Implications of Photostability on the Manufacturing, Packaging, Storage, and Testing of Formulated Pharmaceutical Products

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The authors evaluate the implications of product photosensitivity and how it influences various aspects of product development. They discuss a product photosensitivity classification system and present a photosensitive pharmaceutical product case study.

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Photostability testing in the pharmaceutical industry has evolved rapidly, particularly since the May 1997 publication of the ICH Q1B guidance "Photostability Testing of New Drug Substances and Products" in the *Code of Federal Regulations* (hereafter referred to in this article as Q1B) (1). Although some notable criticisms have been leveled against the document for its perceived shortcomings (2–4), Q1B has provided much-needed input to pharmaceutical applicants about regulatory requirements for photostability testing. Significantly, Q1B alleviates much of the ambiguity around spectral range and irradiance-level requirements, harmonizes global pharmaceutical laboratory practice, and provides a sequential approach to follow when examining protective packaging requirements for photosensitive pharmaceutical products. Thatcher *et al.* have recently published a two-part article that provides a practical interpretation of the guideline and offers important insights into satisfying Q1B requirements (5, 6).

Although Q1B identifies the need for forced-degradation photostability studies to help define method selectivity, its primary focus is to outline the confirmatory photostability testing required for drug substances and finished pharmaceutical products. Q1B is somewhat vague, however, about the experimental design and data interpretation of photostability studies, especially as they pertain to protecting photosensitive products during manufacturing, packaging, shelf storage, testing, and administration. Despite the significant lack of direction in the Q1B, the appropriate conduct of such supporting photostability studies and implementation of necessary protective measures remain an important responsibility of pharmaceutical applicants. This article summarizes important practical considerations for acquiring and using photostability data to address the effect of product photosensitivity in each critical area of product development.

Sample preparation

Compound 1 solution samples. Compound 1 solution samples were prepared by dissolving 365 mg of Compound 1 and 30 mg of sodium carbonate in a 50-mL low-actinic volumetric flask (Kimax Type A, Kimble Glass Company, Vineland, NJ) in the absence of light (pH 8.7). One-milliliter aliquots of the solution (7.3 mg/mL in Compound 1, 5.7 mM in sodium carbon-

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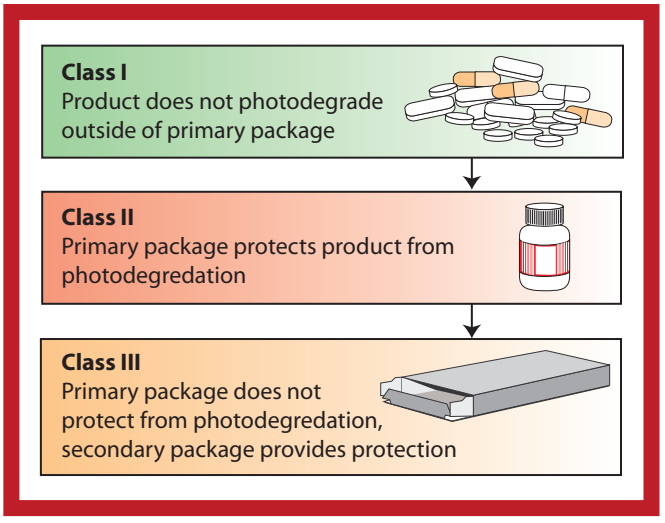

Figure 1: A pharmaceutical product photosensitivity classification system.

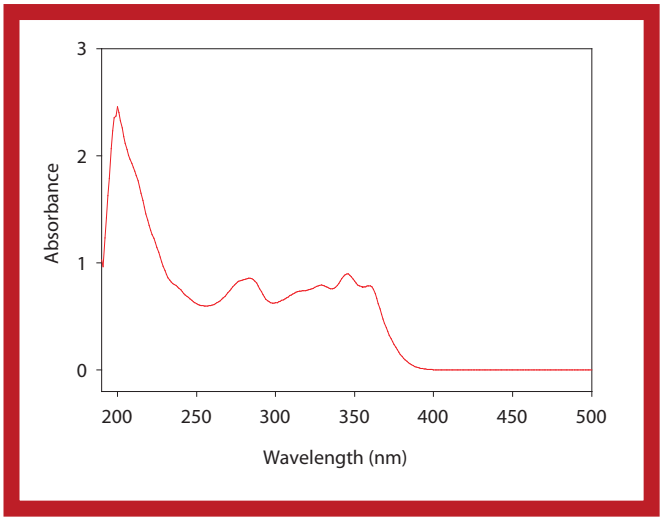

Figure 2: UV–vis absorbance spectrum for Compound 1 at an aqueous solution concentration of 18.3 μg/mL.

ate) then were transferred to 30-mL Type I USP amber vials (Schott Cat. No. 68000376, 30-mm diameter, 75-mm height, Schott Glass, Yonkers, NY) and tightly capped with 20-mm aluminum flip-top rubber stoppers (West Cat. No. 10142779, S-87-J mold 4405/50 gray lyo, West Pharmaceutical Services, Lionville, PA) for lyophilization or photostability testing studies.

Compound 1 lyophilized samples. A subset of Compound 1 solution samples was placed into a freeze dryer with stoppers partially inserted in the vials. The samples were frozen on lyophilizer shelves at −50 °C and held at this temperature for 4 h. Primary drying was subsequently performed for more than 14 h at a pressure of 100 mTorr with shelf and condenser temperatures at −15 and −50 °C, respectively. Secondary drying then was conducted for more than 4 h at a shelf temperature of 20 °C with the lyophilization chamber pressure maintained at 20 mTorr. Stoppers then were seated under 300-Torr nitrogen (scientific grade). Vials were sealed by hand-crimping with 20-mm aluminum flip-top cap rubber stoppers after removal from the lyophilization chamber.

Compound 1 reconstituted solution samples. Compound 1 solutions with 0.365-mg/mL concentrations were prepared by reconstituting Compound 1 lyophilized cake samples with 20 mL of 3.3% dextrose/0.3% NaCl (Abbott Laboratories, lot No. 70009WS) using a 20-mL syringe.

Instrumentation and experiments

Photostability studies. Each set of prepared samples (solution, lyophilized, and reconstituted) were loaded into a photostability chamber (ESI 2000, Environmental Specialties Inc., Raleigh, NC) and the chamber was adjusted to 25 °C and 40% RH for light-exposure experiments. The vials were spaced ~2 in. apart to avoid shadowing. For experiments involving only visible light, the light intensity of the photostability chamber was set to deliver 8.3 klx. Samples were pulled at 25, 50, 75, 100, 200, 300, 600, 900, and 1200 klx-h of visible light exposure and assayed for active and degradate levels by high performance liquid chromatography (HPLC). For experiments involving combined UV–vis light, the prepared samples were exposed for 1, 2, 3, 4, and 6 h with the photostability chamber set to deliver 8.1 klx visible and 4.3 W/m^2 UV light. Following exposure, the samples were assayed for active and degradate levels by HPLC. In all experiments, foil-wrapped controls were placed alongside experimental samples to account for thermal effects.

Absorbance measurements. UV–vis absorbance measurements were performed on a 30-μM solution of Compound 1 in water using a HP8453 UV–vis diode array spectrophotometer (Hewlett Packard, Palo Alto, CA) over the wavelength range of 190–500 nm. The spectrum of the compound was not dependent on pH.

Transmission measurements. UV–vis light-transmission measurements were obtained by placing a portion of the sample to be analyzed in the light beam of a HP8453 UV–vis diode array spectrophotometer (Hewlett Packard) and collecting the transmission of the specimen as a function of wavelength. Samples were obtained for transmission measurements by fracturing a portion of the glassware or other specimen and removing a sample for measurement. Commercial light-filtering film (amber 3, Cat. No. 362931902U, 40 × 150 in., Team Plastics, Inc., Cleveland, OH) was obtained for light-transmission measurements.

Spectral power distribution measurements. Lamp spectral-power distribution measurements were recorded with a spectroradiometer (McMahan Light Spex, McMahan Instruments, Chapel Hill, NC) on a T-5 biax cool white visible lamp (Environmental Specialties, Raleigh, NC) with and without light-filtering material (amber 3, Team Plastics) placed over the light banks.

Active and degradate assay by HPLC. All HPLC analyses were performed on an HPLC instrument with diode array detection (Agilent 1100, Agilent, Wilmington, DE). Compound 1 samples were diluted to 0.6 mM for separations using an Inertsil phenyl column (10 cm × 3.0 mm, 5-μm particle size) and mobile phase consisting of a mixture of 40% acetonitrile (0.2% trifluoroacetic acid) and 60% water (0.2% trifluoroacetic acid). Following isocratic elution, the chromatographed active and degradates were detected by UV absorbance at 255 nm and quantitated against a standard. The described method had been previously validated and shown to be selective for active, impurities, and major degradates.

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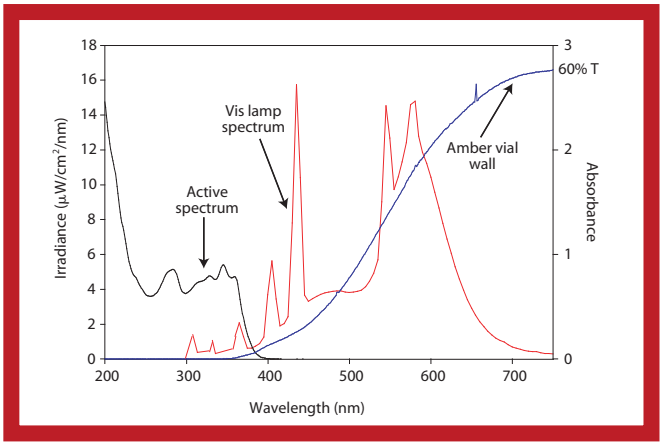

Figure 3: UV–vis absorbance spectra for Compound 1, spectral-power distribution for the ESI T-5 biax cool white lamp, and transmittance curve for a Schott USP Type I amber vial wall.

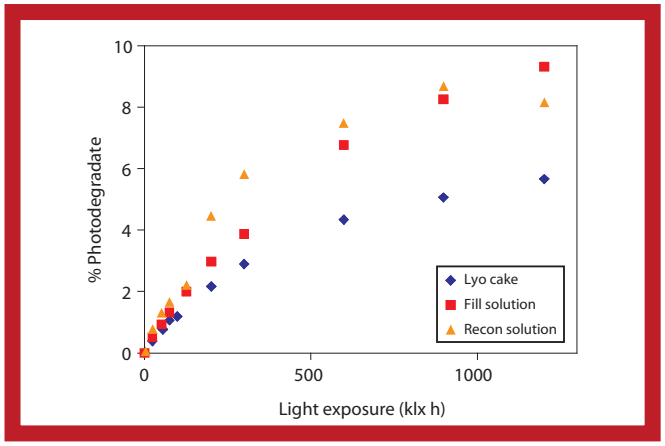

Figure 4: Photodegradate formation for Compound 1 packaged in amber vials (30-mL, Schott USP Type I) in various forms (fill solution, lyophilized cake, reconstituted solution) as a function of visible-light exposure.

A pharmaceutical product photosensitivity classification system

A pharmaceutical product photosensitivity classification system is a potentially useful construct for understanding and managing the implications of product photosensitivity during manufacturing, packaging, shelf storage, testing, and administration. Such a classification system offers a means to establish a common understanding that can be applied across a particular category of photosensitive products for which photostability issues are expected to be similar. One approach for classifying pharmaceutical products according to their photosensitivity is shown in Figure 1. The classification system presented delineates classes of products on the basis of the amount of protection afforded by packaging. Class I represents formulated products that do not chemically and/or physically change to any reasonable extent upon exposure to light. Formulated products that fall into this class are naturally the most straightforward to handle from a photosensitivity standpoint, because there are no photostability implications to consider and testing falls squarely into the limited confirmatory approach described in Q1B (1).

According to the photosensitivity classification system shown in Figure 1, Class II and III products are those that photodegrade or otherwise exhibit significant change upon direct-light exposure. The difference between Class II and Class III products is that although Class II products are fully protected from photo-driven change when placed into an appropriately protecting immediate package, Class III products may be adversely affected by light even when housed in an immediate package. Class III products thus require protection from light with an additional packaging layer (*e.g.,* a cardboard carton). The photostability implications for Class II and Class III products necessitate different approaches (demonstrated later in this article). Class II and Class III products both require carefully designed photostability studies to support effective decision-making for product protection in each of the key areas of product development. Because the described classification system is based on photosensitivity relative to packaging, it is possible for a given product of various packaging configurations (*e.g.,* blister and HDPE) to have different classifications.

The following sections address the various implications of product photosensitivity on manufacturing, packaging, shelf storage, testing, and administration with emphasis on developing the appropriate confirmatory photostability studies and interpreting and using the resultant data. As each area is considered, differences in approach for Case II and Case III products are presented. A product "light budget" also is discussed as a tool used with experimental photostability data for managing product photosensitivity. The concepts developed in the following sections are extended to an example product as a means to demonstrate the potential utility of the approaches. Although the example may or may not represent other active pharmaceutical ingredients, the purpose is to illustrate the application of the described principles.

Product photochemistry: causative wavelengths and the mechanism for photoinduced change

When significant photosensitivity has been established for a formulated product, the spectral range of light responsible for the photosensitivity must be identified. This spectral range typically is referred to as the *causative wavelengths* of light for photo-driven product change. Pharmaceutical product photodegradation usually results from one of two scenarios. The first involves direct absorption of light by the active pharmaceutical ingredient and subsequent conversion to another chemical entity. In this case, the classical first law of photochemistry put forth by Grotthus (1817) and Draper (1843) is maintained (2). The second photodegradation pathway results from photosensitization reactions in which one component of the formulation (which may also include the active pharmaceutical ingredient) absorbs light and activates another component for subsequent chemical reactions, leading to degradation of the active pharmaceutical ingredient (7). Both types of photodegradation pathways must be taken into consideration when examining the photosensitivity of formulated pharmaceutical products.

Other changes besides direct or indirect chemical photodegradation of the active may also occur upon light exposure, including additional chemical and/or physical changes to the formulated product (*e.g.,* a loss of excipient functionality). These

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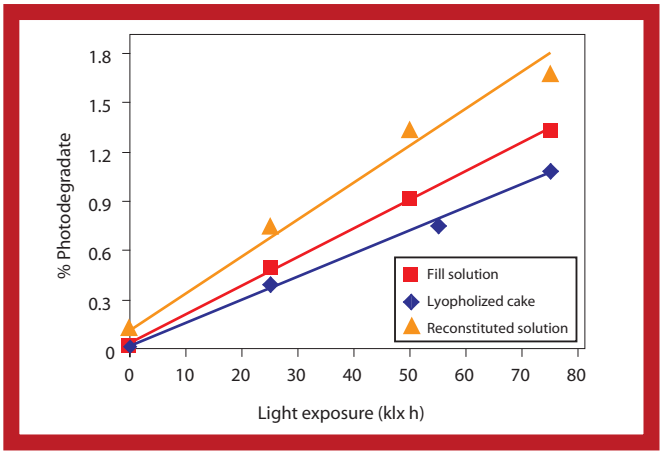

Figure 5: The linear portion of the Figure 4 data showing photodegradate formation for Compound 1 in amber vials (30-mL, Schott USP Type I) in various forms (fill solution, lyophilized cake, reconstituted solution) as a function of visible-light exposure (≤75 klx-h). Lines represent a linear fit to the respective data points.

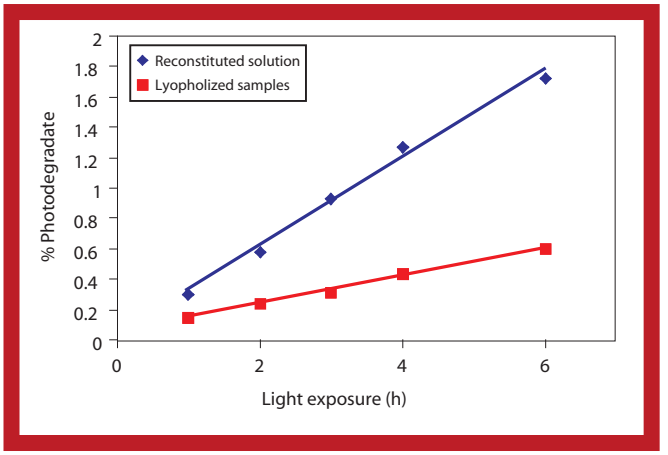

Figure 6: Photodegradate formation for Compound 1 in amber vials (30 mL, Schott USP Type I) in various forms as a function of combined UV- and visible-light exposure. Lines represent a linear fit to the respective data points.

changes must also be taken into consideration (8). For product photosensitivity induced by the direct absorption of light by the active pharmaceutical ingredient, the UV–vis absorbance spectrum offers important guidance as to which wavelength range to avoid (*e.g.,* by packaging, light filtering) to prevent photodegradation, assuming that light absorption at any of the absorbing wavelengths results in degradation. For photosensitization reactions, the causative wavelengths for photodegradation can expectedly be quite different than those associated with the absorbance spectra of the active and must be examined carefully to establish which wavelengths of light are pertinent (9). Understanding the mechanism for photodegradation or other photoinduced changes also may help identify the causative wavelengths.

The UV–vis absorbance spectrum for a proprietary active pharmaceutical ingredient is shown in Figure 2. Compound 1 photodegrades by direct absorption of light to a single direct photodegradation product resulting from a trans-*cis* isomerization reaction. The *cis* isomer photodegradate may then oxidize further, producing a secondary photo-oxidative degradate. Assuming that the absorption of light at any wavelength at which Compound 1 absorbs is sufficient to promote the isomerization reaction, the absorbance spectra indicate that both UV and visible light will induce degradation. The causative wavelengths thus extend out to ~400 nm. Protection against photodegradation is only achieved by preventing absorption across this wavelength range. A central question to be answered at this point is: Does the degradation of the product occur to such a significant extent upon light exposure as to warrant protective measures? To answer this question, attention turns to developing a quantitative relationship between light exposure and the relevant photoinduced change(s).

Product photochemistry: a quantitative relationship between incremental light exposure and product change

Once product development has focused attention on a small number of formulation candidates or the final formulation for market has been identified, a definitive confirmatory photostability study is needed. The study design for confirmatory photostability studies requires careful consideration to ensure that all of the necessary data are provided to support product development decisions. The approach advocated herein is a study design consisting of incremental exposure of the product to decoupled UV and visible light up to the Q1B recommended levels of 200 W-h/m^2 UV and 1.2 ×106 lx-h visible (1).

The study design may further consist of coupled UV–vis light exposure either in a sequential or simultaneous fashion, as required. The suggested study design allows for specific testing of the product at each of the incremental light-exposure levels and produces a light-induced change versus light-exposure level correlation curve that provides a quantitative basis for establishing product protection requirements during manufacture, packaging, shelf storage, testing, and administration. The data produced from these studies also can be used to establish a "light budget" for the product that is the basis for determining a critical threshold of light exposure that, if exceeded, will lead to an unacceptable amount of product change. The "light budget" is a useful concept when judgments are made about the relative costs associated with light exposure during manufacturing, packaging, and long-term storage.

Photostability studies were conducted with the Compound 1 product (lyophilized cake consisting of the drug and sodium carbonate) according to the approach described. To support general scenarios, the quantitative data acquired in the study were categorized as indoor lighting without windows, indoor lighting with windows, or indoor lighting without windows using light filtering.

Indoor lighting without windows. UV-light exposure can be eliminated by operating in facilities without windows or by covering windows. Therefore, in many settings, the effects of UV-light exposure on a product is negligible. Thus, the quantitative relationship between visible-only light exposure and product degradation were studied.

For experiments involving only visible light, the light intensity of the photostability chamber was set to deliver 8.3 klx.

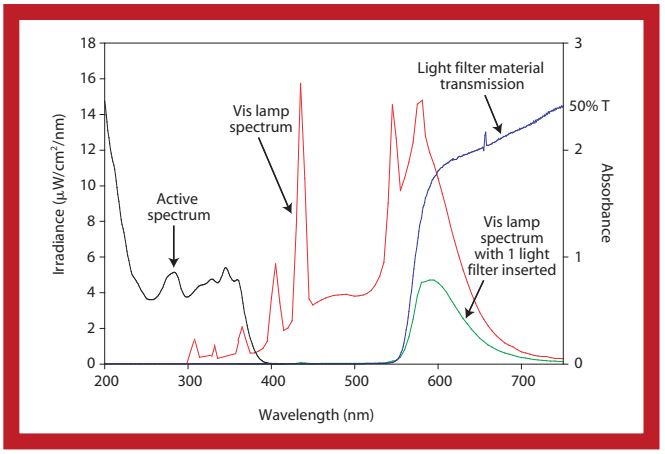

Figure 7: Absorbance spectra for Compound 1, visible-light spectral power distribution for an ESI T-5 biax cool white lamp, transmittance curve for amber light-filter material (amber 3), and visible-light spectral-power distribution for the ESI T-5 biax cool white lamp with light filter inserted over the light banks.

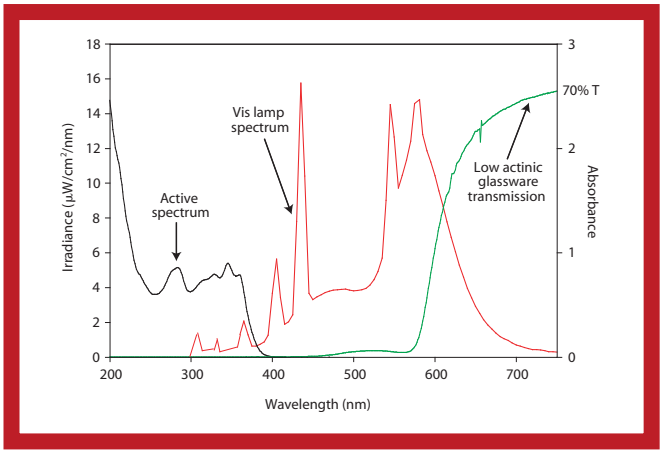

Figure 8: Absorbance spectra for Compound 1, spectral power distribution for ESI T-5 biax cool white lamp, and transmittance curve for low-actinic volumetric flask (Kimax, Type A).

Samples were pulled at 25, 50, 75, 100, 200, 300, 600, 900, and 1200 klx-h of visible-light exposure. Because Compound 1 is a lyophilized cake sample and the photodegradation mechanism was previously established (*cis*-trans isomerization), the battery of tests performed on each sample were congruent with possible changes that might occur for this product type and naturally included an assay for active and degradate levels. In general, the battery of tests should examine the potential for all possible changes that could adversely effect product specifications and performance.

Because various physical forms (*e.g.*, fill and spray solutions, granules) of the active pharmaceutical ingredient and product may exist at various steps during manufacture, the photosensitivity of each relevant form should be independently examined to establish necessary protective measures. Even various polymorphs of a single drug exhibit different photosensitivities (10). In this case, Compound 1 was examined as a fill solution (form before lyophilization), as a lyophilized product in its immediate package, and as a reconstituted solution (form immediately before and during administration). Each relevant product form was exposed to the same light-exposure level and each was housed in a common amber vial package.

Before examining the data, a few underlying considerations must be noted for this particular study. An overlay of the UV-vis absorbance spectra of Compound 1 with the typical spectral power distribution of a fluorescent lamp of the type commonly used to conduct visible-light exposure testing in commercial photostability chambers (ESI T-5 biax cool white lamp) is shown in Figure 3. Note that the spectral power distribution of common indoor fluorescent lighting has a near-identical profile (3). As the figure shows, the overlap between the lamp spectral-power distribution and Compound 1 absorbance spectra is significant, which leads to the prediction that degradation would occur if Compound 1 were exposed to this lamp source.

A transmittance curve for the amber vial (Schott USP Type I, 30 × 75 mm) selected as the immediate package for the Compound 1 lyophilized product also is included (see Figure 3). Comparison of the absorbance spectrum of Compound 1 with the transmittance spectrum of the amber vial leads to the prediction that the vial transmittance cutoff is such that a small amount of causative wavelength light will reach the product when housed in this vial type. If the vial transmittance curve were shifted only ~30–50 nm, the prediction from the Figure 3 data would conversely be that the product is protected adequately against photodegradation.

Photodegradation assay results were graphed for fill solution (7.3 mg/mL in Compound 1), lyophilized product, and reconstituted solutions of Compound 1 (0.365 mg/mL in Compound 1) following visible-light exposure (see Figure 4). As the data show, the growth of the *cis* isomer photodegradate in all three sample types diverges from linearity after ~75 klx-h exposure. Although the absolute levels of the photodegradate were similar for the two solution-phase samples, the lyophilized cake samples had (as expected) significantly less photodegradate growth after light exposure. One plausible explanation for this result is that photo-driven change for solids is typically surface-limited as result of the light's inability to penetrate through the surface to the product interior (8). Note that the prediction made from the Figure 3 data is accurate in that the amber-vial primary package transmits sufficient light to lead to significant photodegradation. According to Figure 1, Compound 1 falls squarely into Class III in the proposed photostability classification system and requires an additional packaging layer to protect the product against photodegradation.

The linear portion of the Figure 4 curve for the three forms of Compound 1 is replotted in Figure 5. Using the equations from the lines obtained, the amount of visible-light exposure required to reach the projected acceptance criteria level for the photodegradate (≤1.0%, determined from safety studies as tolerable) for the three forms is 54 klx-h for the lyophilized cake, 44 klx-h for the fill solution, and 34 klx-h for the reconstituted solution. These values are the limits of the visible "light budget" for Compound 1 and correspond to 60, 48, and 38 h, respectively, of exposure time under "average" visible indoor-light exposure levels (~900 lx lamp output). Examination of

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Table I: Summary and comparison of estimated "light budget" and costs for Compound 1 manufacturing and packaging under visible light without windows.*

	Fill solution preparation and hold before lyophilization (manufacturing)	Postlyophilization (secondary packaging)**
Degradate (% per klx-h)	0.017	0.014
Light budget (klx-h)	44	54
Projected light costs (klx-h)	6.4	3.0
Photodegradate level (%)	0.15	0.06
Maximum time allowed (h)	48	60

*The product would not be expected to degrade during shelf-stability because secondary packaging provides protection.
**Note that if this were a Case II product, the effects of light exposure could be neglected entirely for secondary packaging.

the earlier linear portion data further shows that reconstituted solutions of Compound 1 are slightly more sensitive than the prelyophilized solution, which is slightly more sensitive than the lyophilized cake to visible-light exposure. Note that the reconstituted solution samples are 20-fold less-concentrated than the fill-solution samples. The amount of photoisomerization was only ~25% higher, however, suggesting a minimal concentration dependence on the extent of photodegradation. In addition, similar extents of photoisomerization occur in both liquid and solid states. Because the physical mobilities of the molecule are very different in these two physical states, the rate of photoisomerizations appears to be largely photon limited. The experimental data presented in this section were used to address the implications of visible-light exposure in areas where window lighting can be avoided.

Indoor lighting with windows. For cases in which window-light exposure cannot be avoided, it is important to develop a quantitative understanding of the effect of combined or simultaneous UV- and visible-light exposure on the product. For example, Compound 1 can be administered in a situation in which both UV- and visible-light exposure may occur (*e.g.,* a hospital room). Simultaneous UV- and visible-light exposure consequently was included as part of the photostability study design.

For combined UV- and visible-light exposure experiments, samples were exposed for 1, 2, 3, 4, and 6 h with the photostability testing chamber set to deliver 8.1 klx visible light and 4.3 W/m^2 UV light. For these studies, only the lyophilized cake and reconstituted solution samples were examined because these samples are the only forms of the product to which combined UV- and visible-light exposure were anticipated. The product fill-solution samples are expected to lack window-light exposure during manufacturing and were not considered.

The photodegradate growth versus combined UV- and visible-light exposure level curve is shown in Figure 6. As the data show, similar trends were observed for photodegradate formation under combined UV- and visible-light exposure as were seen in the visible-only light exposure experiments. The reconstituted solution samples were much more photosensitive than the lyophilized cake samples. The data in Figure 6 indicate that the amount of combined UV- and visible-light exposure required to reach the acceptance criteria level for the photodegradate (≤1.0%) for the two sample types is 3.5 h for the reconstituted solution stored in the original amber-vial packaging and 10.8 h (extrapolated from the plot) for the lyophilized product. The sensitivities to UV light are a factor of 10 and 4 higher for the reconstituted solution and lyophilized cake, respectively, than observed for the visible-light exposure. The increased UV photodegradation suggests an increased overlap with "causative wavelengths" and less of a photon-limited reaction rate, particularly for the solid lyophilized cake. The experimental data presented in this section were used later to address the implications of visible-light exposure in areas where window lighting cannot be avoided.

Indoor lighting without windows using light filtering. For compound 1, light filtering was considered as an option for manufacturing and packaging settings. The light-transmission curve of a representative cross-section of the light-filtering material (amber 3, Team Plastics) is shown in Figure 7 relative to Compound 1 absorbance spectra and visible lamp spectral power distribution data. The data in Figure 7 led to the prediction that the Compound 1 product would be well-protected from photodegradation with the light-filtering material inserted. As further evidence of the effect of light-filter insertion, the spectral power distribution of the T-5 biax cool white visible lamp also is shown with the light-filter material positioned over the light banks. Independent photostability experiments with the Compound 1 product showed that the product was indeed indefinitely stable in such a scenario. The understanding described in this section was used to address the implications of light-filtering approaches for product protection during manufacturing and packaging settings.

Implications to manufacturing, packaging, and storage

Protective measures may be required to adequately protect photosensitive products during manufacturing, packaging, and storage.

Mapping the process. A thorough understanding of the manufacturing and packaging processes is needed to develop a plan to protect photosensitive products during these operations. At the outset, it is important to establish what type of light exposure the product will experience (*e.g.,* with or without windows) to develop and refer to the appropriate supportive photostability study data. Required information includes junctions where the product is exposed to light, the time the product is held at each junction under worse-case scenarios, and irradiance and spectral power distribution of light sources at each exposure junction. These data are used to develop the light costs associated with manufacturing and packaging the product.

The "light budget" and hypothetical costs for Compound 1 are summarized in Table I. Compound 1 is manufactured using a relatively straight-forward process involving fill solution preparation, vial filling, and lyophilization steps; however, the general

Table II: Summary of combined UV- and visible-light exposure data for Compound 1, relative to product administration and projected stability of the product.

	Lyophilized product (before reconstitution)	Reconstituted product (for administration)
Degradate (% per klx-h)	0.09	0.29
Maximum time allowed (h) for each step of packaging	10.8 from removal from secondary packaging	3.5 from reconstitution to delivery

approach described herein should be applicable for any manufacturing processes regardless of complexity. UV-light exposure was neglected in the present case because manufacturing and packaging operations were performed under indoor lighting without windows. The worst-case scenario light costs during prelyophilization were estimated at 6.4 klx-h (800 klx-h irradiance levels at a maximum of 8-h exposure) (see Table I). These costs are those accrued during Compound 1 exposure during fill solution preparation and vial filling before lyophilization. Until secured within an appropriate secondary packaging, the product is still subject to photodegradation and thus costs are still being incurred.

The worst-case light costs for secondary packaging were estimated at 3.0 klx-h (600 klx-h irradiance levels at a maximum of 5-h exposure). The light levels experienced at each exposure junction along the process train can be converted to the amount of photodegradate expected to form in comparison with the projected acceptance criteria for the product (see Table I). Note that 0.15% of photodegradate would be expected to form during manufacturing, 0.06% formed during secondary packaging, and none formed on the market shelf because the product is adequately protected from photodegradation within protective secondary packaging. Using this analysis, controls for light exposure may be established at each step to ensure that the aggregate photodegradate level formed (manufacturing and packaging) are comfortably below the projected acceptance criteria threshold established for the product. In this example, worst-case exposure levels during manufacturing and packaging would produce photodegradate levels for Compound 1 of ~0.21%, which are well below the desired threshold levels of ≤1.0%.

For Case II products, those that are fully protected within immediate packages, the costs associated with secondary packaging can be neglected entirely because Case II products are adequately protected upon placement into their immediate packages. Light exposure between the products' removal from the lyophilization chamber (or any manufacturing process) and packaging (immediate or secondary) areas also must be strictly controlled. In this case, the contributions of light exposure during transfer were assumed to be negligible. Transfer and hold steps can be important, however, particularly for products in which manufacturing and packaging may occur at various geographic locations. In such cases, the light protection afforded to the product by the bulk containers also must be established.

This analysis is a potentially useful approach for treating photostability implications during manufacturing, packaging, and storage for Case II and Case III products. Moreover, the approach is one means of using supporting confirmatory photostability data to define acceptable exposure levels by comparing the available light budget with required light costs to establish adequate controls. The important information that must be assembled to address product photostability implications thus can be reduced to the type of light exposure (visible only or combined UV–visible), product class (Class II or Class III), and appropriate supporting quantitative photostability data.

Protective measures. The costs associated with manufacturing and packaging may at times exceed or be uncomfortably close to the available light budget for the product. Thus, additional protective measures may be needed. Conversion of a photosensitive product from Case III to Case II by careful package selection is clearly advantageous because the protective effects of secondary packaging become nonessential. Even some widely available and accepted primary packaging materials (*e.g.,* the USP Type I amber glass presented herein or HDPE), however, may provide insufficient protection to extremely light-sensitive products. Moreover, for sterile liquid products, clear colorless packaging is desired whenever possible to facilitate quality inspection, release testing, and administration (11). For some products, Case III categorization is unavoidable and secondary packaging such as cardboard cartons or other light-protective overwraps are required to achieve full product protection.

Other approaches can be used to decrease the overall costs of light exposure during manufacturing and packaging, including operating with partial or indirect lighting and inserting color filters to reduce the transmission of causative-wavelength light. If the manufacturing and packaging is conducted under filtered-lighting conditions, the spectral power distribution and irradiance of the filtered light must be studied to understand and maximize the potential benefits of light filtration. The spectral power distribution of the photostability chamber visible lamp with a filter inserted indicates that the causative wavelengths were removed (see Figure 7). Independent photostability experiments with Compound 1 showed that the product was indeed stable indefinitely in such a scenario. With such a filter inserted in the manufacturing and/or packaging setting, the costs associated with these two areas would be expected to be inconsequential and much greater process flexibility afforded.

Implications to product testing

The implications of product photosensitivity during laboratory testing can be significant. Care must be taken to ensure that photosensitive product samples remain in a fully protected state (immediate package for Class II and immediate/secondary combination for Class III) until sample preparation and analysis are performed.

Once the product is removed from protective packaging, the irradiance levels and time of exposure must be controlled to ensure that testing measurements are not artificially biased. Color-filtered or partial-lighting conditions may be needed to avoid photoinduced changes during sample preparation and analysis

operations, particularly if the laboratory area has windows that allow exposure to UV light. As with manufacturing and packaging operations, it is anticipated that UV-light exposure can be strictly controlled or eliminated in typical testing areas.

Protective measures may also be needed during sample transport from various facilities to the testing laboratories (internal or contract). Special low-actinic laboratory glassware or sample vials may be used to protect prepared samples from further photodegradation. It is important to understand the transmission properties of such glassware in relation to the causative wavelengths for photodegradation to ensure adequate protection. Protection also may be needed while samples are in queue in analytical instrumentation, and special covers or filters may be needed. Appropriate conditions must be established for standard preparation and storage as well as system suitability as part of methods development and validation activities. Testing laboratories should document special procedures for handling the samples during transfer to ensure uniformity in practices. The key to handling the implications of product photostability during testing is to institute procedures to ensure that exposure to causative wavelengths is minimized or altogether eliminated.

For Compound 1, partial lighting conditions in which four of five overhead fluorescent light banks were switched off were sufficient for sample protection during the preparation steps involving reconstitution of the product and dilution. Several sample storage containers were evaluated and low-actinic volumetric flasks (Kimax Type A) were chosen for sample storage. The light transmission of the low actinic glassware used for Compound 1 samples were compared with a spectral power distribution of the T-5 biax cool white lamp—which mimics indoor fluorescent lighting without windows—and Compound 1 absorbance spectra (see Figure 8). The data show that the low-actinic glassware selected should adequately protect the samples. During chromatographic analysis of Compound 1 samples, a protective light-filtering cover was used on the HPLC autosampler to ensure that the samples were not exposed to light while in queue for analysis. The protective steps used for Compound 1 from sample preparation through analysis were sufficient to protect the product against degradation during testing. Although this discussion focuses on chromatographic assays, the same general considerations are applicable to any type of product test. Each operation must be examined and the need for light protection must be determined.

Implications to product administration

Thus far, this article has focused on the approaches to conduct photostability studies, properly interpret data, and institute controls to ensure that photosensitive products can be manufactured, packaged, stored, and tested with high quality. Attention now turns to ensuring that appropriate consideration is given to the implications of product photostability in administration settings.

The primary focus of any controls instituted for product administration, including precautionary product-labeling statements, is that product efficacy and safety is maintained. Adverse safety can result from photoinduced product degradation. de Vries *et al.,* for example, reported on the adverse pharmacological effects of degradation products formed during administration of chloramphenicol (12). The following discussion highlights only some of the considerations when administering photosensitive products and will not attempt to provide definitive position statements. The overall driver for product safety margins for administration settings may be quite different than final product acceptance criteria, because safety tolerance levels may be qualified at higher levels.

Whereas the effects of UV light on product degradation typically can be neglected for manufacturing, packaging, and testing operations, product administration is largely under the control of patients or clinicians and the effects of combined UV and visible light on the product should be considered. For Case II oral dosage forms packaged in HDPE bottles, photoinduced product change commences immediately upon removal of the product from its protective immediate packaging. *USP 25–NF 20* indicates that where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended (13). For particularly photosensitive products, a more appropriate statement might be "store in original container" in that misinterpretations might be avoided. A consumer misunderstanding might lead to repackaging the product in convenience dispensers and assuming that this package type offers as sufficient protection as the original package. Hung recently pointed out the deficiencies in label and package insert contents for a series of photosensitive pharmaceutical products (11). When possible, it would be most prudent to use formulation techniques to design the photosensitivity out of oral dosage forms to avoid labeling and potential misuse of the product (14).

Case III oral products should be stored in protective secondary or marketing packaging until required removal for administration. In this case, precautionary statements might include to "store in carton" or some other similarly appropriate language. For either Case II or Case III products, the value of supporting studies and precautionary statements is that they may help promote consumer storage of the product in its most stable form between doses. Certainly, the language for Case III products should be clear to avoid the product being left exposed to light in the absence of secondary packaging for prolonged periods of time.

For sterile liquid products, additional studies may be needed with respect to administration for Case II and Case III products. Using special administration equipment (*e.g.,* amber tubing, syringes) and/or time limits for administration of injectable products may be considered. Sterile-product administration may require changing the physical form of the product, for example from lyophilized cake to reconstituted solution. Evaluation of photostability profiles of each form would then be necessary to provide proper guidance for administration. Creams, ointments, and ophthalmics may require additional examination to directly simulate product use to support administration. These products may exhibit enhanced photosensitivity and have administration routes that promote prolonged light contact or be used in particularly photosensitive regions (*e.g.,* eyes). Baertschi *et al.* have presented a discussion about the implications of administering transdermal patches containing photosensitive active ingredients (15).

Before considering the implications of both UV- and visible-light exposure for the Compound 1 example, it is worth considering the sequential process of product administration for Compound 1. Because Compound 1 is a Class III product and is protected in secondary packaging, exposure commences when the immediate package is removed for reconstitution. For this product type, exposure of the Compound 1 product between removal of the secondary package and reconstitution should be minimized. Likewise, upon reconstitution, the product should be delivered to the patient in a timeframe that would prevent significant degradation. Thus, the quantitative relationship between simultaneous UV- and visible-light exposure and photodegradate formation for both the lyophilized cake and reconstituted product are important and need examination to provide guidance on the implications of photosensitivity for this particular product case. The relevant data derived from Figure 6 is summarized in Table II.

A few assumptions can be made about how long the product would be expected to be below acceptable levels (≤1.0%, established from safety) for the photodegradate (see Table II). As the data show, the amount of time that the product can be held under the scenarios listed vary dramatically and provide a worst-case guide to product stability in relation to acceptable photodegradate levels. Compound 1 under simultaneous UV- and visible-light exposure is relatively stable in relation to the time that might be reasonably required to administer the product (see Table II). For example, assuming that Compound 1 will be removed from packaging and quickly reconstituted, the product can then be administered over an approximate.y 3.5-h period without photodegradate levels exceeding acceptable levels.

As the data and preceding discussion indicate, it would seem prudent for some products to include detailed language on the packaging insert to provide directions for its safe, effective use. The downside, of course, is compliance with detailed instructions. Thus, for some cases, it may make sense to offer kits that include the appropriate materials to safely administer the product. Examples include light-protective syringes and tubing. For product administration, combined UV- and visible-light exposure is a worst-case scenario but must be assumed because limiting to visible indoor lighting only is out of the control of the pharmaceutical applicant.

Just as with manufacturing, packaging, and testing, the individual operations involved in product administration must be examined and related to appropriately designed photostability study data to rationally approach the implications of product photosensitivity. The intangible difficulties in protecting photosensitive products in administration settings are the variability of potential light spectral-power distribution (*e.g.,* from direct sunlight to indoor lighting with no windows) and that patient and clinical compliance cannot be guaranteed. Thus, it would be worthwhile to ease product administration by means of appropriate development activities and labeling considerations.

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