Implications of In-Use Photostability: Proposed Guidance for Photostability Testing and Labeling to Support the Administration of Photosensitive Pharmaceutical Products, Part 2: Topical Drug Product

STEVEN W. BAERTSCHI,[1] DAVID CLAPHAM,[2] CHRIS FOTI,[3,4] MARK H. KLEINMAN,[5] SOLVEIG KRISTENSEN,[6] ROBERT A. REED,[7] ALLEN C. TEMPLETON,[8] HANNE HJORTH TØNNESEN[6]

[1]Eli Lilly and Company, Lilly Research Laboratories, Indianapolis, Indiana 46285
[2]GlaxoSmithKline Pharmaceuticals, Ware SG12 0DP, UK
[3]Pfizer Inc., Analytical Research and Development, Eastern Point Road, Groton, Connecticut 06340
[4]Gilead Sciences, Foster City California 94404
[5]GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania 19406-0940
[6]School of Pharmacy, University of Oslo, Oslo 0316, Norway
[7]Celsion Corporation, Lawrenceville, New Jersey 08648
[8]Merck Research Laboratories, Merck and Company, Inc., West Point, Pennsylvania 19486

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ABSTRACT: Although essential guidance to cover the photostability testing of pharmaceuticals for manufacturing and storage is well-established, there continues to be a significant gap in guidance regarding testing to support the effective administration of photosensitive drug products. Continuing from Part 1, (Baertschi SW, Clapham D, Foti C, Jansen PJ, Kristensen S, Reed RA, Templeton AC, Tønnesen HH. 2013. J Pharm Sci 102:3888–3899) where the focus was drug products administered by injection, this commentary proposes guidance for testing topical drug products in order to support administration. As with the previous commentary, the approach taken is to examine "worst case" photoexposure scenarios in comparison with ICH testing conditions to provide practical guidance for the safe and effective administration of photosensitive topical drug products. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2688–2701, 2015

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INTRODUCTION

Part 1 of this series of commentary papers[1] outlined the importance of photostability testing to support in-use handling and administration of pharmaceutical products intended for injection. In particular, a systematic approach to evaluating realistic light exposure scenarios, information to develop a photostability testing plan, and the generation of a dataset to provide valuable insight into the safe and effective administration to a patient was proposed. This initial paper in the series laid much of the foundation for how to think about in-use photostability testing, including an in-depth discussion on relevant light sources, supply chain considerations, and a recommended photostability testing strategy. The interested reader is referred to Part 1 for additional background information on these topics as these will only be treated in a cursory fashion in the present work. The current paper applies the concepts and principles outlined in Part 1 to the testing of pharmaceutical products that are administered topically. Expanding the principles of photostability testing to support use of this class of drug products is important for a number of reasons:

- A deficit continues to exist in the literature and in general understanding of the photostability testing needed to support the administration of pharmaceutical products;
- Product light exposure during handling and use can adversely impact the efficacy and safety of a pharmaceutical product;
- Topical drug products are administered by application to external body surfaces and, as a result, have the potential to be exposed to a significant amount of light during use by the patient;
- Formulations are often applied as thin films maximizing the surface to volume ratio and hence increasing the potential to react with incident light;
- For some indications (e.g., psoriasis), exposure of the skin to sunlight, high-intensity UV, or simulated solar light after application of a topical drug is part of the treatment;
- Increasing the dialogue in the scientific community on the topic will lead to improved testing approaches, more effective labeling, better patient and practitioner education, and hence ultimately improved health outcomes.

Our analysis of topical products in the USP[2] showed that 95 of the 342 products (28%) listed have monograph language that indicates storage in a light-protective container. The situation is similar in Europe[3] with many topical products labeled as requiring protection from light (Table 1); however, the label

Correspondence to: David Clapham (Telephone: +44 1920 883943; E-mail: david.clapham@gsk.com); Allen C. Templeton (Telephone: +215 652-0041; E-mail: allen_templeton@merck.com)

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Table 1. Topical Products with a Protect from Light Designation or Light Protective Immediate Pack

Active Pharmaceutical Ingredient	Dosage Form	Immediate Container	Source	Administration Route
Topical light mineral oil	Oil	Preserve in tight, light-resistant containers	USP	Skin
5-Aminolevulinic acid hydrochloride	Gel	Aluminum tube	UK[a]	Skin
Acetylcysteine	Solution	Type I amber glass	UK[a]	Eye
Aminobenzoic acid gel	Gel	Preserve in tight, light-resistant containers	USP	All exposed skin (i.e., nose)
Aminobenzoic acid topical solution	Solution	Preserve in tight, light-resistant containers	USP	All exposed skin (i.e., nose)
Anthralin cream	Cream	Preserve in tight containers, in a cool place; Protect from light	USP	Skin
Anthralin ointment	Ointment	Preserve in tight containers, in a cool place; protect from light	USP	Scalp
Atropine sulfate	Solution	NS	UK[a]	Eye
Azithromycin dihydrate	Solution	LDPE	UK[a]	Eye
Beclometasone dipropionate	Suspension	HDPE	UK[a]	Nose
Benzethonium chloride tincture	Tincture	Package in tight, light-resistant containers	USP	Skin (hands)
Benzethonium chloride topical solution	Solution	Preserve in tight, light-resistant containers	USP	Skin
Benzocaine cream	Cream	Preserve in tight containers, protected from light, and avoid prolonged exposure to temperatures exceeding 30°C	USP	Skin, mouth
Benzocaine ointment	Ointment	Preserve in tight containers, protected from light, and avoid prolonged exposure to temperatures exceeding 30°C	USP	Skin
Benzocaine topical solution	Solution	Preserve in tight containers, protected from light, and avoid prolonged exposure to temperatures exceeding 30°C	USP	Ear
Betamethasone dipropionate	Gel	HDPE	UK[a]	Scalp
Betamethasone valerate	Solution	Plastic bottle	UK[a]	Scalp
Betamethasone valerate lotion	Lotion	Preserve in tight, light-resistant containers, and store at controlled room temperature	USP	Skin
Betaxolol hydrochloride	Solution	LDPE	UK[a]	Eye
Brimonidine tartrate	Solution	LDPE	UK[a]	Eye
Calcipotriol monohydrate	Gel	HDPE	UK[a]	Scalp
Carbamide peroxide topical solution	Solution	Preserve in tight, light-resistant containers, and avoid exposure to excessive heat	USP	Ear
Carbol–Fuchsin topical solution	Solution	Preserve in tight, light-resistant containers	USP	Skin
Chloramphenicol	Solution	LDPE, HDPE, white bottle	UK[a]	Eye
Chlorhexidine acetate topical solution	Solution	Preserve in well-closed containers, protected from light	USP	Mouth
Chlorhexidine gluconate solution	Solution	Preserve in tight containers, protected from light, at controlled room temperature	USP	Skin
Chlorhexidine gluconate topical solution	Solution	Preserve in well-closed containers, protected from light; store at controlled room temperature	USP	Skin
Chlortetracycline hydrochloride ointment	Ointment	Preserve in collapsible tubes or in well-closed, light-resistant containers	USP	Eye
Ciclopirox topical solution	Solution	Preserve in well-closed containers, protected from light; store at controlled room temperature	USP	Skin (nails)
Clioquinol and hydrocortisone cream	Cream	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin
Clioquinol and hydrocortisone ointment	Ointment	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin
Clioquinol cream	Cream	Preserve in collapsible tubes or tight, light-resistant containers	USP	Skin
Clioquinol ointment	Ointment	Preserve in collapsible tubes or tight, light-resistant containers	USP	Skin
Clocortolone pivalate cream	Cream	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin

Continued

Table 1. Continued

Active Pharmaceutical Ingredient	Dosage Form	Immediate Container	Source	Administration Route
Cocaine and tetracaine hydrochlorides and epinephrine topical solution	Solution	Package in sterile, tight, light-resistant containers; store in a refrigerator	USP	Skin (face), scalp
Cocaine hydrochloride tablets for topical solution	Solution	Preserve in well-closed, light-resistant containers	USP	Mouth, nose
Compound benzoin tincture	Tincture	Preserve in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat	USP	Skin (blisters)
Compound clioquinol topical powder	Powder	Preserve in well-closed, light-resistant containers	USP	Skin
Crotamiton cream	Cream	Preserve in collapsible tubes or tight, light-resistant containers	USP	Skin
Cyclopentolate hydrochloride	Solution	LDPE	UK[a]	Eye
Dexamethasone sodium phosphate	Solution	LDPE, PE	UK[a]	Eye
Dibucaine cream	Cream	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin
Dibucaine ointment	Ointment	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin
Dimethyl sulfoxide gel	Gel	Preserve in tight, light-resistant containers	USP	Skin
Dimethyl sulfoxide irrigation	Sterile solution	Preserve in single-dose containers, and store at controlled room temperature, protected from strong light	USP	Skin
Dimethyl sulfoxide topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Dorzolamide hydrochloride	Solution	HDPE, LDPE	UK[a]	Eye
Dyclonine hydrochloride gel	Gel	Preserve in collapsible, opaque plastic tubes, or in tight, light-resistant glass containers	USP	Skin, mouth
Dyclonine hydrochloride topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin, mouth
Epinastine hydrochloride	Solution	PE	UK[a]	Eye
Estradiol hemihydrate	Patch	Paper/aluminum/PE foil pouch	UK[a]	Skin
Estradiol transdermal system	Transdermal patch	Preserve in hermetic, light-resistant, unit-dose pouches	USP	Skin
Estradiol transdermal system	Transdermal	Preserve in hermetic, light-resistant, unit-dose pouches	USP	Skin
Ethinylestradiol	Patch	Sachet composed of four layers: a LDPE film (innermost layer), an aluminum foil, a LDPE film, and an outer layer of bleached paper	UK[a]	Skin
Felbinac	Foam	Aluminum	UK[a]	Skin
Ferric subsulfate solution	Solution	Preserve in tight, light-resistant containers, and store at temperatures above 22°C	USP	Skin
Ferric sulfate	Solution for compounding	Preserve in tight, light-resistant containers, and store at controlled room temperature	USP	Skin
Fluorescein sodium	Solution	PP	UK[a]	Eye
Flurandrenolide cream	Cream	Preserve in tight containers, protected from light	USP	Skin
Flurandrenolide lotion	Lotion	Preserve in tight containers, protected from heat, light, and freezing	USP	Skin
Flurandrenolide ointment	Ointment	Preserve in tight containers, protected from light	USP	Skin
Fluticasone propionate cream	Cream	Preserve in collapsible tubes or tight containers, protected from light; store between 2 and 30°C	USP	Skin
Fluticasone propionate ointment	Ointment	Preserve in collapsible tubes or tight containers, protected from light; store between 2 and 30°C	USP	Skin
Gentamicin sulfate	Solution	LDPE	UK[a]	Ear
Glyceryl trinitrate	Patch	Polyester	UK[a]	Skin
Hexachlorophene cleansing emulsion	Cleaning emulsion	Preserve in tight, light-resistant, nonmetallic containers	USP	Skin
Hexachlorophene liquid soap	Soap	Preserve in tight, light-resistant containers	USP	Skin
Hydrogen peroxide	Solution	Amber glass bottle	UK[a]	Skin, mouth

Continued

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Table 1. Continued

Active Pharmaceutical Ingredient	Dosage Form	Immediate Container	Source	Administration Route
Hydrogen peroxide concentrate	Concentrate	Preserve in tight, light-resistant containers, at controlled room temperature	USP	Skin
Hydrogen peroxide topical solution	Topical solution	Preserve in tight, light-resistant containers, at controlled room temperature	USP	Skin
Hydroquinone cream	Cream	Preserve in well-closed, light-resistant containers	USP	Skin
Hydroquinone topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Hypromellose	Solution	LDPE	UK[a]	Eye
Ibuprofen	Gel	Aluminum tube	UK[a]	Skin
Indomethacin topical gel	Gel	Preserve in tight, light-resistant, wide-mouth containers, or ointment jars; store at controlled room temperature	USP	Skin
Iodine topical solution	Topical solution	Preserve in tight, light-resistant containers, at a temperature not exceeding 35°C	USP	Skin
Iodoform	Powder	Preserve in tight, light-resistant containers, store at controlled room temperature, and prevent exposure to excessive heat	USP	Skin
Latanoprost	Solution	PE, LDPE	UK[a]	Eye
Levobunolol hydrochloride	Solution	LDPE	UK[a]	Eye
Mafenide acetate cream	Cream	Preserve in tight, light-resistant containers, and avoid exposure to excessive heat	USP	Skin
Mafenide acetate for topical solution	Topical solution	Preserve in tight, light-resistant containers, at controlled room temperature; for prepared solutions, use within 48 h of preparation	USP	Skin
Meclocycline sulfosalicylate cream	Cream	Preserve in tight containers, protected from light	USP	Skin
Methoxsalen topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Methylprednisolone acetate cream	Cream	Preserve in collapsible tubes or in tight containers, protected from light	USP	Skin
Miconazole nitrate	Powder	Aerosol container with epoxy lining	UK[a]	Skin
Minoxidil	Solution	HDPE	UK[a]	Scalp
Neomycin and polymyxin B sulfates and bacitracin ointment	Ointment	Preserve in tight, light-resistant containers, preferably at controlled room temperature	USP	Eye
Neomycin sulfate and bacitracin ointment	Ointment	Preserve in tight, light-resistant containers, preferably at controlled room temperature	USP	Eye
Neomycin sulfate and flurandrenolide cream	Cream	Preserve in collapsible tubes or in tight containers, protected from light	USP	Skin
Neomycin sulfate and flurandrenolide lotion	Lotion	Preserve in tight containers, protected from light	USP	Skin
Neomycin sulfate and flurandrenolide ointment	Ointment	Preserve in collapsible tubes or in tight containers, protected from light	USP	Skin
Neomycin sulfate and methylprednisolone acetate cream	Cream	Preserve in collapsible tubes or in tight containers, protected from light	USP	Skin
Neomycin sulfate and prednisolone acetate ointment	Ointment	Preserve in collapsible tubes or in tight containers, protected from light	USP	Skin
Nicotine transdermal system	Transdermal patch	Preserve in the hermetic, light-resistant, unit-dose pouch	USP	Skin
Nitrofurazone ointment	Ointment	Preserve in tight, light-resistant containers; avoid exposure to direct sunlight, strong fluorescent lighting, and excessive heat	USP	Skin
Nitrofurazone topical solution	Topical solution	Preserve in tight, light-resistant containers; avoid exposure to direct sunlight and excessive heat	USP	Skin
Nitromersol topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Norelgestromin	Patch	Sachet composed of four layers: a LDPE film (innermost layer), an aluminum foil, a LDPE film, and an outer layer of bleached paper	UK[a]	Skin

Continued

Table 1. Continued

Active Pharmaceutical Ingredient	Dosage Form	Immediate Container	Source	Administration Route
Oxybuprocaine hydrochloride	Solution	PP	UK[a]	Eye
Oxytetracycline hydrochloride and hydrocortisone ointment	Ointment	Preserve in collapsible tubes or in well-closed, light-resistant containers	USP	Skin
Oxytetracycline hydrochloride and polymyxin B sulfate ointment	Ointment	Preserve in collapsible tubes, or in well-closed, light-resistant containers	USP	Eye
Padimate O lotion	Lotion	Preserve in tight, light-resistant containers	USP	Skin
Papain tablets for topical solution	Topical solution	Preserve in tight, light-resistant containers in a cool place	USP	Skin
Phenylephrine hydrochloride	Solution	PP	UK[a]	Eye
Pilocarpine nitrate	Solution	NS	UK[a]	Eye
Piroxicam cream	Cream	Preserve in a tight, light-resistant plastic resealable container, and store at controlled room temperature	USP	Skin
Podophyllum resin topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Warts
Povidone iodine	Solution	PP	UK[a]	Eye
Prednicarbate cream	Cream	Preserve in tight, light-resistant containers, and store at controlled room temperature	USP	Skin
Prednicarbate ointment	Ointment	Preserve in tight, light-resistant containers, and store at controlled room temperature	USP	Skin
Prednisolone sodium phosphate	Solution	PP	UK[a]	Eye
Rose water ointment	Ointment	Package in tight, light-resistant containers	USP	Skin
Silver sulfadiazine cream	Cream	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin
Sodium hypochlorite topical solution	Topical solution	Preserve in tight, light-resistant 1-L plastic containers, and store at controlled room temperature	USP	Skin
Strong iodine tincture	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Tetracaine hydrochloride topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Tetracycline hydrochloride for topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Thimerosal tincture	Topical solution	Preserve in tight, light-resistant containers, and avoid exposure to excessive heat	USP	Skin
Thimerosal topical aerosol	Topical aerosol	Preserve in tight, light-resistant, pressurized containers, and avoid exposure to excessive heat	USP	Skin
Thimerosal topical solution	Topical solution	Preserve in tight, light-resistant containers, and avoid exposure to excessive heat	USP	Skin
Timolol maleate	Solution	LDPE	UK[a]	Eye
Timolol maleate	Gel	LDPE	UK[a]	Eye
Tolu balsam tincture	Tincture	Package in tight, light-resistant containers, and store at controlled room temperature. Avoid exposure to direct sunlight and to excessive heat	NF	Skin
Tretinoin cream	Cream	Preserve in collapsible tubes or in tight, light-resistant containers	USP	Skin
Tretinoin gel	Gel	Preserve in tight containers, protected from light	USP	Skin
Tretinoin topical solution	Topical solution	Preserve in tight, light-resistant containers	USP	Skin
Tropicamide	Solution	NS	UK[a]	Eye

[a]Electronic Medicine Compendium (UK).
LDPE, low-density polyethylene; HDPE, high-density polyethylene; PE, polyethylene; PP, polypropylene; NS, not specified.

language for protecting the product from light during handling and use is often inadequate and sometimes virtually nonexistent. Furthermore, the indication for a drug in different formulations is not always consistent in regards to the necessary precautions to protect from light (such as the use of light-protective containers). Although a formulation and its excipients can have a significant effect on the photostability of its active pharmaceutical ingredient, the inconsistent distribution of information

across different formulation types is unlikely to be fully explained by actual differences in product photostability that varies with compositional changes. Moreover, the lack of label language or specific instructions to practitioner or patients is somewhat surprising. Several possible reasons could explain this gap in information, including a general lack of understanding of the topic within the scientific community and the absence of a systematic approach to arrive at appropriate instructions, label language, and practical recommendations.

SCOPE

The present work seeks to address the limitations described above. It does not cover photostability testing for topical products in the context of the ICH Q1B[4] as this has been discussed previously in the literature.[5–11]

For the purposes of this commentary, the term topical drug products is taken to mean any pharmaceutical product applied to an external surface of the body such as creams, ointments, lotions, pastes, eye drops, transdermal formulations, and patches.[12,13] Although some of these formulations are designed to deliver the API systemically, in general this paper will concern itself with in-use testing relevant to direct exposure on the surface of the body (e.g., skin, eye, within a patch delivery system). It is acknowledged, however, that light does penetrate the skin (the depth of penetration being dependent on wavelength),[14] and this should be taken into account if the topical compound or one of its photoproducts is known to accumulate in the surface layers of the skin or the eye.[14,15] Products intended for subcutaneous injection were covered in our previous work.[1]

Sunscreen formulations will not be considered even though they are topically applied and may interact with pharmaceutical products, either enhancing stability via providing some reduction in photoexposure or leading to reduced stability via chemical–physical interaction. A significant literature already exists on the stability of sunscreens and their interactions[16–22] and the reader is referred to these papers for further information. Though not covered as part of this work, it should be noted that there is a potential for concomitant use of a sunscreen with a pharmaceutical product and any impact may need to be considered as part of a careful evaluation of the implications of photostability on topical product use on a case-by-case basis.

Similarly, the interaction of topical pharmaceutical products with cosmetics is outside the scope of this paper. Once again, there is a significant body of literature concerned with the formulation of cosmetics.[23,24] Given the similarity of many cosmetic formulation types with those used for pharmaceuticals, there is a considerable degree of overlap in the formulation concepts employed and a potential risk of destabilizing the formulation of either or both agents. Many cosmetic products deliberately contain colored materials with potentially complex photochemical behavior that may have the potential to initiate instability in an otherwise stable pharmaceutical product. As with sunscreen usage, if the topical drug product could be anticipated to be used concomitantly with cosmetics, the impact of photostability on the combined products should be considered in order to ensure appropriate instruction and label language to support effective therapeutic usage.

Considering the wide range of topical product types and their often complex multiphasic formulations, this paper will discuss some overarching factors that could be of relevance to any topical formulation type and then provide sections that discuss photostability testing considerations and the implications of photostability as it pertains to the handling and therapeutic use of a product. The summation will be recommended testing considerations in two broad groups of topical formulations, namely:

- Formulations intended for direct topical administration.

Relevant pharmaceutical product applications include but are not restricted to creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, solutions, douches, contact lens care products, soaks, eye drops, and colloidal suspensions. Products in this category of topical formulations may range from visually transparent to opaque. Common packaging approaches range from fully light impenetrable to clear containers.

- Patch and transdermal drug delivery systems.

These drug delivery systems comprise patches that are affixed to the body surface of a patient. In general, patch products target local delivery, whereas transdermal systems target systemic delivery via a dosage form applied topically.[25]

This is a somewhat arbitrary distinction but it provides a convenient method of grouping the suggested photostability testing approach required.

It should be noted that formulation composition can have a dramatic impact on the photostability of the product.[26–32] Thus, every effort should be taken during the formulation development process to optimize formulation compositional components so as to reduce or eliminate photostability concerns by design and avert the need for controls in label language and practice.

GENERAL CONSIDERATIONS

Administration of topical pharmaceutical products comprises a large range of formulation types and administration sites. In Part 1 of this series, six sequential steps along the pharmaceutical product supply chain from the manufacturer to the patient were described. For all topical products, these same steps should again be considered with the exception that dilution is rare except in the case of extemporaneous compounding in response to a specific prescription (e.g., dilution of potent steroids). Of particular note among these steps is the need to understand the light-protective nature of packaging components employed (both immediate and secondary packaging), how the product is typically stored within distribution channel settings (e.g., hospital, commercial pharmacy), and how patients typically will use and store the product. One significant risk that should be considered when commercial formulations are diluted for use by a patient is the possibility that stabilizing components of the formulation could be diluted below their effective level.[33]

For many topical drug products, the primary pack is either light proof (e.g., cream or ointment in a metal tube with a screw cap) or light protective (e.g., cream or ointment in an opaque plastic tube). Light-protective containers can provide very different levels of protection (Fig. 1). It should be remembered that even though a package appears to be opaque, it may still

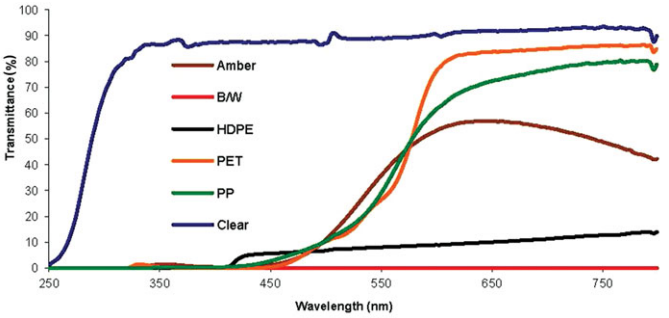

Figure 1. Light-protective effect of various packaging materials. (Amber, Amber Glass; B/W, Black lined HDPE; HDPE, High Density Polyethylene; PET, Amber Polyethylene Terephthalate; PP, Polypropylene; Clear, Clear Glass- USP/EP Type 1)

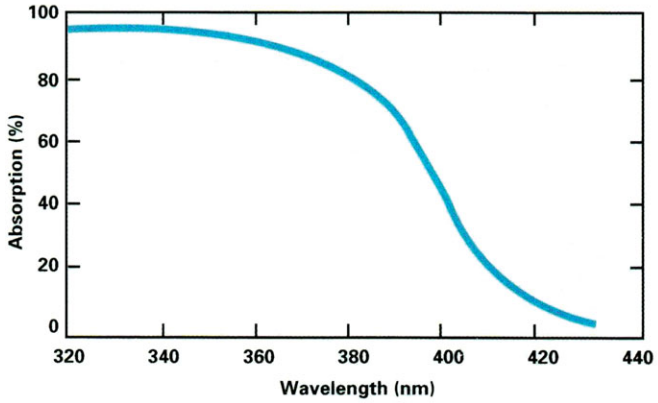

Figure 2. Absorption spectrum of TiO_2.

transmit significant amounts of light. As one example, plastic tubes that employ titanium dioxide (TiO_2) as an opacifier may show significant transmission in the wavelength range above 380 nm[34,35] (Fig. 2). A secondary package consisting of a cardboard box is often employed and the product is completely protected from light when stored within this additional packaging. Recent developments in delivery options for topical formulations may include both protective and less protective elements.[36]

Packaging aspects should have been evaluated during the standard ICH Q1B compliant testing, but it may be wise to consider the photostability of the product within primary and secondary packaging in the environment where the product will be used. Nevertheless, for most formulations, the in-use period effectively starts either when the product is subdispensed into a clear container or when the product is applied to the skin or other external sites.

Not all topical products can be packed into opaque containers as it is often important to be able to visually inspect the product for homogeneity before use (e.g., eye drops, ear drops, etc.), and in this case the in-use period will commence once the primary pack is exposed to light and will continue until the product usage period is complete. Extemporaneous compounding of creams and ointments is common and hence it is important to emphasize that compounding pharmacists need appropriate awareness and guidance on handling light-sensitive compounds in order to prevent photodegradation during preparation. Patient education is also required to ensure that the product is handled and administered in a manner that minimizes photostability issues. For products packaged and distributed from pharmaceutical companies, active education of pharmacy staff and patients could also be important because label language for light-sensitive topical products is often ambiguous or lacking, as noted previously. An additional factor to consider is that many topical products are made available for direct purchase by the patient from a pharmacy and may be kept for some considerable time unless the stability of the product once the pack is opened (and hence the use by date) precludes this.

Before proceeding to a discussion of the recommended testing for each class of topical formulations, it is also important to consider that physical and/or technical performance aspects other than chemical instability of the API in topical formulations may be affected by light. These may be as important, or in some cases more important, than light-induced reduction in content of the drug substance itself. Factors to consider include viscosity, changes of semisolid formulations because of degradation of stabilizing polymers, photo-induced precipitation of suspended materials, change in droplet charge and size of emulsions (particularly lipid emulsions), embrittlement of polymeric packaging, and color changes.[37–40] In addition, it is important to remember that many topical formulations are biphasic (or even multiphasic). Effects on the physical state of the formulation could potentially lead to dramatic changes in chemical degradation from all sources including photo-induced degradation.

PHOTOTOXICITY AND BIOLOGICAL CONSIDERATIONS

Certain medications, both oral and topical, are known to cause localized phototoxicity through direct action by the drug (or one of its degradation products). An example is tretinoin, a drug used to treat acne, where patients have been found to develop increased sun sensitivity and are more prone to sunburn as a result. Others drugs can elicit a disseminated photo allergenic response following interaction between the photo-activated drug/formulation and endogenous/exogenous substances. The effects on skin can be in the form of a rash or burn and can persist and spread in the case of photo allergenic responses.[41,42]

The *in vitro* phototoxicity testing described in the ICH S10 (Step 4) guidance[43] may give valuable additional information on photochemical reaction mechanisms to aid understanding of in-use photostability of topical and ophthalmic products. Of particular interest for the purposes of this paper is the proposed test for the detection and quantification of any reactive oxygen species (ROS) such as singlet oxygen and superoxide that may be formed. These species may go on to react with endogenous molecules, other components in the formulation or *in vivo*, and lead to a phototoxic response or photodegradation.[44–46] The UV exposure requirements of this test are " a UVA dose ranging from 5 to 20 J/cm^2" typically 7.2 J/cm^2 (~20 Wh/m^2) integrated UV radiation, approximately 10-fold less than required for the ICH confirmatory test. As a guide, exposure at the 250 W/m^2 setting (i.e., the total output integrated over the range 200–800 nm) in a Suntest CPS+/XLS+ cabinet for approximately 35 min will provide the photoexposure required for this test. Guidance for the photoexposure conditions required using other solar simulators is given in the literature.[47,48] It may be wise to combine the "worst case" testing proposed in *Summary of Recommended Photostability Testing Conditions* with a test under the reduced radiation levels required for the ROS assay so that both stability and safety aspects can be considered in a single study.

Table 2. Skin Depth to Achieve Reduction of 99% Incident Light[16]

Wavelength (nm)	Depth to Achieve Reduction of 99% of Light (μm)
250–280	40
300	100
360	190
400	250
700	400

The pharmacological response to dermal preparations requires skin penetration followed by transport to the site of action, which can be followed by a number of techniques including coherent Raman scattering.[49] Skin penetration is a complex process dependent on many factors, including the constituents of the formulation. Literature reviews highlight the key steps in skin penetration: (1) release of drug into solution, (2) permeation through the skin, (3) transfer from epidermis to dermis, and (4) pharmacokinetics and metabolism.[50,51]

For light to interact with the drug substance, photons need to be absorbed by the active ingredient, the formulation, or perhaps the skin itself. Skin contains many light absorbing materials (e.g., some lipids, proteins, and pigments such as melanin, carotene, and hemoglobin). The epidermis is the top layer of skin and has a thickness of around 70 μm. From Table 2, it can be extrapolated that photons of wavelength of more than 280 nm will be able to penetrate through the entire outermost layer of skin. Therefore, when evaluating the effects of light on the medicinal product on skin, one should consider the ability of the API (and excipients where appropriate) to penetrate to the different skin layers. Depending on the depth of penetration and other molecular properties, light/radiation may either have a significant or no effect.[14] The absorption of photons by the skin itself may gain increasing importance with age. It has been demonstrated that skin ageing is associated with the formation and accumulation of products of oxidative stress, including cross-links between amino acids and lipid peroxidation products, which may have photo-sensitizing properties.[52–54]

RELEVANT LIGHT SOURCES

There is a broad range of possible light sources that the product might be exposed to during in-use conditions. This topic was discussed in some detail in Part 1 and the interested reader is referred to that work. In particular, Table 1 in that document details the range of light intensities that are encountered under various climatic conditions, whereas Table 2 provides information about light intensities that are recommended for various environments by the IESNA. Part 1 also provides an overview of the light sources used in ICH Q1B testing in terms of relating these to "real world" scenarios and testing approaches. A recent paper provides some guidance on the UV radiation from various energy-efficient light sources.[55]

As before, the approach taken in this paper is to cover the broad diversity of light sources to which topical products might be exposed by leveraging light sources that cover the broad categories of artificial indoor lighting, outdoor daylight, and window filtered daylight. As noted elsewhere, topical formulations may be exposed to direct sunlight, which is highly variable both in intensity and spectral power distribution based on a number of factors such as time of day, season, weather conditions, geographical location, and so on.[56] If many of the variables are known, or can be reasonably estimated, the solar radiation impinging on a product over time can be modeled through use of commercial software packages such as Atlas' CESORA (Calculation of Effective Solar Radiation).

Figure 3 shows the relative spectral power distribution of D65 (i.e., simulated outdoor daylight) and ID65 (simulated window glass-filtered daylight). As can be seen, the proportion

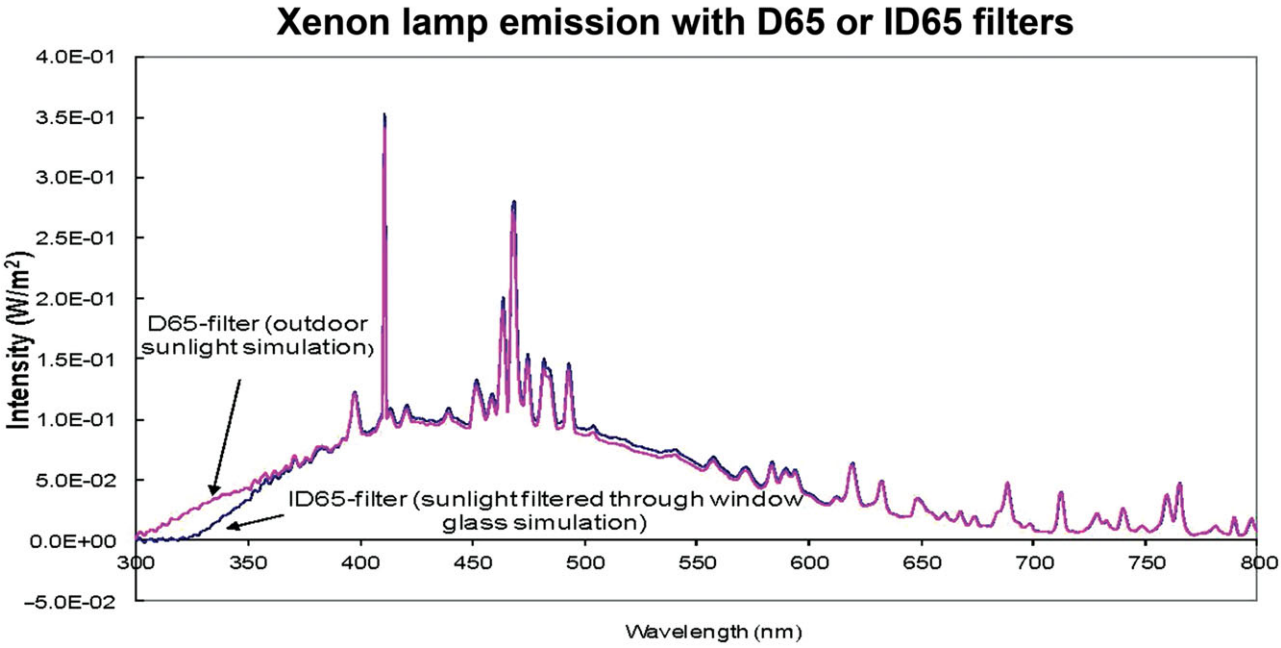

Figure 3. Spectral irradiance for the Atlas Suntest Photochamber for filtered sunlight (D65) and window filtered sunlight (ID65) showing the primary change in the irradiance occurs between 300 and 350 nm resulting from the glass absorption of light in this wavelength region.[60]

of higher energy wavelengths (~290–360 nm) is significantly higher in the former compared with the latter. This can have important implications for the stability of formulations, particularly as topical formulations tend to be applied as thin layers maximizing the surface area available for light interaction. The situation may be further exacerbated by the fact that patients with several skin conditions (that are often treated with topical drugs) sometimes deliberately expose themselves to bright light or sun beds either as part of the therapeutic regimen or for perceived psychological benefits.[57,58] Users of topical formulations can be exposed to significant levels of UV radiation during everyday outdoor tasks even when they do not consciously expose themselves to the sun.[59]

In addition to considering the relevant light sources/doses, it can be useful to understand, as much as possible, the relationship between photostability and wavelength of light in order to ascertain whether the product would be particularly susceptible to degradation in certain lighting conditions. Clothing and/or bandages might be expected to provide some protection against light exposure, but light transmission through clothing could be considerable and there may also be restrictions suggested that disallow clothing or bandages because of concerns that the product would be absorbed or removed by these materials, thus limiting therapeutic benefit.[61,62]

In the following sections, we will consider how the implications of topical product light exposure translate to photostability testing and risk mitigation strategies for the various common topical product types.

SUMMARY OF RECOMMENDED PHOTOSTABILITY TESTING CONDITIONS

The general approach taken in this paper is to establish a typical "worst case" light exposure for each formulation type/packaging configuration and typical lighting conditions. This information can in turn be used to recommend a set of photostability testing conditions to identify the appropriate controls to articulate in product labeling and usage instructions. Given the inherent diversity of topical products and light exposure scenarios, it is impractical to cover all possible product and package permutations but the realistic "worst case" conditions proposed in Table 3 below should serve as a useful framework to cover a vast majority of cases.

Figure 4 provides a flow chart to describe the recommended approach. Depending on whether the product is provided directly by a pharmaceutical manufacturer (part a) or is produced/modified by a pharmaceutical practitioner (part b), the flow chart describes how to employ existing knowledge about the photostability of the product or how to test the product to understand its likely in-use photostability. It then provides guidance on how to use the information gained to aid safe use of the product. In alignment with ICH Q1B, the figure uses the term "acceptable change" requiring the user to employ good scientific judgment to evaluate the relevance/implications of any changes that might occur. The term "acceptable change" can be taken to mean any change that can be justified as having no significant adverse effect on efficacy, patient safety, or perceived quality. An example would be a small reduction of the level of the API provided that therapeutic efficacy is still assured or a small increase in a nontoxic degradation product/impurity that are within relevant safety/GMP specification limits.

Table 4 describes a categorization of products intended for topical administration as well as patch drug delivery systems. The categorization in terms of in-use photostability considerations is driven by the light-protective character of packaging components prior to actual application of the product to the site of action. Topical formulations are often presented in tubes as the primary pack that can be categorized into light impenetrable (e.g., metal foil tubes) or light penetrable (e.g., a nonmetallic tube), which may or may not be sufficient to protect the product. In the latter case, a cardboard box (secondary packaging) may be required to protect the product from light. The same approach applies for other common primary packaging types for topical products such as, for example, bottles or jars. By consulting this table, one can arrive at the relevant product presentations for photostability testing. In the case of secondary packaging not being required for light protection, the initiation of the in-use product period starts with the removal of the product from the primary packaging, whereas in the case of secondary packaging being required, the initiation of the in-use period begins upon removal from the secondary packaging.

Table 3 takes the relevant product presentations for photostability testing and applies the typical light intensities found within indoor artificial lighting, indoor artificial lighting with window-filtered daylight, and outdoor lighting to arrive at recommended photostability testing conditions and approaches. The proposed light intensities are based on data from Table 2 in Part 1 of this commentary series.[1] Clearly, an important consideration in understanding worst case light exposure is an estimate of hold times (i.e., the time a sample could be exposed to a particular set of conditions) for the product during in-use conditions in the various settings. For product use indoors, with or without the presence of windows, a typical hold time of the product of 24 h is recommended for evaluation as a worst case. For outdoor lighting, it is recommended to consider a range of hold times in order to understand the nature of light impact on product degradation. Of course, if the treatment regimen involves removal of the product after a certain time (e.g., wiping off a cream or removal of a transdermal patch), then the hold time should be adjusted accordingly.

In terms of product presentation, formulated products within secondary and primary packaging should be in final form with the packaging material composition, shape, color, labeling, and other markings representative of those intended for commercial distribution. For the formulated product removed from packaging, it is important to mimic the application of the product to the site of action in the photostability test. For formulations other than patches, the product should be spread as a thin layer on a glass dish (or other suitable surface) in order to be similar to what a patient would apply to the skin. For particularly photosensitive products where clothing would be recommended to be employed during use, it might be necessary to overlay the thin film of product on the dish with a single layer of cloth of representative composition(s) in order to understand the protective nature of such materials. However, we recommend evaluating and establishing controls in the absence of such material as the range of material types and thicknesses vary greatly and are seen as introducing too much variability in recommendations on how to deal with the implications of data generated during in-use photostability studies.

A second major type of formulation is the patch or transdermal drug delivery systems. These drug delivery systems have been evaluated for a number of indications and offer patient

Table 3. Light Exposure, Hold Times, and Recommended Testing Conditions[a] for topical drug products[b]

Light Source(s)	Typical Light Intensity	Relevant Product Presentation for Photostability Testing		Typical Hold or In-Use Times (h)[c]	Realistic Worst Case Light Exposure[d]	Recommended Photostability Testing Approach
Indoor artificial lighting	400–1000 Lux (home setting)	Company	• Formulated product in secondary packaging • Formulated product in primary packaging	24	24,000 Lux h	Cool white fluoresesent as per ICH Option 2[e]
		Pharmacy or patient	• Formulated product removed from primary packaging			
		Company	• Patch delivery system upon removal from secondary packaging • Patch removed from primary packaging	Recommended attachment time	Recommended attachment time x 1000 Lux	
Indoor lighting with window-filtered daylight	400–1000 Lux, 17 W/m^2[f]	Company	• Formulated product in secondary packaging • Formulated product in primary packaging	24	24,000 Lux h, and 200 Wh/m^2[g]	ICH option 1 or option 2
		Pharmacy or patient	• Formulated product removed from primary packaging			
		Company	• Patch delivery system upon removal from secondary packaging • Patch removed from primary packaging	Recommended attachment time	Recommended attachment time x (1000 Lux and 17 W/m^2)	
Outdoor lighting	475[h] W/m^2 (average location on earth and worst case time during day)	Company	• Formulated product in secondary packaging • Formulated product in primary packaging	1	475 Wh/m^2[i]	ICH option 1 with UV exposure consistent with worst case
		Pharmacy or patient	• Formulated product removed from primary packaging	2	950 Wh/m^2[i]	
		Company	• Patch delivery system upon removal from secondary packaging • Patch removed from primary packaging	4 Recommended attachment time	1900 Wh/m^2[i] Recommended attachment time x 475 W/m^2[i]	ICH option 1 with UV exposure consistent with worst case

[a] Simulated in-use conditions would include, for example, evaluating the product photostability characteristics when covered by bandage or clothing.

[b] Select the test conditions appropriate to the product, pack, and patient usage conditions.

[c] Artificial lighting lamps produce limited emission in the UV with typical intensity of 0.1–0.3 W/m^2 at 1000 Lux and this should be factored for products with severe sensitivity to UV light. Option 1 could also be used but the UV intensity delivered will be far higher than using option 2. Filters could be employed with option 1 to attenuate the UV exposure received.

[d] Hold time conditions should be adjusted based on specific product circumstances such as rapid absorption or cases of significant phototoxicity concerns.

[e] Visible light exposure only.

[f] UV light exposure calculation based on ICH Q1B guidance approach of 200 Wh/m^2 equivalence to 1–2 days of window-filtered UV light exposure. Assuming 1 day corresponds to 12 h of daylight, and 1 day corresponds to a UV light exposure of 200 Wh/m^2, an intensity of 16.7 W/m^2 is calculated.

[g] Integrated UV radiation between 295 and 400 nm.

[h] Value based on measured data from the Eppley Total UV Radiometer, Miami, Florida, July 24, 1996 (the clearest, highest UV day in 1996). The UV dose recorded (295–400 nm) for the entire day was 473 Wh/m^2. Between 10 am and 2 pm, the total was 245 Wh/m^2. Information provided by Atlas Material Testing Technology, LLC, 1500 Bishop Court, Mount Prospect, Illinois 60056.

[i] Integrated total UV/Vis radiation across the wavelength range 295–800 nm.

convenience for extended-release systemic indications or prolonged localized delivery to a site of action. The patch delivery system is typically housed within primary packaging consisting of a plastic or metallic foil (e.g., Mylar®) sleeve. The patch system within primary packaging is often further housed within a cardboard box or carton. As before, patch systems may or may not be adequately protected from light when stored within primary packaging and thus the initiation of the in-use period will either be upon removal from secondary packaging (where this is required for full light protection) or when removed from primary packaging. The relevant product presentations for the patch drug delivery system are then exposed to light of the various sources in the same manner as other formulations intended for topical administration. An important factor to consider is the recommended attachment time for the product in establishing the typical hold time and thus duration for which to expose the relevant product presentations to light of typical intensities for indoor and outdoor settings. The recommended

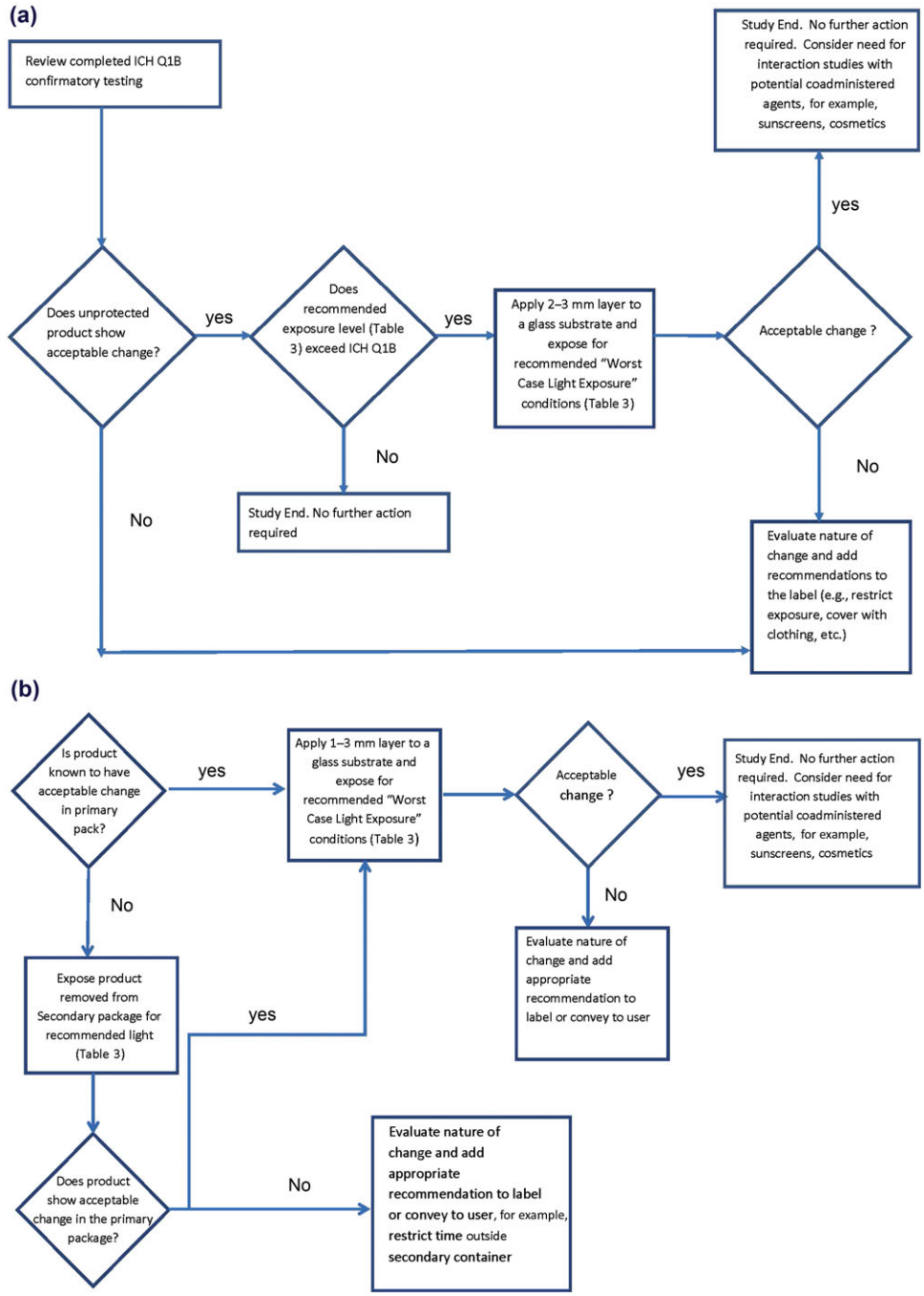

Figure 4. Example decision tree for in-use testing of topical pharmaceuticals (a) using product as supplied by manufacturer and (b) using a product produced or modified by a pharmaceutical practitioner.

attachment time for patch drug delivery systems will vary by product type and intended indication.[63]

As an example of how the concepts in this section may be applied, let us suppose that a hospital physician has had excellent results in the treatment of a psoriatic condition using a 1% cream formulation of Compound X and now wishes to use that API in a pediatric population. In order to avoid overdosing the pediatric patients, a 0.25% cream formulation is desired for this patient group. As no such strength is commercially available, the hospital pharmacy is requested to dilute the commercial product with a compatible cream base. To cover the length of the testing of the efficacy of the compound in this patient group, this preparation needs to be available for at least 1 year and so a "one-time" ad hoc formulation is not appropriate. Although the commercial 1% cream formulation of Compound X does not have a "protect from light" designation, the compounding pharmacist is aware that dilution could have an adverse effect on stability; thus, testing the chemical, physical, microbiological, and light stability of dilutions made with the chosen cream base (or possibly to use such tests as one significant factor in the choice of which base to use) would be appropriate. In order to test the photostability of the product, the pharmacist will

Table 4. In-Use Photostability Categorization of Topical Drug Products by Product Type and Packaging Protection Offered to Light

Formulation Type[a]	Primary Packaging	Secondary Packaging Required for Light Protection?	Initiation of the In-Use Product Period	Relevant Product Presentation for Photostability Testing
Formulations intended for topical administration	Light impenetrable container	N	Removal from primary packaging	Formulated product in primary packaging
				Formulated product removed from primary packaging
	Light penetrable container	Y	Removal from secondary package	Formulated product in secondary packaging
				Formulated product in primary packaging
				Formulated product removed from primary packaging
		N	Removal from primary package	Formulated product in primary packaging
				Formulated product removed from primary packaging
Patch drug delivery systems	Patch delivery system	Y	Removal from secondary package	Patch delivery system upon removal from secondary packaging
				Patch removed from primary packaging
		N	Patch within use setting	Patch removed from primary packaging

[a] Extemporaneous formulations require light protection during preparation within the compounding pharmacy and subsequent steps up to and during patient administration.

refer to Figure 4b for guidance. As this 0.25% cream is a new product, it is not known whether change in the primary pack will be acceptable and so it will be necessary to consult Table 3 to determine the required light conditions to use for the test. In this case where the treatment is chronic, the patient may well take the packed product with them so it may be exposed to outdoor lighting; hence, the product should be exposed in the proposed pack to ICH Option 1 lighting with UV exposure consistent with worst case (as determined by the practitioner based on their knowledge of the likely patient behavior) for 2–4 hours.

If this level of light exposure produces unacceptable change, for example, excessive loss of API, significant color change, generation of a significant level of impurity, and so on, then the pharmacist should seek an alternative diluent base that does not cause these changes, explore alternative approaches to satisfying the clinicians requirements, or evaluate the severity of the changes produced and provide guidance on how the product should be stored, for example, by keeping it in a light proof outer container or limiting the shelf life of the product in the primary pack.

If the product is stable for the required time in the primary pack (note that this "shelf life" will inevitably be relatively short unless all aspects of product stability following dilution have been assured, for example, that the product remains adequately preserved), the next step is to evaluate any potential degradation that may occur when the patient applies the product to their skin. For this step, the pharmacist should apply a 1–3-mm layer to a suitable substrate and expose it to the appropriate conditions as determined from Table 3 (in this case outdoor lighting) for 1 or 2 hours depending on what is dictated by the treatment regimen. Hopefully, this test will confirm that any changes produced by exposure to this level of light will be acceptable (i.e., not deleterious to product efficacy, safety, or quality). However, if the changes seen are not acceptable, then the pharmacist must use their professional judgment to decide whether those changes can be ameliorated by some realistic behavior changes by the user (e.g., completely covering the treated area with clothing, sunscreen, etc.), whether an alternative formulation approach may ameliorate the changes or whether they will need to inform the clinician that a suitable formulation may not be available.

By contrast, if a commercial 0.25% cream formulation of Compound X does exist, then Figure 4a should be consulted. In this case, if ICH Q1B confirmatory testing shows the product to be stable when not protected by the pack and the expected level of light exposure by the patient does not exceed that required for the ICH Q1B confirmatory test (e.g., if the only product exposure will be to indoor lighting perhaps in an "in patient" setting), then the dispensing pharmacist can rely on data provided by the manufactures and does not need to undertake any further stability tests.

CONCLUSIONS

This document suggests conditions for in-use testing of topical preparations according to estimated worst case scenarios. Though photostability testing per ICH Q1B has been in place for more than a decade, there remains a clear gap in photostability testing aimed at ensuring the safety and efficacy of pharmaceutical products while they are being used by the patient. This manuscript has extended the previous guidance provided on pharmaceuticals intended for injection to topical drug products. The same principles as in Part 1 were employed and involve establishing the in-use photoexposure starting point and typical in-use conditions in order to design testing that mimics the light exposures experienced by the product. An area of differentiation for topical drug products relative to injectables and other pharmaceutical products is the potential for them to be exposed to direct sun environments. This clearly creates a heightened level of concern because of the potentially

high levels of photoexposure. Table 4 provides a summary of product types and how in-use conditions are defined. Table 3 evaluates the product types under various common light categories to derive testing recommendations and takes into account the likely configuration, location, lighting intensities, and hold times. Conducting photostability testing to support in-use conditions as per Table 3 is recommended to help understand the risks of light exposure to the product during the course of administration.

The data collected from in-use photostability testing should be used to assess and manage risks for adverse consequences of light exposure during administration. As discussed in Part 1, risk mitigation strategies could involve inclusion of label language, detailed product usage instructions, or including additional items (e.g., light protective covering for application site) with the product in a combination pack to ensure successful products usage. For topical products, the label or patient information may also involve advice to patients to limit skin exposure to sunlight and/or to cover treated areas with clothing or to wear sunscreen and eye protection.[64,65]

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