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3 GUIDELINE FOR THE STABILITY TESTING
4 OF NON-PRESCRIPTION (OTC) DRUG PRODUCTS NOT REGULATED BY AN NDA/ANDA
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20 ***INTRODUCTION***

21 Prior to this guideline, the non-prescription industry did not have directly applicable stability
22 testing guidance for OTC monograph drug products not regulated by an NDA/ANDA.
23 Historically, non-prescription drug companies developed their stability testing programs based
24 upon their best interpretation and practical application of the most current FDA guidance for new
25 drug products. Because of the unique requirements associated with new drug products, the direct
26 application of the FDA guidance is frequently inappropriate and impractical. Drug products with
27 an OTC monograph will typically be well characterized with a significant body of information, a
28 well known safety profile, and a long history of use in multiple dosage forms. For this reason, the
29 OTC industry is proposing this guideline for non-prescription (OTC) drug products not regulated
30 by an NDA/ANDA. For simplicity, non-prescription (OTC) drug products not regulated by an
31 NDA/ANDA will be referred to as OTC monograph drug products.

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44 ***OBJECTIVES OF THE GUIDELINE***

45 To define the minimum stability data package to support the commercial distribution of OTC
46 monograph drug products in the United States per climatic zone II. The stability data package
47 will be based on development stability studies. These studies will be used to establish the
48 tentative expiration dating period and label storage statement for the OTC monograph drug
49 product.

50 This guideline recognizes that a significant body of scientific information may exist for OTC drug
products. Alternative approaches may be used when there are scientifically justifiable reasons.

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64 ***SCOPE OF THE GUIDELINE***

65 This guideline applies specifically to OTC monograph drug product stability. This guideline does
66 not currently seek to cover the stability testing of:

- 67 - Non-prescription drug products regulated by an NDA/ANDA
- 68 - Drug substances
- 69 - Drug products used in clinical trials
- 70 - Marketed product stability

71 Additionally, this guideline is not applicable to:

- 72 - Specific details of the sampling and testing for particular dosage forms in their proposed
73 container closures
- 74 - Safety studies

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88 ***GENERAL PRINCIPLES***

89 The purpose of product stability testing is to provide evidence on how the quality of a drug
90 product in a specific package configuration varies with time under the influence of a variety of
91 environmental factors such as temperature, humidity, and light, and to establish a shelf-life period
92 for the drug product and recommended storage conditions.

51 The choice of test conditions defined in this guideline is based on an analysis of the effects of
52 climatic conditions only in the United States.

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54 The design of the stability studies for the OTC monograph drug product should be based on
55 knowledge of the behavior and properties of the drug substance and drug products that use the
56 same active ingredient(s), manufacturing process, quantity of excipients, and container / closure
57 system. The likely changes on storage and the rationale for the selection of attributes to be tested
58 in the formal stability studies should be stated.

60 ***PHOTOSTABILITY TESTING***

61 Stability data should be available to demonstrate that the drug product is not susceptible to light.
62 At least one batch of the drug product packaged in the container closure proposed for market
63 should be tested for photostability effects. This testing may be omitted, if a scientific
64 justification can be provided to show that the drug product in the container closure proposed for
65 market will not be susceptible to photostability effects.

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67 The irradiation of the packaged drug product is to be conducted according to the ICH Q1B
68 guidance for photostability testing of drug products. Generally, not all test parameters are
69 required in order to assess photostability effects. Scientific judgment should be used in order to
70 determine the appropriate subset of parameters required for the photostability assessment.

72 ***SELECTION OF BATCHES***

73 Stability data should be available on at least one primary batch of the drug product. Primary
74 batches may be necessary for new product formulations and instances where no similar
75 formulations exist. The primary batch(es) should be of the same formulation and packaged in the
76 same container closure system as proposed for marketing. The manufacturing process used for
77 primary batch(es) should simulate that to be applied to production batches and should provide
78 product of the same quality and meeting the same specification as that intended for marketing.
79 The batch(es) should be at least pilot scale (1/10 Production Scale); a scientific rationale may be
80 used to justify a smaller batch size. Where practical, if multiple batches are studied, the drug
81 product should be manufactured using different batches of the drug substance. Stability studies
82 should be performed on each individual strength, container size, or other attribute unless a
83 reduced sampling and testing program can be scientifically justified (e.g. bracketing and/or
84 matrixing approaches can be used).

86 ***CONTAINER / CLOSURE SYSTEM***

87 Stability testing should be conducted on the dosage form packaged in the container closure
88 system proposed for marketing.

90 ***SPECIFICATIONS***

91 A specification is composed of a list of tests with references to analytical procedures and the
92 proposed acceptance criteria. The acceptance criteria can be numerical limits or ranges, textual
93 descriptions, or other requirements depending on the type of test specified.

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95 The list of tests should include an assessment for all of the drug product attributes that are
96 susceptible to change during storage and that are likely to influence quality, safety, and/or
97 efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and
98 microbiological attributes. Analytical test procedures should be fully validated and stability
99 indicating. There are some test methodologies where it may not be necessary or appropriate,
100 using good scientific judgment, to validate a test procedure (e.g. tablet hardness, where a
101 calibrated test instrument is used).

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Acceptance criteria for shelf-life specifications should be based on all of the available stability information and compendial requirements. Specifications for product release may be more restrictive than shelf-life specifications in order to account for changes observed during storage of stability samples.

For multi-dose liquid and semi-solid drug products, antimicrobial preservative effectiveness testing (AET) should be demonstrated in the multi-dose container(s). If differences between the release and shelf-life acceptance criteria for AET are necessary, the difference should be scientifically justified based on a correlation between preservative content and preservative effectiveness.

TESTING FREQUENCY

The frequency of testing, for the primary stability studies, should be designed in order to adequately determine the stability profile for the drug product. This testing frequency will typically be 0, 3, 6, 12, and 24 months, and annually thereafter through the proposed shelf-life. Other time points (such as 9, 18, 30 months) may also be appropriate.

At the accelerated storage condition, a minimum of three time points are recommended to be tested over a three month period (including the initial and final time; e.g. 0, 1, and 3 months). When the drug product fails to meet the established shelf-life criteria at the accelerated storage condition (such as 40C/75%RH), alternative accelerated conditions may be used to insure that at minimum, some acceptable accelerated data is available to show that the product can withstand the typical excursions experienced in the distribution chain once the product is marketed. In addition, a drug product that fails to meet shelf-life specifications for accelerated conditions will require additional data from long term and/or alternate accelerated conditions in order to establish an acceptable tentative expiration dating period for market.

STORAGE CONDITIONS

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Long term and accelerated storage conditions for drug products are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

Container orientation should be considered when designing stability study protocols for liquid and semi-solid products.

STORAGE CONDITIONS – GENERAL CASE

Study	Storage Condition
Long Term	25 ± 2°C / 60 ± 5% RH
Accelerated	40 ± 2°C / 75 ± 5% RH

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146 If at the accelerated storage condition the drug product fails to meet the established shelf-life
147 criteria, alternative accelerated conditions may be used to insure that at minimum, some
148 acceptable accelerated data is available to show that the product can withstand the typical
149 excursions experienced in the distribution chain once the product is marketed.

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151 ***STORAGE CONDITIONS –***

152 ***DRUG PRODUCTS PACKAGED IN IMPERMEABLE CONTAINERS***

153 Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in
154 impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus,
155 stability studies for products stored in impermeable containers can be conducted under any
156 controlled or ambient humidity condition.

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158 ***STORAGE CONDITIONS –***

159 ***DRUG PRODUCTS PACKAGED IN SEMI-PERMEABLE CONTAINERS***

160 Aqueous-based products packaged in semi-permeable containers should be evaluated for potential
161 water loss in addition to physical, chemical, biological, and microbiological stability. This
162 evaluation can be carried out under conditions of low relative humidity, as discussed below.
163 Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable
164 containers can withstand low relative humidity environments. Other comparable approaches can
165 be developed and reported for non-aqueous, solvent-based products.

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Study	Storage Condition
Long Term	25 ± 2°C / 40 ± 5% RH
Accelerated	40 ± 2°C / NMT 25% RH

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168 A 5% loss in water from the initial value is recommended to be the limit of acceptability for a
169 product packaged in a semi-permeable container after an equivalent of 3 months' storage at
170 40°C/NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a
171 water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be
172 appropriate, if justified.

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174 An alternative approach to studying at the reference relative humidity as recommended in the
175 table above (for either long term or accelerated testing) is performing the stability studies under
176 higher relative humidity and deriving the water loss at the reference relative humidity through
177 calculation. This can be achieved by experimentally determining the permeation coefficient for
178 the container closure system or, as shown in the example below, using the calculated ratio of
179 water loss rates between the two humidity conditions at the same temperature. The permeation
180 coefficient for a container closure system can be experimentally determined by using the worst
181 case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

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183 Example of an approach for determining water loss:

184 For a product in a given container closure system, container size, and fill, an appropriate approach
185 for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate
186 measured at an alternative relative humidity at the same temperature by a water loss rate ratio
187 shown in the table below. A linear water loss rate at the alternative relative humidity over the
188 storage period should be demonstrated. For example, at a given temperature, e.g., 40°C, the
189 calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75%
190 RH multiplied by 3.0, the corresponding water loss rate ratio.

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Alternative Relative Humidity	Reference Relative Humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

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Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

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STORAGE CONDITIONS – SPECIAL CASE

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Drug products intended for storage in a refrigerator, freezer, below -20°C, or under other conditions should be treated on a case-by-case basis.

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POST-LAUNCH STABILITY REQUIREMENTS

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Post-launch marketed product stability testing will be conducted to confirm the assigned expiration dating period as required by the current Good Manufacturing Practices (cGMPs).

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EVALUATION

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A scientific approach should be adopted in the presentation and evaluation of stability information for establishing a tentative expiry period. Results from research and development batches on similar or closely related formulations, on similar or closely related marketed products, and data published in the literature, as well as results from the specific stability study may be considered a body of knowledge that can be used in the scientific assessment. Results from physical, chemical and microbiological tests as appropriate for the dosage form should be included in this evaluation.

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The purpose of the accelerated stability study is to establish, based on testing a minimum of one batch of the drug product, a tentative expiry period and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances.

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When the data from an accelerated stability study remains within established limits, while maintaining potency, a tentative expiry period can be assigned prior to marketing the product. A twenty-four month expiry period may be assigned upon successful completion of three months accelerated testing. Using sound scientific judgment, shorter expiry periods may be assigned based on less than three months of accelerated testing and longer tentative expiry periods may be justified using extended periods of accelerated testing. Any longer tentative expiry period or extension of an expiration dating period should be made based on the previous histories of similar products, sound scientific judgment, calculations using the Arrhenius equation, all with appropriate documentation.

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When the data clearly exhibits no change or stability trend over time, a formal statistical analysis is not necessary.

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An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean intersects the acceptance criterion. If analysis shows that the batch-to-batch or among package configuration variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of

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235 rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the
236 individual batches or package configurations. If it is inappropriate to combine data from several
237 batches, the overall shelf life should be based on the minimum time a batch can be expected to
238 remain within acceptance. If it is inappropriate to combine data from several package
239 configurations, then each configuration should be evaluated separately with an expiry period
240 being assigned to the individual package configuration rather than to the product as a whole.

241

242 **STATEMENTS/LABELING**

243 A storage statement should be established for the labeling in accordance with current FDA or
244 USP requirements. The statement should be based on the stability evaluation of the drug product.
245 Where applicable, specific instruction should be provided, particularly for drug products which
246 require special storage conditions.

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248 **GLOSSARY**

249 The following definitions are provided to facilitate interpretation of the guideline.

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251 **Accelerated testing**

252 Studies designed to increase the rate of chemical or physical change of a drug product by using
253 exaggerated storage conditions as part of the formal stability studies. Data from these studies, in
254 addition to long term stability studies, can be used to assess longer term chemical effects at non-
255 accelerated conditions and to evaluate the effect of short term excursions outside the label storage
256 conditions such as might occur during shipping. However, results from accelerated studies are
257 not always representative of similar results from the long-term label storage studies.

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259 **Bracketing**

260 The design of a stability schedule such that only samples on the extremes of certain design
261 factors, e.g., strength, package size, are tested at all time points as in a full design. The design
262 assumes that the stability of any intermediate levels is represented by the stability of the extremes
263 tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are
264 identical or very closely related in composition (e.g., for a tablet range made with different
265 compression weights of a similar basic granulation, or a capsule range made by filling different
266 plug fill weights of the same basic composition into different size capsule shells). Bracketing can
267 be applied to different container sizes or different fills in the same container closure system.

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269 **Container / Closure system**

270 The sum of packaging components that together contain and protect the dosage form. This
271 includes primary packaging components and secondary packaging components, if the latter are
272 intended to provide additional protection to the drug product. A packaging system is equivalent to
273 a container closure system.

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275 **Development studies**

276 Stability studies initiated during the development of a drug product. If these studies are to be
277 used for the purpose of assigning a tentative expiration dating period, they are sometimes called
278 "formal" stability studies.

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280 **Dosage form**

281 A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug
282 substance generally, but not necessarily, in association with excipients.

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284 **Drug product**

285 The dosage form in the final immediate packaging intended for marketing.

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287 **Drug Substance**
288 The unformulated active pharmaceutical ingredient that may subsequently be formulated with
289 excipients to produce the dosage form.
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291 **Excipient**
292 Anything other than the drug substance in the dosage form.
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294 **Expiration date**
295 The date placed on the container label of a drug product designating the time prior to which a
296 batch of the product is expected to remain within the approved shelf life specification if stored
297 under defined conditions, and after which it must not be used.
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299 **Formal stability studies**
300 Stability studies initiated during the development of a drug product in a specific package
301 according to a prescribed stability protocol in order to establish or confirm the shelf life or
302 expiration dating period for the product.
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304 **Impermeable containers**
305 Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed
306 aluminum tubes for semi-solids, sealed glass ampoules for solutions.
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308 **Long term testing**
309 Stability testing of samples that have been stored at the proposed (or approved) labeled storage
310 condition for a drug product in a specific package. Samples are stored and tested through the
311 entire shelf life period.
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313 **Matrixing**
314 The design of a stability schedule such that a selected subset of the total number of possible
315 samples for all factor combinations is tested at a specified time point. At a subsequent time point,
316 another subset of samples for all factor combinations is tested. The design assumes that the
317 stability of each subset of samples tested represents the stability of all samples at a given time
318 point. The differences in the samples for the same drug product should be identified as, for
319 example, covering different batches, different strengths, different sizes of the same container
320 closure system, and, possibly in some cases, different container closure systems.
321
322 **Pilot scale batch**
323 A batch of a drug product manufactured by a procedure fully representative of and simulating that
324 to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is
325 generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules,
326 whichever is the larger.
327
328 **Primary batch**
329 A batch of a drug product used in a formal stability study for the purpose of establishing an
330 expiration dating period. A primary batch of a drug product should be at least a pilot scale batch;
331 a scientific rationale may be used to justify the use of a smaller batch.
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333 **Production batch**
334 A batch of drug product manufactured at production scale using production equipment in a
335 production facility.
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337 **Semi-permeable containers**
338 Containers that allow the passage of solvent, usually water, while preventing solute loss. The
339 mechanism for solvent transport occurs by absorption into one container surface, diffusion
340 through the bulk of the container material, and desorption from the other surface. Transport is
341 driven by a partial-pressure gradient.
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343 **Shelf life (also referred to as expiration dating period)**
344 The time period during which a drug product is expected to remain within the approved shelf life
345 specification, provided that it is stored under the conditions defined on the container label.
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347 **Specification – Release**
348 The combination of physical, chemical, biological, and microbiological tests and acceptance
349 criteria that determine the suitability of a drug product at the time of its release.

350 **Specification - Shelf life**
351 The combination of physical, chemical, biological, and microbiological tests and acceptance
352 criteria that determine the suitability of a drug product throughout its shelf life.
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354 **Storage condition tolerances**
355 The acceptable variations in temperature and relative humidity of storage facilities for formal
356 stability studies. The equipment should be capable of controlling the storage condition within the
357 ranges defined in this guideline. The actual temperature and humidity (when controlled) should
358 be monitored during stability storage. Short term spikes due to opening of doors of the storage
359 facility are accepted as unavoidable. The effect of excursions due to equipment failure should be
360 addressed, and reported if judged to affect stability results. Excursions that exceed the defined
361 tolerances for more than 24 hours should be described in the study report and their effect
362 assessed.
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364 **Supporting data**
365 Data, other than those from formal stability studies, that support the analytical procedures, the
366 proposed shelf life, and the label storage statements. Such data include (1) stability data on small
367 scale batches of materials, investigational formulations not proposed for marketing, related
368 formulations, and product presented in containers and closures other than those proposed for
369 marketing; (2) information regarding test results on containers; and (3) other scientific rationales.
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371 **Tentative Expiry Period**
372 A shelf-life for a drug product in a specific package that has been established using either
373 accelerated or less than full term stability data. A tentative expiry period becomes a shelf-life
374 period once acceptable long term stability data are available to confirm the tentative period.
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376 **REFERENCES**
377 *ICH Q1B: "Photostability Testing of New Drug Substances and Products"*
378