Photostability of Pharmaceuticals

Conforming to the ICH Guideline for the Photostability Testing of New Drug Substances and Products (ICH Q1B) Using the SUNTEST® XXL+FD

1. *Executive Summary*

"The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration." From the official website for ICH, www.ich.org.

The result of this effort was a guideline, the ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products (ICH Q1A). Photostability testing is further addressed in a separate official ICH document (ICH Q1B). This applies to both forced degradation stress testing and confirmatory studies of the active drug substance, drug product and excipients. ICH Q1B is applicable to small molecules; large molecules (proteins, monoclonal antibodies, etc.) are addressed in the separate document, Stability Testing of Biotechnological/Biological Products (ICH Q5C). Additionally, the Q1B protocol has been adopted as the VICH Tripartite Harmonized Guideline covering the Photostability Testing of New Drug Substances and Products in the Veterinary Field.

Despite Implementation of the ICH stability and Photostability guidelines, issues remain that are not specifically covered in the documents and left to the researcher's discretion. Additionally, several non-equivalent options are available, reflecting different practices for handling drug products on different continents.

2. *Summary of key ICH Q1B contents*

Note: The numbers and letters correspond to the sections of the official ICH Q1B document; however, not all sections are listed.

2.1 General

The ICH Harmonized Guideline on Stability Testing of New Drug Substances and Products requires that photostability testing be an integral part of stress testing. The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that light exposure does not result in unacceptable change.

2.2 Light Sources, Option 1

ICH recommends the following light sources that emit an output *similar to* D65/ID65 emission standard. "D65 is the internationally recognized emission standard for outdoor daylight as defined in ISO 10977:1993 standard. ID65 is

the equivalent indoor indirect daylight standard [(1)]." Light sources conforming to D65/ID65 emission standard should contain UV and visible spectrum, such as:

- Xenon lamps
- Artificial daylight fluorescent lamp combining visible and UV outputs
- Metal-halide lamps

2.3 Procedure

ICH requires the following two exposure criteria for confirmatory photostability studies:

- Not less than 1.2 million Lux hours of Visible (400-800 nm) exposure
- Not less than 200 Watt • hours / m² of UV (320-400 nm) exposure

The ICH Guideline states that "The minimum Visible light exposure level represents approximately 3 months of continuous exposure to artificial visible light in the pharmacy, warehouse or home with the protective container removed from the product. The UV light exposure roughly corresponds to 1 to 2 days inside close to a window with sunlight exposure [(1)]." However, the ratio of UV to VIS radiation that the ICH estimates to represent the "real" storage conditions differs from the UV/VIS ratio defined in the standard for indoor direct daylight (ID65). ID65 is generally selected as more representative of actual exposure conditions; however, the more severe D65 conditions may be useful for "forced degradation" studies.

3. *Option 1 xenon light source*

Filtered (D65 or ID65) xenon discharge lamps are full-spectrum light sources and simultaneously expose in the UV, Visible and IR spectral regions. Because the spectral distribution of the selected radiation source must conform to the D65 or ID65 standard (Option 1), a total irradiance of 200 W•hours/m² in the UV region (320-400 nm) simultaneously underexposes the visible by ca. 55 %, and a total irradiance of 1.2 million Lux-hours in the Visible (400-800 nm) simultaneously overexposes the UV by ca. 220 %.

At present, no single source provides the combination of simultaneous UV and Visible exposure levels required by the ICH Q1B (D65/ID65) without overexposure to the UV or underexposure to the Visible. However, since the recommended exposures are only **minimums**, and not absolute endpoints, exceeding the minimum exposure in the UV or Visible is perfectly acceptable.

Overexposure can be avoided by (1)

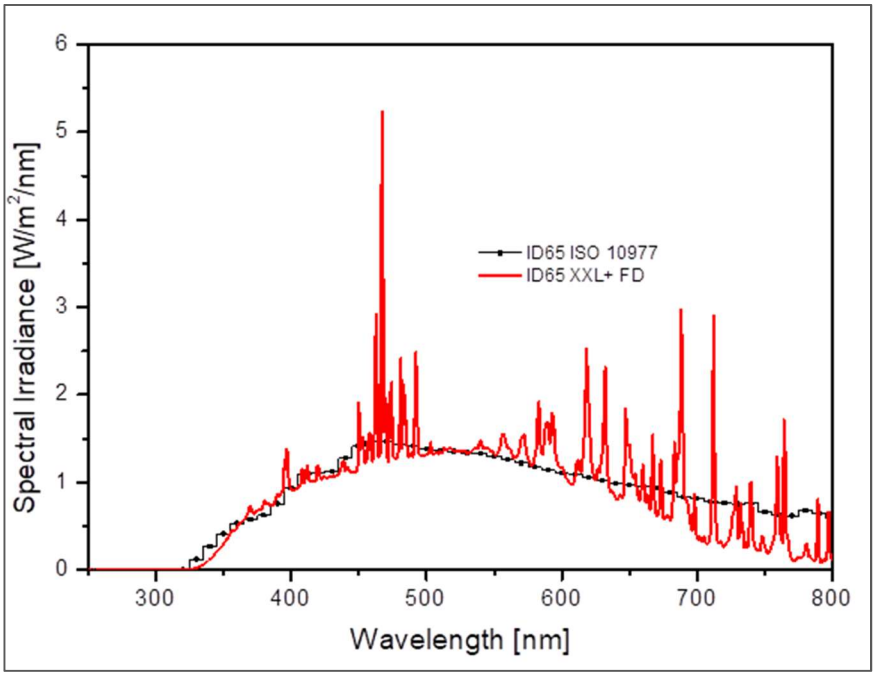


Figure 1: Spectrum Comparison between ID65 (ISO 10977 / ISO DIS 18909) and SUNTEST XXL+ FD with Solar ID65 filter system.

excluding the excess of UV radiation by the use of UV blocking filters around the specimen upon reaching the desired UV dose; (2) remove one half of the specimens after reaching the UV dose and continuing exposure to the Visible dose on the remaining specimens; or (3) running two separate tests, one for each criterion (UV and Visible), with identical specimens. Exceeding the minimum UV dosage is acceptable according to the guidelines, and may actually be a better simulation of end use conditions where the product is exposed to direct daylight or daylight filtered through window glass.

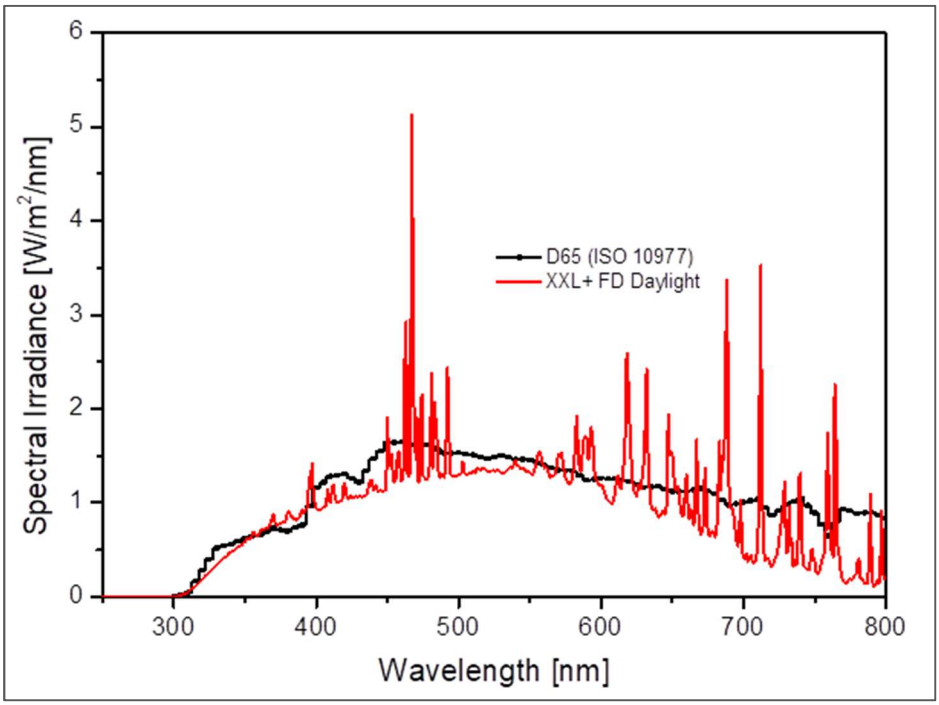


Figure 2: Spectrum Comparison between D65 (ISO 10977 / ISO DIS 18909) and SUNTEST XXL+ FD with Daylight filter system.

The Atlas SUNTEST XXL+ FD meets the ID65 (Figure 1) spectral criterion with an optical filter system consisting of an uncoated quartz base filter (chamber-integrated standard feature) and two Solar ID65 filters (accessory). The XXL+ FD filtered xenon light source is a full spectrum light containing both UV and Visible outputs as required in Option 1, with a UV cut-on of approx. 320 nm and a spectral distribution corresponding to ID65 per ISO 10977.

The following filter set is required to provide ID65 for the SUNTEST XXL+ FD:

P/N 56079177	Solar ID65, cut-on ca. 320 nm, simulating exposure behind 6 mm window glass

The following filter set is required to provide the more severe Daylight D65 (Figure 2) for the SUNTEST XXL+ FD:

P/N 56079174	Daylight filter, cut-on ca. 295 nm, simulating solar radiation outdoors

4. *Determining test duration*

The test procedures mentioned previously describe *minimum* exposure levels for confirmatory testing. The Atlas SUNTEST XXL+FD is available in two configurations regarding the light monitor – Wideband 300-800 nm or Broadband 300-400 nm:

P/N 55008093 XXL+FD BB 300-400 nm; 400 V, 50/60 cycles, 3/N/PE
P/N 55008094 XXL+FD BB 300-400 nm; 200-240V, 50/60 cycles, 3/PE

P/N 55008099 XXL+FD WB 300-800 nm; 400 V, 50/60 cycles, 3/N/PE
P/N 55008100 XXL+FD WB 300-800 nm; 200-240V, 50/60 cycles, 3/PE

SUNTEST XXL+FD WB 300-800 nm:

Exposure dosage in a Wideband 300-800 nm controlled XXL+FD is measured in radiometric units Kilojoules in a range of 300-800 nm or can be switched to Lux control, enabling exposure dosage in Kilolux in the visible range.

Exposure duration may be expressed in chronological time (hours). Remember, exposure duration is dependent on the irradiance (radiation intensity) settings.

1) Based on an irradiance level between 300-800 nm, the irradiance level between 320-400 nm can be approximated by the following equation (for ID65):

W/m² (320-400 nm) = W/m² (300-800 nm) ÷ 12.0

2) The illuminance level in Kilolux (klx) can be approximated by the following equation (for ID65):

1 klx = 4.4 W/m² (300-800 nm)

Radiation (Dosages) for XXL+FD; light monitor WB 300-800 nm (allows also Lux control):

1) UV minimum requirement

200 Wh/m² is approximately 9,150 kJ/m² @ 300-800 nm

2) VIS minimum requirement

1.2 million Lux•hours is approximately 24,060 kJ/m² @ 300-800 nm

SUNTEST XXL+FD BB 300-400:

Exposure dosage in the Broadband 300-400 nm controlled XXL+FD is measured in radiometric units Kilojoules in a range of 300-400 nm and cannot be switched to Lux control.

Exposure duration may be expressed in chronological time (hours). Remember, exposure duration is dependent on the irradiance (radiation intensity) settings.

The illuminance level in Kilolux (klx) can be approximated by the following equation (for ID65):

1 klx = 0.37 W/m² (300-400 nm)

Radiation (Dosages) for XXL+FD; light monitor BB300-400 nm:

1) UV minimum requirement

- 200 Wh/m² equals 720 kJ/m² @ 300-400 nm

2) VIS minimum requirement

- 1.2 million Lux•hours equals 1600 kJ/m² @ 300-400 nm

5. SUNTEST XXL+ FD conditions for the ICH Q1B protocol

5.1 Filters

The ID65 requirements in the ICH guideline can be achieved by using the SUNTEST ID65 filter system as described on page 4.

5.2 Irradiance and Exposure Duration

The ICH guideline does not recommend a specific irradiance (light intensity) setting. The SUNTEST XXL+ FD with the above filter system can accommodate a range of irradiance values from a minimum of 250 W/m^2 to a maximum of 600 W/m^2 in the wavelength range of 300-800 nm; a minimum of 55 klx to a maximum 130 klx between 400-800 nm. Or, with light monitors 200-400nm, a minimum of 25 W/m^2 to a maximum of 50 W/m^2 between 300-400 nm.

Lux, as used in the ICH guideline, is a photometric intensity unit for the visible bandwidth between 400-800 nm, weighted to the spectral response of the human eye. Higher irradiance settings result in shorter test durations to reach a given exposure. However, from a practical consideration, higher irradiance results in higher chamber air and specimen temperatures because the xenon emission includes infrared radiation.

The following provides an estimation of test durations at minimum and maximum SUNTEST XXL+FD irradiance levels to reach the ICH minimum exposure requirements.

SUNTEST XXL+FD BB 300-400 nm (ID65 filter system):

1) The UV minimum requirement: 200 Wh/m² (between 320-400 nm):

- At minimum irradiance: 200 Wh/m² ÷ 20 W/m² = 10.0 h SUNTEST XXL+FD exposure
- At maximum irradiance: 200 Wh/m² ÷ 48 W/m² = 4.2 h SUNTEST XXL+FD exposure

2) The Visible minimum requirement: 1.2 million lxh (between 400-800 nm):

- At minimum illuminance: 1200 klxh ÷ 54 klx * = 22.2 h SUNTEST XXL+FD exposure

  (20 W/m² ÷ 0.37)
- At maximum illuminance: 1200 klxh ÷ 130 klx ** = 9.2 h SUNTEST XXL+FD exposure

  (48 W/m² ÷ 0.37)

SUNTEST XXL+ FD WB 300-800 nm (ID65 filter system):

1) The UV minimum requirement: 200 Wh/m² (between 320-400 nm):

- At minimum irradiance: 200 Wh/m² ÷ 20.8 W/m² * = 9.6 h SUNTEST XXL+FD exposure;

(250 W/m² ÷ 12.0)

- At maximum irradiance: 200 Wh/m² ÷ 50.0 W/m² **= 4.0 h SUNTEST XXL+FD exposure;

(600 W/m² ÷ 12.0)

2) The Visible minimum requirement: 1.2 million lxh (between 400-800nm):

- At minimum illuminance: 1200 klxh ÷ 57 klx * = 21.0 h SUNTEST XXL+FD exposure

(250 W/m² ÷ 4.4)

- At maximum illuminance: 1200 klxh ÷ 136 klx ** = 8.8 h SUNTEST XXL+FD exposure;

(600 W/m² ÷ 4.4)

- At maximum illuminance: 1200 klxh ÷ 130 klx *** = 8.4 h SUNTEST XXL+FD exposure;

****maximum instrument setting for klx = 130 klx***

****Note: SUNTEST XXL+ FD WB 300-800 nm (model 2018) allows control in Lux. Programming and setting the Visible minimum requirement - 1,2 Mlxh (1200 klxh) as a dosage is possible!***

5.3 Temperature

Determining thermal stability of drug substances and products is a separate requirement and is conducted independently from the photostability portion of the ICH guideline. However, the infrared energy emitted from the xenon lamp causes the chamber and sample temperature to rise above the ambient temperature. ICH Guideline Q1B requires that care be taken to avoid degradation of thermally labile products. To avoid excessive temperatures, SUNTEST XXL+FD is connected to an Atlas SunCool air chiller to achieve lower test chamber and black standard temperatures. Using the SunCool, even at maximum irradiance of XXL+FD will allow chamber air temperatures of ca. 15 °C. (XXL+FD by itself typical chamber air temperature in the range of ca. 30-35 °C).

The SUNTEST XXL+FD offers selectable temperature control either by chamber air temperature (CHT) or by dual control - CHT and Black Standard Temperature (BST) simultaneously. The BST sensor is a widely used surface temperature probe for monitoring maximum possible surface temperature of a black surface. To achieve the ambient temperature requirement, Atlas recommends setting the BST as well as the Chamber air temperature CHT to their minimum.

Note that photo-degradation rates should increase linearly with the photon flux (irradiance intensity) while thermal degradation rates will not increase linearly with increasing temperature, but rather will follow typical Arrhenius kinetics. Therefore, more thermal degradation can occur in a longer test at lower irradiance and temperature than at higher ones. The ICH Guideline recommends the use of a “dark control” sample shielded from the light exposure.

The ICH Guideline states that the purpose of “forced degradation” studies is to evaluate the overall photosensitivity of the material for method development purposes and/or to elucidate the degradation pathways and to validate

stability-indicating assays. Unlike conformance testing, no specific testing criteria or minimums are recommended. However, the forced degradation experiment on the drug substance should be conducted using a visible light and UV exposure in excess of that used for formal product testing (e.g., by a factor of 3- to 5-fold). Alternatively, exposure may be continued until significant degradation has occurred. These studies are usually conducted on solid drug substances and also on solutions that are usually more susceptible to degradation.

Calibration

As chemical actinometers have shown inaccuracies, it is advised to calibrate the SUNTEST with approved radiometers (e.g. Atlas XenoCal®). Best laboratory practice would dictate that calibration of any device be verified before and after each test. However, due to the stability of the integral radiometer measuring system of the XXL+FD, common practice is to have the unit calibrated at intervals of 6 or 12 months by an accredited, Atlas-authorized service representative (check for local availability of ISO 17025 accreditation). If the equipment is moved to another location or the electrical supply is changed, Atlas recommends recalibration. Please note, the user is obliged to have the device recalibrated at appropriate intervals.

Cautionary Note: Radiometers and spectroradiometers must be calibrated for the specific type of lamp and power supply. Atlas manufactures specific Atlas XenoCal irradiance calibrators for use with SUNTEST instruments and the use of third-party devices may result in inaccurate measurements and calibrations.

6. References

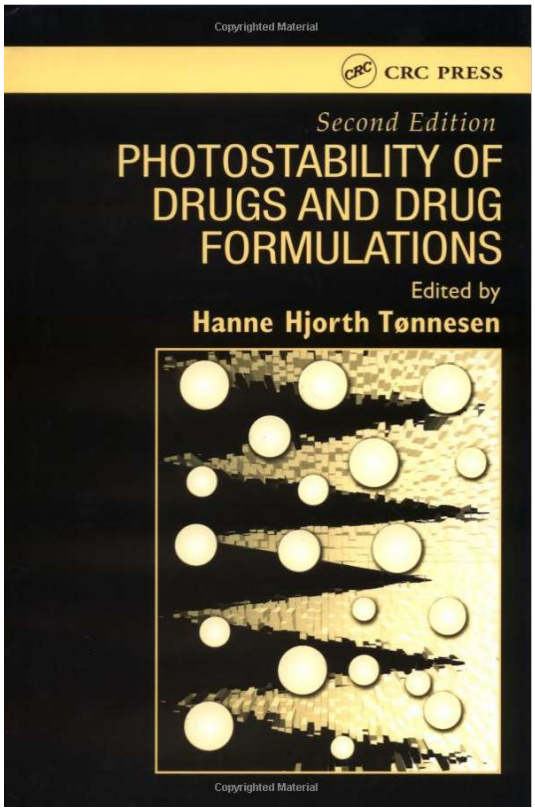
[1] S.R. Thatcher, R.K. Mansfield, R.B. Miller, C.W. Davis, and S.W. Baertschi, "A Technical Guide and Practical Interpretation of the ICH Guidelines and Its Application to Pharmaceutical Stability." *Pharmaceutical Technology*, March 2001: 102.

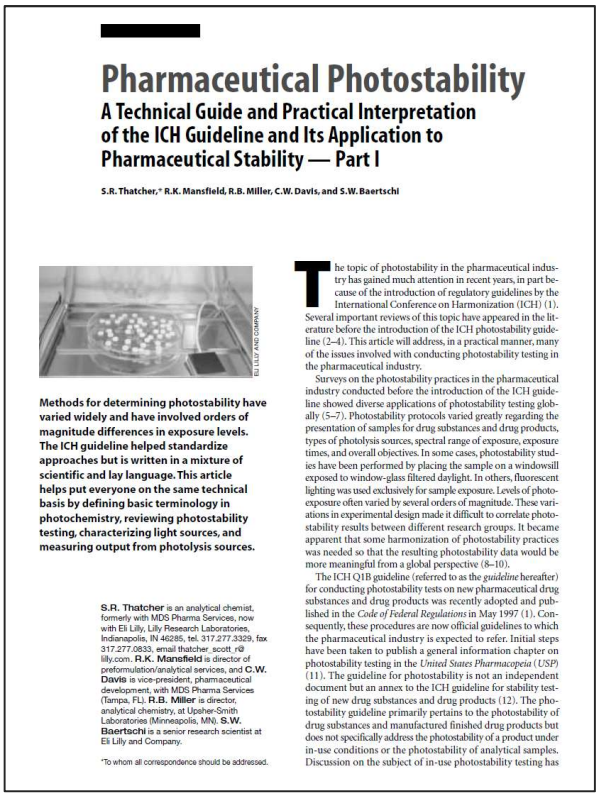
7. Library

1) A more thorough discussion of photostability testing and the ICH Q1B Guideline can be found in: Photostability of Drugs and Drugs Formulations 2nd edition, edited by Hanne Hjorth Tonnesen, CRC Press, ©2004, www.crcpress.com.

2) A summary of Q1B photostability testing may be found in: S.R. Thatcher, R.K. Mansfield, R.B. Miller, C.W. Davis and S.W. Baertschi, "*A Technical Guide and Practical Interpretation of the ICH Guideline and Its Application to Pharmaceutical Stability" Part 1 & 2.* Pharmaceutical Technology, March & April 2001.

3) A detailed critique of the original ICH Q1B Guideline is provided in*:* S.W. Baertschi, K.M. Alsante, H.H. Tønnesen*, A Critical Assessment of the ICH Guideline on Photostability Testing of New Drug Substances and Products (Q1B): Recommendation for Revision.* Journal of Pharmaceutical Sciences, Vol.99, No.7, July 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22076.





Pharmaceutical Photostability

A Technical Guide and Practical Interpretation of the ICH Guideline and Its Application to Pharmaceutical Stability — Part I

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Methods for determining photostability have varied widely and have involved orders of magnitude differences in exposure levels. The ICH guideline helped standardize approaches but is written in a mixture of scientific and lay language. This article helps put everyone on the same technical basis by defining basic terminology in photochemistry, reviewing photostability testing, characterizing light sources, and measuring output from photolysis sources.

The topic of photostability in the pharmaceutical industry has gained much attention in recent years, in part because of the introduction of regulatory guidelines by the International Conference on Harmonization (ICH) (1). Several important reviews of this topic have appeared in the literature before the introduction of the ICH photostability guideline (2–4). This article will address, in a practical manner, many of the issues involved with conducting photostability testing in the pharmaceutical industry.

Surveys on the photostability practices in the pharmaceutical industry conducted before the introduction of the ICH guideline showed diverse applications of photostability testing globally (5–7). Photostability protocols varied greatly regarding the presentation of samples for drug substances and drug products, types of photolysis sources, spectral range of exposure, exposure times, and overall objectives. In some cases, photostability studies have been performed by placing the sample on a windowsill exposed to window-glass filtered daylight. In others, fluorescent lighting was used exclusively for sample exposure. Levels of photoexposure often varied by several orders of magnitude. These variations in experimental design made it difficult to correlate photostability results between different research groups. It became apparent that some harmonization of photostability practices was needed so that the resulting photostability data would be more meaningful from a global perspective (8–10).

The ICH Q1B guideline (referred to as the *guideline* hereafter) for conducting photostability tests on new pharmaceutical drug substances and drug products was recently adopted and published in the *Code of Federal Regulations* in May 1997 (1). Consequently, these procedures are now official guidelines to which the pharmaceutical industry is expected to refer. Initial steps have been taken to publish a general information chapter on photostability testing in the *United States Pharmacopeia* (*USP*) (11). The guideline for photostability is not an independent document but an annex to the ICH guideline for stability testing of new drug substances and drug products (12). The photostability guideline primarily pertains to the photostability of drug substances and manufactured finished drug products but does not specifically address the photostability of a product under in-use conditions or the photostability of analytical samples. Discussion on the subject of in-use photostability testing has

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