchange-HPLC (Figs. 8, 9) representing a change in the charged species. In a similar fashion, an increase in the yellow index (Figs. 7, 11) is reflective of degradation of the mAb polypeptide, the small molecule (e.g., quinine), or the amino acid (e.g., tryptophan). Further, a change in the absorbance of the quinine is reflective of a change in the small molecule. In each case, while the color change between the photosensitive material and the measure of the degradation of the sample may not be the same for all characteristics examined, it is true that there is a direct relationship between the change in color of the photosensitive material and the measure of the degradation of the active ingredient, such that the photosensitive material may be used as a real-time indicator for changes occurring to an active ingredient in a container.

[0068] The use of a correlation between the degradation of the material (e.g., polypeptide) disposed within the interior chamber 114 and the property (e.g., color) change of the photosensitive layer 140 as a real-time indication and indicator of the changes and/or degradation of the material within the interior chamber 114 provides a number of opportunities for optimization of the product 100 through selection of the photosensitive material for the layer 140. A number of factors may also need to be accounted for in providing a stable and reliable indication and indicator. Certain

examples of opportunities for optimization and factors to be accounted for are provided herein; the list is not intended to be exhaustive.

[0069] For example, where the material (e.g., polypeptide) within the interior chamber 114 undergoes degradation in reaction to light of a particular wavelength or range of wavelengths, the photosensitive material may be selected to be responsive only to light of that wavelength or to range of wavelengths. In fact, the sensitivity of the material to the wavelength of interest may be selected so as to match or relate a more sensitive (reactive) material for the photosensitive layer 140 with a more sensitive (reactive) material (e.g., a more sensitive polypeptide) disposed within the container 110 relative to the wavelength under consideration.

[0070] Alternatively, the material (e.g., polypeptide) within the interior chamber 114 may experience degradation as a consequence of a number of reactions, each of which is attributable to light of a different wavelength. It may be the case that all of these factors contribute to the reduced efficacy of the material for treatment of a particular medical condition, and no one factor predominates. Based on this analysis, a photosensitive material reactive to a wide range of wavelengths may be used for the layer 140.

[0071] It is also possible that while the material or substance (e.g., polypeptide) in the interior chamber 114 may exhibit degradation when exposed to a light over a particular range of wavelengths, it may be possible that the environment will selectively eliminate or provide only certain wavelengths within that range. As a consequence, rather than selecting a material based on the entire range of wavelengths known to cause degradation of the material disposed within the interior chamber 114, the photosensitive material may be selected according to the wavelengths known to exist within a given environment. As a consequence, the photosensitive material selected for a layer 140 applied to a container 110 that will predominantly be used within a manufacturing facility, such as a carboy, may differ from the photosensitive material selected for a layer 140 applied to a container 110 that will be carried by paramedics or the like for use in the field.

[0072] On the other hand, factors such as temperature may affect the performance of the photosensitive material, and thus the stability or robustness of the correlation derived between the property change of the photosensitive material and the change of the material disposed in the container 110. Along such lines, Fig. 15

illustrates the change in colorimeter readings for a photosensitive material that may be used in the layer 140 over a range of light exposures and a plurality of temperatures. It may be observed from Fig. 15 that the change in colorimeter reading may vary less dramatically at lower temperatures (e.g. 4°C) than at higher temperatures (37°C). Consequently, not only may a material be selected for the layer 140 according to the reactivity of the material (e.g., polypeptide) in the container 110, the material for the layer 140 may also be selected according to the performance characteristics of the photosensitive material over the operational range of temperatures expected. In the alternative, the knowledge of variations in colorimeter readings based on temperature may be used to create corrections for correlations between the changes in the material of the layer 140 and the changes in the material in the container 110 that are temperature dependent, which further corrections may enhance the stability and reliability of the correlations.

[0073] While it is believed that temperature may affect the rate of color change, Figs. 28 and 29 illustrate that little reversibility is believed to exist in the color change of photosensitive material that has been exposed and then subsequently stored in a space without further light exposure (i.e., in the dark) over a wide range of temperatures (e.g., 4°C (Fig. 28) or 25°C (Fig. 29)). That is, there is little difference in the color measurements for a control sample and a sample stored at the specified temperature in the dark for a prolonged period of time (e.g., approximately 48 hours)). The samples were controlled for humidity, and the measurements were made using an X-Rite spectrodensitometer, which device is exemplary of the types of color-measuring equipment that may be used in such an experimental set-up.

[0074] The size and placement of the layer 140 may also be selected to improve the stability of the readings. This in turn may affect the reliability of the derived correlation, as well as reliability of an assessment of the condition of the material (e.g., polypeptide) in the chamber 114 made in reliance on the correlation. In particular, readings obtained from a layer 140 that is planar or appears substantially planar relative to the measuring device or equipment used to take the color reading of the layer 140 may be more consistent than readings obtained from a layer 140 with a curved profile. As a consequence, when dealing with a generally cylindrical object (such as a vial or a carboy) having a particular length and diameter, wider layers 140 are believed to appear to have a more curved profile relative to measurement

equipment, resulting in greater variation in readings that narrower layers 140. As a consequence, this potential source of variation may be addressed by more extensive mapping of the potential curvature of the layer 140 as applied to the container 110, or by selecting the size and/or dimensions of the layer 140 to minimize the effects of the curvature of the layer 140 on the variation in the readings obtained (i.e., make the layer 140 appear more planar relative to the equipment used to take the reading).

[0075] As a consequence of these various considerations and factors, while an exemplary embodiment has been illustrated in Fig. 1 in which a single layer 140 of material is disposed on the exterior surface 112 of the container 110, more than one layer of material may be disposed on the exterior surface 112 of the container 110, or may be associated with the container 110, as explained in greater detail below. According to such an embodiment, each layer may be useful in determining exposure to a different wavelength of light, may have different sensitivity to temperature, or may be of different sizes and shapes. Of course, the presence of multiple layers 140 on a single container 110 may lead to user confusion in certain circumstances, so the layers 140 may be disposed on portions of the exterior surface 112 of the container 110 remote from each other, or in such a manner that at least one of the layers 140 may be removed from the exterior surface 112, for example, once the photosensitive material in the layer no longer is capable of undergoing a property change, e.g., a colorimetrically detectable property change.

[0076] As mentioned above, the layer 140 may be exposed to environmental conditions contemporaneous with the polypeptide being disposed in the interior chamber 114. That is, the layer 140 may be disposed on the exterior surface 112 of the container 110 and exposed to the same conditions the material (e.g., polypeptide) is exposed to at the same time the material is disposed into the interior chamber 114 of the container 110, or within some time period before or after the material is disposed into the chamber 114. The length of the time period considered to be contemporaneous may be determined by the sensitivity of the material in the chamber 114 and/or the sensitivity of the material used to define the layer 140, for example.

[0077] As was mentioned above and will be explained in greater detail below, the layer 140 may be exposed to environmental conditions at some point in time that is not considered contemporaneous with the material (e.g., polypeptide) being disposed in the interior chamber 114. Where the reaction of material disposed within the

container 110 happens rapidly, even the passage of a limited period of time may be considered to be non-contemporaneous. However, in more general terms, this may encompass a situation wherein the layer 140 is purposefully shielded from exposure to the same conditions as the material disposed in the chamber 114, for example through the use of a physical barrier or photoresistive material.

[0078] Returning again to the embodiment of Fig. 1, it will be recognized that the layer 140 is disposed on the exterior surface 112 through the use of a label 160. The label 160 may include a substrate 162 having a first surface 164 and a second surface 166, which surfaces 164, 166 are disposed on opposite sides of the substrate 162. The size of the substrate 162 relative to the size of the layer 140 has been purposely exaggerated in Fig. 1 so that the substrate 162 may be more easily visualized and identified. According to a preferred embodiment, the layer 140 extends to the edges of the substrate 162; however, it is possible for the edges of the layer 140 to be spaced from the edges of the substrate 162 as shown. Also, a corner of the substrate 162 is turned back in Fig. 1 to expose the surface 166, although this corner would typically lie along the surface 112 as assembled.

[0079] The substrate 162 may be a paper product, but also may be made of plastic or other polymer, for example. On one surface (surface 166, as illustrated) may be disposed an adhesive or other compound that may be used to affix, adhere or attach the label 160 to the surface 112. Of course, for that matter, the substrate 162 may be attached to the exterior surface 112 by applying a material over the surface 164 of the label, which material would be selected to be sufficiently transparent such that the layer 140 may be visualized or scanned and such that the operation of the layer 140 (i.e., the photosensitivity of the layer 140) would not be affected. For example, a clear, single-side tape product may be used to attach the substrate 162 (and thus the label 160) to the surface 112. The application of additional layer may not only attach the substrate 162 to the surface 112, but may protect the layer from environmental conditions (e.g., humidity) as well; consequently, the additional layer may be present even when not used to attach the substrate 162 to the surface. The use of an adhesive-backed label 160 may also facilitate the assembly of the product 100 including the label 160 during manufacturing.

[0080] As one alternative, Fig. 16 illustrates an embodiment wherein the layer 140 of photosensitive material is applied directly to the exterior surface 112 of the

container 110. According to such an embodiment, the surface 112 may need to be prepared prior to application of the layer 140 to the surface 112. The preparation of the surface 112 may require the application of other chemicals to the surface 112 to permit a satisfactory joining or bonding to occur between the material of the layer 140 and the material of the container 110. It will be recognized that while such chemicals may technically present an intermediate layer between the layer 140 and the surface 112 of the container 110, the layer 140 may still be understood as being applied to the surface 112 of the container 110 for the purposes of this disclosure.

[0081] The label 160 may also include other elements beyond the layer 140. For example, the label 160 may include indicia to identify the material (e.g., polypeptide) disposed within the chamber 114, such as the name of the material, the name of the manufacturer, instructions relating to use of the material, etc. As a further example, the label 160 may include indicia relevant to the layer 140, such as a color scale, so that a user would know without further reference to additional materials how to interpret the layer 140 so as to know if the material (e.g., polypeptide) within the chamber 114 should be safe to administer or not. This color scale may be based on the correlations between the changes in the material of the layer 140 and in the material in the chamber 114 discussed above.

[0082] The label 160 may also include other structures that cooperate with the layer 140. For example, as alluded to previously, the layer 140 may be shielded or concealed from exposure to light. Consequently, Fig. 17 illustrates a label 160 including the substrate 162 on which the layer 140 is disposed, and a further layer 180 of removable photo-resistive material applied over the layer 140 of photosensitive material. According to certain embodiments, the photo-resistive material of the layer 180 may block all light exposure; according to other embodiments, the photo-resistive material of the layer 180 may block only a portion of the light exposure. In the particular embodiment illustrated, the layer 180 of removable photo-resistive material comprises a cover removably attached to the exterior surface 112 of the container 110 over the layer 140 of photosensitive material to block light of all wavelengths, and may be made of coated paper, coated plastic, or metallic (e.g., aluminum) foil having a releasable adhesive applied to at least a portion of the surface 182 facing the layer 140. This cover 180 may be removed as required. While the cover 180 may be removably attached directly to the exterior surface 112 of the container 110 according

to certain embodiments, according to the embodiment illustrated in Fig. 17, the cover 180 is removably attached to the substrate 162, which is in turn disposed on the surface 112 of the container 110.

[0083] A further example of an alternative structure for a label 160 is illustrated in Fig. 18. According to this embodiment, the label 160 has a first region 190 disposed on the exterior surface 112 of the container 110 with a layer 191 of photosensitive material applied thereto and a second region 192 removably disposed on the exterior surface 112 of the container 110 with a layer 193 of the photosensitive material applied thereto. The first region 190 and the second region 192 of the label may be integrally attached (i.e., formed as a single piece), but the boundary between the first and second regions 190, 192 may be defined by a perforation 194, which may facilitate the separation of the first and second regions 190, 192. According to other embodiments, the boundary between the first and second regions 190, 192 may simply be defined by a marking on the label 160.

[0084] According to the illustrated embodiment, the first and second regions 190, 192 may be exposed to environmental conditions contemporaneous with the material (e.g., polypeptide) being disposed in the interior chamber 114. As such, the layer 191 and the layer 193 should experience roughly the same exposure to light as the material in the chamber 114. Therefore, the regions 190, 192 and the respective layers 191, 193 may be referred to in much the same manner to determine the overall exposure history of the material in the chamber 114.

[0085] As to how a label 160 such as the one illustrated in Fig. 18 may be used, consider that while the container 110 may be used for storage of the material, it is likely that the material will be removed from the container 110 and disposed in a delivery device before the material is administered to the patient. For example, where the container 110 is a single-dose vial, for example, the material disposed in the container 110 may be removed from the container using a syringe 200 with a needle (see Fig. 19) or a syringe with a luer tip and a vial adapter. In either case, it may be some time before the material in syringe is administered to the patient. Because the exposure to light will continue throughout this time, it may be advantageous to continue the monitoring of the light exposure by removing the second region 190 of the label 160, and attaching the second region 192 to the syringe 200, such that the layer 193 may be observed. As a consequence, the monitoring of the light exposure

of the material in the syringe 200 may continue even after the material is removed from the container 110 using such a system.

[0086] It will be further recognized that it is possible to incorporate features from the label illustrated in Figs. 18 and 19 with those of the label illustrated in Fig. 17. For example, a further embodiment of a label 160 is illustrated in Fig. 20. According to this embodiment, the label 160 includes a substrate 162 having a first portion 190 and a second portion 192, each with its respective layer 191, 193 of photosensitive material. However, a cover 210 in Fig. 21 is disposed over the layer 193 arranged on the second portion 192 of the substrate 162. This cover 210 may be similar in nature to the cover 182 discussed above in that the cover 210 may be defined by a layer of photo-resistive material removably attached to the exterior surface 112 of the container 110 over the layer 193 of photosensitive material. As illustrated, the cover 210 may be removably attached to the portion of the substrate 162 that defines the second portion 192 of the label, such that the second section 192 and the cover 210 may be removed as a single item from the container 110.

[0087] The label illustrated in Fig. 20 may be used in a fashion similar to that of the label illustrated in Figs. 18 and 19. That is, when the material in the chamber 114 of the container 110 is transferred to a syringe 220 (see Fig. 21), the second section 192 and the cover 210 may be removed from the container 110 and applied to the syringe 220. The cover 210 may then be removed from the second section 192 of the label 160 to expose the layer 193 of photosensitive material beneath the cover 210. The monitoring of the light exposure of the material in the syringe 220 may thus continue with the layer 193. It will be recognized that a similar effect may be achieved if the cover 210 is first removed from the second section 192 of the label 160 (and thus the layer 193) prior to application of the second section 192 to the syringe 220.

[0088] A label such as that illustrated in Figs. 20 and 21 may be advantageous, for example, when the material used to make the container 110 has a filtering or a blocking effect on the light to which the container 110 is exposed, but that same material is not used in the manufacture of the syringe 220. According to such an embodiment, it may be appropriate to use a layer 191 of photosensitive material that has been selected to more closely correlate the light exposure of the material (e.g. polypeptide) when disposed in the container 110, and to use a layer 193 of

photosensitive material that has been selected to more closely correlate the light exposure of the material (e.g., polypeptide) when disposed in the syringe 210. To prevent the layer 193 from providing an inaccurate representation of the light exposure of the material in the syringe 220, the cover 210 is removed contemporaneously with the transfer of the material from the container 110 to the syringe 220, rather than when the polypeptide or other substance is disposed into the chamber 114.

[0089] It is also possible to design a label or labeling system that incorporates the layer of photosensitive material in combination with a layer of material reactive to other environmental conditions, such as temperature or humidity. For example, Figs. 22 and 23 illustrate a container 250 in which a polypeptide, for example, is disposed. The container 250 is used in conjunction with a label or labeling system that permits monitoring of light exposure and temperature, for example. Such a device may be useful where the polypeptide has a photosensitive property that changes based on exposure to light having a wavelength within the range between X and Y, and also has a temperature-sensitive property. Alternatively, the temperature-sensitive layer may be used to signal the user to use a different correlation for the photosensitive layer 252 where the photosensitive material of the photosensitive layer 252 is temperature-sensitive (see Fig. 15, above).

[0090] To address the photosensitivity, or potential photosensitivity, of the material (e.g., polypeptide) in the container 250, a layer 252 of photosensitive material may be disposed on an exterior surface 254 of the container 250 and exposed to environmental conditions contemporaneous with the polypeptide being disposed in the interior chamber, for example. The photosensitive material may be reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the polypeptide. It will be recognized that any of the variations in regard to the layer of photosensitive material illustrated and/or discussed above may be used in conjunction with the layer 252.

[0091] In addition, a label 256 including a layer 258 of temperature sensitive material may be disposed on the exterior surface 254 of the container 250. The layer 258 may experience a property change (e.g., a colorimetrically detectable property

change) at a threshold of temperature exposure related to a change in a temperature-sensitive property of the material in the container 250, i.e., the polypeptide according to the present embodiment. This layer 258 may be disposed on or against a background 260 of varying colors to facilitate detection or visualization of the change of the layer 258 (compare Fig. 22 to Fig. 23, for example). In fact, a similar mechanism may be used in combination with the layer of photosensitive material, in this or the other embodiments described herein, to facilitate detection or visualization of the property change of the photosensitive material wherein this property change is a color change.

[0092] Having thus described numerous embodiments of a product according to the present disclosure with reference to Figs. 1-23, a number of uses may now be described for these embodiments.

[0093] Initially, it will be recognized that one use that may be made of the product according to the present disclosure is to determine the status of a material disposed in the chamber 114 in real time. This determination may be made, for example, once a correlation has been defined between the property change of the material in the layer 140 and the photosensitivity of the material in the chamber 114. Once known, the correlation may be used to define a scale (e.g., a color scale) that will permit inspection of the layer 140 to be used to determine that status of the material disposed in the chamber 114. The correlation may be determined, for example, by disposing material in the chamber 114 contemporaneous with disposing a label 160 on the exterior surface 112 of the container 110, monitoring both the property change of the material in the layer 140 and the photosensitive property of the material in the chamber 114, for example, at a series of time increments over a test period, and collecting the data. The data collected for the material in the layer 140 and for the material in the chamber 114 may be compared, and a correlation or relationship may be defined. Based on the defined relationship, a scale may be determined to permit a level of light exposure for the material in the chamber 114 to be identified with changes in the property of the material in the layer 140 for real-time assessment of the status of the substance in the chamber 114.

[0094] The monitoring and/or determination of the change in the property of the photosensitive material in the layer 140 will vary according to the material used. For example, if the photosensitive material in the layer 140 experiences a color change,

then the change in the property may be determined visually by the user or by an optical colorimetric sensing device, such described above. The optical sensing device may be coupled to a computerized system, which system may be programmed with the correlation or relationship between the property change and the status of the material (e.g., polypeptide) in the chamber 114, and which system may be further programmed to remove a container from inventory if the determination of status suggests that the material is no longer safe and/or effective to administer.

[0095] The pharmaceutical product thus described may also be used in a method of confirming correct handling of photosensitive material (e.g., polypeptide) in the container. According to such a method, the layer 140 of photosensitive material would be applied to the exterior surface 112 of the container 110 having the polypeptide or other material disposed therein, the polypeptide or other material having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y and the photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change (e.g., a colorimetrically detectable property change) at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the polypeptide. The container 110 would then be delivered to and collected from a recipient within the manufacturing or distribution chain of the pharmaceutical product, for example, but not limited to, a warehouse, a packaging or filling plant, a distributor, a testing lab, a pharmacy, a dispensary, a clinic, a hospital or other healthcare facility, a healthcare provider, or a patient. The layer of photosensitive material may be examined to determine if the photosensitive material has experienced the property change, and the container may be identified as mishandled if the photosensitive material has experienced the property change.

[0096] For example, the product 100 may be packaged within a box or wrapper that is intended to be removed only when the material in the container 110 is to be administered to the patient. In such a setting, the box or packaging may be used to limit the light exposure of the material in the container 110. If, however, the layer 140 has undergone a colorimetrically detectable property change, this may be suggestive of the fact that the product 100 has been prematurely taken out of the protective packaging in contravention of the express instructions.

[0097] While all of the embodiments illustrated in Figs. 1-23 relate to products where in the photosensitive layer is disposed on the exterior surface of the container, it is also possible to dispose the photosensitive layer within the interior chamber of the container, as mentioned in the introductory paragraphs. According to the embodiment illustrated in Fig. 24, a pharmaceutical product 300 is illustrated, the product 300 including a container 310 having an interior chamber 314, the container 310 constructed from a material that is photo-resistive. As noted above, the material may filter or block light of one or more ranges of wavelengths. As such, the exposure of a material disposed in the chamber 314 of the container 310 may be different than if the material was exposed to environmental conditions.

[0098] The product may also include a layer 340 of photosensitive material disposed in the interior chamber 314 of the container 310. As illustrated, the layer 340 may be disposed on monitoring card 360 including a substrate 362 having a first side 364 and a second side 366. According to other embodiments, the material may be applied to both sides 364, 366 of the substrate 362. As illustrated, the substrate 362 may be made of a rigid material, such as a rigid cardstock or plastic, which will permit the substrate 362 to remain upright within the chamber 314 when the container 310 is placed on a surface, thereby facilitating the readability of the layer 340. According to other embodiments, the surface 366 may have an adhesive applied thereto, and the card 360 may be attached at a particular location within the chamber 314.

[0099] As was the case with the layer 140, the material of the layer 340 may be a photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in a photosensitive property of a polypeptide. While the polypeptide or other material may be disposed in the chamber 314 with the card 360, it may also be the case that the card 360 is disposed within the chamber 314 without the material also being present in the chamber 314.

[00100] For example, consider the situation where the photo-resistivity of the material used for the container 310 is unknown or not well known, or at least where the photo-resistivity of the material used for the container 310 is unknown or not well known relative to the photo-sensitivity of the material that will be disposed within the

chamber 314 of the container 310. In such a setting, the card 360 may be disposed in the chamber 314 of the container 310, and then the container 310 may be exposed to a light source of interest. The card 360, and in particular the layer 340, may be monitored for changes as to the property change (e.g., a colorimetrically detectable property change) while exposed to the light. The correspondence of the property change of the layer 340 may be collected, for example, at a series of time increments over a test period.

[00101] The collected data may be used for a variety of uses. For example, data collected may be compared with data collected with the instance of the card 360 disposed in another container 310 made of another material for which the photo-resistivity is known (perhaps, at least relative to the photo-sensitivity of the material that will be disposed in the chamber 314 is known). Based on the comparison, a determination may be made either to use the material for the container 310 or not to use the material for the container 310.

[00102] Fig. 25 illustrates an example where a system similar to that illustrated in Fig. 24 was used to measure light exposure (as reflected in colorimeter readings) for a variety of materials: glass, polycarbonate, and Teflon. As illustrated, the lowest plot of data points corresponds to the card 360 disposed in a glass vial, while the upper two plots correspond to the cards disposed in containers of polycarbonate and Teflon. As a consequence, it appears that greater light exposure occurs in glass vials rather than in containers of polycarbonate or Teflon.

[00103] This conclusion is further supported by the graph of Fig. 30, wherein the UV intensity measurements from inside and outside of teflon, polycarbonate ("PC") and glass containers have been plotted. In this testing, a 3UV-38 3UV Lamp from UVP LLC of Upland, California was used, and the measurements inside and outside the container were taken using PMA 2110 UVA detectors from Solar Light Co. of Glenside, Pennsylvania. The inside and outside detectors were placed approximately 47 to 48 cm from the lamp, with the inside detector placed inside the container with the cap or lid on. The smallest difference between the values measured inside and outside the container occurred with regard to the glass container, suggesting that less light is absorbed by the glass walls than by the walls of other containers, such that greater light exposure occurs within the glass vials as opposed to those made of other materials.

[00104] As another example of a use of the product illustrated in Fig. 24, the material may be disposed in the chamber 314 at the same time as the card 360, and both the property change of the material in the layer 340 and the photosensitive property of the material in the chamber 314 may be monitored and collected, for example, at a series of time increments over a test period. The data collected for the material in the layer 340 and for the material in the chamber 314 may be compared, and a correlation or relationship may be defined. Based on the defined relationship, a scale may be determined to permit a level of light exposure for the material in the chamber 314 to be identified with changes in the property of the material in the layer 340.

[00105] Still another system and use for the present technology may be described according to the schematic of a facility, such as a manufacturing facility for example, according to Fig. 26, and may involve a system and method for analyzing light exposure of a pharmaceutical product passing through the facility. This system and use may be particularly helpful when and where it is not possible to limit the light exposure of the product passing through the facility because of regulatory directives, for example. For instance, European Council Directive 89/654/ECC (of Nov. 30, 1989) requires that workplaces must, as far as possible, receive sufficient natural light and be equipped with artificial lighting adequate for protections of workers' safety and health. As such, it may not be possible to limit light exposure to the product, and yet comply with the light requirements of the Council Directive relative to the workers' safety and health.

[00106] In particular, the manufacturing facility or plant 400 may include at least one space (according to the illustrated embodiment of Fig. 26, a plurality of spaces) through which a pharmaceutical product according to the present disclosure may pass. These spaces may be physically separated from each other through the presence of walls or other barriers; in other instances, the spaces may be demarked from an organizational standpoint, but there may no physical barrier demarking one space, area or region from the other. The product may include a label as according to any of the preceding embodiments. However, in addition to such a label affixed to the pharmaceutical product, additional photosensitive devices 402, or phototrackers, may be disposed about the plant 400 once a path P along which the product passes through the plant has been identified. The information regarding light exposure developed

through the use of the devices 402 may be used in conjunction with information from the labels associated with the product, or may be used separately instead.

[00107] As illustrated, the plant 400 includes a first space 410, wherein the pharmaceutical product is prepared. For example, a polypeptide that represents the active component in the product may be combined within the space 410 with a media in which the polypeptide will be stored and administered to a patient. The polypeptide may have a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y. The active component and the media may be disposed in a container such as that illustrated in Fig. 2 at this time. The active component and the media may then pass from the space 410 into space 412, wherein the active component and media is filled into a smaller containers, such as those illustrated in Fig. 1.

[00108] The filled containers may then pass into a transfer space 414 before moving to an inspection space 416 or a storage (or warehouse) space 418. As indicated by the arrows along the flow path, P, product may flow from the filling space 410 directly through the transfer space 414 to the inspection space 416, or may detour through the storage space 418. Additionally, before moving along the path P from the inspection space 416, the product may be returned to the warehouse space 418.

[00109] Once the containers have passed inspection within the inspection space 416, the product may be assembled with other items to define a system or a kit within assembly space 420. As illustrated, the product may arrive at assembly space 420 either from the inspection space 416 or the warehouse space 418. The product may be combined with a syringe, such as is illustrated in Figs. 19 or 21, to define a system or to be packaged as part of a kit, in an injection kit clam shell, for example. Alternatively, the product may be assembled as part of system in the form of a medical device, such as an autoinjector (as illustrated in Figs. 22 and 23), microinfuser, or the like. Once assembly is complete, the system or kit may pass through a loading dock 422, prior to removal from the plant 400.

[00110] It will be observed that devices 402 are disposed along the path P that the product takes through the spaces 410, 412, 414, 416, 418, 420, 422. The devices 402 may include a layer of photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change (e.g., a

colorimetrically detectable property change) at a threshold of cumulative exposure to light received within the range between X and Y. In many cases, such as in spaces 410, 412, 418, 420, 422, the devices 402 are disposed on either side of the path P. In certain spaces, such as spaces 414, 416, the devices 402 are disposed only on one side of the path P. The number of devices may differ between spaces, such that spaces 414, 416 have only a single device, while spaces 410, 412 have two devices, space 420 has three devices, space 422 has four devices, and space 418 has six devices. The devices 402 may be attached through the use of an adhesive backing, for example, to particular structures, equipment or machinery disposed within the spaces 410-422, such as mixing tanks or syringe/cartridge filling machines for example.

[00111] It will be recognized that the placement and number of devices used may be dictated by a number of factors. For example, in certain rooms, certain equipment or other environmental light sources (lamps, overhead lighting, windows, etc.) may be disposed primarily to one side of the path or the other. Additionally, it may be more desirable to place additional devices in a larger room, or a room in which the path has multiple entry and exit points, or a more complex path. For example, space 418 might qualify under all of these criteria for the inclusion of more devices 402 than in other spaces.

[00112] However, there is at least one significant advantage of using the phototrackers or photosensitive devices along the path P. Disposing the devices 402 along the path P permits identification and isolation of points along the path P at which light of a particular wavelength or intensity impacts the product. Through the use of the devices 402, this identification and isolation may be performed in real time. For example, the photosensitive devices 402 may be read for evidence of a property change using an optical sensing device proximate to the device 402, the optical sensing device coupled to a computing device that displays an indication of light exposure experienced by the at least one device 402. As a consequence, changes may be made to the equipment (e.g., using different mixing tanks, syringe fillers, etc.), environment surrounding the path P (e.g., erecting walls, screens, etc.), the product (e.g., changing the container used), or to the path P (e.g., modifying the path P between or within the various spaces 410, 412, 414, 416, 418, 420, 422) to minimize or eliminate light exposure at points along the path P.

[00113] That is, a label affixed to a product may be used to determine the cumulative exposure of the individual product, and as a consequence whether the product should be used or discarded. However, the label will not provide a history of where the product has received the exposure that has been recorded through the use of the label on the product. Even if a label attached to a product were to be inspected for cumulative light exposure at various points along the path P, using the light exposure information obtained in this fashion may still make identification and isolation of a localized spaces, areas or regions of increased light exposure or light exposure of particular wavelengths difficult. This is particular true given that certain spaces, such as space 420, may have product passing through it after having passed through any of a number of preceding spaces, because of the manner in which product may be transported between the transfer, inspection and warehouse spaces 414, 416, 418.

[00114] By contrast, through the use of the phototrackers or photosensitive devices 402 disposed along the path P, the light exposure of the product within the plant 400 may be analyzed separately from the product itself, and considered without having to account for the movement of the product along the path P. For example, readings obtained from the devices 402 disposed in the space 418 suggest that product moving along the path P are exposed to considerable amounts of light having a wavelength or wavelengths of interest relative to that product in the portion of the space where the product is stored between the inspection and assembly spaces 416, 420. Additional devices 402 may then be disposed in the space 418 to further identify the source of the light, or along alternative paths within the space 418 to determine the viability of these alternative paths for the product prior to modification of the path P within the space 418. If the labels were used only on the product, the identification of such sources or alternative paths may only occur through the exposure of additional amounts of light exposure that may result in the degradation of the product and the need for its disposal.

[00115] This is not to suggest that information from photosensitive labels might not play a role in conjunction with the photosensitive devices 402, but it is not necessary to attempt to back track the exact travel of a particular instance of the product along the path P. For instance, while the devices 402 may be used to identify the level of exposure of product to light along the path P, the spacing of the devices 402 may be such that it is not possible to capture every possible source of undesirable

light exposure. Alternatively, conditions along the path P may change relative to a previously adequate distribution of devices 402 that makes the previous distribution inadequate to identify and isolate undesirable sources of light exposure. To this end, the label associated with the product may be inspected, and the results of that inspection compared against the readings determined at various points along the path P to determine, for example, if the distribution needs to be altered relative to placement or number of devices 402 used.

[00116] It will also be recognized that many of the comments made above will be of general usefulness in selecting the material used in the devices 402, as well as the shape and placement of the devices 402. For example, while the devices 402 may provide a real time reading of the cumulative light exposure in a given portion of the plant, the devices 402 may not be monitored continuously. As a consequence, it may be desirable to select a less sensitive material for use in the devices 402, as it is intended that the device 402 be exposed to environmental lighting conditions for long periods of time between being monitored. Fig. 27 illustrates the range and nature of color change possible for five different sensitivities of a material that may be used in the devices 402 when exposed to varying amounts of visible light, the color change being measured according to the L^*a^*b index. It will also be recognized that the use of this system and method is not limited to a production facility, but might be used in other buildings or structures as well, such as a healthcare facility, testing lab, hospital or clinic.

[00117] As will be recognized, the devices according to the present disclosure may have one or more advantages relative to conventional technology, any one or more of which may be present in a particular embodiment in accordance with the features of the present disclosure included in that embodiment. Other advantages not specifically listed herein may also be recognized as well.

We claim:

1. A pharmaceutical product comprising:
 - a container having an exterior surface and an interior chamber;
 - an active ingredient disposed in the interior chamber, the active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y; and
 - a layer of photosensitive material disposed on the exterior surface of the container and exposed to environmental conditions contemporaneous with the active ingredient being disposed in the interior chamber,

the photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the active ingredient.
2. The product according to claim 1, wherein the layer of photosensitive material is applied to a label that is affixed to the exterior surface of the container.
3. The product according to claim 1, wherein the layer of photosensitive material is applied directly to the exterior surface of the container.
4. The product according to any one of claims 1 to 3, further comprising a layer of removable photo-resistive material applied over the layer of photosensitive material.
5. The product according to claim 4, wherein the layer of removable photo-resistive material comprises a label removably attached to the exterior surface of the container over the layer of photosensitive material.

6. The product according to any of claims 1 to 5, wherein the property change of the photosensitive material in the layer on the exterior surface of the container is a colorimetrically detectable property change.

7. The product according to any of claims 1 to 6, wherein the active ingredient is a polypeptide, amino acid, or small molecule.

8. The product according to claim 7, wherein the polypeptide is an antibody polypeptide.

9. The product according to claim 8, wherein the antibody polypeptide is a monoclonal antibody polypeptide.

10. The product according to claim 9, wherein the photosensitive property change comprises an increase in an amount of high molecular weight species present in the active ingredient.

11. The product according to claim 9, wherein the photosensitive property change comprises an increase in an amount of low molecular weight species present in the active ingredient.

12. The product according to claim 9, wherein the photosensitive property change is a colorimetrically detectable property change.

13. The product according to claim 12, wherein the photosensitive property change comprises a yellow-index color change.

14. The product according to claim 9, wherein the photosensitive property change comprises a change in an amount of charged species present in the active ingredient.

15. The product according to claim 7, wherein the active ingredient is a small molecule.

16. The product according to claim 15, wherein the photosensitive property change is a change in light absorbance.

17. The product according to claim 15, wherein the photosensitive property change comprises a yellow-index color change.

18. The product according to any of claims 1 to 6, wherein the active ingredient is a virus.

19. The product according to any of claims 1 to 6, wherein the active ingredient is a diagnostic reagent.

20. The product according to any of claims 1 to 19, wherein the range is between 190 to 1100 nm.

21. The product according to claim 20, wherein the range is between 315 to 400 nm.

22. The product according to claim 20, wherein the range is between 401 to 750 nm.

23. A pharmaceutical product comprising:

a container having an interior chamber, the container constructed from a material that is photo-resistive; and

a layer of photosensitive material disposed in the interior chamber of the container,

the photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in a photosensitive property of an active ingredient.

24. The product according to claim 23, wherein the property change of the photosensitive material in the layer disposed in the interior chamber of the container is a colorimetrically detectable property change.

25. The product according to claim 23 or 24, wherein the active ingredient is a polypeptide, amino acid or small molecule.

26. The product according to claim 23 or 24, wherein the active ingredient is a virus.

27. The product according to claim 23 or 24, wherein the active ingredient is a diagnostic reagent.

28. A pharmaceutical product comprising:

a container having an exterior surface and an interior chamber;

an active ingredient disposed in the interior chamber, the active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y; and

a label having a first region affixed to the exterior surface of the container with a layer of photosensitive material applied thereto and a second region removably attached to the exterior surface of the container with a layer of the photosensitive material applied thereto, the first and second regions exposed to environmental conditions contemporaneous with the active ingredient being disposed in the interior chamber,

the photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the active ingredient.

29. The product according to claim 28, wherein the property change of the photosensitive material in the layers applied to the label is a colorimetrically detectable property change.

30. The product according to claim 28 or 29, wherein the active ingredient is a polypeptide, amino acid, or small molecule.

31. The product according to claim 30, wherein the polypeptide is an antibody polypeptide.

32. The product according to claim 31, wherein the antibody polypeptide is a monoclonal antibody polypeptide.

33. The product according to claim 32, wherein the photosensitive property change comprises an increase in an amount of high molecular weight species present in the active ingredient.

34. The product according to claim 32, wherein the photosensitive property change comprises an increase in an amount of low molecular weight species present in the active ingredient.

35. The product according to claim 32, wherein the photosensitive property change is a colorimetrically detectable property change.

36. The product according to claim 35, wherein the photosensitive property change comprises a yellow-index color change.

37. The product according to claim 32, wherein the photosensitive property change comprises a change in an amount of charged species present in the active ingredient.

38. The product according to claim 30, wherein the active ingredient is a small molecule.

39. The product according to claim 38, wherein the photosensitive property change is a change in light absorbance.

40. The product according to claim 38, wherein the photosensitive property change comprises a yellow-index color change.

41. The product according to claims 28 or 29, wherein the active ingredient is a virus.

42. The product according to claims 28 or 29, wherein the active ingredient is a diagnostic reagent.

43. The product according to any of claims 28 to 42, wherein the range is between 190 to 1100 nm.

44. The product according to claim 43, wherein the range is between 315 to 400 nm.

45. The product according to claim 43, wherein the range is between 401 to 750 nm.

46. A method of confirming correct handling of photo-sensitive material, comprising:

applying a layer of photosensitive material to an exterior surface of a container having an active ingredient disposed therein, the active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y and the photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y related to the change in the photosensitive property of the active ingredient;

delivering the container to a recipient;

collecting the container from the recipient;

examining the layer of photosensitive to determine if the photosensitive material has experienced the property change; and

identifying the container as mishandled if the photosensitive materials has experienced the property change.

47. The method according to claim 46, wherein the property change of the photosensitive material in the layer on the exterior surface of the container is a colorimetrically detectable property change.

48. The method according to claim 46 or 47, wherein the active ingredient is a polypeptide, amino acid, or small molecule.

49. The method according to claim 48, wherein the polypeptide is an antibody polypeptide.

50. The method according to claim 49, wherein the antibody polypeptide is a monoclonal antibody polypeptide.

51. The method according to claim 50, wherein the photosensitive property change comprises an increase in an amount of high molecular weight species present in the active ingredient.

52. The method according to claim 50, wherein the photosensitive property change comprises an increase in an amount of low molecular weight species present in the active ingredient.

53. The method according to claim 50, wherein the photosensitive property change is a colorimetrically detectable property change.

54. The method according to claim 53, wherein the photosensitive property change comprises a yellow-index color change.

55. The method according to claim 50, wherein the photosensitive property change comprises a change in an amount of charged species present in the active ingredient.

56. The method according to claim 48, wherein the active ingredient is a small molecule.

57. The method according to claim 56, wherein the photosensitive property change is a change in light absorbance.

58. The method according to claim 56, wherein the photosensitive property change comprises a yellow-index color change.

59. The method according to claims 46 or 47, wherein the active ingredient is a virus.

60. The method according to claims 46 or 47, wherein the active ingredient is a diagnostic reagent.

61. The method according to any of claims 46 to 60, wherein the range is between 190 to 1100 nm.

62. The method according to claim 61, wherein the range is between 315 to 400 nm.

63. The method according to claim 61, wherein the range is between 401 to 750 nm.

64. A method of analyzing light exposure of a pharmaceutical product, comprising:

identifying a path for the pharmaceutical product within a facility comprising at least one space through which the pharmaceutical product passes, the pharmaceutical product comprising an active ingredient having a photosensitive property that changes based on at least cumulative exposure to light having a wavelength within the range between X and Y;

disposing at least one photosensitive device along the path, the at least one photosensitive device comprising a layer of photosensitive material reactive to light having a wavelength within the range between X and Y to experience a property change at a threshold of cumulative exposure to light received within the range between X and Y;

reading the at least one photosensitive device after being disposed along the path for evidence of the property change to the photosensitive material of the photosensitive device; and

changing the path for the pharmaceutical product through the facility if the property change occurs to the photosensitive material of the photosensitive device.

65. The method according to claim 64, wherein the facility is a manufacturing facility.

66. The method according to claim 64, wherein reading the at least one photosensitive device being disposed along the path comprises disposing an optical sensing device proximate to the photosensitive device, the optical sensing device coupled to a computing device that displays an indication of light exposure experienced by the at least one photosensitive device.

67. The method according to claim 64, wherein the property change of the photosensitive material in the layer is a colorimetrically detectable property change.

68. The method according to any of claims 64 to 67, wherein the active ingredient is a polypeptide, amino acid, or small molecule.

69. The method according to claim 68, wherein the polypeptide is an antibody polypeptide.

70. The method according to claim 69, wherein the antibody polypeptide is a monoclonal antibody polypeptide.

71. The method according to claim 70, wherein the photosensitive property change comprises an increase in an amount of high molecular weight species present in the active ingredient.

72. The method according to claim 70, wherein the photosensitive property change comprises an increase in an amount of low molecular weight species present in the active ingredient.

73. The method according to claim 70, wherein the photosensitive property change is a colorimetrically detectable property change.

74. The method according to claim 73, wherein the photosensitive property change comprises a yellow-index color change.

75. The method according to claim 70, wherein the photosensitive property change comprises a change in an amount of charged species present in the active ingredient.

76. The method according to claim 68, wherein the active ingredient is a small molecule.

77. The method according to claim 76, wherein the photosensitive property change is a change in light absorbance.

78. The method according to claim 76, wherein the photosensitive property change comprises a yellow-index color change.

79. The method according to any of claims 64 to 67, wherein the active ingredient is a virus.

80. The method according to any of claims 64 to 67, wherein the active ingredient is a diagnostic reagent.

81. The method according to any of claims 64 to 80, wherein the range is between 190 to 1100 nm.

82. The method according to claim 81, wherein the range is between 315 to 400 nm.

83. The method according to claim 81, wherein the range is between 401 to 750 nm.