CARON
Opening Doors for Scientists

WHITE PAPER

RAPID & REPEATABLE PHOTOSTABILITY RESULTS IN AN ICH Q1B OPTION II CHAMBER

Bob Dotterer, Engineering Director, and Alan Campbell, VP Marketing

Abstract

There are a wide variety of alternate design approaches to construct and configure a pharmaceutical-grade photostability test chamber. Companies performing photostability testing on new drugs face a wide range of choices when it comes to selecting a product that best meets the requisite ICH Q1B guideline. Understanding the differences between these design approaches is key, if the user is to select a unit that provides the best balance of test speed, repeatability, and flexibility, and avoid compromised test results. Caron's 7540 Series chambers provide unequalled blend of best-in-class speed to exposure and repeatability of results, through careful lamp selection, chamber configuration, light control, and control of all potential test environment variables.

ICH Introduction

ICH's Q1B guideline is a harmonized standard for photostability testing of new pharmaceutical drug substances and drug products. For companies developing or manufacturing pharmaceutical drugs, a robust photostability testing process is essential to ensure product quality and regulatory compliance. Inadequate or substandard testing equipment can result in costly delays and lost revenue. Whether performing forced degradation or confirmatory studies, the solution is a carefully designed photostability testing chamber that creates environmental test conditions in accordance with ICH Q1B.

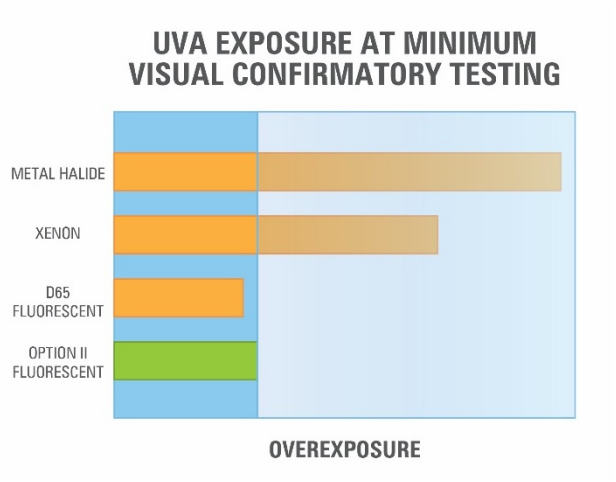
In the two decades since its release, ICH Q1B's importance has increased. Manufacturers of nutraceuticals, cosmetics, personal care products, and food are also turning to the ICH's quality guidelines, including Q1B, as tools to help improve the quality and consistency of their products.

Q1B Options 1&2: Light Source Selection

ICH Q1B allows either single lamp (Option I: fluorescent D65, metal halide or xenon) or dual lamp types (Option II: fluorescent near-UV (UVA) and cool white). Both options are intended (for confirmatory studies) to meet the same exposure levels – 1.2 million lux hours for

visible (VIS) spectrum light, and 200 watt hours/square meter for near ultraviolet (UVA) energy. Option I lamps emit both UVA and visual irradiance, thus the UVA to visual irradiance ratio is fixed.

Since the exposure requirements for photopic and UVA levels are independent, this fixed ratio causes one of the Option I dose levels to overexpose. This fixed ratio varies according to lamp type. At the minimum confirmatory testing requirement, UVA overexposure is around 540 W-h/m2 for xenon and 2500W-h/m2 for metal halide (1). This corresponds to 270% and 1250% overexposure, respectively.



Due to fluorescent D65 lamp's lower UVA irradiance, they overexpose in the visual region. Ideally, illuminance and UVA irradiance would be controlled independently. Selective overexposure can lead to false results, and mistaken and potentially costly product packaging solutions based on that data. This problem is only alleviated by using two different light sources, as specified in Option II.

In addition to UVA overexposure, xenon and metal halide lamps produce significant amounts of heat. At elevated temperatures, dark controls are needed to segregate photochemical degradation from thermal degradation. Large internal cooling fans are necessary to dissipate this heat and can pose presentation problems (particularly at the formulation stage) by blowing around samples. In addition, high temperatures can cause sample color changes that are difficult to compensate for.(2)

Issues with xenon and metal halide are not limited to overexposure and excessive heat generation. Xenon and metal halide lamps have a short life span and typically need to be replaced every 750 to 1500 hours.(1) They require light filters to eliminate radiation below 320mn. Over time, the filters become solarized and the wavelength of the UV cutoff increases.(1) They also have a relatively small maximum illumination level area, reducing uniformity within the test chamber.

The advantages of Option II cool white and UVA fluorescent lighting outshine other options. Independent control of illuminance and UVA irradiance eliminates unanticipated overexposure for confirmatory tests and provides flexibility for forced degradation and research studies. Fluorescent lamps generate minimal heat and eliminate the need for expensive light filters and dark controls. Small internal fans can be employed to subtly maintain proper air temperature without disturbing sample presentation. Fluorescent lamps typically last over ten thousand hours, have low replacement costs, and provide a large illumination area.

Correctly Measuring & Controlling Irradiance

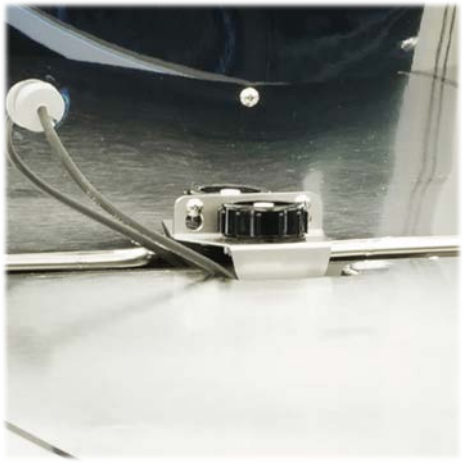
Traditionally, chemical actinometers were used to measure sample dose as part of a timed exposure test. Selecting suitable chemical actinometers involved tradeoffs. Each chemical actinometer used must be calibrated for the light source used.(3) Absorption spectra of the test compound and actinometer should be similar (4). ICH describes the use of quinine hydrochloride dehydrate as an example of a chemical actinometer. Quinine has a 'dark reaction' where the reaction continues after it is used.(5) Not only is quinine wavelength dependent, it is affected by temperature and pH variations.(1) Due to these characteristics, quinine has been shown to be inaccurate with lamps that produce significant amounts of heat, such as xenon lamps.(6)

Chemical actinometers also have an inherently limitation when used in a photostability chamber; they do not provide a mechanism to automatically turn the lamps off or alert the operator when the desired exposure level is reached. What if confirmatory testing completes while the chamber is unattended? Chemical actinometers cannot record irradiance levels throughout the test. As lamps age, their intensity decreases. This causes irradiance levels of full-power light sources to fluctuate over time. Because timed tests are unable to compensate for irradiance level changes, a timed test based on initial light intensity would terminate prematurely compared to the desired dose. This dose uncertainty is particularly troublesome for confirmatory studies.

Ideally, a physical actinometer (radiometer) with irradiance integration would continually monitor dose and control the photostability test duration accordingly. Selecting the proper radiometer, however, is also challenging. Irradiance measurements with instrumental radiometers have high margins of uncertainty; 10% is not uncommon.(7) Unless using a spectral radiometer, two radiometers configured specifically for each wavelength region (UVA and visual) are required. The radiometer should have a wide bandwidth and be cosine corrected.(8) Radiometers need to be calibrated or certified before use. Spectral radiometers are cumbersome to use and awkward to integrate with photostability chamber lamp controls.

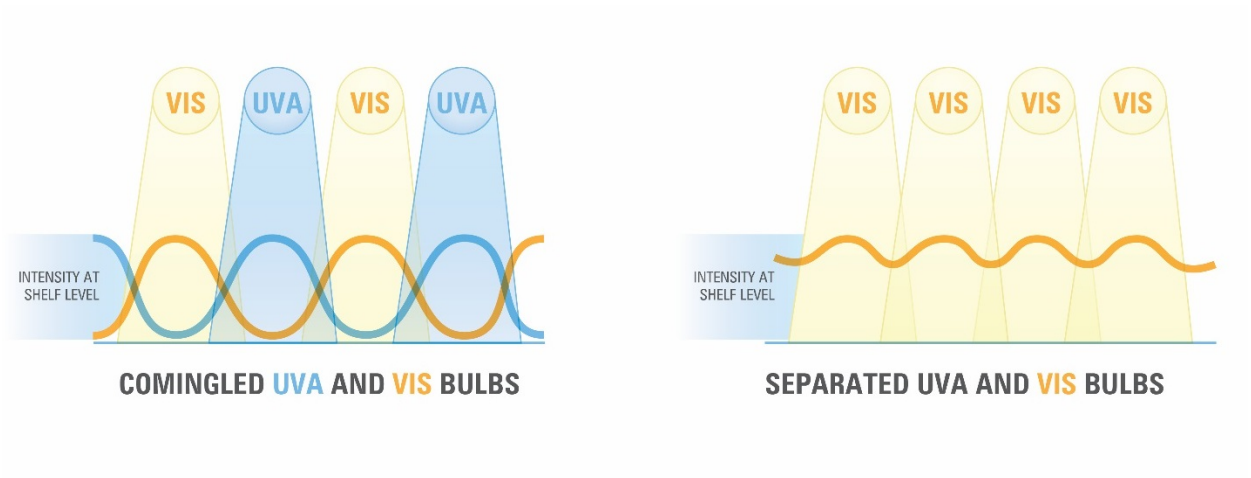
Accurate illuminance and UVA irradiance measurements are best achieved with a built-in radiometer. Photopic detectors have a wide bandwidth and spectral response that closely follows the CIE photopic action spectrum. Near-UV irradiance is then measured by an independent UVA light detector. Detectors utilizing a Teflon diffuser may result in an exceptionally good cosine response. Detectors should be both cosine corrected and calibrated to NIST or other traceable standards. It is best if radiometer displayed units for illuminance and UVA irradiance are consistent with ICH documentation.

An integrating radiometer combined with chamber controls should be used to ensure precise dose levels at test completion. Lamps can then be programmed to automatically shut-off based on an exposure level (dose). Advanced systems are capable of running based on exposure level or timed tests. Whether operating at full power or dimmed condition, the programmable exposure level should automatically adjust testing time to compensate for influencing factors like lamp aging as well as pause testing for sample evaluation. During both exposure level and time based testing, the radiometer should show irradiance, test time remaining and accumulated dose levels.



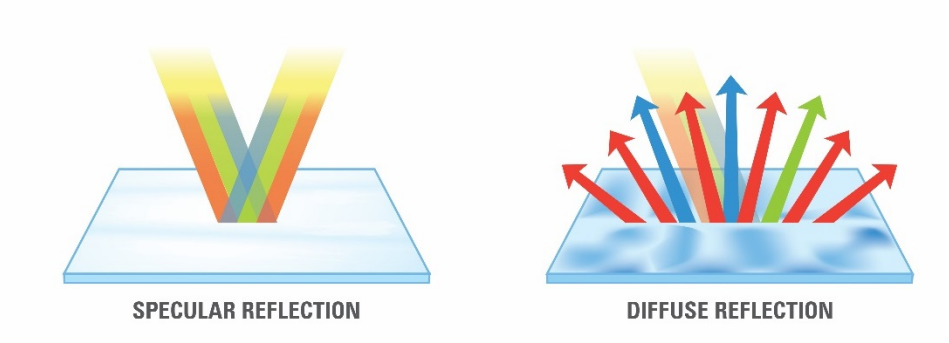
Design for Light Uniformity

ICH Q1B doesn't specify light source (or product sample) layouts. As a result, some Option II chambers alternate UVA and VIS bulbs above the target shelf. While it might seem convenient to run a single-step cycle, comingling different spectrally-specific light sources creates uniformity issues within a chamber that are very difficult to anticipate and address. Sample exposure levels are highest when directly under a bulb. If bulbs are installed alternating between UVA and VIS, the effect is to vary product exposure levels by spectra based on their specific shelf position. Achieving the required exposure at a 'lower light level' location will result in over exposure at a 'higher light level' location. Therefore, reduced uniformity will lead to overexposed product.



The simplest and most repeatable way, therefore, to avoid varying UV/VIS exposure ratios within a test batch is to divide UV and VIS exposure into separate physical areas, each separately measured and controlled.

In addition to light source positioning, interior chamber materials are also a factor in achieving good exposure uniformity. Materials that reflect light onto samples should reflect and absorb radiation uniformly across the UVA and photopic spectrums. Diffuse reflection will subject samples to light with a different spectral power distribution than that specified by ICH. This is especially true comparing reflective properties of UVA verses visual irradiance. Chamber interior materials such as mirrored stainless steel and white paint distort reflected light by absorbing different amounts of irradiance over the relevant spectra.



The lamp's spectral power distribution is best preserved by using specular aluminum on interior reflective surfaces. Specular aluminum uniformly reflects light across both UVA and photopic spectrums. It is available with a 95% total reflection (DIN 5036-3) and only 0.01% diffuseness at 15º. Specular aluminum's superior reflective properties outshine mirrored stainless steel and white painted surfaces for not only illuminance reflection but also UVA irradiance.

Option II designs built with standard stainless steel interiors or with comingled light source spectra tend to compensate for their uneven light distribution by limiting the area that can be used for test purposes, decreasing unit utility and productivity.

Test Speed as a Design Factor

Q1B specifies cumulative test exposures, not elapsed time. Optimizing unit design to maximize intensity while preserving chamber uniformity can dramatically reduce test time, improving throughput. This balance between throughput and accuracy is essential. Users who once needed a large upright chamber to perform photostability studies at low light levels can achieve the same through-put with high-intensity benchtop units.

As previously discussed, Option I chambers produce very high intensities, leading to minimized test time. Their use of one or two bulbs, however, produces substantial uniformity variance within the chamber, and greatly limits the space available for test materials. Selective overexposure and thermal effects make this approach even less favorable.

Option II chambers are offered in two primary configurations; dedicated Q1B, and hybrid Q1A/Q1B. Hybrid chambers, that attempt to offer both Q1A and Q1B testing environments within a single unit, typically include design compromises such as a reduced number of bulbs, minimized light diffusers, and conventional painted or stainless steel interiors. While

these hybrid chambers can eventually produce ICH-specified light exposures, they tend to either greatly extend test duration, or limit the area within each shelf that can reliably be used. Typically, purpose-built Q1B Option II chambers feature more technical bulb and interior panel layouts, including features such as light diffuser panels and densely spaced bulbs that produce both maximum intensity and uniformity across the sample shelf. As a result, some dedicated Option II chambers rival the overall test speed of their Option I counterparts, while providing far larger test surfaces and a more favorable overall test environment.

Low Temperature as a Potential Test Criteria

An often overlooked potential test setpoint is the photostability companion to ICH Q1A's required test conditions for "drug substances intended for storage in a refrigerator". This Q1A conducted in the Long term study at 5C for 12 months, is substantially different than the ambient to above ambient test conditions required for General case storage drugs. These refrigerated drugs should also be tested for photodegradation, requiring comparable test conditions to avoid introducing thermal variables. While most drugs don't require this test condition, few Q1B chambers offer it as a feature or option. Testers, particularly those performing contract services, should seriously consider including low temperature to their requirements listing, in case the need arises.

Humidity as a Potential Test Criteria

While not required by ICH for confirmatory studies, the state of hydration affects the photostability of some samples.(2) This means identical drug substances subjected to identical irradiance and temperature conditions can have very different results if exposed to different humidity levels. When product presentation is such that samples are exposed to ambient (chamber) air, the effects of humidity must be considered. Uncontrolled, humidity can alter photostability testing results and cloud their interpretation. Controlling humidity in a photostability chamber requires proper equipment and associated controls.

Using steam to raise the humidity level adds more heat into the chamber and requires long warm-up times. Steam boilers also introduce additional serviceability complications, since they accumulate any soluble or insoluble deposits present within the feed water, deposits that can cause premature boiler heat element failure. Atomizers and ultrasonic nebulizers respond quickly to changes in humidity setpoint or chamber conditions, and produce no waste heat. Nebulizers use sound waves generated by a vibrating membrane to excite water molecules into vapor. They have the capacity to respond quickly to changes in humidity within a smaller chamber, but are less capable within the context of larger walk-in designs. Atomizers force water through a fine nozzle under pressure, flashing the water off into vapor as it exits the orifice. Either technology would be suitable for use in a smaller benchtop-scale chamber.

Caron's Solution: 7540 Series Photostability Chambers

The 7540 Series' dedicated Q1B Option II design provides the best combination of speed, accuracy, space utilization, and flexibility in a photostability chamber. These units utilize cool white and near-UV lamps, arranged in two independent banks. Integral radiometers accurately measure and control lighting for each bank. Specular aluminum panels line the chamber interior, and special light diffusers are employed, maintaining proper spectral power distribution and placing over 75% of the shelf space within a tight ±10% (UVA)/±10 (VIS) uniformity specification (-2 & -3 models).

By combining tight uniformity with closely spaced bulbs, the full Q1B-specified exposures can be achieved within 42 hours (35 hours VIS, 7 hours UVA, -2 and -3 models only).

For usage flexibility, humidity and low test temperature condition options are also provided. Optional ultrasonic nebulizers provide tight humidity control, and refrigeration capacity and chamber insulation is provided to allow units to reliably operate down to 5C.

All controls are programmed through an eye-level icon-based color touchscreen interface that tracks lamp life, and permits easy program modification, including 3X, 10X or similar calculated overexposure testing for forced degradation studies.

Drug photostability is a specialized and complex environmental control application; requiring a specialized technical solution for best results. Companies choosing an ICH Q1B photostability chamber for ICH guideline Q1B should select a purpose-built solution, such as Caron's 7540 Series chambers. By combining an optimized approach to ICH lighting options with practical solutions to general environmental control challenges, Caron's chambers enhance the testing process, ensuring both product quality and regulatory compliance.

Bibliography and References

S.R. Thatcher et al., "Pharmaceutical Photostability: A Technical Guide and Practical Interpretation of the ICH Guideline and Its Application to Pharmaceutical Stability" Pharmaceutical Technology, 25 (2001)

J. Piechocki, "Pharmaceutical Photostability Testing Protocols" presented at CBI's Design and Qualify Photostability Studies in Stability Testing, June 2001

International Conference on Harmonization, "Guidelines for the Photostability Testing of New Drug Substances and Products," Federal Register 62, 27115-27122 (1997)

T.D. Rhines, "Pharmaceuticals Design Photostability Studies within FDA and ICH Guidelines" presented at CBI's Regulatory Compliance and Expedited Design and Execution of International Stability Programs, June 2000.

T.C. Kester, Z. Zhan, and D.H. Bergstorm, "Quinine Actinometry Studies Under Two Photolysis Sources Specified by the ICH Guideline on Photostability Testing", presented at the AAPS National Meeting (Seattle, WA, 1996)

H. Drew et al., "Quinine Photochemistry: A proposed Chemical Actinometer System to Monitor UVA Exposure in Photostability Studies of Pharmaceutical Drug Substances and Drug Products", Pharm. Forum 24, 6334-6346 (1998)

B. Angelo, "Radiometry/Photometry", presented at Photostability 99: 3rd International Conference on the Photostability of Drug Substances and Drug Products (Washington, DC, 10-14 July 1999)

J. Piechocki, "Radiometry Photometry Actinometry and Spectroradiometry", presented at Photostability of Drugs and Drug Products, July 2001

CARON PRODUCTS & SERVICES, INC. PO Box 715 / Marietta OH 45750 / **PHONE** 740 373 6809 / 800 648 3042 / **FAX** 740 374 3760