1.2

ICH Q1B Guideline

Photostability Testing of New Drug Substances and Products

Comments for its Application

Preamble

The intrinsic photostability characteristics should be evaluated to demonstrate that light exposure does not result in unacceptable change.

Photostability testing is carried out on a
- single registration batch of drug substance and drug product

A systematic approach is recommended:

- Tests on the drug substance,
- Tests on the exposed drug product outside the immediate pack,
- Tests on the drug product in the immediate pack if unacceptable change outside immediate pack,
- Tests on the drug product in the marketing pack If unacceptable change in immediate pack.

Acceptable change is change within limits justified by the applicant.

Actually it has to be differentiated between:

- Change in appearance which is justified by the applicant,
- decomposition the limits of which are described in the ICH Guidelines Impurities in New Drug Substances and New Drug Products.

B Light Sources

To distinguish between:

- the effect of light and temperature
- the temperature should be appropriate controlled or a dark sample used as reference.

☐ **Option I**

Any light source that is designed to produce an output similar to the D 65/ID 65 emission standard such as an
- artificial daylight fluorescent,
- lamp combining visible and ultraviolet. (UV) outputs,
- Xenon or metal halide lamp.

D 65 internationally recognized standard for outdoor daylight (ISO 10977, 1993)
(D 65 is applied for photographic material).
ID 65 is the equivalent indoor indirect daylight standard.

B Light Sources

☐ **Option 2**

For option 2 the same sample should be exposed to both

- The cool white fluorescent lamp specified in ISO 10977(1993) and
- A near UV fluorescent lamp with spectral distribution from 320 nm to 400 nm

The spectral distribution of Xenon is still the best light source

It has to be differentiated between illuminance and irradiance.

Illuminance (how bright a light source Iooks) is measured in lux.

1 lux = 1 luman per square meter.

Irradiance (how much energy a light source has) is measured in Watts per square meter.

1 Watt = 1 Joule per second.

(Illuuminace = Beleuchtungsstärke
Irradiance = Bestrahlung)

C Procedure I

For confirmatory studies, samples should be exposed to light providing an

- overall illumination of not less than 1.2 million lux hours
- and an integrated near ultraviolet energy of not less than 200 Watt hours/square meter.

Samples may be exposed side-by-side with a validated chemical actinometric system or calibrated radiometers/lux meter.

These requirements are fulfilled by the application of the Suntest CPS (Atlas corp.).
It is equipped with a Xenon lamp.

C Procedure

The required radiant exposure

- **200 Wh/m²**
  is given for a wavelength range from 320 nm to 400 nm (UV range)

  The cut-off in the UV at approx. 320 is achieved by a filter system consisting out of a coated quartz glass dish and a window glass filter.

The second mentioned radiant exposure,

- **1.2 million lux hours,**
  is limited to the visible range from approx. 400 nm to 800 nm.

The irradiance level in the Suntest may be adjusted from min. 250 to max. 765 W/ m² between 320 nm and 800 nm.

With the a.m. filter systems installed these limits correspond:
- to approx. 22.5 W/m² to 68.9 W/m² in the UV range and
- to approx. 55 k lux to 170 k lux in the visible range.

C Procedure

❒ **Confirmatory studies 320 - 400 nm 200 Wh/m²**

At min. irradiance level:

200Wh/m²:: 22.5 W/ m² = 8.9 hours

At max. irradiance level:

200 Wh/m² : 68.9 W/m^2 = 2.9 hours

❒ **Confirmatory studies 1.2 million lux hours**

At min. irradiance level:

1.2 million lux hours : 55 klux = 21.8 hours

At maximum irradiance level

1.2 million lux hours: 170 klux = 7.1 hours

Higher irradiance levels shorten the test duration by the factor 3, but the temperature increases if the irradiance is raised.

Therefore it is recommended to apply the minimum irradiance level of 22.5 W/m^2.

2. Drug Substance I

Photostability should consist of two parts:

❒ **Forced degradation testing in early stage of development with one batch**

Evaluation of overall photosensitivity of the material:
- for method development purposes
- and/or degradation pathway elucidation

Drug substance and/or solution/suspension is tested. Exposure should be limited if extensive decomposition occurs.

For photostable materials studies may be terminated after an appropriate exposure level has been applied.

Decomposition products observed under forcing conditions but not formed in the confirmatory studies need not be further examined.

2. Drug Substance II

❒ **Confirmatory testing on single registration batch**

Provide information necessary for:

- Handling,
- Packaging,
- Labelling

A Presentation of Samples

Change in physical states as sublimation or evaporation or melting should be minimised.

An appropriate amount of sample is placed in a

- suitable glass or plastic dish and
- spread across the container
- to give a thickness of not more than 3 mm.

B Analysis of Samples

Samples are examined for any changes in:

- appearance
- clarity
- colour of solution
- assay
- decomposition.

Sampling of representative portion, if necessary homogenisation of entire sample.
For comparison always a protected dark control sample.

C Judgment of Results

- **Forced degradation studies should provide**
  - analytical procedures for confirmatory studies in resolving and detecting photolytic degradants that appear during confirmatory studies.
  - The forced degradation studies form part of the stress testing and are not designed to establish qualitative or quantitative limits for change.
- **The confirmatory studies should identify**
  - precautionary measures needed in manufacturing
  - or in formulation of the drug product and
  - if light resisting packaging is needed.

Drug Substance

- **Example Forced Degradation Studies**
  - **Test samples**:
    - Drug substance spread in colourless and brown glass across the container to give a thickness of not more than 3 mm
    - 1% aqueous solution (or inert organic solvent) with and without N2 gassing in colourless glass.
    - 1% aqueous solution (or organic inert solvent) in brown glass.

- **Test attributes**
  - appearance
  - clarity of solution
  - colour of solution
  - assay
  - decomposition

- **Storage period:**
  - 48 h 22.5 W/m² = 1080Wh/m², = 2.6 million lux hours

- **Evaluation**

  Decomposition: ≤ 0.1 not photosensitive
  > 0.1% test repeated 24 h

Drug Substance

☐ **Example Confirmatory Testing**

- **Test samples:**

  - Drug substance spread in colourless and brown glass across the container to give a thickness of not more than 3 mm

  - 1% aqueous solution (or inert organic solvent) with and without N2 gassing in colourless glass.

  - 1% aqueous solution (or organic inert solvent) in brown glass.

- **Test attributes**
  - appearance
  - clarity of solution
  - colour of solution
  - assay
  - decomposition

- **Storage period:**
  - 23 h 22.5 W/m² = 495 Wh/m², = 1.2 million luxhours

- **Evaluation**

  Decomposition: ≤ 0.1 % test end
  > 0.1% structure elucidation

3. Drug Product

Studies should be carried out in sequential manner:

- Drug product fully exposed, if unacceptable change:
- Drug product in immediate pack, if unacceptable change.
- Drug product in marketing pack.

Results should demonstrate

- that drug product is protected from exposure to light.

One batch during development phase. One registration batch.

Drug product should be exposed to standard conditions. Aluminium tube as packaging only with direct exposed drug product.

A Presentation of Samples

Care should be taken to prevent or minimise physical characteristics of sample

Sample should be positioned to provide maximum area to exposure to light source

B Analysis of Sample

❒ **Test attributes:**

- Physical properties
  - appearance
  - clarity of solution
  - colour of solution
- assay
- decomposition

❒ **Sampling consideration**

- Testing should be conducted on an appropriately composite of samples

C Judgement of Results

Special labelling may be needed to mitigate expose to light

Consider other formal stability studies to ensure that product will be within specifications during shelf life