

Photostability in New Drug Products

'...evaluating photostability is foremost for new chemical entities only - not in generic drugs, provided the container-closure protection is the same...'

INTRODUCTION

In June 1998 the FDA issued for comment, a lengthy 110 page *draft* guidance titled '**Stability Testing of Drug Substance and Drug Products**'. The stability guidance interweaves the requirements of NDAs and ANDAs for both drug substance and drug product and borrows heavily from the European Stability Guidelines.

Photostability Draft Guidelines do not readily affect Generic Development

The New Draft Guidance to industry is extremely comprehensive and is intended to replace the ageing 1987 guidelines, thus harmonising the requirements for US, EU and Japan. They contain detailed recommendations on all current aspects of stability testing, photostability, including reduced testing procedures via the use of bracketing and matrixing protocols.

This Part III article deals with the proposed guidance namely aspects affecting the photostability stability testing in New Drug Applications.

Photostability Draft Guidelines do not readily affect generic development providing that the packaging configuration and protection against

light is equal or better than the reference and one of the two standardized caution phrases 'PROTECT FROM LIGHT' appears on the package labeling.

GENERAL

The ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the *parent guidance*) notes that light testing should be an integral part of stress testing.

The ICH Q1B guidance **Photostability Testing of New Drug Substances and Products** primarily addresses the generation of photostability information for new molecular entities and associated drug products and the use of the data in determining whether precautionary measures in manufacturing, labeling, or packaging are needed to mitigate exposure to light.

Generic Developers should at least be aware of the Draft Photostability Guidelines

Q1B does not specifically address other photostability studies that may be needed to support, for example, the photostability of a product under in-use conditions or the photostability of analytical samples.

Because data are generated on a directly exposed drug substance alone and/or in simple solutions and drug products when studies are conducted as described in the **Q1B** guidance, knowledge of photostability characteristics may be useful in determining when additional studies may be needed or in providing justification for not performing additional studies.

Generic Developers
should check the
reference drug's
labelling and literature
for photo-instability



Light stress testing
is part of
the stress testing
ANY stability indicating
assay development



For example, if a product has been determined to photodegrade upon direct exposure but is adequately protected by packaging, an in-use study may be needed to support the use of the product (e.g., a parenteral drug that is infused over a period of time).

The test conditions for in-use studies will vary depending on the product and use but should depend on and relate to the directions for use of the particular product.

Photostability studies are usually conducted only in conjunction with the first approval of a new molecular entity.

Under some circumstances, photostability studies should be repeated if certain post-approval or supplemental changes, such as changes in formulation or packaging, are made to the product, or if a new dosage form is proposed.

Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of changes made.

For example, if initial studies demonstrate that an active moiety in a simple solution degrades upon exposure to light and the tablet drug product is stable, a subsequent filing requesting approval of a liquid dosage form may warrant additional studies to characterize the photostability characteristics of the new dosage form.

Photostability studies need not be conducted for products that duplicate a commercially available listed drug product provided that the packaging (immediate container/closure and market pack) and labeling storage statements regarding light duplicate those of the **reference listed drug**.

If deviations in packaging or labeling statements are made, additional studies may be recommended.

The decision as to whether additional studies should be conducted will be made on a case-by-case basis by the agencies chemistry review team.

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described in the section Selection of Batches, in the parent guidance.

Under some circumstances, these studies should be repeated if certain variations and changes are made to

the product (e.g., formulation, packaging).

Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation and / or change made. [ICH Q1B] 1992.

Four Stages for Light Stress Testing exist::

Exposed Active material
Drug Product - outside pack
Drug Product - in Primary Pack
Drug Product - Final Marketing Pack

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as: (See flow chart attached.)

- Tests on the drug substance;
- Tests on the exposed drug product outside of the immediate pack; and if necessary,
- Tests on the drug product in the immediate pack; and if necessary,
- Tests on the drug product in the marketing pack (with secondary carton and label - where required). [ICH Q1B]

The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing as described in the **Decision Flow Chart for Photostability Testing of Drug Products**. Acceptable change is change within limits justified by the applicant. [ICH Q1B]

The formal labeling requirements for photolabile drug substances and drug products are established by national / regional requirements. [ICH Q1B]

LIGHT SOURCES

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified.

For both options 1 and 2, a pharmaceutical manufacturer / applicant can rely on the spectral distribution specification of the light source manufacturer. [ICH Q1B]

Standard Light Sources
for light chambers
are set with controlled
exposure temperatures

Option 1

Any light source that is designed to produce an output similar to the D65 / ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard.

For a light source emitting significant radiation below 320 nanometers (nm), an appropriate filter(s) may be fitted to eliminate such radiation. [ICH Q1B]

Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp.

■ A cool white fluorescent lamp designed to produce an output similar to that specified in ISO10977 (1993); and;

■ A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy

emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm. [ICH Q1B]

PROCEDURE [ICH Q1B]

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 to allow direct comparisons to be made between the drug substance and drug product.

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters.

An example of an actinometric procedure is provided.

If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample. [ICH Q1B].

DRUG SUBSTANCE [ICH Q1B]

For drug substances, photostability testing should consist of two parts: Forced degradation testing and confirmatory testing.

The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

This testing may involve the drug substance alone and/or in simple **solutions / suspensions** to validate the analytical procedures. In these

studies, the samples should be in chemically inert and transparent containers.

In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used.

For development and validation purposes, it is appropriate to limit exposure and end the studies if extensive decomposition occurs.

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

The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified. Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies.

This information may be useful in developing and validating suitable analytical methods.

If in practice it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be examined further. Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling (see Presentation of Samples, for information on the design of these studies Section VIII.J.3., Procedure, and 4.a. in guidelines).

Normally, only **one batch** of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guidance if the drug is clearly photostable or photolabile.

If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. Samples should be selected as described in the parent guidance.

[a.] Presentation of Samples [ICH Q1B]

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account, and efforts should be made, such as cooling and/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation, or melting are minimized.

All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

As a direct challenge for samples of **solid drug substances**, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary.

Spread Active Materials
3 mm thick in a covered
glass petri dish.
(plastics can affect wavelength)

Solid drug substances should be spread across the container to give a thickness of typically not more than 3 millimeters.

Drug substances that are liquids should be exposed in chemically inert and transparent containers.

[b.] Analysis of Samples - At the end of the exposure period, the samples should be examined for any changes

in physical properties (e.g., **appearance, clarity, color of solution**) or **assay** and **degradants** by a method suitably validated for products likely to arise from photochemical degradation processes.

Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations, such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure.

The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark control if these are used in the test.

[c.] Judgement of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies.

These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies.

When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

Generic Developers
must perform light
stress studies on the
stability indicating assay

The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product and if light resistant packaging is needed.

When evaluating the results of confirmatory studies to determine whether change due to exposure to

light is acceptable, it is important to consider the results from other formal stability studies to ensure that the drug will be within justified limits at time of use (see the relevant ICH stability and impurity guidance).

DRUG PRODUCTS [ICH Q1B]

Normally, the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack.

Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light.

The drug product should be exposed to the light conditions described.

Normally, only **one batch** of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guidance if the product is clearly photostable or photolabile.

If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted on directly exposed drug product.

It may be appropriate to test certain products, such as **infusion liquids** or **dermal creams**, to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

[a.] Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account, and efforts, such as cooling and/or placing the samples in sealed containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting.

All precautions should be chosen to provide minimal interference with the irradiation of samples under test.

Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

Where practicable when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance.

Spread Tablets & Capsules
in a single layer
in a covered glass petri dish
for maximum exposure

The samples should be positioned to provide maximum area of exposure to the light source.

For example, **tablets and capsules** should be spread in a single layer.

If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz).

If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples.

Some adjustment of testing conditions may have to be made when testing large volume containers (e.g., dispensing packs).

[b.] Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g.,

- appearance
- clarity of solution
- color of solution
- dissolution / disintegration for dosage forms such as capsules)
- assay
- degradants



Suitably validated methods for degradants likely to arise from photochemical degradation processes should be used.

When powder samples are involved, sampling should ensure that a representative portion is used in individual tests.

For solid oral dosage form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules.

Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions).

The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

[c.] Judgement of Results

Depending on the extent of change, special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies to ensure

that the product will be within proposed specifications during the shelf life (see the relevant ICH stability and impurity guidance).

QUININE CHEMICAL ACTINOMETRY

Details of an actinometric procedure for monitoring exposure to a near UV fluorescent lamp, based on the draft guidance are provided in the attached Standard Operating Procedure.

ACCEPTABLE & UNACCEPTABLE PHOTOSTABILITY CHANGE

The extent of the drug product photostability testing depends on the change that has occurred at the end of each test tier described in the Decision Flow Chart for Photostability (See chart.)

Testing of Drug Products.

Test results that are outside the proposed acceptance criteria for the product would not be considered acceptable change.

This is a stress test designed to determine the intrinsic photostability characteristics of new drug substances and products, and no correlation has been developed to equate a within specification result to an expiration dating period.

Evaluate Light Stress and Heat Stress Degradation Separately

The acceptability of any observed changes should be justified in the application. It may be important to consider other degradative processes (e.g., thermal) when justifying a photostability change as acceptable because the processes may be independent and additive.

For example, a 5 percent loss in potency due to photodegradation may be considered acceptable if that is the only type of degradation observed.

If the product is also expected to degrade **5 percent** over the shelf-life *due to thermal degradation*, the photo-

degradation may then be considered unacceptable based on the potential additive effect of the changes. In this case, precautions should be taken to mitigate the product's exposure to light.

Under the intense light exposure conditions included in the **Q1B** guidance, certain colors in solid dosage forms may fade.

Quantitative analysis of the color change is not recommended as these changes are not likely to occur under actual storage conditions.

In the absence of change in other parameters such as assay, these color changes may be acceptable.

Two Standardized labeling instructions recommended to PROTECT FROM LIGHT

PHOTOSTABILITY LABELING

The data generated using the procedure described in the ICH Q1A guidance is useful in determining when special handling or storage statements regarding exposure to light should be included in the product labeling (21 CFR 201.57(k)(4)).

The labeling guidance provided below pertains only to products as packaged for distribution. Instructions and stability statements that may be needed to address in-use conditions pursuant to 21 CFR 201.57(j) are not covered.

Change after direct exposure:

If changes that are observed when the product is directly exposed under the light conditions described in the **Q1B** guidance are acceptable, no labeling storage statement regarding light is needed.

Change after exposure in the immediate container/closure:

If changes observed when the product is directly exposed are unacceptable, but are acceptable when the product is tested in the immediate container / closure under the conditions described in the **Q1B** guidance, the

inclusion of a labeling storage statement regarding light would depend on the likelihood of the product being removed from the immediate package during the distribution process.

■ For those products that are unlikely to be removed from the immediate container, such as creams or ointments in tubes dispensed directly to the patient, and ophthalmic products, the use of a labeling storage statement regarding light is optional.

■ For products that may be removed from the immediate pack, such as pharmacy bulk packs, a light storage statement should be included such as "PROTECT FROM LIGHT. Dispense in a light-resistant container."

Change after exposure in the market pack:

If changes that are observed are acceptable only when the product in the market pack is exposed under the conditions described in the **Q1B** guidance, labeling storage statements regarding light should be included.

Examples of typical labeling cautions for single-dose and multiple-dose products respectively are either,

Labeling Caution - Type Single Dose

■ "PROTECT FROM LIGHT. Retain in carton until time of use."

Labeling Caution - Type Single Dose

■ "PROTECT FROM LIGHT. Retain in carton until contents are used."

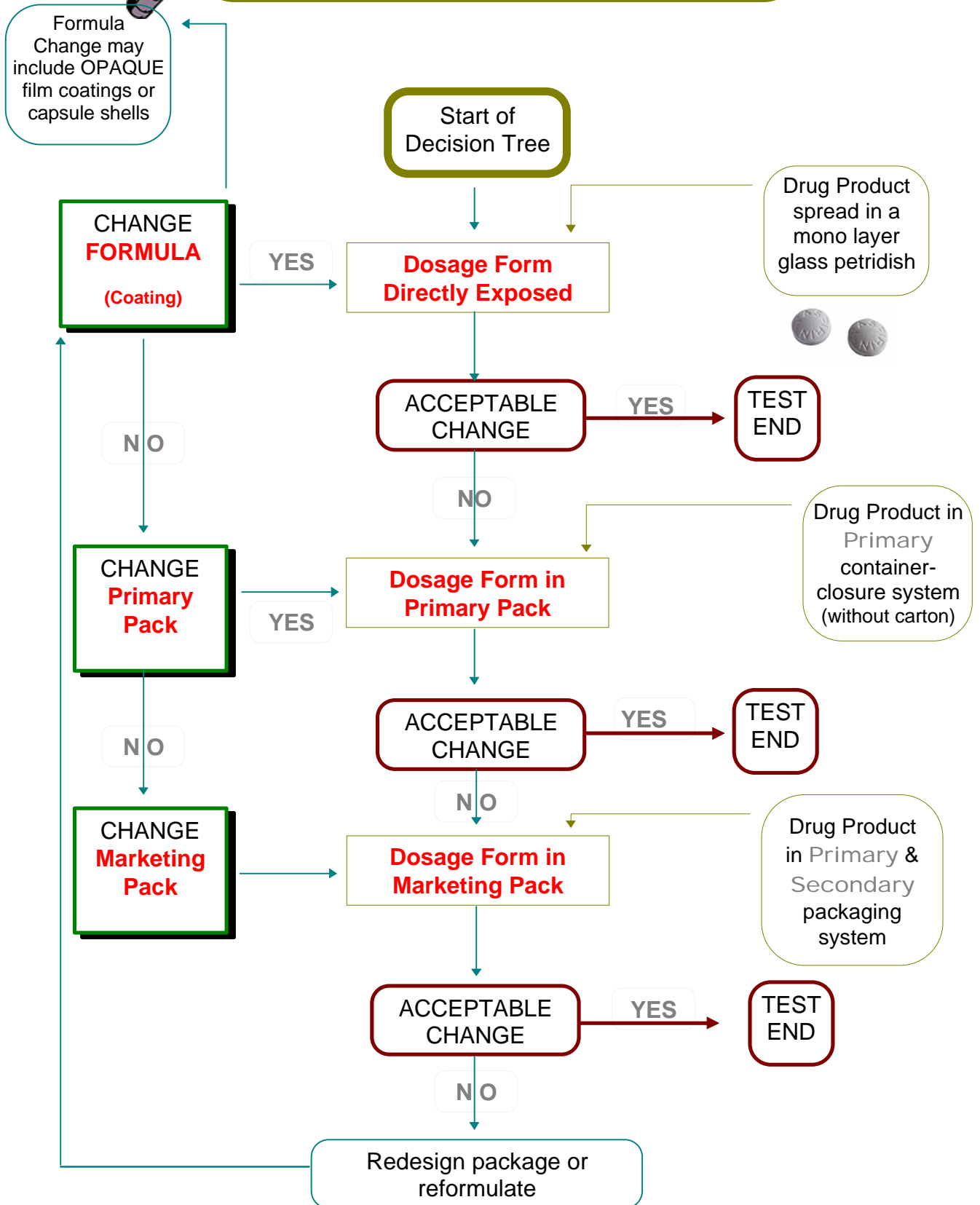
SOPS and 'Guidance for Industry'

■ Violating an in-house SOP is a GMP violation and you can be cited for SOP violations.

■ Violating a agency 'Guidance for Industry' in **NOT** a GMP violation and you **cannot** be cited for a violation.

■ Violating an in-house SOP which is based on a 'Guidance for Industry' is a standard GMP violation.
The photostability example supplied is a SOP based on the current draft guideline.

Decision Flowchart for Photostability of Drug Products



HIGHLIGHTS



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IMPURITIES
QUALIFYING IMPURITIES IN
GENERIC BULK
DRUG SUBSTANCES
(Impact of Q3A and Q3B)

Intelligent
Drug Development

Topical Bioequivalent Studies

New Smarter Ways
of achieving
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